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ORIGINAL RESEARCH

Population-Based Analysis of Rare Genetic Variants in Sudden Cardiac Arrest

Evan P. Kransdorf, MD, PhD,[a] Marco Mathias, BS,[a] Kotoka Nakamura, PhD,[a] Harpriya Chugh, BE, MSHS,[a] David Nguyen, BS,[a] Jonathan Tyrer, PhD,[b] Paul D. Pharoah, MD, PhD,[c] Kyndaron Reinier, MPH, PhD,[a] Zeynep Akdemir, PhD,[d] Eric Boerwinkle, PhD,[d] Bing Yu, PhD,[d] Sumeet S. Chugh, MD[a]

ABSTRACT

BACKGROUND More than 360,000 Americans experience sudden cardiac arrest (SCA) annually. A subgroup is caused by rare genetic variants, but existing studies are not population based and have been limited to nonsurvivors.

OBJECTIVES This study sought to establish the prevalence of disease-causing rare genetic variants in both survivors and nonsurvivors of SCA in the general population.

METHODS Patients with SCA (n = 3,264) were accrued from 2 community-based studies in Oregon and California and compared with control participants (n = 13,258) from the ARIC (Atherosclerosis Risk in Communities) study. Whole genome sequencing was performed. Disease-causing (likely pathogenic or pathogenic) variants in 63 candidate genes associated with arrhythmia/cardiomyopathy were identified using updated American College of Medical Genetics and Genomics criteria. Gene-collapsing case-control analysis and variant proportion comparison with the Genome Aggregation Database was performed.

RESULTS Disease-causing variants were present in 130 patients (4.0%) in the SCA group as compared with 323 participants (2.4%) in ARIC (OR: 1.59; $P < 0.001$). In the subgroup of patients with a nonischemic SCA, 39 of 638 patients (6.1%) harbored a disease-causing variant (OR: 2.52; $P < 0.001$). We identified 15 genes associated with an increased risk of SCA: *ACTC1*, *BAG3*, *CACNA1C*, *DES*, *DSG2*, *DSP*, *FLNC*, *KCNH2*, *KCNQ1*, *LMNA*, *MYBPC3*, *MYH7*, *PKP2*, *RBM20*, and *TTN*.

CONCLUSIONS Specific disease-causing variants identified in 15 arrhythmia and cardiomyopathy genes were associated with an increased risk of SCA in the community. These findings will enable targeted SCA prevention strategies in family members harboring variants in these SCA-associated genes. (JACC Clin Electrophysiol. 2026;■:■–■) © 2026 by the American College of Cardiology Foundation.

From the [a]Center for Cardiac Arrest Prevention, Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, California, USA; [b]Center for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom; [c]Department of Computational Biomedicine, Cedars-Sinai Medical Center, Los Angeles, California, USA; and the [d]Department of Epidemiology, School of Public Health, University of Texas Health Science Center at Houston, Houston, Texas, USA.

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ABBREVIATIONS AND ACRONYMS

ACMG = American College of Medical Genetics and Genomics

ClinGen = National Institutes of Health Clinical Genome Resource

DCM = dilated cardiomyopathy

GCEP = Gene Curation Expert Panel

gnomAD = Genome Aggregation Database

LP/P = likely pathogenic/pathogenic

SCA = sudden cardiac arrest

VUS = variant of undetermined significance

Each year 360,000 Americans will suffer a sudden cardiac arrest (SCA) with a mortality rate of 90%.[1] Without the use of genetic testing, the cause of SCA remains unidentified in approximately 30% of patients in whom an autopsy is performed.[2] Studies using gene-panel or exome sequencing have identified rare, heterozygous variants in genes associated with Mendelian causes of arrhythmia and cardiomyopathy in 10% to 20% of patients with SCA.[3-6]

Previous studies examining the genetic basis of SCA may have been affected by several biases. First, these studies primarily studied individuals of European ancestry who were referred to specialized cardiogenetic centers.[5,7] Other studies were performed using participants in longitudinal cohort studies, in which genetic analysis was limited to deceased individuals determined retrospectively and survivors of SCA could not be included. Also, ischemic vs nonischemic etiology could not be established.[8] Last, previous genetic studies of victims of SCA used the American College of Medical Genetics and Genomics (ACMG) 3.0 sequence variant interpretation criteria[9] and several updates have been made to these criteria by the National Institutes of Health Clinical Genome Resource (ClinGen) consortium since that time.[10]

We have evaluated and previously reported the epidemiology of the detailed SCA phenotype in 2 ongoing community-based studies: SUDS (the Oregon Sudden Unexpected Death Study) (since 2002)[11,12] and the PRESTO (PREdiction of Sudden death in mulTi-ethnic cOmmunities) study (since 2015).[13] Both studies ascertain SCA prospectively for all ages and include both survivors and nonsurvivors of SCA. We sought to 1) establish the population prevalence of rare disease-causing variants in a set of candidate genes and 2) confirm the association of disease-causing variants in these genes with SCA in these 2 prospective population-based studies.

METHODS

SCA AND CONTROL SAMPLES. This study was performed under an approved protocol of the Cedars-Sinai, Oregon Health and Science University, and Ventura County Medical Center Institutional Review Boards. Patients with SCA were accrued from the SUDS, Multnomah County, Oregon (n = 2,512),[11,12] and the PRESTO study Ventura County, California (n = 966)[13] (**Figure 1**). Detailed ascertainment, adjudication, and phenotyping methods have been published and are identical for both studies.[11,14,15] Patients were excluded if DNA sequencing did not meet quality control criteria (n = 148 from SUDS and 66 from PRESTO). Based on review of available medical records, the cause of SCA was assigned as definite or probable ischemic, definite or probable nonischemic, or unassigned if no records were available. Methods used for classification have been published previously[16] and are detailed in the Supplemental Material.

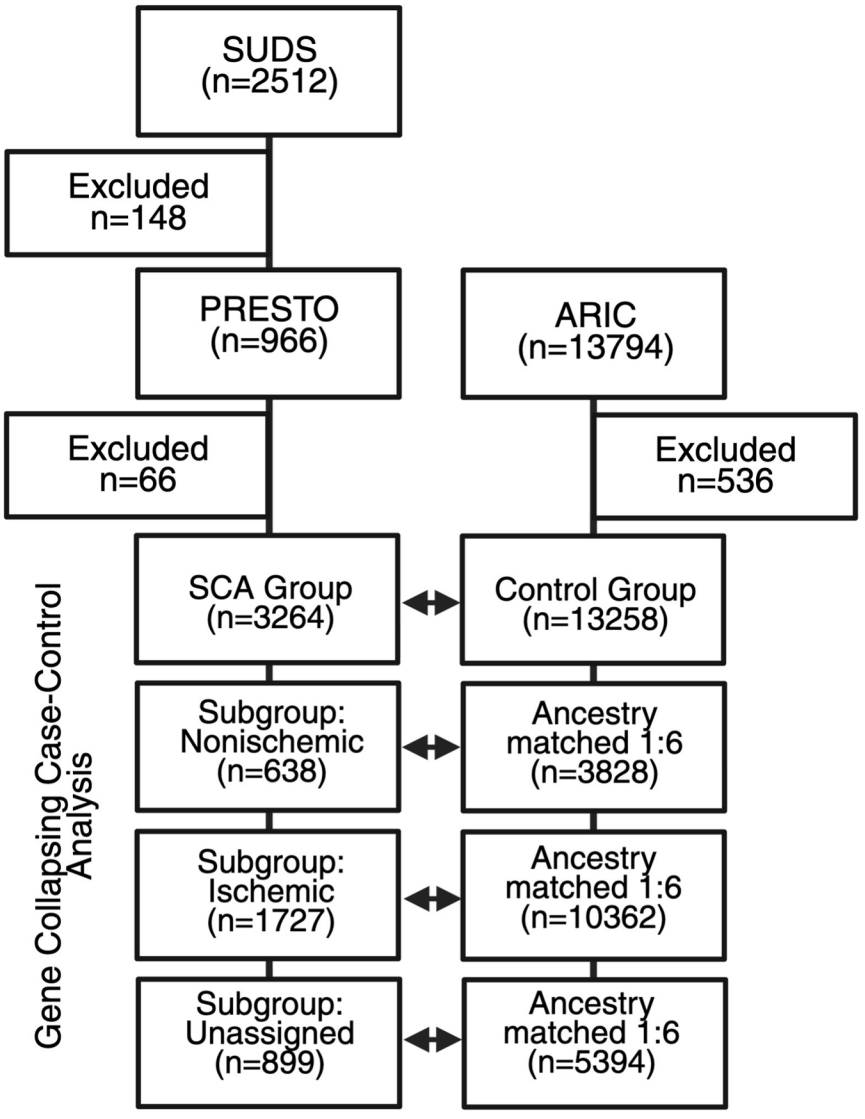
Control participants (n = 13,713) were obtained from the ARIC (Atherosclerosis Risk in Communities) study and were persons without cardiac disease and aged at least 45 at baseline.[17] Participants were excluded if DNA sequencing did not meet quality control criteria (n = 81) and if they experienced SCA during follow-up (n = 455).

WHOLE GENOME SEQUENCING AND VARIANT CALLING. Whole genome sequencing was performed at the Baylor College of Medicine Human Genome Sequencing Center. DNA samples were constructed into libraries according to the manufacturer's protocol. All samples underwent paired-end sequencing using NovoSeq instruments (Illumina). Variant calling was performed jointly for the SCA and control groups using the DRAGEN 4.0 pipeline (Illumina).

GENE SELECTION AND FILTERING. We identified 6 cardiac phenotypes associated with SCA and used the National Institutes of Health ClinGen Gene Curation Expert Panels (GCEPs) to identify genes associated with each cardiac phenotype. We specifically used the GCEPs for 1) arrhythmic right ventricular cardiomyopathy,[18] 2) Brugada syndrome,[19] 3) catecholaminergic polymorphic ventricular tachycardia and short QT syndrome,[20] 4) dilated cardiomyopathy (DCM),[21] 5) hypertrophic cardiomyopathy,[22] and 6) long QT syndrome.[23] Genes classified by each GCEP as being definitively, strongly, moderately, or of limited association were included (Supplemental Table 1). The analysis was restricted to genes with autosomal dominant, semidominant, and x-linked inheritance mechanisms. Variants were excluded if they were present in the Genome Aggregation Database (gnomAD) exomes v4.1 or genomes v4.0 with total population frequency that was ≥0.1%[24] and if genotype quality was <20.

VARIANT INTERPRETATION. Variants were assigned as benign/likely benign (B/LB) or likely pathogenic/pathogenic (LP/P) if the variant had that classification in ClinVar (version July 6, 2025)[25] and a review status of "reviewed_by_expert_panel" or "criteria_provided,_multiple_submitters,_no_conflicts." The

FIGURE 1 Design of the SCA and Control Groups



CONSORT diagram showing composition of the SCA and control groups. ARIC = Atherosclerosis Risk in Communities; PRESTO = PREdiction of Sudden death in mulTi-ethnic cOmmunities; SCA = sudden cardiac arrest; SUDS = Oregon Sudden Unexpected Death Study.

latter ClinVar review status requires that the variant was interpreted as LP/P by at least 2 independent laboratories and appropriate assertion criteria were included in the submission. If no applicable ClinVar classification was present, variant interpretation was performed using the ACMG 3.0 criteria[9] with updates by ClinGen. A full specification of our variant interpretation criteria, including specialized criteria for variants in *TTN*, can be found in the Supplemental Material. Variant effect was determined using Ensembl Variant Effect Predictor[26] on Matched Annotation from the National Center for Biotechnology Information and European Molecular Biology Laboratory-European Bioinformatics Institute (MANE) transcripts.[27] Proband counts were taken from eligible submissions to ClinVar (version July 2025). Final variant pathogenicity classification was based on the sum of points awarded from all criteria.[28]

AUTOMATED VARIANT INTERPRETATION. We developed a computational method termed Python Automatic Variant Interpretation (PAVI) to apply our ACMG interpretation method to whole genome

TABLE 1 Characteristics of the SCA and Control Groups

	SCA Group (n = 3,264)	Control Group (n = 13,258)	*P* Value
Age, y	66.0 [53.8-78.2]	54.0 [49.0-59.0]	<0.001
Race (self-reported)			<0.001
White	2,885 (88.4)	10,110 (76.3)	
Black	166 (5.09)	3,133 (23.6)	
Asian	119 (3.65)	9 (0.07)	
Other/Unknown	94 (2.88)	6 (0.05)	
Sex			<0.001
Women	963 (29.5)	7,451 (56.2)	
Men	2,301 (70.5)	5,807 (43.8)	
Phenotype subgroup			
Definite/Probable ischemic	638 (19.5)		
Definite/Probable nonischemic	1,727 (52.9)		
Unassigned	899 (27.5)		
Study site			
SUDS	900 (27.6)		
PRESTO	2,364 (72.4)		

Values are n (%) unless otherwise noted.

PRESTO = PREdiction of Sudden death in mulTi-ethnic cOmmunities; SCA = sudden cardiac arrest; SUDS = Oregon Sudden Unexpected Death Study.

sequences in the SCA and control groups. We validated PAVI by comparing automated interpretation against manual interpretation on an independent dataset of 60 patients with DCM and demonstrated 100% concordance of the manual and computational variant interpretation methods.

GENOME AGGREGATION DATABASE. We used the gnomAD as an additional control dataset.[29] Variant Call Format files for gnomAD v4.1 exomes and v4.0 genomes were downloaded and the variant interpretation strategy described previously was applied to the 63 candidate genes. The number of disease-causing (LP/P by ACMG sequence variant interpretation criteria) was aggregated by gene. For genes without LP/P variants, allele number was taken from the allele number for B/LB variants.

STATISTICAL ANALYSIS. Genetic ancestry was determined using principal component analysis applied to 33,661 uncorrelated single nucleotide polymorphisms (pairwise $r^2 < 0.1$) with minor allele frequency >0.05 using an in-house program.[30] Four major ancestry groups—White, Black, Asian, and Other/Unknown—were estimated from the first 3 principal components, using the 4 vertices of a tetrahedron. The proportions of each ancestry for each sample were determined by identifying the nearest point on the tetrahedron and applying barycentric coordinates. Genetic ancestry correlated well with self-reported race (Supplemental Figure 1 and Supplemental Table 2).

For the total SCA group, patients were matched to those in ARIC 1:4. For the SCA phenotype subgroups, patients were matched to those in ARIC 1:6 by the first 6 principal components of genetic ancestry using the R package "optmatch."[31] Logistic modeling was used to assess the association between rare variants in the total SCA group and SCA phenotype subgroups and SCA using the "b.collapse" function in EPACTS (Efficient and Parallelizable Association Container Toolbox) with the first 4 principal components of genetic ancestry as covariates.[32] Gene-collapsing rare variant case-control analysis was performed using conditional logistic regression-sequence kernel association test as implemented in CLoMAT (Conditional Logistic Model Association Tests)/EPACTS.[33]

Data from gnomAD v4.1 exomes and v4.0 genomes were utilized. For each gene, 1) allele count was calculated as the sum allele count in both exomes and genomes for each LP/P variant, 2) null alleles was calculated as the average allele number for that gene minus the allele count, and 3) allele frequency was calculated as follows:

$$\sum allele\ count\ for\ LP\ and\ P\ variants \Big/ \overline{allele\ number}$$

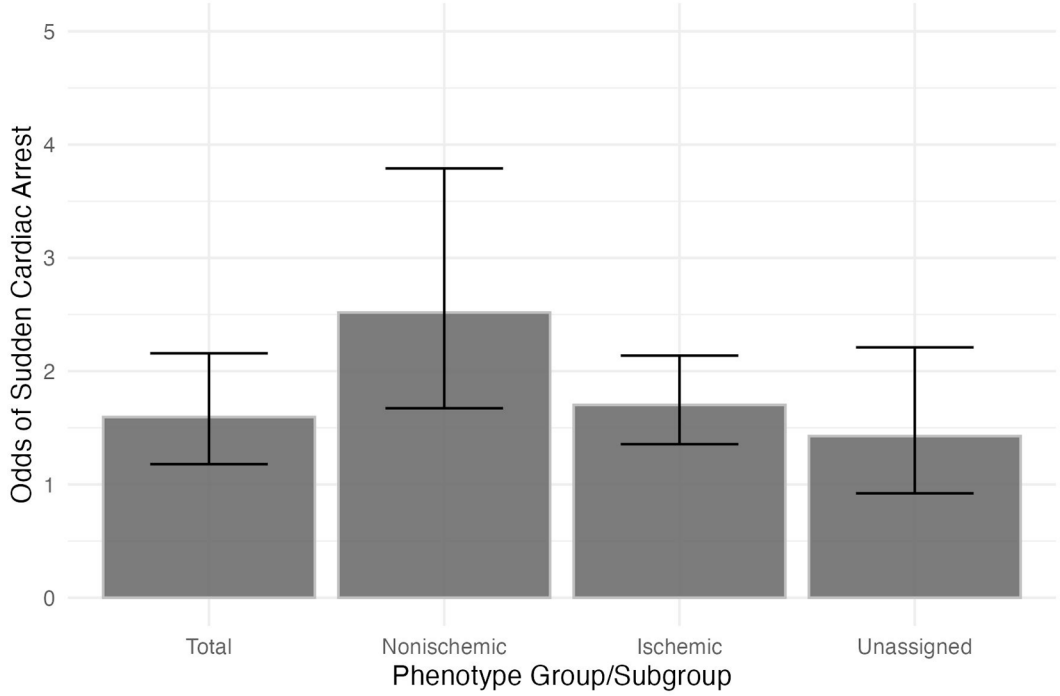
Variant proportion for each gene was compared between the gnomAD and SCA groups using the Fisher exact test. All analyses and data visualizations were carried out using R as implemented in R Studio with the R packages dplyr and ggplot2.

RESULTS

SCA AND CONTROL GROUPS. We included 3,264 patients with SCA from the SUDS (n = 2,364 or 72%) and PRESTO (n = 900 or 28%) study and 13,258 control participants from the ARIC study (**Figure 1**). The patients with SCA and ARIC control participants exhibited significant epidemiologic differences (**Table 1**), with patients with SCA being older (66 vs 54 years, $P < 0.001$), less frequently women (30% vs 56%, $P < 0.001$), and more frequently self-reporting as White (88% vs 76%, $P < 0.001$). Genomic ancestry closely matched to self-reported race (Supplemental Figure 1 and Supplemental Table 2). Cause of SCA was determined to be definite/probable nonischemic in 638 (20%), definite/probable ischemic in 1,727 (53%), and unassigned in 899 patients (27%) in the SCA group. Of the 3,264 patients with SCA, 423 (13%) survived and 2,834 (87%) did not survive the arrest (status was missing in 7 patients).

GENE VARIANTS. We evaluated for disease-causing variants (LP/P by ACMG sequence variant interpretation criteria) in 63 candidate genes associated with

FIGURE 2 **Prevalence of Rare, Disease-Causing Genetic Variants Based on Ischemic vs Nonischemic Etiologies of SCA**



OR of SCA with disease-causing variants, by group and phenotype subgroup. Barplot showing the OR of SCA in patients harboring at least 1 disease-causing (likely pathogenic/pathogenic) variant in a candidate arrhythmia or cardiomyopathy gene for the total SCA group, nonischemic SCA subgroup, ischemic SCA subgroup, and unassigned SCA subgroup. Bars indicate 95% CIs. Abbreviation as in Figure 1.

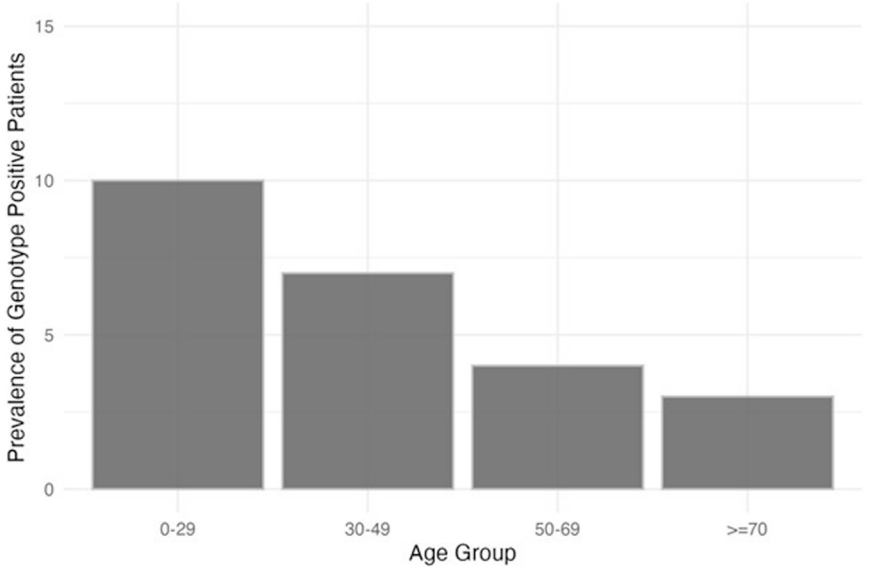
Mendelian arrhythmia and cardiomyopathy (Supplemental Table 1) within the SCA and ARIC control groups. We identified a total of 725,963 variants in these genes with population frequency <0.1% (Supplemental Table 3), of which 317 (0.04%) were classified as LP/P. We classified the remainder as B/LB (6,020; 0.8%) or uncertain (719,626; 99.2%).

The 317 LP/P variants were present in 38 candidate genes (Supplemental Table 4); 157 (50%) were previously classified in ClinVar as LP/P with high confidence and 160 (50%) were novel. Variant consequence was frameshift/stop-gain in 176 (56%), missense in 94 (30%), canonical splice site in 34 (11%), and other consequence in 13 (4%). There was no difference in the frequency of variant consequences between previously classified in ClinVar and novel variant groups ($P = 0.301$; Supplemental Table 5).

The number of LP/P variants per gene varied between 1 for *EYA4*, *ILK*, *KCNJ2*, *LAMA4*, *MYL3*, *SLC4A3*, *TBX20*, and *TCAP* and 96 for *TTN*. There were 447 variant allele heterozygotes, 130 in patients with SCA and 317 in ARIC control participants, as well as 6 variant allele homozygotes, all in ARIC control participants. Any individual LP/P variant was uncommon in the SCA group; the 2 most frequent LP/P variants, *MYBPC3* c.2373dup (p.Trp792ValfsTer41) and *MYBPC3* c.1624G>C (p.Glu542Gln), were present in 3 (0.09%) patients each. Individual LP/P variants were also uncommon in the ARIC control group with the most frequent variant, MYL2 c.401A>C (p.Glu134Ala), present in 11 patients (0.08%).

VARIANTS PER PATIENT. We identified 130 patients (4.0%) in the total SCA group harboring 115 LP/P variants: 127 patients with a single variant and 3 patients each harboring 2 variants. In these 130 patients, 39 (30%) suffered nonischemic SCA, 62 (48%) suffered ischemic SCA, and 29 (22%) suffered SCA of unassigned cause. We identified 323 participants (2.4%) in the ARIC control group harboring 228 LP/P variants: 301 participants with a single variant and 22 participants each harboring 2 LP/P variants. The odds of harboring at least 1 LP/P variant was 1.59 (Figure 2; 95% CI: 1.18-2.16; $P = 4.75 \times 10^{-6}$) for the SCA group as compared with ARIC controls.

FIGURE 3 Prevalence of Genotype-Positive Patients in the Sudden Cardiac Arrest Group by Age



Prevalence of patients harboring any disease-causing (likely pathogenic/pathogenic) variant in 4 groups by age at the time of cardiac arrest: 10% in patients 0-29 years, 7% in patients 30-49 years, 4% in patients 50-69 years, and 3% in patients 70 years or older.

There were 39 of 638 patients (6.1%) with LP/P variants in the nonischemic SCA subgroup, 62 of 1,727 patients (3.6%) in the ischemic SCA subgroup, and 29 of 899 patients (3.2%) in the unassigned subgroup. The odds of harboring at least 1 LP/P variant was significantly higher in the nonischemic (**Figure 2**; OR: 2.52; 95% CI: 1.67-3.79; $P = 9.65 \times 10^{-6}$) and ischemic (OR: 1.70; 95% CI: 1.36-2.14; $P = 0.002$) SCA subgroups than in the ARIC control group, but similar in the unassigned SCA subgroup (OR: 1.43; 95% CI: 0.92-2.21; $P = 0.111$).

Given the lower frequency of genotype-positive patients with SCA in the ischemic subgroup but the higher likelihood of ischemia with increasing age, we assessed the frequency of genotype-positive patients with SCA according to 4 groups of increasing age: 0-29, 30-49, 50-69, and ≥70 years (**Figure 3** and Supplemental Table 6). We found that the frequency of genotype-positive patients was highest in the 0- to 29-year age group at 12 of 122 (9.8%) and decreased with increasing age, whereas the frequency of definite/probable ischemic SCA increased with age (Supplemental Table 6).

We also compared the frequency of disease-causing variants between survivors and nonsurvivors of SCA. We identified 15 patients harboring at least 1 LP/P variant in the 423 SCA survivors (3.5%) as compared with 115 patients harboring at least 1 LP/P variant in the 2,834 nonsurvivors (4.1%), a difference that was not statistically significant ($P = 0.713$).

GENE-BASED ANALYSIS. We then collapsed LP/P variants by gene and performed case-control analysis, while controlling for genomic ancestry, to assess the association between candidate genes harboring LP/P variants and the risk of SCA. For the total SCA group, 1 arrhythmia gene (*CACNA1C*) and 2 cardiomyopathy genes (*LMNA* and *MYBPC3)* were associated with a significantly increased risk of SCA (**Table 2** and Supplemental Table 7). In the nonischemic SCA subgroup, 2 arrhythmia genes (*KCNH2* and *KCNQ1)* and 6 cardiomyopathy genes (*BAG3*, *FLNC*, *LMNA*, *MYBPC3, PKP2*, and *RBM20*) were associated with a significantly increased risk of SCA (**Table 2** and Supplemental Table 8). In the ischemic SCA subgroup, 1 arrhythmia gene (*CACNA1C*) and 5 cardiomyopathy genes (*ACTC1*, *DSG2*, *LMNA, MYBPC3*, and *TTN*) were associated with a significantly increased risk of SCA (**Table 2** and Supplemental Table 9). Finally, in the unassigned SCA subgroup, 1 arrhythmia gene (*KCNH2*) and 2 cardiomyopathy genes (*DES* and *MYBPC3*) were associated with a significantly increased risk of SCA (**Table 2** and Supplemental Table 10).

COMPARISON WITH THE GENOME AGGREGATION DATABASE. Given that 2.4% of participants in the control group harbored an LP/P variant, we compared the proportion of disease-causing variants in the SCA group with a second control group, the gnomAD. We identified a total of 1,969,594 variants in the 63 candidate genes with population frequency <0.1% (Supplemental Table 11), of which 1,078 (0.05%) were classified as LP/P. We classified the remainder as B/LB (12,601; 0.6%) or uncertain (1,955,915; 99.3%).

For the SCA group, disease-causing LP/P variants were present in 47 genes (Supplemental Table 11). Although each of these 47 genes harbored disease-causing LP/P variants in gnomAD, we found a significantly higher proportion of disease-causing variants in the SCA group for 9 genes: *CACNA1C, DSG2, DSP, FLNC, KCNQ1, LMNA, MYBPC3, MYH7,* and *TTN* (**Table 3**). Of these 9 genes, 7 had been identified previously using gene-based case-control analysis with the ARIC group serving as controls, whereas 2 genes (*DSP* and *MYH7*) were novel.

TABLE 2 Genes Associated With Sudden Cardiac Arrest in Gene-Collapsing Case-Control Analysis

Gene	Primary Disease Association	Association Between Gene and Sudden Cardiac Arrest (*P* Values <0.05 From CLR-SKAT)			
		Total	Nonischemic Subgroup	Ischemic Subgroup	Unassigned Subgroup
Genes associated with Mendelian arrhythmic diseases					
CACNA1C	LQTS	0.047		0.003	
KCNH2	LQTS		0.014		0.002
KCNQ1	LQTS		9.2E-05		
Genes associated with Mendelian cardiomyopathic diseases					
ACTC1	HCM			0.049	
BAG3	DCM		0.043		
DES	ARVC				0.040
DSG2	ARVC			3.1E-04	
FLNC	DCM		0.040		
LMNA	DCM	0.034	5.6E-04	0.032	
MYBPC3	HCM	0.013	4.3E-04	0.010	1.5E-04
PKP2	ARVC		0.033		
RBM20	DCM		0.045		
TTN	DCM			0.038	

ARVC = arrhythmic right ventricular cardiomyopathy; CLR-SKAT = conditional logistic regression-sequence kernel association test; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; LQTS = long QT syndrome.

DISCUSSION

In this community-based study of 63 candidate genes associated with Mendelian arrhythmia and cardiomyopathy, we identified disease-causing variants in 4.0% of patients with SCA, which was significantly higher than 2.4% in the ARIC control group. In patients with nonischemic SCA, the percentage was higher at 6.1%. We identified 13 genes that were associated with a significantly increased risk of SCA in the total SCA group or its subgroups compared with the ARIC control group. Using a second control group, we identified an additional 2 genes with a significantly higher proportion of disease-causing variants in the SCA group (**Central Illustration**). To our knowledge, this is the first comprehensive, population-based analysis of SCA rare genetic variants in which individuals were ascertained prospectively, both survivors and nonsurvivors of SCA were included, and phenotyping for ischemic vs nonischemic etiologies was available.

Our results have important implications for the role of genetic testing in SCA. The 2017 American Heart Association/American College of Cardiology/Heart Rhythm Society Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death[34] indicate that postmortem genetic testing is reasonable for SCA victims "with an autopsy that implicates a potentially heritable cardiomyopathy or absence of structural disease, suggesting a potential cardiac channelopathy." Indeed, data suggest that there is a significant rare genetic variant burden in autopsy-inconclusive SCA cases,[4] as well as in cardiac arrest survivors with an unexplained cause of SCA.[5] Because we identified specific genes that were associated with SCA among all 3 SCA etiologic subgroups (nonischemic, ischemic, and unassigned), a genetic testing panel that includes at a minimum the genes identified here may be beneficial in evaluating SCA of any cause. However, because additional genes such

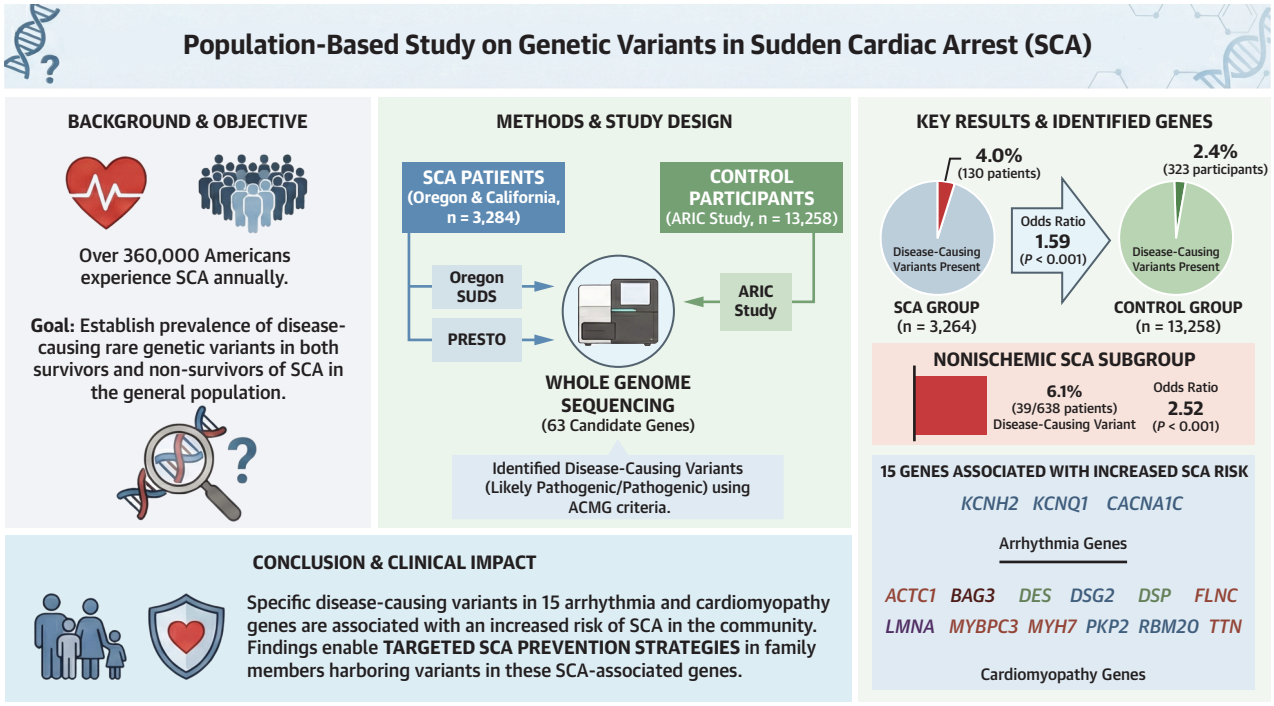
TABLE 3 Proportion of Disease-Causing Variants in Patients With SCA as Compared With the Genome Aggregation Database

Gene	SCA Group			gnomAD			*P* Value
	LP/P AC	Null AC	Allele Frequency	LP/P AC	Null AC	Allele Frequency	
Genes associated with Mendelian arrhythmic diseases							
CACNA1C	2	6,526	0.306	42	1,567,954	0.0268	0.014
KCNQ1	12	6,516	1.838	1311	1,591,745	0.8229	0.014
Genes associated with Mendelian cardiomyopathic diseases							
DSG2	7	6,520	1.073	352	1,586,474	0.2218	8.0E-04
DSP	6	6,522	0.919	499	1,611,317	0.3096	0.018
FLNC	8	6,520	1.225	623	1,605,110	0.388	0.005
LMNA	4	6,524	0.613	214	1,604,460	0.1334	0.012
MYBPC3	21	6,507	3.217	1408	1,587,156	0.8863	8.9E-07
MYH7	10	6,518	1.532	678	1,613,273	0.4201	5.8E-04
TTN	26	6,501	3.984	1949	1,604,303	1.2134	3.1E-07

Frequency is provided as $\times 10^{-4}$.

AC = allele count; gnomAD = Genome Aggregation Database; LP/P = likely pathogenic/pathogenic variants; other abbreviation as in **Table 1**.

CENTRAL ILLUSTRATION **Population-Based Analysis of Rare Genetic Variants in Sudden Cardiac Arrest**



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In this study we sought to establish the prevalence of disease-causing rare genetic variants in both survivors and nonsurvivors of SCA in the general population. We accrued patients with SCA from 2 community-based studies in Oregon and California and compared with control participants from the ARIC study. Whole genome sequencing was performed. Disease-causing (likely pathogenic or pathogenic) variants in 63 candidate genes associated with arrhythmia/cardiomyopathy were identified using updated ACMG criteria. Gene-collapsing case-control analysis and variant proportion comparison with the Genome Aggregation Database (gnomAD) was performed. Disease-causing variants were present in 130 patients (4.0%) in the SCA group as compared with 323 participants (2.4%) in ARIC (OR: 1.59; $P < 0.001$). In the subgroup of patients with a nonischemic SCA, 39 of 638 patients (6.1%) harbored a disease-causing variant (OR: 2.52; $P < 0.001$). We identified 15 genes associated with an increased risk of SCA: *ACTC1*, *BAG3*, *CACNA1C*, *DES*, *DSG2*, *DSP*, *FLNC*, *KCNH2*, *KCNQ1*, *LMNA*, *MYBPC3*, *MYH7*, *PKP2*, *RBM20* and *TTN*. These findings will enable targeted SCA prevention strategies in family members harboring variants in these SCA-associated genes. ACMG = American College of Medical Genetics and Genomics; ARIC = Atherosclerosis Risk in Communities; PRESTO = PREdiction of Sudden death in mulTi-ethnic cOmmunities; SCA = sudden cardiac arrest; SUDS = Oregon Sudden Unexpected Death Study.

as *RYR2*[20] and *SCN5A*[19] have previously been associated with SCA but were not found to be associated with SCA in our study, the utilization of more broad gene panels remains prudent. In fact, the possibility remains that analysis of a sufficiently larger cohort would have identified other important rare genetic variants in additional candidate genes.

Our results also have important implications for the role of genetic testing in patients with DCM and hypertrophic cardiomyopathy. Of the 15 genes we identified as being associated with SCA, 12 (80%) were associated with cardiomyopathies. In the United States, 80% of implantable cardioverter-defibrillator implants are for primary prevention of SCA.[35] The current approach to risk stratification for SCA in DCM and hypertrophic cardiomyopathy, as supported by relevant guidelines,[34,36,37] is to perform genetic testing after a cardiac phenotype has been established. Once established, specific clinical factors such as ejection fraction or the presence of nonsustained ventricular tachycardia are used to determine the risk of SCA and the ensuant management strategy. However, studies suggest that phenotype and risk factors such as ejection fraction may not always be a reliable starting point for risk stratification for SCA.[38-40] Moreover, genes that cause

arrhythmia or cardiomyopathies are frequently associated with more than 1 phenotype (Supplemental Table 1); 10 of the 15 (67%) genes we identified as being associated with SCA are associated with more than 1 phenotype. Thus, our data highlight the relevance of an integrated approach incorporating both genotype and phenotype into the interpretation of genetic testing results in patients with arrhythmia or cardiomyopathy and their family members.

Our current results are consistent with our previous study of the genetics of SCA in young patients in the community,[6] which yielded a lower prevalence of disease-causing variants as compared with studies performed in referral populations, in which the typical prevalence of disease-causing variants is approximately 10% to 20%.[3,7] Similarly, Khera et al[8] identified disease-causing variants in 4 arrhythmia and cardiomyopathy genes in 9 of 600 (1.5%) SCA cases. However, in the latter study, the mean age of patients with SCA was 72 years, which could explain the significantly lower prevalence of rare genetic variants. Within the SCA group of the current study, we identified disease-causing variants in only 27 of 63 candidate genes, and only 15 of these genes were associated with a significantly increased risk of SCA or exhibited a higher proportion of disease-causing variants in patients with SCA.

Consistent with previous epidemiologic studies, definitive/probable ischemia was the most common phenotype of SCA. We identified 6 genes associated with an increased risk of SCA in the ischemic SCA subgroup, suggesting that disease-causing variants can contribute to ischemic SCA in a small percentage of cases. The mechanistic basis for this contribution is unclear, but previous studies have identified an increased risk of ischemic SCA in families,[41,42] suggesting that it may have a rare variant genetic basis. The concept of "mixed" cardiomyopathy, wherein myocardial dysfunction is due to both genetic variants and coronary artery disease, is well established[43-45] and our findings suggest that the clinical entity of "mixed" SCA is also an important cause of SCA.

STUDY STRENGTHS. Ours is one of the first studies of the genetics of SCA to enroll both survivors and nonsurvivors. Next, given the large number of SCA cases in our study, we have been able to determine gene-based risks of SCA that, to the best of our knowledge, has not previously been accomplished. The availability of phenotyping for the cause of SCA in our study has allowed us to identify novel gene associations with causes of SCA, for example, our observation of an association between disease-causing variants in *ACTC1*, *CACNA1C*, *DSG2*, *LMNA*, *MYBPC3,* and *TTN* and ischemic SCA.

STUDY LIMITATIONS. The SCA and control groups were significantly different in several characteristics, including age, race, and sex distribution, and these disparities could have confounded our results. Extensive and detailed phenotyping of SCA is challenging because of the inherent limitations of community-based studies focused on out-of-hospital SCA. At least 40% of individuals present with SCA as their first manifestation of heart disease. Therefore, pre-SCA medical records may not be available in many SCA victims. In addition, autopsy rates have decreased significantly nationwide and these are not performed in most SCA victims. Taken together, these factors limited our ability to perform comprehensive and detailed phenotypic characterization of SCA cases. Therefore some specific clinical data such as findings from the electrocardiogram and echocardiogram were not presented because of significant levels of missingness.

Disease-causing genetic variants were found in 2.4% of ARIC control participants. Although this prevalence is higher than might be expected from a healthy control population, a similar frequency of disease-causing genetic variants in cardiomyopathy genes has been observed in biobank studies.[46,47] Nevertheless, to provide rigorous controls for the frequency of variants, we utilized ARIC participants without a history of SCA as well as gnomAD as a second control group. We used a candidate gene approach considering only genes with known associations with arrhythmia and cardiomyopathy and thus high a priori likelihood of association with SCA, but because we did not perform adjustment for multiple comparisons, we acknowledge the possibility of type I error. Likewise, there are likely additional genes that when dysfunctional due to rare genetic variants contribute to an increased risk of SCA that were not included in our analysis and should be the subject of future study. We used a rigorous variant interpretation approach that classified the vast predominance of variants (99%) as variant of undetermined significance (VUS); as such in our effort to maximize specificity it is likely that a small portion of VUSs were actually LP/P. Further

studies focused on reclassification of VUS are likely to identify additional rare variants associated with an increased risk of SCA.

CONCLUSIONS

In a community-based study of victims of SCA, we identified 15 genes associated with an increased risk of SCA. Inclusion of these genes in genetic testing for SCA will lead to improved identification of persons at risk for SCA.

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ADDRESS FOR CORRESPONDENCE: Dr Evan P. Kransdorf, Center for Cardiac Arrest Prevention, Smidt Heart Institute, Cedars-Sinai Medical Center, 8670 Wilshire Boulevard, Suite 200, Beverly Hills, California 90211, USA. E-mail: evan.kransdorf@cshs.org. OR Dr Sumeet S. Chugh, Cedars-Sinai Health System, Smidt Heart Institute, Department of Cardiology, Division of Artificial intelligence in Medicine, Department of Medicine, Bard Pavilion, 127 South San Vicente Boulevard, Suite A3100, Los Angeles, California 90048. E-mail: sumeet.chugh@csmc.edu.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In this prospective, community-based study, disease-causing variants in 3 arrhythmia and 12 cardiomyopathy genes were associated with SCA, demonstrating that persons in the general population harboring disease-causing variants in these genes are at an increased risk of SCA.

TRANSLATIONAL OUTLOOK: These findings suggest that a gene-centered approach, rather than a phenotype-driven approach, can identify individuals at risk for SCA.

REFERENCES

1. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart disease and stroke statistics-2022 update: a report from the American Heart Association. *Circulation*. 2022;145:e153–e639.

2. Bagnall RD, Weintraub RG, Ingles J, et al. A prospective study of sudden cardiac death among children and young adults. *N Engl J Med*. 2016;374:2441–2452.

3. Guo L, Torii S, Fernandez R, et al. Genetic variants associated with unexplained sudden cardiac death in adult White and African American individuals. *JAMA Cardiol*. 2021;6:1013–1022.

4. Isbister JC, Nowak N, Yeates L, et al. Concealed cardiomyopathy in autopsy-inconclusive cases of sudden cardiac death and implications for families. *J Am Coll Cardiol*. 2022;80:2057–2068.

5. Grondin S, Davies B, Cadrin-Tourigny J, et al. Importance of genetic testing in unexplained cardiac arrest. *Eur Heart J*. 2022;43:3071–3081.

6. Holmstrom L, Chaudhary NS, Nakamura K, et al. Rare genetic variants associated with sudden cardiac arrest in the young: a prospective, population-based study. *Circ Genom Precis Med*. 2023;16:404–405.

7. Neves R, Tester DJ, Simpson MA, Behr ER, Ackerman MJ, Giudicessi JR. Exome sequencing highlights a potential role for concealed cardiomyopathies in youthful sudden cardiac death. *Circ Genom Precis Med*. 2022;15:e003497.

8. Khera AV, Mason-Suares H, Brockman D, et al. Rare genetic variants associated with sudden cardiac death in adults. *J Am Coll Cardiol*. 2019;74:2623–2634.

9. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17:405–424.

10. Abou Tayoun AN, Pesaran T, DiStefano MT, et al. Recommendations for interpreting the loss of function PVS1 ACMG/AMP variant criterion. *Hum Mutat*. 2018;39:1517–1524.

11. Chugh SS, Jui J, Gunson K, et al. Current burden of sudden cardiac death: multiple source surveillance versus retrospective death certificate-based review in a large U.S. community. *J Am Coll Cardiol*. 2004;44:1268–1275.

12. Stecker EC, Vickers C, Waltz J, et al. Population-based analysis of sudden cardiac death with and without left ventricular systolic dysfunction: two-year findings from the Oregon Sudden Unexpected Death Study. *J Am Coll Cardiol*. 2006;47:1161–1166.

13. Reinier K, Moon JY, Chugh HS, et al. Risk factors for sudden cardiac arrest among Hispanic or Latino Adults in Southern California: Ventura PRESTO and HCHS/SOL. *J Am Heart Assoc*. 2023;12:e030062.

14. Chugh SS, Reinier K, Uy-Evanado A, et al. Prediction of sudden cardiac death manifesting with documented ventricular fibrillation or pulseless ventricular tachycardia. *JACC Clin Electrophysiol*. 2022;8:411–423.

15. Reinier K, Sargsyan A, Chugh HS, et al. Evaluation of sudden cardiac arrest by race/ethnicity among residents of Ventura County, California, 2015-2020. *JAMA Netw Open*. 2021;4:e2118537.

16. Stecker EC, Teodorescu C, Reinier K, et al. Ischemic heart disease diagnosed before sudden cardiac arrest is independently associated with improved survival. *J Am Heart Assoc*. 2014;3:e001160.

17. Wright JD, Folsom AR, Coresh J, et al. The ARIC (Atherosclerosis Risk In Communities) study: JACC focus seminar 3/8. *J Am Coll Cardiol*. 2021;77:2939–2959.

18. James CA, Jongbloed JDH, Hershberger RE, et al. International evidence based reappraisal of genes associated with arrhythmogenic right ventricular cardiomyopathy using the clinical genome

resource framework. *Circ Genom Precis Med*. 2021;14:e003273.

19. Hosseini SM, Kim R, Udupa S, et al. Reappraisal of reported genes for sudden arrhythmic death: evidence-based evaluation of gene validity for Brugada syndrome. *Circulation*. 2018;138:1195-1205.

20. Walsh R, Adler A, Amin AS, et al. Evaluation of gene validity for CPVT and short QT syndrome in sudden arrhythmic death. *Eur Heart J*. 2022;43:1500-1510.

21. Jordan E, Peterson L, Ai T, et al. Evidence-based assessment of genes in dilated cardiomyopathy. *Circulation*. 2021;144:7-19.

22. Ingles J, Goldstein J, Thaxton C, et al. Evaluating the clinical validity of hypertrophic cardiomyopathy genes. *Circ Genom Precis Med*. 2019;12:e002460.

23. Adler A, Novelli V, Amin AS, et al. An international, multicentered, evidence-based reappraisal of genes reported to cause congenital long QT syndrome. *Circulation*. 2020;141:418-428.

24. Pedersen BS, Brown JM, Dashnow H, et al. Effective variant filtering and expected candidate variant yield in studies of rare human disease. *NPJ Genom Med*. 2021;6:60.

25. Landrum MJ, Chitipiralla S, Brown GR, et al. ClinVar: improvements to accessing data. *Nucleic Acids Res*. 2020;48:D835-D844.

26. McLaren W, Gil L, Hunt SE, et al. The ensembl variant effect predictor. *Genome Biol*. 2016;17:122.

27. Morales J, Pujar S, Loveland JE, et al. A joint NCBI and EMBL-EBI transcript set for clinical genomics and research. *Nature*. 2022;604:310-315.

28. Tavtigian SV, Harrison SM, Boucher KM, Biesecker LG. Fitting a naturally scaled point system to the ACMG/AMP variant classification guidelines. *Hum Mutat*. 2020;41:1734-1737.

29. Chen S, Francioli LC, Goodrich JK, et al. A genomic mutational constraint map using variation in 76,156 human genomes. *Nature*. 2024;625:92-100.

30. Phelan CM, Kuchenbaecker KB, Tyrer JP, et al. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. *Nat Genet*. 2017;49:680-691.

31. Hansen BB, Klopfer SO. Optimal full matching and related designs via network flows. *Journal of Computational and Graphical Statistics*. 2006;15:609-627.

32. Kang H. EPACTS. Accessed February 25, 2026. https://genome.sph.umich.edu/wiki/EPACTS

33. Cheng S, Lyu J, Shi X, et al. Rare variant association tests for ancestry-matched case-control data based on conditional logistic regression. *Brief Bioinform*. 2022;23:bbab572.

34. Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS Guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2018;138:e272-e391.

35. Yousuf OK, Kennedy K, Russo A, et al. Appropriateness of implantable cardioverter-defibrillator device implants in the United States. *Heart Rhythm*. 2024;21:397-407.

36. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022;79:e263-e421.

37. Ommen SR, Ho CY, Asif IM, et al. 2024 AHA/ACC/AMSSM/HRS/PACES/SCMR Guideline for the management of hypertrophic cardiomyopathy: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *Circulation*. 2024;149:e1239-e1311.

38. Zhang Y, Guallar E, Blasco-Colmenares E, et al. Changes in follow-up left ventricular ejection fraction associated with outcomes in primary prevention implantable cardioverter-defibrillator and cardiac resynchronization therapy device recipients. *J Am Coll Cardiol*. 2015;66:524-531.

39. Pelliccia F, Gersh BJ, Camici PG. Gaps in evidence for risk stratification for sudden cardiac death in hypertrophic cardiomyopathy. *Circulation*. 2021;143:101-103.

40. Paldino A, Dal Ferro M, Stolfo D, et al. Prognostic prediction of genotype vs phenotype in genetic cardiomyopathies. *J Am Coll Cardiol*. 2022;80:1981-1994.

41. Kaikkonen KS, Kortelainen ML, Linna E, Huikuri HV. Family history and the risk of sudden cardiac death as a manifestation of an acute coronary event. *Circulation*. 2006;114:1462-1467.

42. Hookana E, Junttila MJ, Kaikkonen KS, et al. Comparison of family history of sudden cardiac death in nonischemic and ischemic heart disease. *Circ Arrhythm Electrophysiol*. 2012;5:757-761.

43. Povysil G, Chazara O, Carss KJ, et al. Assessing the role of rare genetic variation in patients with heart failure. *JAMA Cardiol*. 2021;6:379-386.

44. Jones RE, Hammersley DJ, Zheng S, et al. Assessing the association between genetic and phenotypic features of dilated cardiomyopathy and outcome in patients with coronary artery disease. *Eur J Heart Fail*. 2024;26:46-55.

45. Cao L, Rushakoff J, Williamson I, et al. Similar burden of rare genetic variants in ischemic and non-ischemic dilated cardiomyopathy. *Front Cardiovasc Med*. 2025;12:1542653.

46. Asatryan B, Shah RA, Sharaf Dabbagh G, et al. Predicted deleterious variants in cardiomyopathy genes prognosticate mortality and composite outcomes in the UK Biobank. *JACC Heart Fail*. 2024;12:918-932.

47. Lee DSM, Cardone KM, Zhang DY, et al. Common-variant and rare-variant genetic architecture of heart failure across the allele-frequency spectrum. *Nat Genet*. 2025;57:829-838.

KEY WORDS cardiomyopathy, channelopathy, population-based study, rare genetic variant, sudden cardiac arrest

APPENDIX For the Criteria for Sudden Cardiac Arrest Phenotypes, Variant Interpretation Criteria, the supplemental tables, and the supplemental figure, please see the online version of this paper.