

ORIGINAL RESEARCH

Prevalence of Pathogenic Genetic Variants Across Heart Failure Etiologies in an Admixed Population

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ABSTRACT

BACKGROUND Heart failure (HF) has multiple etiologies, but genetic testing remains mainly recommended for selected subgroups with suspected inherited cardiomyopathy.

OBJECTIVES This study identified and classified genetic variants in patients within a HF cohort with reduced ejection fraction or mildly reduced ejection fraction from diverse etiologies in an admixed population.

METHODS The authors analyzed whole-genome sequencing data from 1,013 unrelated individuals in the GENIUS-HF (Genetic and ElectroNic medical records to predict oUtcomeS in Heart Failure patients) cohort. Rare variants in 123 ClinGen-curated cardiovascular genes were classified according to American College of Medical Genetics and Genomics (ACMG) criteria. Local ancestry inference evaluated associations with variant distribution.

RESULTS Overall, 6.5% of individuals carried at least one pathogenic/likely pathogenic variant considered causal (no significant difference between HF cohort with reduced ejection fraction and HF with mildly reduced ejection fraction, $P = 0.500$), 77.7% had at least 1 variant of uncertain significance, and 15.8% had only benign/likely benign variants observed. *TTN* variants accounted for nearly half of the causal findings, including 13 novel variants, with additional causal variants in *MYBPC3*, *FLNC*, *BAG3*, and *DSP*. Idiopathic dilated cardiomyopathy showed the highest yield (9.9%), but pathogenic variants were also detected in ischemic (4.6%), Chagasic HF (4.9%), and hypertensive (3.8%). Local ancestry analyses showed that variant of uncertain significance were significantly more frequent in regions with African and Native American ancestry.

CONCLUSIONS These findings replicate a significant diagnostic yield of molecular genetic testing in individuals with dilated cardiomyopathy but extend the relevance of genetic testing beyond traditionally selected HF subgroups. They also underscore the importance of including non-European and admixed populations in cardiovascular genomics to reduce interpretation bias and improve equity in precision medicine. (JACC Adv. 2026;■:103123) © 2026 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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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

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**ABBREVIATIONS
AND ACRONYMS****AD** = autosomal dominant**AR** = autosomal recessive**B** = benign**DCM** = dilated cardiomyopathy**HCM** = hypertrophic
cardiomyopathy**HF** = heart failure**LB** = likely benign**LoF** = loss-of-function**LP** = likely pathogenic**P** = pathogenic**PSI** = percentage spliced in**VUS** = variant of uncertain
significance

Hear failure (HF) is a progressive disorder that is characterized by structural and/or functional impairment of the heart, leading to insufficient cardiac output, which results in high hospitalization and mortality rates.¹ In 2023, it affected approximately 64 million people worldwide, including 2 million in Brazil.² HF can have diverse etiologies, including coronary artery disease, hypertension, Chagas disease, valvopathy, and cardiomyopathies.^{3,4}

The genetic contribution to HF is heterogeneous and complex. Increasing evidence shows that causes previously thought to be purely environmental are, in reality, determined by a complex interplay between genetic and nongenetic causes.⁵⁻⁷ Previous studies have shown that the genetic diagnostic yield ranges from 3% to 35% across HF cohorts, depending on the cohort design, inclusion criteria, etiology, and ancestral background, reflecting the genetic heterogeneity of HF.^{8,9} However, most information on the prevalence of pathogenic (P) genetic variants in HF individuals is mostly restricted to cohorts of primary cardiomyopathies, such as hypertrophic and dilated cardiomyopathy (DCM), and it is still unknown what role, if any, genetic testing has in HF from different etiologies.

Moreover, allele frequency and variant effect differ across diverse ancestry groups, as current genomic knowledge has been derived primarily from European individuals, leading to an underrepresentation of admixed individuals in genetic databases and literature.^{10,11}

Here, we conducted a comprehensive analysis to identify and classify rare and potentially P variants in 1,013 admixed patients with HF with reduced ejection fraction or mildly reduced ejection fraction of various etiologies. We focused on genes previously implicated in cardiac disease, and evaluated the frequency of P and uncertain variants across ancestries.

METHODS

STUDY DESIGN AND PATIENTS. This is a retrospective cohort study based on the analysis of genetic and clinical data previously collected from the GENIUS-HF (Genetic and ElectroNic medical records to predict oUtcomeS in Heart Failure patients) cohort,¹² conducted at the Heart Institute (Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo) and part of the DNA do Brasil study.¹³

We included 1,013 Brazilian adults, unrelated, between 18-80 years of age, with HF of different etiologies and ejection fraction $\leq 50\%$. We excluded patients with impaired cognition, without telephone access, or who refused to participate, as previously published in the GENIUS-HF baseline description.¹² All enrolled patients were followed and treated at the Heart Institute (São Paulo, Brazil).

HF etiology was the one considered at enrollment in the protocol. HF etiology was determined based on clinical records and confirmed by 3 board-certified cardiologists. An etiological definition was made after all diagnostic tests deemed initially necessary were available. Chagas disease etiology was confirmed by serological evidence of immunoglobulin G antibodies to *Trypanosoma cruzi* by immunoenzymatic and indirect immunofluorescence assays. Ischemic HF etiology was defined as a history of myocardial infarction, coronary artery bypass graft surgery, or obstructive coronary artery disease. Patients classified as idiopathic were considered to have DCM of unknown cause. Medication dosage was recorded from the most recent prescriptions at enrollment. Patients signed an informed consent form, and the study was approved by the local ethics committees (Comitê de Ética e Pesquisa HC-FMUSP CAAE #85633324.0.0000.0068).

**WHOLE-GENOME SEQUENCING, VARIANT CALLING,
AND ANNOTATION.**

We extracted DNA from whole blood samples, prepared whole-genome sequencing libraries following the prespecified high-coverage ($>35\times$) protocol for DNA polymerase chain reaction-free by Illumina, and sequenced using the NovaSeq system. After sequencing, as described elsewhere,¹³ we processed sequence data with Genome Analysis Toolkit (GATK) Docker v4.1.8.0. Per-sample variants were called with HaplotypeCaller followed by Variant Quality Score Recalibration according to GATK Best Practices to obtain a cohort joint Variant Call Format (VCF) file. Variants failing GATK's PASS filter were excluded. In addition, genotype calls with a read depth $<10\times$ were removed from the analyses. Variants were annotated with the Ensembl Variant Effect Predictor¹⁴ v113 using the Genome Reference Consortium Human Build 38 (GRCh38). After annotation, variants with intrastudy minor allele frequency <0.01 were retained using bcftools. Only the variants predicted by Variant Effect Predictor as having high and moderate impact on the transcript were retained (ie, splice sites, stop gained, transcript ablation, frameshift, stop lost, start lost, transcript amplification, inframe insertion, inframe deletion, protein altering, and missense variants).¹⁴

GENE SELECTION AND RARE VARIANT ANALYSIS.

Cardiovascular genes were selected according to different ClinGen Cardiovascular Curation Expert Panels.¹⁵⁻²⁰ We selected only the genes presented in cardiovascular panels with supportive evidence, defined as “limited,” “moderate,” “strong,” and “definitive,” excluding the genes defined as “no evidence” or “contradictory evidence.” The list of selected genes (123 in total) is provided in [Supplemental Table 1](#).

All variants identified were interpreted and classified according to the ACMG (American College of Medical Genetics and Genomics)²¹ following the ACGS (Association for Clinical Genomic Science)²² specifications and ClinGen gene-specific Variant Curation Expert Panel recommendations, when available. General population data were obtained using the total allele frequencies from the gnomAD database (version 4.1), which contains data from different populations, and from ABraOM (version 2.1), a repository containing population data only from Brazilian elderly individuals.²³ In silico prediction for missense variants was assessed using the REVEL (Rare Exome Variant Ensemble Learner) meta-predictor.²⁴ We applied the PP3 (supporting evidence for pathogenicity) criteria for a REVEL score of ≥ 0.64 and the BP4 (supporting evidence for benign effect) for a REVEL score of ≤ 0.29 , as recommended by ClinGen.²⁵

After evaluating each criterion from the American College of Medical Genetics and Genomics guideline, the variants were classified as benign (B), likely benign (LB), uncertain (variant of uncertain significance [VUS]), likely pathogenic (LP), and P. A second analyst independently reviewed variant classifications to ensure consistency and accuracy.

We defined LP/P findings as causal when they occurred in genes with definitive, strong, and moderate evidence levels and curated as autosomal dominant (AD) or x-linked by ClinGen, or when biallelic in autosomal recessive (AR) genes. Heterozygous LP/P variants in genes with AR evidence were treated as carrier findings and LP/P variants in genes classified as limited by ClinGen were considered secondary findings, and, therefore, were excluded from the diagnostic yield.

Novel variants were defined as absent from ClinVar, gnomAD v4.1, ABraOM v.2.1, and dbSNP at the time of analysis (December 2025).

LOCAL ANCESTRY INFERENCE. We used genomic ancestry information to evaluate its influence on HF etiology and the distribution of genetic variants. As previously described,¹³ we inferred local ancestry using GNOMIX, a method that infers local ancestry by

training a supervised machine learning model on reference panels to classify genomic segments along phased haplotypes, leveraging linkage patterns and neighboring markers to assign ancestry at a fine scale across the genome.²⁶

Local ancestry was derived from the GNOMIX output file (.msp), which encodes ancestry assignments along each phased haplotype across the genome. To determine local ancestry at the variant level, we integrated a phased VCF file, generated using Shapeit5,²⁷ with corresponding ancestry segments by mapping each variant position to its respective genomic interval in the msp file. This allowed assignment of ancestry to each allele at each variant site.

After the variant classification, we evaluated the distribution of local ancestry across LP/P and VUS variants. We calculated the proportion of ancestry-specific segments overlapping the variants and compared observed vs expected ancestry frequencies across variant classes (the observed proportion corresponds to the ancestry distribution among variant-containing segments, and the expected proportion reflects the ancestry distribution across all genomic segments).

STATISTICAL ANALYSIS. Categorical variables were described as frequencies and compared using the chi-square test. Quantitative variables were described using the median (Q1-Q3), and comparisons were made using the Kruskal-Wallis rank-sum test. CIs for diagnostic yield estimates were calculated using the exact binomial method.

We set a statistically significant threshold at $P < 0.05$ for these analyses. All the analyses were performed using R, version 4.5.1.

RESULTS

INDIVIDUALS. We performed a whole-genome analysis in 1,013 Brazilian adults with HF ([Table 1](#)), who were categorized based on genetic findings. The median age was 57 years, and 35% of individuals were female. Median genomic local ancestry proportions revealed a predominant European component (62.3%), followed by African ancestry (23.8%), Native American (9.4%), and East Asian (0.4%). Regarding cardiac function, the median ejection fraction was 30%, and most patients were classified as having idiopathic (considered here as DCM) HF etiology (29.9%), followed by ischemic (21.2%), hypertensive (18.1%), and Chagasic (16.1%). Ancestry analysis demonstrated that, although European ancestry was predominant across all etiology groups, its proportion

TABLE 1 Individuals' Clinical and Demographic Characteristics

	All Individuals (N = 1,013)	Causal Variant (n = 66)	Uncertain (n = 787)	No Evidence for Causal Variant (n = 160)	P Value ^a
Age, y	57 (48-65)	52 (43-61)	57 (48-65)	57 (50-66)	0.010
Female	356 (35)	25 (38)	276 (35)	55 (34)	0.9
HF classification					0.5
HFmrEF	178 (18)	9 (14)	137 (17)	32 (20)	
HFrEF	834 (82)	57 (86)	650 (83)	127 (80)	
LVEF, %	30 (25-40)	30 (25-35)	31 (25-39)	33 (28-40)	0.2
Local ancestry proportions, %					
European	62.2 (47.6-77.2)	63.2 (51.9-74.8)	61.3 (46.6-77.2)	66.4 (53.7-79.2)	0.061
African	23.7 (11-39.5)	22.0 (13.6-36.6)	24.9 (11.1-40.9)	21.5 (9.4-37.3)	0.15
Native American	9.4 (5.8-12.9)	9.0 (6.2-13.4)	9.2 (5.6-12.7)	9.7 (6.6-13.2)	0.6
East Asian	0.4 (0-0.9)	0.5 (0.04-1.0)	0.4 (0.0-0.9)	0.4 (0.0-0.8)	0.6
Obesity					0.2
No	591 (59)	39 (62)	469 (60)	83 (53)	
Grade I	215 (22)	11 (17)	171 (22)	33 (21)	
Grade II	134 (13)	7 (11)	98 (13)	29 (18)	
Grade III	57 (5.7)	6 (9.5)	39 (5)	12 (7.6)	
BMI, kg/m ²	26.8 (23.7-30.4)	26.5 (24.3-30.2)	26.7 (23.6-30.1)	27.4 (24.4-32.3)	0.040
Systolic BP, mm Hg	120 (107-140)	118 (103-137)	120 (106-140)	122 (110-140)	0.2
Diastolic BP, mm Hg	74 (65-85)	70 (62-86)	75 (65-84)	75 (66-88)	0.6
Dyslipidemia					0.15
Yes	616 (62)	32 (51)	481 (62)	103 (65)	
Arrhythmias					0.2
No	845 (84)	52 (80)	660 (85)	133 (84)	
Atrial fibrillation	140 (14)	11 (17)	109 (14)	20 (13)	
Flutter	9 (0.9)	2 (3.1)	5 (0.6)	2 (1.3)	
VT/NSVT	8 (0.8)	0 (0)	5 (0.6)	3 (1.9)	
Myocardial infarction					0.090
Yes	257 (25)	10 (15)	201 (26)	46 (29)	
HF etiology					0.030
Idiopathic	303 (29.9)	30 (45)	235 (30)	38 (23.8)	
Ischemic	215 (21.2)	10 (15)	171 (22)	34 (21.2)	
Hypertensive	183 (18.1)	7 (11)	142 (18)	34 (21.3)	
Chagasic	163 (16.1)	8 (12)	130 (17)	25 (15.6)	
Alcoholic	87 (8.6)	3 (4.5)	68 (8.6)	16 (10)	
Other	62 (6.1)	8 (12)	41 (5.2)	13 (8.1)	
Cardiac disease family history ^b					0.034
Yes	564 (56)	41 (62)	421 (54)	102 (64)	

Values are median (Q1-Q3) and tested with the Kruskal-Wallis rank-sum test or n (%) and compared using Pearson chi-squared test, unless otherwise indicated. **Bold** indicates statistically significant differences ($P < 0.05$). A total of 1,013 Brazilians with heart failure were part of the study. ^aP values correspond to the statistical test comparing the groups (Causal Variant, Uncertain, and No Evidence for Causal Variant). ^bFamily history: myocardial infarction, HF, sudden cardiac death, or other cardiovascular causes in first-degree relatives.

BMI = body mass index; BP = blood pressure; HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; NSVT = nonsustained ventricular tachycardia; VT = ventricular tachycardia.

was higher in ischemic and idiopathic HF and lower in alcoholic and hypertensive HF, which showed relatively higher African ancestry proportion (Supplemental Table 5).

RARE VARIANT ANALYSIS. After excluding low-quality variants, we assessed and classified 3,286 single-nucleotide variants. Most variants were

classified as LB or B (54%), or as a VUS (44%), with only 2% classified as LP or P. A summary of variant classification is shown in Supplemental Table 2, and the complete list of variants and their final classifications is provided in a Supplemental data file.

Among the 1,013 individuals, 76 carried at least one LP/P variant. Of these, 3 harbored heterozygous variants in genes with an AR inheritance pattern and

were therefore considered carriers only. Five individuals carried LP/P variants in genes with limited evidence (*OBSCN* and *TGFB3*), and 2 carried LP/P variants in a gene primarily associated with long-QT syndrome (*KCNQ1*). These findings were considered secondary and were not included in the analysis (Supplemental Table 6). The remaining 66 individuals (6.51%; 95% CI: 5.1%-8.2%) met the criteria for causal LP/P findings in genes with definitive disease association and with an AD inheritance pattern. One of these individuals carried 2 distinct variants, yielding 67 causal LP/P occurrences in the cohort. Among the HF etiologies, the highest diagnostic yield was observed in idiopathic HF (9.9%; 95% CI: 6.8%-13.8%), followed by Chagasic (4.9%; 95% CI: 2.1%-9.4%), ischemic (4.7%; 95% CI: 2.3%-8.4%), hypertensive (3.8%; 95% CI: 1.6%-7.7%), and alcoholic HF (3.4%; 95% CI: 0.7%-9.7%) (Supplemental Table 10).

In total, these occurrences corresponded to 52 distinct causal variants, summarized in Table 2. Of the 52 distinct causal variants, 28 were identified in *TTN*, of which nearly half were novel (not present in ClinVar, gnomAD, ABraOM, or dbSNP) (Figure 1). All causal variants in *TTN* were truncating variants located in exons with a percentage spliced in (PSI) of 100%, according to the Cardiodb.²⁸ Two additional truncating *TTN* variants were identified; however, because they were located in exons with PSI values of 62% and 75% they were classified as VUS (Supplemental Table 3). Additional novel causal variants were also identified in other genes, such as *BAG3*, *DSP*, *FLNC*, and *MYBPC3*.

Figure 2 summarizes the distribution of the causal variants across genes. *TTN* was the most frequently affected gene, followed by *MYBPC3* and *FLNC*.

As several variants were observed in more than one individual, we made a pairwise kinship analysis using KING,²⁹ which showed no evidence of relatedness up to the third degree among carriers of recurrent variants in *KCNQ1*, *MYBPC3*, *TTN*, and *TTR* (Supplemental Table 9).

GROUPS. We categorized the individuals according to the variant's classification. The group in which a VUS was identified was named the "Uncertain" group (77.7%). Those with only B or LB variants were in the "No Evidence for Causal Variant" group (15.8%). Individuals with at least one P or LP variant in AD genes and with definitive association by ClinGen were classified as "Causal Variant," representing 6.5% of the total. After categorization, we tested the statistical differences between clinical and demographic variables (Table 1). There was no statistical difference in sex, genomic ancestry, HF cohort with reduced

ejection fraction or HF with mildly reduced ejection fraction, or other clinical measurements. Yet, we did find statistical differences in age ($P = 0.010$), body mass index ($P = 0.040$), HF etiology ($P = 0.030$), and family history of cardiac disease ($P = 0.034$). A detailed familial history comparison is provided in Supplemental Table 8.

LOCAL ANCESTRY INFERENCE—GENOMIC INTERVALS AND VARIANT LEVEL ANALYSIS. We evaluated the local ancestry distribution within genomic intervals harboring LP/P and VUS variants. Across all categories, European ancestry showed the highest mean proportion compared to African and Native American ancestries. No significant difference was observed between expected and observed frequencies of LP/P variants across ancestry groups (chi-square test 0.146, $P = 0.929$). In contrast, genomic regions containing uncertain variants showed a significant enrichment of African and Native American ancestries (chi-square test: 60.453, $P < 0.001$) (Figure 3).

At the individual variant level, we evaluated the local ancestry of the haplotype carrying the alternative allele. Among the 67 LP/P variants, 39 mutated alleles had European local ancestry (58.2%), 20 had African ancestry (29.85%), 6 had Native American ancestry (8.95%), and 2 cases were missing (Supplemental Table 4).

DISCUSSION

We identified 52 distinct causal variants across cardiac disease-associated genes in 1,013 Brazilian unrelated adult individuals with ejection fraction $\leq 50\%$ from different etiologies, 18 of which were novel. As expected, the distribution of HF etiologies differed between groups, with a higher proportion of causal variants observed among individuals classified as having idiopathic DCM ($P = 0.030$) (Central Illustration).

At the gene level, *TTN* accounted for nearly 50% of LP/P findings, all of which were loss-of-function (LoF) variants. Several previous studies have demonstrated that *TTN* truncating variants are the most common cause of DCM,³⁰⁻³² and a study published in 2025³³ showed that individuals with *TTN* LoF variants have a 21-fold increased risk of developing DCM when compared with *TTN*-negative individuals. Moreover, all *TTN* LP/P were located in constitutive exons, with a PSI of 100%. Two additional truncating *TTN* variants were identified; however, these variants were located in exons with PSI values of 62% and 75%. Previous studies have shown that *TTN* truncating variants associated with DCM are enriched in highly expressed exons (commonly defined as PSI $> 90\%$), whereas

TABLE 2 Distinct Causal Variants (Pathogenic or Likely Pathogenic in Genes With Definitive Evidence-Level and With AD Inheritance) Identified

Gene	ClinGen Phenotype	ClinGen Evidence Level	Novel	Reference SNP ID (rsID)	Chromosome	Genomic Position (GRCh38)
BAG3	DCM	Definitive	Yes	—	10	119669894
BAG3	DCM	Definitive	No	rs387906875	10	119670037
BAG3	DCM	Definitive	Yes	—	10	119676863
DES	DCM	Definitive	No	—	2	219419041
DSC2	ARVC	Definitive	No	rs2510951125	18	31086588
DSG2	ARVC	Definitive	No	rs1187924885	18	31524752
DSP	ARVC	Definitive	Yes	—	6	7574655
FLNC	DCM	Definitive	Yes	—	7	128848961
FLNC	DCM	Definitive	No	—	7	128850484
FLNC	DCM	Definitive	No	rs1808781579	7	128850924
FLNC	DCM	Definitive	No	rs748416758	7	128854661
MYBPC3	HCM	Definitive	No	rs727504287	11	47342686
MYBPC3	HCM	Definitive	No	rs200411226	11	47342718
MYBPC3	HCM	Definitive	Yes	—	11	47343490
PKP2	ARVC	Definitive	No	rs78897684	12	32824163
PLN	INTCM	Definitive	No	rs754782171	6	118558947
RBM20	DCM	Definitive	No	rs796734066	10	110812297
SCN5A	DCM; BrS; LQTS	Definitive	No	rs199473605	3	38560374
SCN5A	DCM; BrS; LQTS	Definitive	No	rs199473153	3	38597737
SCN5A	DCM; BrS; LQTS	Definitive	No	rs199473556	3	38630342
TNNT2	DCM	Definitive	No	rs397516456	1	201365298
TPM1	HCM	Definitive	No	rs730881151	15	63042891
TTN	DCM	Definitive	Yes	—	2	178560461
TTN	DCM	Definitive	Yes	—	2	178533818
TTN	DCM	Definitive	No	rs752697861	2	178534092
TTN	DCM	Definitive	No	rs2468686204	2	178537825
TTN	DCM	Definitive	No	—	2	178548444
TTN	DCM	Definitive	No	—	2	178552137
TTN	DCM	Definitive	Yes	—	2	178552622
TTN	DCM	Definitive	Yes	—	2	178553152
TTN	DCM	Definitive	No	rs762411631	2	178553933
TTN	DCM	Definitive	No	—	2	178557326
TTN	DCM	Definitive	No	rs1060500525	2	178559797
TTN	DCM	Definitive	No	rs756499458	2	178560639
TTN	DCM	Definitive	No	rs770038577	2	178561042
TTN	DCM	Definitive	Yes	—	2	178566243
TTN	DCM	Definitive	Yes	—	2	178569070
TTN	DCM	Definitive	No	rs794729281	2	178577085
TTN	DCM	Definitive	Yes	—	2	178580535
TTN	DCM	Definitive	Yes	—	2	178588565
TTN	DCM	Definitive	Yes	—	2	178588606
TTN	DCM	Definitive	No	rs769912484	2	178599063
TTN	DCM	Definitive	No	rs1343120755	2	178609301
TTN	DCM	Definitive	No	rs2057454001	2	178617003
TTN	DCM	Definitive	No	rs2060187635	2	178634576
TTN	DCM	Definitive	No	—	2	178635462
TTN	DCM	Definitive	Yes	—	2	178738353
TTN	DCM	Definitive	Yes	—	2	178741889
TTN	DCM	Definitive	Yes	—	2	178768880
TTN	DCM	Definitive	Yes	—	2	178777811
TTR	ATTR	Definitive	No	rs28933979	18	31592974
TTR	ATTR	Definitive	No	rs76992529	18	31598655

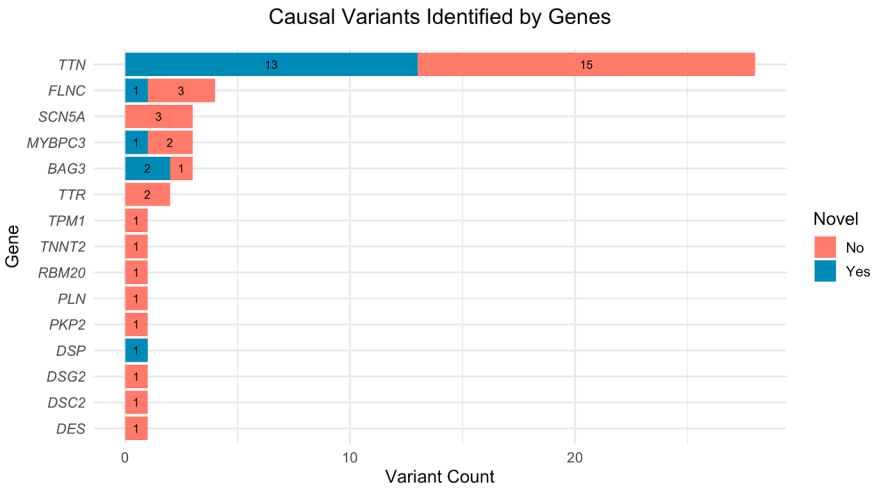
AA = amino acid; ACMG = American College of Medical Genetics and Genomics; AD = autosomal dominant; AF = allele frequency; ARVC = arrhythmogenic right ventricular cardiomyopathy; ATTR = transthyretin amyloidosis; BrS = Brugada syndrome; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; INTCM = intrinsic cardiomyopathy; LP = likely pathogenic; LQTS = long QT syndrome; N = number of individuals; P = pathogenic.

Continued on the next page

TABLE 2 Continued

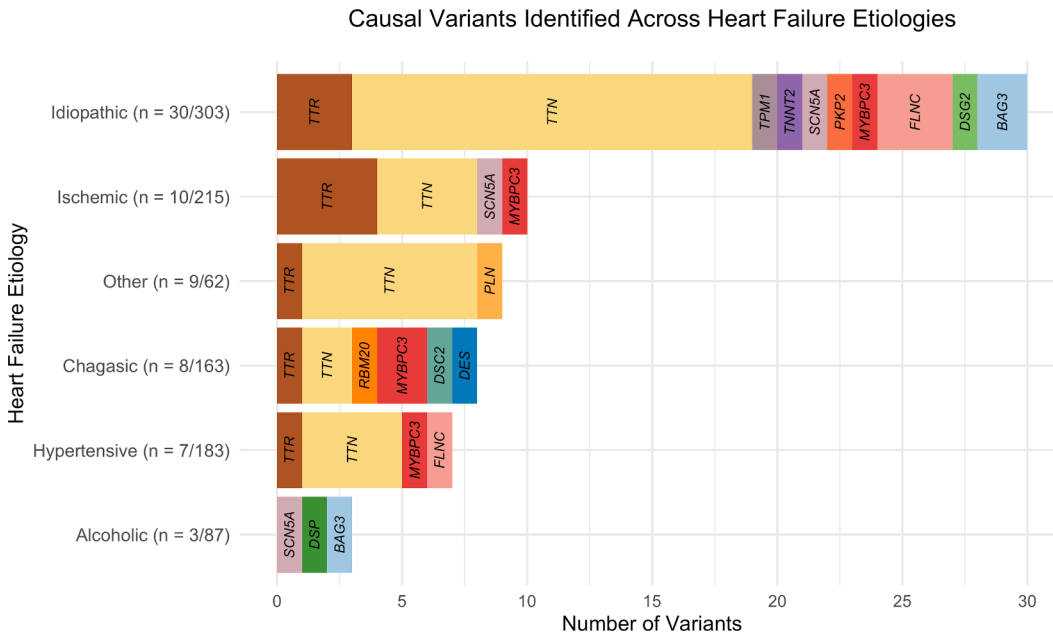
Nucleotide Change	AA Change	gnomAD Total AF	ABraOM Total AF	ClinVar	ACMG Classification	N
c.228_237del	p.Pro77Glyfs*131	Absent	Absent	Absent	LP	1
c.367C>T	p.Arg123*	0.0003%	Absent	LP/P	P	1
c.1309C>T	p.Gln437*	Absent	Absent	Absent	LP	1
c.578+1G>A	—	0.0002%	Absent	Absent	P	1
c.929delinsTT	p.Gln310Hisfs*8	Absent	Absent	LP	LP	1
c.882dup	p.Val295Serfs*6	0.0003%	Absent	LP/P	P	1
c.2298-2A>G	—	Absent	Absent	Absent	LP	1
c.4908del	p.Ser1637Alafs*29	Absent	Absent	Absent	LP	1
c.5398+1G>A	—	0.0000006%	Absent	Absent	LP	1
c.5520T>A	p.Tyr1840*	0.0000006%	Absent	P	P	1
c.6976C>T	p.Arg2326*	0.0001%	Absent	P	P	1
c.1513_1515del	p.Lys505del	0.0009%	Absent	LP	LP	3
c.1484G>A	p.Arg495Gln	0.0024%	Absent	LP/P	P	1
c.1223+2T>A	—	Absent	Absent	Absent	P	1
c.1557-1G>C	—	0.0005%	Absent	P	P	1
c.26G>A	p.Arg9His	0.0007%	Absent	Conflicting	LP	1
c.1900C>T	p.Arg634Trp	Absent	Absent	P	P	1
c.4015G>A	p.Val1339Ile	0.0023%	Absent	Conflicting	LP	1
c.2254G>A	p.Gly752Arg	0.0004%	Absent	LP/P	P	1
c.361C>T	p.Arg121Trp	0.0001%	Absent	LP/P	LP	1
c.304C>T	p.Arg102Trp	0.0005%	Absent	P	P	1
c.62G>T	p.Arg21Leu	0.0009%	Absent	Conflicting	P	1
c.85670del	p.Leu28557Trpfs*6	Absent	Absent	Absent	LP	1
c.102795_102796dup	p.Asn34266Ilefs*7	Absent	Absent	Absent	LP	1
c.102523C>T	p.Arg34175*	0.0004%	Absent	LP/P	P	1
c.99381del	p.Arg33127Serfs*34	Absent	Absent	LP	LP	1
c.93181del	p.Arg31061Valfs*33	Absent	Absent	LP	LP	4
c.90762del	p.Gly30255Glufs*35	Absent	Absent	LP	LP	1
c.90277del	p.Lys30094Argfs*18	Absent	Absent	Absent	LP	1
c.89725_89747del	p.Lys29909Trpfs*4	Absent	Absent	Absent	LP	1
c.89178C>G	p.Tyr29726*	Absent	Absent	LP	LP	3
c.87931_87935dup	p.Tyr29313Glyfs*90	Absent	Absent	LP	LP	1
c.86335C>T	p.Arg28779*	0.0001%	Absent	LP/P	LP	1
c.85493G>A	p.Trp28498*	0.0001%	0.0427%	LP	LP	1
c.85090C>T	p.Arg28364*	0.0001%	Absent	LP/P	P	1
c.79888del	p.Glu26630Lysfs*14	Absent	Absent	Absent	LP	1
c.77062C>T	p.Gln25688*	Absent	Absent	Absent	LP	1
c.69250C>T	p.Arg23084*	0.0000006%	Absent	LP/P	LP	1
c.66843dup	p.Tyr22282Ilefs*16	Absent	Absent	Absent	LP	1
c.63160A>T	p.Arg21054*	Absent	Absent	Absent	LP	1
c.63118del	p.Ala21040Glnfs*23	Absent	Absent	Absent	LP	1
c.56648-1G>A	—	0.0001%	Absent	Conflicting	LP	1
c.52009C>T	p.Arg17337*	0.0001%	Absent	LP/P	P	1
c.47885dup	p.Met15963Asnfs*7	Absent	Absent	LP	LP	1
c.42205C>T	p.Arg14069*	Absent	Absent	LP	LP	1
c.41861dup	p.Tyr13954*	0.0000006%	Absent	Absent	LP	1
c.14099dup	p.Val4701Serfs*22	Absent	Absent	Absent	LP	1
c.11344G>T	p.Glu3782*	Absent	Absent	Absent	LP	1
c.8955del	p.Ile2986Leufs*5	Absent	Absent	Absent	LP	1
c.4371_4372del	p.Val1458Leufs*19	Absent	Absent	Absent	LP	1
c.148G>A	p.Val50Met	0.0057%	Absent	P	P	1
c.424G>A	p.Val142Ile	0.0887%	0.3416%	LP/P	P	9

FIGURE 1 Distribution of Causal Variants

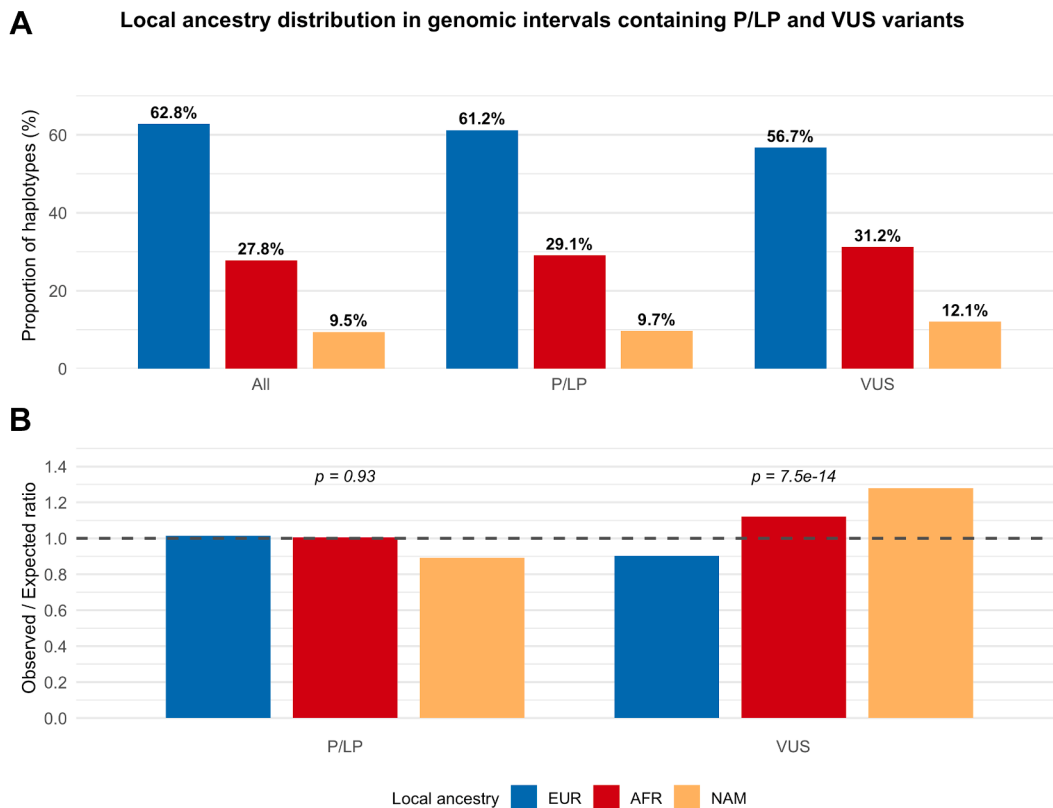


Distribution of distinct causal variants across genes. Bars indicate the number of pathogenic or likely pathogenic variants identified in each gene. Colors denote novelty status, with novel variants defined as those absent from ClinVar, gnomAD, ABrOM, and dbSNP.

FIGURE 2 Causal Variants Across HF Etiologies



Distribution of causal variants across heart failure etiologies. Each bar represents the number of causal variants identified within each etiology stratified by gene. Etiology-specific sample sizes are shown in parentheses as the number of individuals carrying at least one causal variant relative to the total number of individuals in that etiological group. HF = heart failure.

FIGURE 3 Local Ancestry Distribution Across Intervals Containing Pathogenic/Likely Pathogenic and VUS Variants

Local ancestry proportions were derived using inferred segments from GNOMIX (.msp file output). (A) Proportion of segments assigned to each ancestry group stratified by variant classification (ie, all, pathogenic/likely pathogenic, and variant of uncertain significance). (B) Observed-to-expected ratio of local ancestry proportions in segments containing pathogenic/likely pathogenic and variant of uncertain significance. The observed proportion corresponds to the ancestry distribution within segments containing variants, whereas the expected proportion corresponds to the ancestry distribution across all genomic segments. The dashed line indicates a ratio = 1, with no enrichment. P values were obtained using a chi-square test using the ancestry distribution across all variants as a reference. AFR = African; EUR = European; LP = likely pathogenic; NAM = Native American; P = Pathogenic; VUS = variant of uncertain significance.

truncating variants in exons with lower PSI are more frequently observed in the general population.^{28,34} Therefore, based on the PSI values, these 2 variants were here classified as VUS. Notably, 71% of *TTN* LP/P variants were absent from the gnomAD database, and 46% were novel, reflecting the high mutational burden of *TTN* and the expected enrichment of rare variants in cardiomyopathy cohorts.³⁵

Novel variants were also identified in *MYBPC3*, *FLNC*, *BAG3*, and *DSP*, genes previously implicated in cardiomyopathies. *MYBPC3* is a well-established gene associated with hypertrophic cardiomyopathy (HCM), accounting for approximately 50% of the P variants identified in HCM cases.³⁶ *FLNC* and *BAG3* are both linked to DCM. *FLNC* encodes a cytoskeletal protein that maintains the structural integrity of the cardiac sarcomere,³⁷ while *BAG3* plays an important

role in myofibrillogenesis and is widely associated with DCM, often with variable age of onset and phenotypic expressivity.³⁸⁻⁴⁰ Together, these findings reinforce that sarcomeric and cytoskeletal disruption are contributing mechanisms in the genetic susceptibility to HF.

P *TTR* variants were identified in 10 individuals, including 9 carriers of the p.Val142Ile variant. Although none had a diagnosis of cardiac amyloidosis at enrollment, it is important to highlight that the disease presentation is age-dependent. Indeed, one of our participants carrying the p.Val142Ile variant was diagnosed as an amyloidosis patient after the development of new symptoms pointed to this etiology (Supplemental Table 7). It remains to be determined if individuals with a different HF etiology than amyloidosis might benefit from the

CENTRAL ILLUSTRATION Genetics of Heart Failure Across Diverse Etiologies in an Admixed Population

1,013 individuals with heart failure with systolic dysfunction of diverse etiologies

1. Cohort Characteristics

LVEF ≤50%



Median Local Ancestry



62% EUR



24% AFR

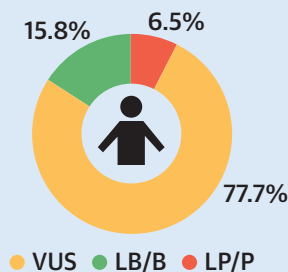


9% NAM

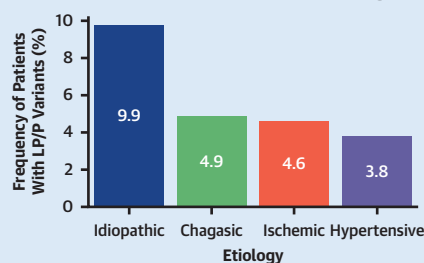
● Idiopathic ● Ischemic ● Hypertensive ● Chagasic ● Others



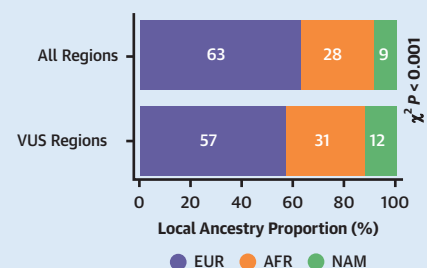
Etiologies Proportions

2. Genomic and Ancestry AnalysisRare variant analysis in 123
ClinGen-Curated
Cardiovascular GenesLocal Ancestry Inference:
GNOMIX**3. Overall Results****Results Per Individual**

● VUS ● LB/B ● LP/P

Causal Variants by Etiology

Etiology

Local Ancestry in Genomi Segments

Local Ancestry Proportion (%)

 $\chi^2 P < 0.001$ 

LP/P Variants are identified in individuals with diverse etiologies of heart failure.

VUS were more frequent in genomic regions with African and Native American ancestries, highlighting an interpretative bias in non-European populations.

Lima IR, et al. JACC Adv. 2026;■(■):103123.

A total of 1,013 individuals with HFrEF from diverse etiologies underwent rare variant analysis in 123 ClinGen-curated cardiovascular genes and local ancestry inference. Pathogenic or likely pathogenic variants were identified across multiple heart failure etiologies, with the highest frequency observed among individuals with idiopathic heart failure. Variants of uncertain significance were more frequently observed in genomic regions with African and Native American local ancestries compared with the genome-wide ancestry distribution, highlighting the challenges of variant interpretation in underrepresented populations. AFR = African; B = benign; EUR = European; HFrEF = heart failure with reduced ejection fraction; LB = likely benign; LVEF = left ventricular ejection fraction; LP = likely pathogenic; NAM = Native American; P = pathogenic; VUS = variant of uncertain significance.

availability of disease-modifying therapies for amyloidosis, but our study provides an empirical estimate of this prevalence in a diverse HF cohort.

Other findings, although detected in individuals with a HF diagnosis, were considered secondary, as they do not influence HF directly. *TGFB3*, for example, currently has limited gene-disease evidence for arrhythmogenic right ventricular cardiomyopathy,¹⁵ though it is an established gene associated with Syndromic Aortic Aneurysms.⁴¹ Likewise, *KCNQ1* is a major gene for Long QT Syndrome cases, and its association with HF or cardiomyopathies is rare.⁴² Five LP/P variants were identified in the *OBSCN*, a gene

primarily involved in sarcomere assembly with a LoF mechanism and an AR inheritance pattern.⁴³ Although the ClinGen Expert Panels classifies *OBSCN* as having limited evidence for AD hypertrophic and DCM,^{17,18} recent studies have shown an enrichment of truncating variants in individuals with HCM and DCM.^{44,45} These data suggest that *OBSCN* LoF variants may act as a contributing factor, often with variable or late penetrance. However, the biological mechanisms in this gene remain unclear, and further studies are needed to clarify the role of *OBSCN* in cardiomyopathy and HF. Thus, P variants in *OBSCN*, *TGFB3*, and *KCNQ1* were considered secondary findings.

Interestingly, some patients classified as having nongenetic etiologies, such as Chagasic and hypertensive cardiomyopathy, also carried LP/P variants in well-established cardiomyopathy genes. It is important to note that we cannot determine whether the clinically assigned etiology caused HF or whether these individuals had an underlying genetic cardiomyopathy with a coexisting condition, such as positive serology for Chagas or hypertension. Although our data do not support observation of a gene-environment interaction, a “second-hit” mechanism has been proposed in other contexts, such as viral myocarditis.⁴⁶

Our results showed that a causal variant was found in 6.5% of the individuals. This overall diagnostic yield is lower than that reported in cohorts enriched for genetic cardiomyopathies or advanced HF. For instance, Linnér et al⁹ identified a higher yield of P variants (about 30%) in a Swedish population with different HF etiologies. However, the subjects in that study consisted of individuals with early-onset HF who were eligible for a heart transplantation. Similarly, Dellefave-Castillo et al⁴⁷ identified causal variants in 20% of the individuals with cardiomyopathy and arrhythmia, etiologies associated with a higher prevalence of monogenic disease. In contrast, Povysil et al⁸ reported a diagnostic yield of nearly 4% in a cohort of individuals with midrange and reduced HF of different etiologies, mostly ischemic. These differences highlight that the genetic yield clearly depends on the cohort composition. Our study included individuals with diverse HF etiologies, including ischemic, hypertensive, and Chagasic, many of which are predominantly multifactorial and in which the monogenic contribution is less pronounced, if ever considered. Consequently, the monogenetic contribution in this type of cohort is inherently lower than in studies focused on familial or early-onset cardiomyopathies. When we restricted the analysis to patients with idiopathic/dilated HF, the diagnostic yield increased to approximately 10% (30/303), compared with about 5% in nonidiopathic etiologies. As such, we propose that the presence of non-DCM HF together with a family history of HF should be seen as a risk predictor for DCM (or of HF associated with a P/LP genetic variant) and, thus, a candidate for genetic testing.

We did not observe statistical differences in local genetic ancestry distribution in regions containing LP/P variants, suggesting no evidence of ancestry-specific enrichment for P variants. However, a difference was observed in regions harboring uncertain variants, with lower rates in European ancestry.

Other studies have also shown that non-European individuals have a higher rate of uncertain variants than Europeans, highlighting a knowledge bias in genomic data from different ancestries, as non-Europeans and admixed individuals remain underrepresented in genomic databases.^{48,49} This is expected, and we extend this observation to admixed individuals, even if they self-report as from European ancestry. These results underscore the need to increase the representation of diverse populations in genomic studies, which can improve the accuracy of genetic tests.⁵⁰ Our results also highlight the role of local ancestry interrogation in population studies from admixed individuals, since self-referred ancestry might not completely capture the bias in available genetic information in public datasets.

STUDY LIMITATIONS. First, it was conducted at a single tertiary hospital in São Paulo state, which may have biased the sample toward more severe HF phenotypes. The sample size remains modest for rare-variant association and ancestry testing. Finally, we did not analyze copy number variants or large structural variants, which can significantly contribute to HF. Other analyses, including non-coding variants or regulatory regions, should be performed. Also, functional assays such as RNA-Seq or Mini-gene editing can help determine the impact of some variants, especially those classified as VUS, which might be unequally distributed among patients with different types of HF.

CONCLUSIONS

In a Brazilian HF cohort with diverse etiologies and ancestries, we observed a significant monogenic contribution to HF in 6.5% of the cohort. *TTN* accounted for the largest number of LP/P variants, with an enrichment among idiopathic cases, consistent with a stronger monogenic component in this subgroup. We also identified previously unreported variants across other established cardiomyopathy genes. Local ancestry analyses showed a higher proportion of VUS in genomic regions of non-European ancestry, highlighting disparities in variant interpretation. These results raise the discussion on the use of genetic testing in HF from different etiologies and illustrate the expected diagnostic yield in cohorts with varied etiologies. It reinforces the need to increase representation of diverse populations in genomic studies of HF.

DATA AVAILABILITY The data that support the findings of this study are available from the corresponding author upon reasonable request.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE:

Pathogenic or likely pathogenic variants are present in a subset of patients with heart failure with an ejection fraction $\leq 50\%$, including those with nonidiopathic etiologies, supporting a role for genetic evaluation beyond classical cardiomyopathies.

TRANSLATIONAL OUTLOOK: The implementation of genetic testing in heterogeneous heart failure populations remains limited by challenges in variant interpretation, particularly in admixed individuals, where a higher proportion of variants of uncertain significance persists. Increasing the representation of non-European and admixed populations in genomic databases and studies could improve the interpretation of rare variants in these populations.

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KEY WORDS admixed population, cardiogenetics, heart failure, local ancestry, pathogenic variants, uncertain variants

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