CONTEMPORARY REVIEW

Racial Disparities in Ion Channelopathies and Inherited Cardiovascular Diseases Associated With Sudden Cardiac Death

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ABSTRACT: Cardiovascular disease (CVD) continues to be the most common cause of death worldwide, and cardiac arrhythmias account for approximately one half of these deaths. The morbidity and mortality from CVD have been reduced significantly over the past few decades; however, disparities in racial or ethnic populations still exist. This review is based on available literature to date and focuses on known cardiac channelopathies and other inherited disorders associated with sudden cardiac death in African American/Black subjects and the role of epigenetics in phenotypic manifestations of CVD, and illustrates existing disparities in treatment and outcomes. The review also highlights the knowledge gaps that limit understanding of the manifestation of phenotypic abnormalities across racial or ethnic groups and discusses disparities associated with device underuse in the management of patients at risk for sudden cardiac death. We discuss factors related to reports in the United States, that the overall mortality attributed to CVD and the number of out-of-hospital cardiac arrests are higher among African American/Black subjects when compared with other racial or ethnic groups. African American/Black subjects are disproportionately affected by CVD, including cardiac arrhythmias and sudden cardiac death, thus highlighting a major concern in this population that remains underrepresented in clinical trials with limited genetic testing and device underuse. The proposed solutions include (1) early identification of genetic variants, which is crucial in tailoring a preventive management strategy; (2) inclusion of diverse racial or ethnic groups in clinical trials; (3) compliance with guideline-directed medical treatment and referral to cardiovascular subspecialists; and (4) training and mentoring of underrepresented junior faculty in cardiovascular health disparities research.

Key Words: ethnicity ■ genetics ■ implantable cardioverter-defibrillator ■ ion channelopathies ■ race ■ *SCN5A* ■ sudden cardiac death

The discussion of race and ethnicity and the appropriate use of descriptors have been recognized as germane and relevant to the biomedical literature. Accuracy and appropriate characterization of race and ethnicity serve to avoid stereotypes, provide specificity, attain suitable risk profiles, design appropriate research studies and trials for the purpose of inclusivity, and allow equitable allocation of resources that would lead to improved health care outcomes. Historically, race is considered a social construct unrelated to the individual's genetic makeup and largely not representative of disease predilection. Ethnicity is defined as those attributes that are related to one's cultural makeup reflected in language, practices, and beliefs. The disconnect between race and genetic or biological predisposition to disease compromises the ability to make diagnostic conclusions and inferences strictly based on race.

However, the sociobiological aspects of individuals within a given race or ethnicity may impact the quality of care received within the health care system and influence outcome. Recently, recommendations for journal editors, authors, researchers, clinicians, and others reporting study results, opinions and perspectives, reviews, and other information in the biomedical literature have been developed and aimed at providing

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Nonstandard Abbreviations and Acronyms

AA	African American
ARVC	arrhythmogenic right ventricular cardiomyopathy
BrS	Brugada syndrome
ERS	early repolarization syndrome
HCM	hypertrophic cardiomyopathy
LQTS	long-QT syndrome
OHCA	out-of-hospital cardiac arrest
P/LP	pathogenic/likely pathogenic
POST SCD	Postmortem Systematic Investigation of Sudden Cardiac Death
SAD	sudden arrhythmic death
SCA	sudden cardiac arrest
SCD	sudden cardiac death
SUD	sudden unexpected death
VUS	variants of uncertain significance
WHO	World Health Organization

uniformity and proper decorum in conducting research and in communicating results.[1] These recommendations are expected to enable meaningful communication and interpretation of data on race and ethnicity in a uniform manner and allow accurate assessment of the impact of such data on the health care system, particularly when studying socioeconomic, sociopolitical, demographic, cultural, and institutional factors in disease management. In this review, we were attentional in being consistent with recommendations on nomenclature in discussing race and ethnicity. Although the recommendations are mostly applicable to original research, it behooves all to comply irrespective of the nature of the publication. As such, we are constrained in that the data we present on race and ethnicity can only be reported in a manner consistent with information provided by the authors and the nomenclature used during data collection. For that purpose and uniformity, we elected to use the term "African American (AA)/ Black" subjects as a descriptor of racial or ethnic subjects. Although this review was not written as a "systematic review," an extensive review of the literature to date was undertaken using a combination of PubMed and Google scholar.

Despite the fact that the focus of this review is on ion channelopathies and inherited cardiovascular diseases (CVDs) associated with sudden cardiac death (SCD), we believe that a discussion of disparities and the management of SCD would not be complete without a parallel discussion on the management of at-risk populations with other conditions. Because of the paucity of data in racial or ethnic groups including AA/Black subjects, and the increasing belief that

epigenetic factors play a major role in phenotypic manifestation of disease in genotype-negative individuals, a brief discussion of epigenetic factors appears appropriate. In addition, a discussion on underuse of cardiac implantable electronic devices in AA/Black subjects will sharpen the disparity discussion and hopefully lead to improved treatment outcomes in other racial or ethnic groups. A brief mention of the role of social determinants of health on CVD manifestation will be stated, but the absence of data directly linking SCD and ion channelopathies with social determinants of health will not allow speculation and is beyond the scope of this review.

RACE/ETHNICITY AND CVD

CVD remains the most common cause of death worldwide, and SCD attributable to cardiac arrhythmias accounts for ≈50% of deaths.[2] In the United States, SCD is responsible for an estimated 350 000 cardiac deaths annually.[3,4] AA/Black subjects have higher SCD death rates than White, American Indian/Alaskan native, and Asian/Pacific Islander subjects.[5] Despite improvement in morbidity and mortality over the past few decades, racial or ethnic groups experience disproportionate adverse outcomes when compared with non-Hispanic White subjects.[6,7] Notwithstanding the many pronouncements, passing of the revitalization act of 1993 that promotes racial or ethnic inclusion in clinical trials, and financial investments in understanding the reasons for disparities, resolution of these disparities has not occurred. Despite these efforts, proportional representation of racial or ethnic groups in clinical trials has fallen short of their targeted objectives.[8]

DISPARITIES IN SCD: ASSESSMENT, CLASSIFICATION, AND RACIAL IMPLICATIONS

SCD is a major public health concern, and any racial or ethnic disparity in incidence, treatment, and survival outcomes will add to the complexity involved in its prevention and management of those surviving the event. Survival to hospital discharge from an out-of-hospital cardiac arrest (OHCA) is ≈10%, and 25% from an in-hospital cardiac arrest event.[9,10] Approximately 70% to 85% of OHCA events are attributed to a cardiac cause; thus, prevention has been focused on the management of heart disease and the attendant comorbidities.[11,12] Published reports on the cause of SCD have been derived from emergency medical services (EMS), hospital records, death certificates, and other sources that infer a cause of death. Imprecision and inaccuracies from these sources have been acknowledged.[9,13] These reports often attribute higher SCD rates and

poorer outcomes in AA/Black men when compared with White men.[9,13–16] In a systematic review and meta-analysis of 15 studies of OHCA comparing outcomes by race or ethnicity, using adjusted odds ratios (ORs) from the 6 studies in which they were available, Shah et al reported that compared with White subjects, AA/Black subjects were less likely to receive bystander cardiopulmonary resuscitation (CPR) (OR, 0.66; 95% CI, 0.55–0.78), have a witnessed arrest (OR, 0.77; 95% CI, 0.72–0.83), or have an initial ventricular tachycardia/ventricular fibrillation (VT/VF) arrest rhythm (OR, 0.66; 95% CI, 0.58–0.76; all P values <0.00001).[16] AA/Black subjects had lower rates of survival following hospital admission (OR, 0.59; 95% CI, 0.48–0.72; P<0.00001) and survival to discharge (OR, 0.74; 95% CI, 0.61–0.90; P=0.0003). Shah et al found that ORs from adjusted variables yielded less disparate results than those from analysis of unadjusted variables. On the contrary, other investigations have yielded mixed results.[17] For example, in the Oregon SUDS (Sudden Unexpected Death Study) of individuals experiencing sudden cardiac arrest (SCA) in the Portland metropolitan area from 2002 to 2012, the age-adjusted rates of SCA were 2-fold higher among AA/Black men and women compared with White men and women. Despite comparable rates of coronary artery disease, AA/Black subjects had a lower rate of revascularization and longer corrected QT (QTc) intervals when compared with White subjects. AA/Black subjects with SCA had a higher prearrest prevalence of risk factors, with significantly higher rates of diabetes, heart failure, hypertension, left ventricular hypertrophy, and chronic kidney disease. Aside from a younger age, no other significant differences were noted in the circumstances of the cardiac arrest, proportion of witnessed arrests, arrest location, bystander CPR, response time, or presenting arrhythmias.

Among the largest and most comprehensive database available for analysis of OHCA is the CARES (Cardiac Arrest Registry for Enhanced Survival), initiated by the Centers for Disease Control and Prevention.[9] This registry investigated OHCA events only from presumed cardiac cause in individuals who were resuscitated by CPR or defibrillation. Data were collected from 911 dispatched EMS centers and hospitals. OHCA was defined in CARES as a cardiac arrest that happened before hospitalization, of cardiac cause, and involved individuals who were resuscitated by CPR or defibrillation. The registry included 40 274 OHCA records collected from October 1, 2005, to December 31, 2010. The 31 689 OHCA events from presumed cardiac cause (ie, arrhythmias or myocardial infraction) were analyzed. Noncardiac cause arrests and missing hospital outcomes were excluded from the study (n=8585). The average age at cardiac arrest was 64.0±18.2 years, and most who experienced OHCA were men (61.1%). According to EMS protocols,

21.6% of subjects were declared dead after resuscitation was terminated in the prehospital setting. Survival rates to hospital admission and discharge were 26.3% and 9.6%, respectively; although 36.7% of OHCA events were witnessed by a bystander, only 3.8% of all subjects received bystander CPR and 3.7% received bystander treatment with an automated external defibrillator. Subjects who were witnessed to collapse by a bystander were most likely to survive an OHCA and were also found in a shockable rhythm (ie, ventricular fibrillation or pulseless ventricular tachycardia). Survival to discharge was 30% among these subjects. With regard to unwitnessed arrests, White subjects were significantly more likely to receive CPR than AA/Black, Hispanic, or members of other racial or ethnic populations (P<0.001). Overall survival to hospital discharge of subjects whose events were not witnessed by EMS was 8.5%. Of these, subjects who received bystander CPR had a higher rate of overall survival (11.2%) than those who did not (7.0%) (P<0.001).

Subsequent studies also found that AA/Black subjects were less likely to have witnessed SCA events and less likely to receive bystander-initiated CPR, and OHCA events were more common in low-income neighborhoods where AA/Black subjects were less likely to present with a shockable rhythm.[9,18]

Classification of arrhythmic deaths is often limited or inaccurate as it is difficult to delineate sudden arrhythmic death (SAD) from nonarrhythmic death. Because >90% of SCD events occur outside of the hospital and 90% of cases do not undergo autopsy evaluation, definitive data on the cause and terminal events often are not available.[19,20] Rhythm analysis at the time of death would be invaluable in elucidating the cause of SCD and its mechanism. In a study of causes of deaths in 706 patients with an implantable cardioverter-defibrillator (ICD) in Multicenter Automatic Defibrillator Implantation Trial II, documentation of VT/VF can be made at symptom onset.[21] VT/VF and nonarrhythmic deaths were categorized by the presence or absence of VT/VF during the terminal event. Of 109 deaths, 44, which occurred over a 20-month follow-up, were from cardiac causes and had device interrogation data available. Fifteen of these 44 (34%) patients had VT/VF at the time of death. The mode of death was clinically adjudicated using a modified Hinkle-Thaler classification.[22] The mode of death clinically adjudicated was inaccurate when validated by device interrogation. Fifty percent of patients clinically adjudicated as having SCD did not have VT/VF at the time of death; and 25% of patients adjudicated as not having SCD had VT/VF during the terminal event. Factors independently associated with VT/VF included VT/VF >72 hours before the terminal event (hazard ratio [HR], 7.97; 95% CI, 2.5–24.2; P<0.001), hospitalization for heart failure (HR, 6.69; 95% CI, 2.16–20.7; P=0.001), and a history

of hypertension (HR, 3.97; 95% CI, 1.9–13.7; P=0.04). No data on race were reported. Although these patients were deemed high risk for an arrhythmic event by virtue of their guideline indication for an ICD, VT/VF often was not the mode of death.

Delineation of causes of SCD from SAD is vital because these terms are not synonymous and the cardiac substrate may vary widely. SAD may be attributable to VT/VF and responsive to ICD therapy, whereas nonsudden deaths may not be arrhythmic and therefore will not be rescuable with ICD therapy. SCD is defined by World Health Organization (WHO) criteria (WHO-defined SCD) as sudden or unexpected death that occurred either within 1 hour of symptom onset (if witnessed) or within 24 hours of having been observed alive and symptom free if unwitnessed.[23] In the POST SCD (Postmortem Systematic Investigation of Sudden Cardiac Death) Study, a San Francisco countywide prospective study, autopsy characterization of SCD was undertaken.[24] Among 20 440 deaths of subjects aged from 18 to 90 years, which occurred from February 2011 to March 2014, 12 671 were reported to the medical examiner. From these, 912 were OHCA deaths. A total of 541 of these OHCA deaths (59%) met WHO-SCD criteria and 97% of them were autopsied. Investigators found that only 56% of OHCA cases based on WHO definition had autopsy-defined SCD. Autopsy-defined SCD cases were those cases that had no extracardiac causes, such as acute cerebrovascular accidents, vascular rupture, cardiac tamponade, and pulmonary embolism, nor were associated with acute heart failure. Forty percent of deaths attributed to cardiac arrest were not sudden or unexpected. Nearly half of presumed SCDs were not arrhythmic. The authors concluded that their findings have implications for the accuracy of SCDs, as defined by WHO criteria or EMS records, in aggregate mortality data, clinical trials, and cohort studies.

Sex and racial differences in autopsy-defined causes of SCD from the POST SCD Study were evaluated for accuracy and evidence of racial misrepresentation.[25] Among the 541 OHCA cases collected over a 37-month period that met WHO definition of SCD, 15% of subjects were AA/Black and 8% were Hispanic. SCD was further defined as those cases that had no extracardiac causes nor were associated with acute heart failure. The cause of death was classified as SAD (rescuable with an ICD) or non-SAD. Nearly half of the presumed SCDs had an obvious nonarrhythmic cause of death. Men had a 3-fold higher rate of SCD than women, and there were no differences between AA/Black and White men. The proportion of presumed SCD attributable to SAD was higher in men than women (61% versus 45%; P<0.01). Women were more likely than men to have noncardiac causes of sudden death (51% versus 35%; P<0.01).

Among SADs, women were less likely to have ischemic causes than men and more likely to have primary electrical disease than men (4% versus 2%; P<0.02). Black women had higher autopsy-defined SADs than White women. Overall, there were no significant racial differences in EMS response time, proportion of witnessed events, or initial presenting rhythms for all witnessed events.

In a unique study that included both cardiac implantable electronic devices and autopsy analysis of 517 patients with SCD included in the POST SCD Study, 22 of 517 sudden deaths (4.3%) had cardiac implantable electronic devices.[26] Six of 14 pacemaker sudden deaths and 7 of 8 ICD sudden deaths died of VT/VF. Autopsy-defined SAD was concordant with the cause of death noted on device interrogation, although device malfunction was suspected in a significant portion of deaths.

The SCD POST Study finding that 40% of OHCA deaths were not sudden and only 56% of OHCAs with WHO-defined criteria for SCD were arrhythmic is germane relative to results from smaller non–autopsy-defined SAD studies (Figure 1).[24] The presence of a significant number of noncardiac causes of SCD highlights the importance of primordial and primary CVD prevention and guideline-directed management of cardiovascular comorbidities. Autopsy-derived findings of the POST SCD Study revealed no racial differences in SCDs overall, except for the subgroup of AA/Black women, in contradiction to non–autopsy-based data. Incidence rate ratios for WHO-SCD and autopsy-defined SAD were >2- and 3-fold higher in men versus women, respectively (P<0.0001), highest in AA/Black subjects (P<0.0001), and lowest in Hispanic subjects (P=0.0018). AA/Black (45%) and Hispanic subjects (55%) had the lowest proportion of WHO-defined SCDs that were autopsy-defined SADs, suggesting that WHO-defined SCD parameters did not accurately detect true arrhythmic causes of death. The incidence rate ratios of OHCA deaths in AA/Black subjects compared with White subjects did not reach statistical significance (P=0.07; Figure 2).[24] Because in >90% of SCD cases an autopsy is not performed, it is not surprising that discordant results were observed. Studies that do not include autopsy evaluation appear to lack specificity in elucidating causal factors responsible for SCD. Misclassification of the cause of SCD is evident as autopsy-defined SAD was observed in only 56% of cases. AA/Black subjects exhibited the lowest proportion of presumed SCDs attributed to SAD and the largest proportion of cases attributable to noncardiac causes, which would not be rescuable by an ICD. The burden of comorbidities in AA/Black subjects may contribute to these results and calls for reevaluation of the approach to risk stratification and prevention of SCD in this population.
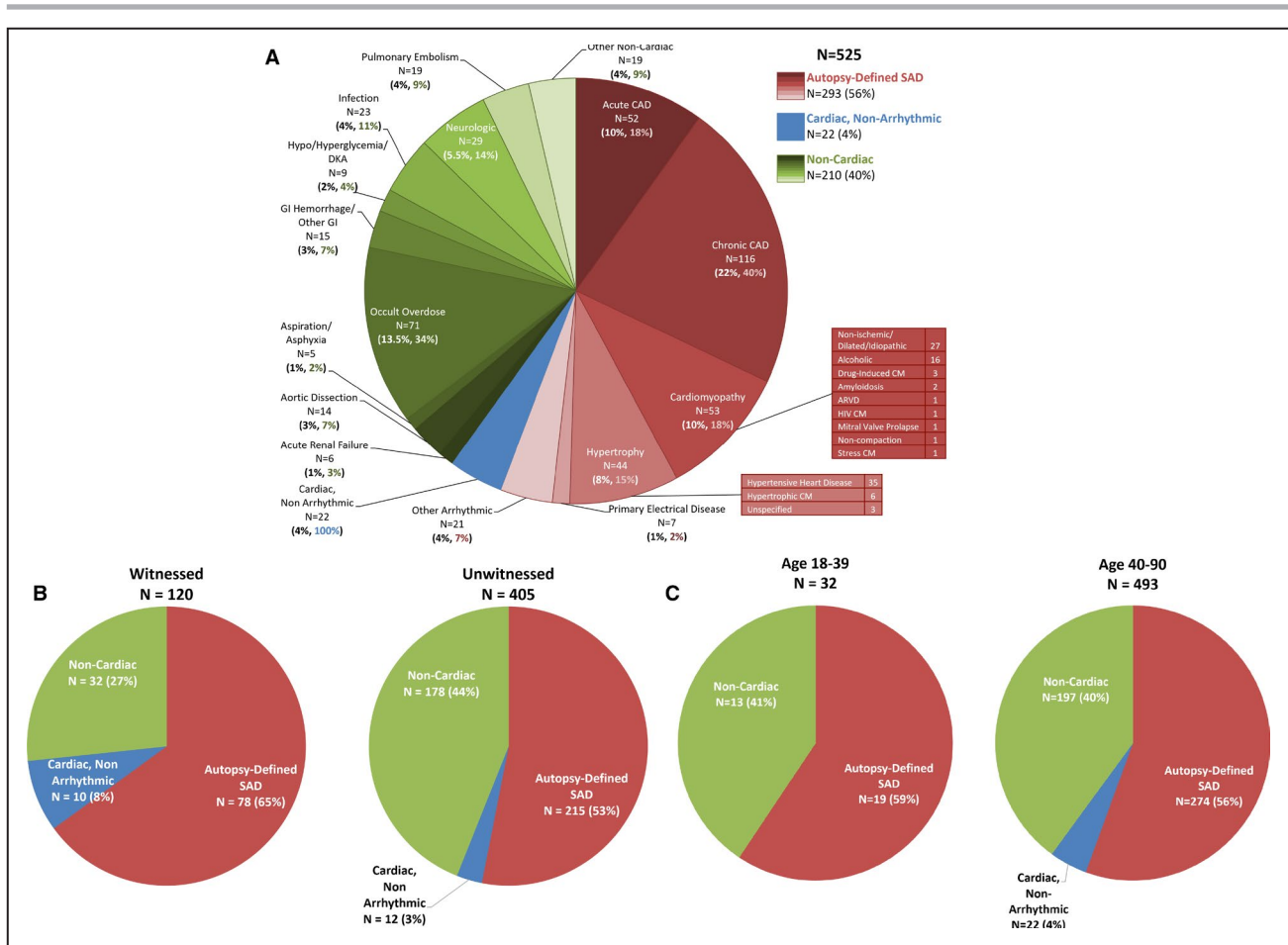
Figure 1. Adjudicated causes of autopsied World Health Organization (WHO)–defined sudden cardiac deaths (SCDs) and adjusted incidence rates per 100 000 person-years for all observed out-of-hospital cardiac arrest deaths, WHO-defined SCDs, and autopsy-defined sudden arrhythmic deaths (SADs) are shown.

A, Adjudicated causes of autopsied WHO-defined SCDs. Autopsy-defined SADs had no identifiable extracardiac or nonarrhythmic cause of death. Among the 525 autopsied cases, autopsy-defined SADs accounted for 56% of all WHO-defined SCDs, 4% were cardiac nonarrhythmic cause of death, and 40% were noncardiac cause of death. Autopsy-defined SAD (N=293). The various causes along with the number of decedents and percentages are shown. **B**, The adjudicated causes of witnessed vs unwitnessed WHO-defined SCDs is noted. Autopsy-defined SADs accounted for 65% of witnessed and 53% of unwitnessed WHO-defined SCDs (odds ratio, 1.62; 95% CI, 1.06–2.48; P=0.024). **C**, Adjudicated causes of WHO-defined SCDs for age 18 to 39 vs ≥40 years is shown. Autopsy-defined SADs accounted for a similar proportion of WHO-defined SCDs age 18 to 39 (19/32 [59%]) vs ≥40 (274/493 [56%]) years (P=0.68). Reprinted from Tseng et al[24] with permission. Copyright ©2021, Wolters Kluwer Health. ARVD indicates arrhythmogenic right ventricular dysplasia; CAD, coronary artery disease; CM, cardiomyopathy; DKA, diabetic ketoacidosis; and GI, gastrointestinal.

Evaluation of factors predisposing to survival from the POST SCD Study cohort revealed that among the 734 OHCA events, 239 met criteria for SCA, 133 (55.6%) were resuscitated to hospital admission, and 19% survived to discharge.[27] Arrhythmic causes accounted for 69% of resuscitated SCA events overall and were documented in 91.5% of survivors when compared with WHO-defined SCD (56%). Statistically significant differences in arrhythmia-related survival were noted between SCA-defined events and WHO-defined SCD (P<0.004). Arrhythmia causes predicted survival, and nearly one half of nonsurvivors had nonarrhythmic causes of OHCA. Multivariable analysis revealed predictors of survival included White race (OR, 4.04; 95% CI, 1.21–13.56; P=0.02), VT/VF as the presenting rhythm (OR, 19.26; 95% CI, 5.25–70.59; P<0.01), and arrhythmic causes (OR, 5.29; 95% CI, 1.38–20.34; P=0.02). Only 5 AA/Black subjects were included among 47 survivors. Given that AA/Black subjects have consistently been found to have a significant number of noncardiac causes of SCD, which may not be sudden or arrhythmic, possibly reflected in a higher percentage of nonshockable rhythms, may represent the availability of external defibrillator therapy for the wrong substrate. Few studies have reported that AA/Black subjects are less likely to undergo
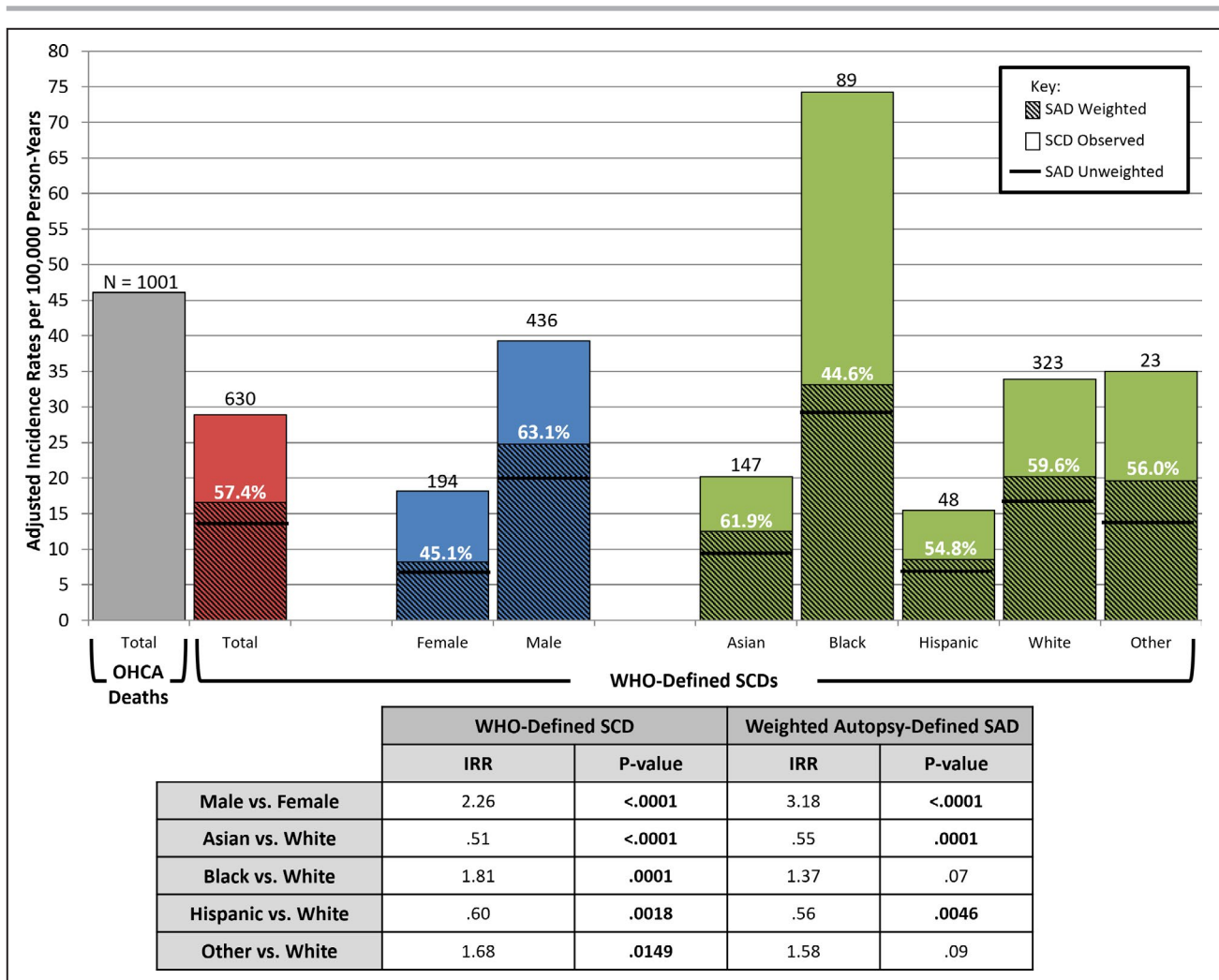
	WHO-Defined SCD		Weighted Autopsy-Defined SAD	
	IRR	**P-value**	**IRR**	**P-value**
Male vs. Female	2.26	**<.0001**	3.18	**<.0001**
Asian vs. White	.51	**<.0001**	.55	**.0001**
Black vs. White	1.81	**.0001**	1.37	.07
Hispanic vs. White	.60	**.0018**	.56	**.0046**
Other vs. White	1.68	**.0149**	1.58	.09

Figure 2. Adjusted incidence rates per 100 000 person-years for all observed out-of-hospital cardiac arrest (OHCA) deaths, World Health Organization (WHO)–defined sudden cardiac deaths (SCDs), and autopsy-defined sudden arrhythmic deaths (SADs).

Adult countywide incidence rates of OHCA death and WHO-defined SCD over 37 months were 46/100 000 and 29.6/100 000 person-years, respectively. OHCA death and WHO-defined SCD incidence rates both include 89 identified WHO-defined SCDs that were attended by the medical examiner (because of recent medical care <3 weeks before death) and 16 OHCA deaths that did not undergo autopsy. Sex- and race-specific incidence rate ratios (IRRs) for all WHO-defined SCD and weighted autopsy-defined SAD are shown. Weighted countywide incidence of autopsy-defined SAD was 17/100 000 person-years, accounting for the 89 WHO-defined SCDs without autopsy. Autopsy-defined SAD accounted for a weighted proportion of 57.4% of all WHO SCDs. IRR for WHO SCD and autopsy-defined SAD were over 2- and 3-fold higher in men vs women, respectively (P<0.0001), and highest in Black subjects (P>0.0001) and lowest in Hispanic subjects (P=0.0018). Black (45%) and Hispanic (54.6%) subjects had the lowest proportion of WHO-defined SCDs that were autopsy-defined SADs. Differences in weighted autopsy-defined SAD rates between African American/Black and White subjects were not significant (P=0.07). Other race includes American Indian/Alaskan natives, native Hawaiians, and other Pacific Islanders. Reprinted from Tseng et al[24] with permission. Copyright ©2021, Wolters Kluwer Health.

bystander-initiated CPR, particularly those who reside in low-income neighborhoods. This should serve as an opportunity to explore the logistical barriers that exist and improve health literacy. The purported disparities may be a manifestation of misclassification of SCD events and misrepresent the true incidence of SCD attributable to VT/VF and response to therapy. A new paradigm for risk stratification, evaluation, and prevention of SCD may be required. In this new paradigm, much needed evidence from autopsy-defined causes of SCD may be included and assist in providing more robust information, thus minimizing misclassification and misrepresentation of the causes of SCD.[20,28] A new approach may allow targeted preventive interventions for cardiac and noncardiac causes of SCD. The importance of a new paradigm cannot be overstated as AA/Black subjects often have several comorbidities, have a long history of disparities in cardiovascular therapies, and receive fewer cardiac procedures than White subjects following survival from a cardiac arrest.[29] The

multiplicity of factors associated with SCD justifies the polypharmacy approach to treating at-risk patients by modulating neurohormonal factors with β blockers, angiotensin-converting enzyme inhibitors, or angiotensin II receptor blockers, neprilysin inhibitors, and other agents. The use of autopsy-defined SCD is a reliable adjunct in characterizing the true incidence of SCD attributable to arrhythmic causes and helps direct appropriate resources and guideline recommendations in the management of patients with CVD. Table 1[30,31] summarizes out-of-hospital cardiac arrest and SCD trials/databases, highlighting disparities and outcomes discussed above.

MOLECULAR GENETICS OF SUDDEN UNEXPECTED DEATH

SCD in adults is a vexing problem and by extension SUD is concerning because of its impact in infants and those without structural heart disease. SUD has a significant societal impact and major implications for surviving families as the role of heritability is brought to the forefront in decision-making and cascade screening. In 2014, Wang et al[32] performed molecular genetic analyses for 6 major cardiac channelopathy genes (KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, and RyR2)

in 274 ethnically diverse SUD cases and found that channelopathies were the cause of death in 13.5% of infant and 19.5% of noninfant victims. The infant cohort had 60% AA/Black, whereas the noninfant cohort had 35% AA/Black subjects. AA/Black subjects carried more SCN5A and KCNQ1 variants than Hispanic and Asian groups, whereas White subjects carried more RyR2 variants. The distribution of 3 SCN5A common variants (S524Y, S1103Y, and H558R) and 2 KCNQ1 variants (G643S and V648I) exhibited patterns of minor allele frequencies higher for AA/Black than for White subjects, whereas the KCNH2 variant (K897T) had a pattern of higher minor allele frequencies for White than for AA/Black subjects (Table 2).

The authors recommended molecular genetic testing for cardiac channelopathies in SUD victims to establish the cause of death and guide decision-making among surviving family members. In a subsequent study by the same group,[33] high-resolution variant interpretation workflow analysis was used to evaluate 89 cardiac disease genes in a cohort of 296 decedent subjects who had SUD (147 AA/Black, 64 Hispanic, 49 White, 22 Asian, and 14 mixed ethnicities) to assess diagnostic accuracy. The diagnostic yield was positive in 21% in mixed ethnicities, 10% White, 5% Asian, 3% Hispanic, and 2% AA/Black subjects.

Table 1. OHCA and SCD Trials/Databases Highlighting Disparities and Outcomes

Study name/investigator	Study design	Study outcome
Systematic Review and Meta-Analysis of Out-of-Hospital Cardiac Arrest and Race or Ethnicity: Black US Populations Fare Worse[16]	Systematic review and meta-analysis	AA/Black subjects less likely to receive CPR; witnessed arrest; initial shockable rhythm than White subjects; AA/Black subjects had lower rates of survival for OHCA following hospital admission and to discharge
Oregon SUDS[17]	Prospective community-based epidemiological study	SCAs were 2-fold greater in AA/Black vs White subjects
Out of Hospital Cardiac Arrest Surveillance-CARES[9]	Large-scale cardiac arrest registry	Witnessed OHCA more likely to survive than unwitnessed; White subjects more likely to receive CPR than AA/Black or Hispanic subjects; bystander CPR associated with greater likelihood of survival than those not receiving bystander CPR
MADIT-II Substudy[21]	MADIT-II substudy	50% of patients with adjudicated SCD and ICD did not have VT/VF at terminal event
Prospective Countywide Surveillance and Autopsy Characterization of Sudden Cardiac Death (Post SCD Study)[24]	Large-scale prospective study	40% of deaths attributed to SCA were not sudden; 56% of SCDs were not arrhythmic; men had 3 times higher SCD rate than women; no difference in SCD rate between AA/Black men and White men; Black women had higher autopsy-defined SAD than White women; women were more likely than men to have noncardiac cause of SCD; no significant racial difference in EMS response time, witnessed events, and presenting rhythm
Amiodarone or an Implantable Cardioverter-Defibrillator for Congestive Heart Failure (SCD-HeFT)[113]	Large randomized multicenter trial	ICD reduces total mortality, in all subjects with reduced LVEF <35%
Effectiveness of the Implantable Cardioverter Defibrillator in Blacks Versus Whites (from MADIT-II)[31]	Prospective randomized multicenter trial, substudy	ICD significantly reduces total mortality, cardiac death, and SCD; SCD 1.7-fold greater in AA/Black subjects than White subjects (underpowered study)

AA indicates African American; CARES, Cardiac Arrest Registry for Enhanced Survival; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MADIT-II, Multicenter Automatic Defibrillator Implantation Trial II; OHCA, out-of-hospital cardiac arrest; SAD, sudden arrhythmic death; SCA, sudden cardiac arrest; SCD, sudden cardiac death; SCD-HEFT, Sudden Cardiac Death in Heart Failure Trial; SUDS, Sudden Unexpected Death Study; VF, ventricular fibrillation; and VT, ventricular tachycardia.

Table 2. Putative Channelopathy-Associated Variant Distributions Among 274 SUDS Decedents

Variables	SCN5A	KCNQ1	KCNH2	KCNE2	KCNE1	RyR2
Ethnicity distribution	11 Black, 5 White, 4 other,* 5 Hispanic, 3 Asian	5 Black, 1 White, 1 Hispanic	3 Black, 1 White, 1 Asian	1 White, 1 Hispanic	1 Hispanic	4 White, 1 Hispanic
Sex distribution	18 men, 10 women	4 men, 3 women	4 women, 1 man	2 men	1 man	4 men, 1 woman
Age distribution	15 (≤1 y), 13 (˃1 y)	3 (≤1 y), 4 (˃1 y)	1 (≤1 y), 4 (˃1 y)	1 (≤1 y), 1 (˃1 y)	1 (˃1 y)	1 (≤1 y), 4 (˃1 y)
Death circumstances	94% sleeping in infants	˜71% sleeping	60% sleeping	100% sleeping	100% sleeping	80% active

SUDS indicates Sudden Unexpected Death Study.
*Other indicates not Black, White, Hispanic or Asian.
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The authors concluded that high-resolution variant interpretation workflow allows for improvement in diagnostic accuracy, but underrepresented groups were few and warrant greater inclusion. A systematic review and meta-analysis by Kong et al[34] assessed the mean allele frequencies of channelopathy genes SCN5A, KCNH2, KCNE1, KCNQ1, and NOS1AP in AA/Black, White, Asian, and Hispanic subjects. Eligible publications were from human studies with reports of SCD for different ethnic populations, that provided allele frequencies of channelopathy genes reporting SDs. The results showed that Asians carried the most alleles of genes associated with SCD, and AA/Black subjects had the highest median value of allele frequencies for SCN5A and NOS1AP (Figure 3). Although AA/Black subjects were reported to be more susceptible to SCD

than White subjects[3,17] and SCD was less prevalent in Asian countries,[5,35–37] Kong's meta-analysis noted that genetics alone without considering environmental and socioeconomic factors cannot account for disparities in health outcomes between racial or ethnic groups. In a more recent comprehensive review of 254 decedents from SCD,[38,39] most of whom were AA/Black subjects (40% AA/Black, 30% Hispanic, 22% White, 5% Asian/Pacific Islander, and 3% mixed/unspecified subjects), a multigene panel composed of 95 genes (Figure 4) associated with cardiac channelopathy and cardiomyopathy were investigated using next-generation sequencing. Twenty-seven pathogenic/likely pathogenic (P/LP) variants and 99 variants of uncertain significance (VUS) were identified in 11% and 39% of decedents, respectively. P/LP and VUS were found in 51 of the
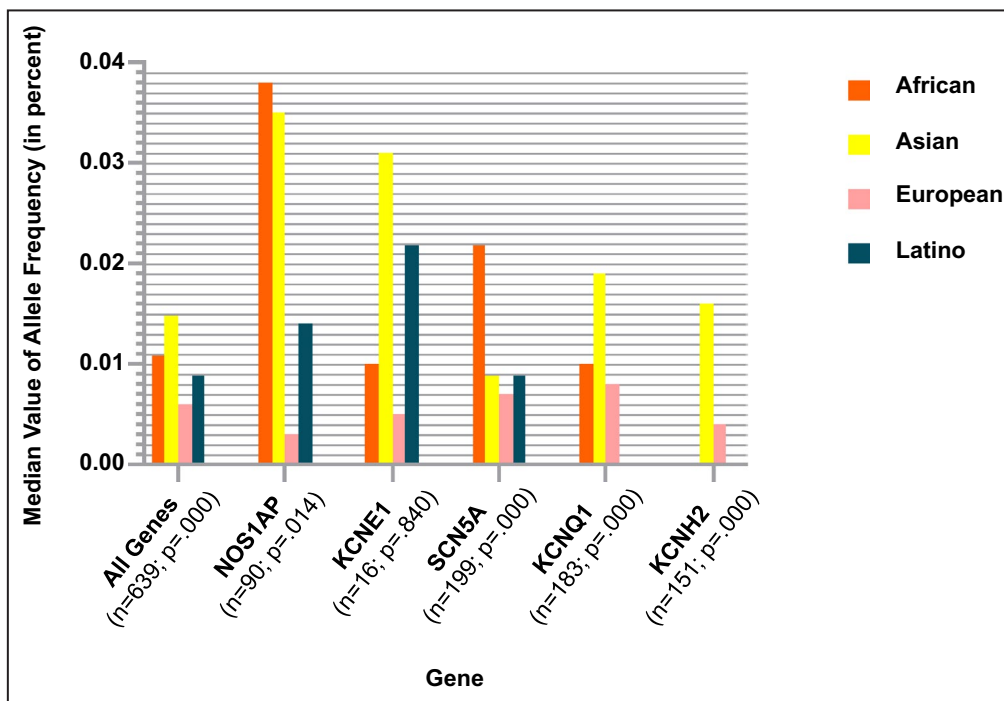

Figure 3. Analysis of genes investigated from the Exome Aggregation Consortium database, showing differences in allele frequency across ethnic groups.
Across all genes, both the number of alleles (n) and the P values are given, and median values of allele frequencies are considered. Reprinted from Kong et al[34] with permission. Copyright ©2021, Elsevier.
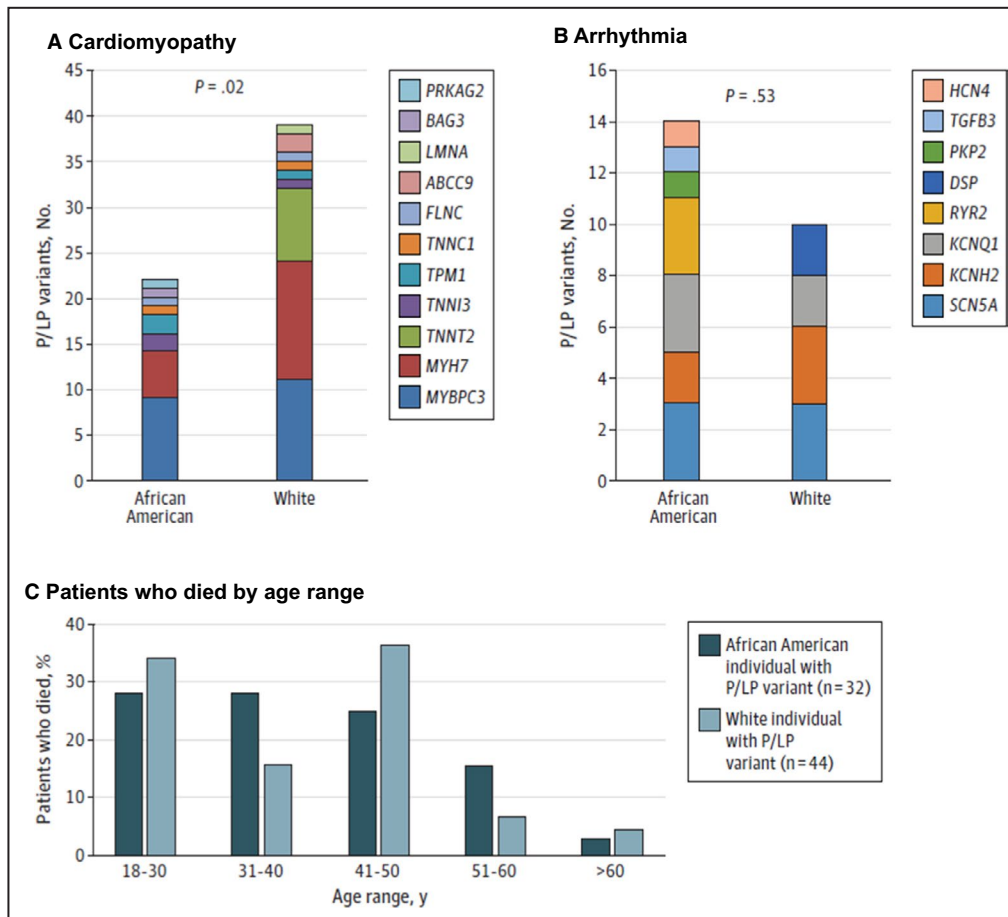
Figure 4. Differences in pathogenic or likely pathogenic (P/LP) gene variants between Black/African American and White Individuals.

A, P/LP gene variant carriers by race showed a significantly higher prevalence of cardiomyopathy variants in White individuals compared with Black/African American individuals (39 of 205 [19.0%] vs 22 of 208 [10.6%]; $P=0.02$). **B**, The total numbers of P/LP gene variant carriers for arrhythmia genes were not different between the 2 groups. Note that *KCNQ1* and *RYR2* were predominant in Black/African American individuals. **C**, There were no differences in age at death between White and Black/African American individuals carrying P/LP variants. Reprinted from Guo et al[39] with permission. Copyright ©2021, American Medical Association.

95 cardiac genes studied. When examining the distribution of the P/PL and VUS by autopsy-determined cause of death, the frequency of P/LP or VUS was high in decedents who were suspected of having cardiac arrhythmia or cardiomyopathy. Among these 73 decedents, 20% had P/LP variants and 48% had VUS. The high rate of VUS and low rate of P/LP variants was thought to be related to combining channelopathy and ion channelopathy genes for analysis and marked heterogeneity of the cohort. AA/Black subjects who are often underrepresented in these analyses are believed to be susceptible to VUS classification. Using the genetic test result as the outcome variable in their multivariable model, none of the independent variables studied (race/ethnicity, age, sex, and cause of death) was predictive of a positive test. The lack of significance was attributed to the limitation of sample size.

In 2021, Guo et al performed genetic analysis of 30 cardiomyopathies and 38 primary arrhythmia genes in 208 (50.4%) AA/Black and 110 White adults who died of unexplained SCD[39] and found that less than one fifth of subjects carried P/LP variants for cardiomyopathies or arrhythmia-related genes. Fifty-two patients (13%) had 49 (P/LP) variants for inherited cardiomyopathies; 22 (5%) had P/LP variants for 23 P/LP variants for arrhythmia, and 2 (0.5%) had P/LP variants for both cardiomyopathies and arrhythmia-related genes. AA/Black and White subjects were equally likely to harbor P/LP variants, but *KCNQ1* and *RYR2* variants were most frequent in AA/Black subjects and *KCNH2* in White subjects. The *SCN5A* variant was equally present in both groups. No significant difference was found in clinical and baseline cardiac characteristics between subjects with or without P/LP variants. These results emphasize

the need for inclusion of diverse racial or ethnic groups to better delineate the presence of disparities.

ION CHANNELOPATHIES AND HEART RHYTHM DISORDERS

Cardiac ion channelopathies may be either acquired or inherited.[40] Inherited channelopathies are attributable to mutations in genes encoding cardiac ion channels, leading to gain or loss of function. Cardiac channelopathies associated with SCD include long-QT syndrome (LQTS) and short-QT syndrome, Brugada syndrome (BrS), early repolarization syndrome (ERS), and catecholaminergic polymorphic ventricular tachycardia. Genetic mutations and channelopathy variants associated with SCD in AA/Black subjects are shown in Table 2. Understanding the link between these mutations and SCD provides opportunities to identify the interplay between genotype-positive individuals without accompanying phenotypes and genotype-negative cases with clinical phenotypes.

Inheritable LQTS

More than 17 LQTS have been reported; however, data from racial or ethnic groups are not always available. The focus herein is on LQTS reported in AA/Black subjects. LQTS is an inherited cardiac disorder, resulting in abnormal cardiac repolarization attributable to a disruption in the balance between inward sodium (I_{Na}) and L-type calcium current (I_{Ca-L}) and outward K^+ currents (rapid K^+ current [I_{Kr}] and slow K^+ current [I_{Ks}]) during phases 2 and 3 of the action potential. LQTS clinically may manifest as a syncopal event or polymorphic ventricular tachyarrhythmia known as torsade de pointes and SCD.

LQT1 disorder is caused by a mutation in the *KCNQ1* K^+ channel gene and responsible for the I_{Ks}. LQT1 is the most common type of LQTS, maps to chromosome 11p15.5-p15.4, and accounts for 50% of genotyped patients.[41] Specific mutations responsible for LQT1 have been reported (Table 3).[42–45]

LQT2 is caused by a mutation of the *KCNH2* (*hERG*) gene that maps on chromosome 7q35-36. This gene encodes the α-subunits of the *hERG* channel that conducts I_{Kr}. It is the second most common variant of LQTS and accounts for 35% to 40% of genotyped patients.[46] A unique feature associated with arrhythmia provocation is an auditory component in which a loud sound, such as an alarm clock, can trigger an arrhythmic event. Several specific mutations in *hERG* channel have been reported in AA/Black subjects (Table 3).

LQT3 is caused by mutations of *SCN5A* gene that maps on chromosome 3q21-24. This gene encodes the α-subunits of the cardiac Na^+ channel ($Na_V1.5$), which conducts I_{Na}.[47] *SCN5A* mutations occurs in ≈10% of genotyped patients with LQTS. This mutation leads to a gain of function of the slow-inward persistent component of I_{Na}. Ventricular arrhythmias are associated with bradycardia during sleep or relaxation

Table 3. Variants Specifically Associated With Heart Rhythm Disorders in Black/African American Population

hNa$_V$1.5	*SCN5A*	3p21	S1102Y R34C H558R	QT prolongation Rare polymorphism Rare polymorphism	Splawski et al[42] Ackerman et al[43] Ackerman et al[43]
hKv7.1	*KCNQ1*	11p15	IAP-56dup V129I V207M G297S F335L R451Q G621S V648I	Potentially QT prolongation Potentially QT prolongation Potentially QT prolongation Potentially QT prolongation Potentially QT prolongation Potentially QT prolongation Potentially QT prolongation Potentially QT prolongation	Ackerman et al[44] Ackerman et al[44] Ackerman et al[44] Ackerman et al[44] Ackerman et al[44] Ackerman et al[44] Ackerman et al[44] Ackerman et al[44]
hKv11.1	*KCNH2*	7q35-36	R181Q G187S GAG187-189del A190T A203T N257H T367S G873S P910L R1035W A1058E Q1068R	Potentially QT prolongation Potentially QT prolongation Potentially QT prolongation Potentially QT prolongation Potentially QT prolongation Potentially QT prolongation Potentially QT prolongation Potentially QT prolongation Potentially QT prolongation Potentially QT prolongation Potentially QT prolongation Potentially QT prolongation	Ackerman et al[44] Ackerman et al[44] Ackerman et al[44] Ackerman et al[44] Ackerman et al[44] Ackerman et al[44] Ackerman et al[44] Ackerman et al[44] Ackerman et al[44] Ackerman et al[44] Ackerman et al[44] Ackerman et al[44]
hKv7.1	*KCNE1*	11p15	G52A K69R	Potentially QT prolongation Potentially QT prolongation	Ackerman et al[44] Ackerman et al[44]
hKv11.1	*KCNE2*	7q35-36	Q9E A66V	QT prolongation Potentially QT prolongation	Lu et al[45] Ackerman et al[43]

The single letter code for amino acids was used.

when the QTc is prolonged. Genetic disorders involving LQT1, LQT2, and LQT3 account for 75% of all LQTS manifestations.

A paucity of LQTS data in AA/Black subjects exist as the first and largest published report was in 2010 in only 41 patients from the US portion of the International LQTS Registry, representing 1.1% of the overall cohort.[48] Participants were evaluated with regard to risk factors and cardiac events. In AA/Black subjects, despite having more severe forms of LQTS and longer QTc values, multivariable Cox analysis with adjustment for decade of birth showed similar risk for cardiac events as non-Hispanic White subjects. Both groups responded equally to treatment with β blockers, and genotype analysis demonstrated positivity for LQT1 in only 2 of 41 AA/Black subjects. Of note, in this study, only 2 of 41 AA/Black subjects had genotype studies, and both had an LQT1 mutation.

Splawski et al identified a variant (Y1102) in the *SCN5A* gene, which encodes Nav1.5 in 13% of AA/Black subjects, but it was not detected in White or Asian subjects (Table 3).[42] The mutation was attributed to a polymorphism in the codon, resulting in the substitution of the amino acid tyrosine for serine. There was no direct effect on the QTc interval; however, in the presence of hypokalemia or antiarrhythmic medications, QTc prolongation may occur. Using computer simulation of a concentration-dependent block of the I_{Kr} current, they predicted that Y1102 would induce action potential prolongation and early afterdepolarizations, a trigger for VT/VF. The biophysical alteration in the Y1102 variant results in a shift of Na$^+$ channel activation to more hyperpolarized potentials and produces a persistent I_{Na}, which may increase the likelihood of abnormal cardiac repolarization. AA/Black subjects with the Y1102 variant may be susceptible to serious life-threatening arrhythmias given a conducive biological environment.[42] Although the electrophysiological effects were subtle, the mathematical models predicted a susceptibility to ventricular arrhythmias, particularly in the presence of hypokalemia or antiarrhythmic drugs that prolong repolarization. Another report noted that the Y1102 variant was rare in White subjects and associated with a major risk for syncope, VT/VF, and SCD.[49] In a prospective study of AA/Black subjects with heart failure and reduced ejection fraction who underwent primary prevention ICD therapy, carriers of Y1102 variant had a 4-fold increase in appropriate ICD therapy than noncarriers.[50] Several polymorphisms in the *SCN5A* gene associated with arrhythmogenic events have been reported (Table 3).[43]

To assess the genetic susceptibility to SCD, Ackerman et al performed a comprehensive mutational analysis in a multiracial cohort and found that 25% of AA/Black subjects exhibited K$^+$ channel variants compared with 14% of White subjects. These findings support the requisite inclusion of AA/Black subjects in genetic studies to better identify and accurately classify variants in racial or ethnic groups.[34]

Brugada Syndrome

BrS is inherited via autosomal dominant transmission and prevalent in southeast Asian populations.[51] Although the *SCN5A* gene has been implicated in 20% to 30% of BrS cases, it is doubtful that a monogenic mutation is responsible for its phenotypic manifestations. The genetic abnormality uniquely involves the epicardial aspect of the right ventricular outflow tract. The clinical manifestation is that of syncope, VT/VF, and SCD. Although BrS is more prevalent in Japan and Southeast Asia, with disease manifestation noted throughout that ancestral diaspora, the syndrome was first reported in "Black African" subjects via a case series of 5 patients published in 2010.[52,53] These patients of Black African ancestry presented with syncope or VT/VF and required prompt medical treatment. All 5 patients in the case series were *SCN5A* genotype negative. These observations support more aggressive inclusion of racial or ethnic groups in genetic and epigenetic studies of genotype-negative patients with a clinical phenotype of known disease entities.

Short-QT Syndrome

Short-QT syndrome is a channelopathy characterized by abnormal shortening of the QTc interval associated with a high incidence of life-threatening ventricular arrhythmias and SCD.[54,55] There are 6 genes responsible for short-QT syndrome. SQT1, SQT2, and SQT3 result in gain-of-function mutations of 3 different K$^+$ channels (*KCNH2*, *KCNQ1*, and *KCNJ2*), thereby leading to increased repolarizing currents and shortening of the action potential duration. SQT4, SQT5, and SQT6 result from loss-of-function mutations in genes encoding L-type Ca^{2+} channels subunits (*CACNA1* and *CACNB2b*), leading to I_{Ca-L} decrease and shortening of the action potential duration.[56–59] In a mega database of 6.4 million ECGs among 1.7 million people, the prevalence of validated machine-read QTc intervals <300 milliseconds per 100 000 people was highest in AA/Black (5.8%), followed by White (3.2%), Latino (1.8%), and Asian/Pacific Islander subjects (1.6%).[55] A validated QTc <300 milliseconds was associated with AA/Black subjects, old age, and marked ECG abnormalities, and was an independent predictor of all-cause mortality.

Early Repolarization Syndrome

ERS, also referred to as early repolarization patterns, has been reported in 10% to 13% of the general population, often affecting young men, athletes, and AA/Black subjects, and associated with VT/VF or SCD.[59,60] ERS

is a channelopathy linked to variants in several genes, resulting in gain of function of the ATP-dependent K$^+$ channel or loss of function of cardiac L-type Ca^{2+} or Na$^+$ channels.[59] In a retrospective study of 752 AA/Black subjects, ECG analysis revealed a high prevalence of ERS associated with syncope.[61] However, no genetic studies were performed to identify variants that may be responsible for ERS. ECG markers of ERS are reportedly more prevalent in AA/Black subjects[62–64] than in other racial or ethnic groups.

CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA

Catecholaminergic polymorphic ventricular tachycardia is a genetic disorder resulting in VT/VF in response to physical activity or emotional stress. The catecholaminergic polymorphic ventricular tachycardia gene is located on chromosome 1 (1q42),[65] and transmission is via an autosomal dominant pattern. Initial genetic studies revealed that the mutation is in the gene encoding the ryanodine type-2 receptor (*RyR2*).[66,67] More recently, 2 groups have reported homozygous mutations in calsequestrin gene-2 (*CASQ2*).[68,69] Arrhythmogenesis has been linked to *RyR2* gain-of-function mutations, although *RyR2* loss-of-function mutations also have been reported.[70] No race-related clinical or genetic studies on catecholaminergic polymorphic ventricular tachycardia were available until a preliminary report described a new mutation in *CASQ2* on the short arm of chromosome 1 in exon 2, which resulted in a nucleotide and amino acid change of 261dupA and Ala88Fs in a 49-year-old AA/Black woman.[71]

STRUCTURAL HEART DISEASES

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is a putative genetic disorder with protean phenotypic manifestations initially ascribed to mutations in 11 genes encoding proteins for cardiac sarcomeres with >1400 notable variants.[72] The fact that only 30% of patients with HCM have a genetic mutation and others may be genotype positive and phenotype negative suggests that significant knowledge gaps exist in understanding the molecular genetic aspects of the disease, and the meaning of incomplete penetrance particularly when considering cascade screening of families of probands.[73] Gene carriers are known to have full life expectancy and absence of disease manifestation. Epigenetic factors and disease-modifying genes may provide an explanation for these observations, but these factors are yet to be proven or validated with

translational data. Furthermore, patients with the prototypical phenotype manifest features that may not be truly typical, as the gain-of-function pathobiology that produces cardiac hypertrophy is asymmetrical, sparing sections of myocardium (and most of the right ventricle, where sarcomeres are present), while coexisting with findings such as left ventricular apical aneurysms, mitral valve leaflet elongation, and cardiac fibrosis, all anatomic regions devoid of sarcomeres.[74] Moreover, variants have been misclassified as pathologic or likely pathologic that were later shown to be benign and unassociated with a clinical phenotype when adequate sample sizes were studied. This misclassification was evident in a study from the National Heart, Lung, and Blood Institute Exome Sequencing Project, which was systematically reviewed for HCM-associated variants labeled "disease causing" or "pathogenic."[75–78] In that database, many more variants were found than expected in the general population, suggesting that disease penetrance might have been lower than previously thought or that misclassification errors might have been present in previous studies of the association between the variants and the condition. The investigators found that 5 high-frequency variants (ie, variants with a minor allele frequency >1%) accounted for most of this overabundance of misclassified variation and that these variants occurred disproportionately among AA/Black subjects. To further study the matter, Manrai et al used publicly accessible sequence data from the National Heart, Lung, and Blood Institute Exome Sequencing Project, 1000 Genomes Project, and Human Genome Diversity Project.[76,79,80] For estimation of minor allele frequency, the National Heart, Lung, and Blood Institute Exome Sequencing Project had exome data for 4300 White and 2203 AA/Black subjects, the 1000 Genomes Project phase 1 had whole-genome data for 1092 people from 14 populations worldwide, and the Human Genome Diversity Project had whole genome single-nucleotide polymorphism data for 938 people from 51 populations worldwide. The authors found that mutations most common in the general population were significantly more common among AA/Black than among White subjects ($P<0.001$). They concluded that misclassification of benign variants as pathogenic illustrates the need for sequencing the genomes of diverse populations, in both asymptomatic controls and the tested patient population. The concept of incomplete penetrance was studied further in the Framingham Study and JHS (Jackson Heart Study) of 3600 probands.[81] The presence of nonsynonymous sarcomere variants not associated with clinical evidence of HCM was found to be 0.5%. This finding would suggest that 1.5 million people in the United States would satisfy the criteria for incomplete penetrance and greatly exceed by 10-fold the number thought to have HCM.[82]

The implications from these data support the need for inclusion of racial or ethnic groups undergoing genetic mutational analysis, better classification of genetic test results, and clarification of differences between P/LP, benign, and VUS. Disparities in management noted in AA/Black subjects with HCM have been related to the paucity of patients referred to specialists for care and the overall reduction in the use of ICDs. Despite the phenomenal contribution of the human genome project and advances in mutational analysis and genomics, genetic testing alone is not sufficient to provide a prognosis for survival as current strategies for SCD prevention are largely dependent on clinical parameters. Genetic testing in AA/Black subjects generally has been lacking, and the existing knowledge gaps should be sufficient to warrant an enhanced effort to study racial or ethnic groups. A novel paradigm derived from translational science that includes epigenetic and environmental factors would be required to provide diagnostic, mechanistic, risk stratification, and prognostic information to guide disease management.

Arrhythmogenic Right Ventricular Cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetic cardiomyopathy affecting about 1 per 5000 individuals. ARVC is characterized by the gradual replacement of muscle tissue by adipocytes and fibrous tissue, causing abnormal impulse conduction and propagation, thus providing the substrate for VT/VF and an increased risk of SCD.[83] Transmission of the condition is via an autosomal dominant mode, with 60% of patients with ARVC having mutations in genes encoding for cardiac desmosomes (*PKP2*, *DSP*, *DSC2*, *DSG2*, and *JUP*). Patients may have mutations in nondesmosomal ARVC-associated genes (*RYR2*, *CTNNA3*, *PLN*, *TMEM43*, *SCN5A*, *CDH2*, and *DES*), which are less prevalent and not well characterized.

The involvement of *SCN5A* in ARVC is somewhat surprising given that mutations in *SCN5A* generally do not only lead to pure arrhythmic disorders, such as LQT3, BrS, and cardiac conduction disease, but may be associated with structural heart disease. Distinct cardiac phenotypes caused by *SCN5A* mutations include dilated cardiomyopathy[84,85] and ARVC.[86] The role of *SCN5A* in ARVC phenotypes can be explained by the fact that the desmosomal protein PKP2 (plakophilin-2) associates with Nav1.5, and the loss of function of PKP2 can alter the biophysical properties of Na$^+$ channels. A recent study showed that Nav1.5 associates with the adherens junction protein N-cadherin as well as connexin 43 at the intercalated discs to form a complex.[87] Mutations in Nav1.5 channels may thus destabilize this complex and result in ARVC structural phenotypes. The principle hypothesis that explains

ARVC is related to a dysfunction of desmosomes. Desmosomes within cardiomyocytes provide an anchor for intermediate filament proteins, creating a network that is essential for the mechanical integrity of cardiomyocytes and rapid transmission of impulses between cells. Dysfunctional desmosomes lead to favorable conditions for reentry circuits and cardiac arrhythmias. The missense and nonsense mutations identified in patients can destabilize this complex and dissociate intercellular junctions.[88] More generally, abnormal desmosomes lead to the rupture of intercellular junctions, resulting in cardiomyocyte apoptosis and, possibly, fibrosis.[83] Another hypothesis to explain ARVC was based on studies of transgenic mice and suggested that cardiac progenitor cells differentiate into adipocytes with high efficiency and into cardiomyocytes with low efficiency,[89] thus resulting in fatty tissue accumulation with myocyte replacement. Other reports have suggested that the mutations cause plakoglobin to migrate into the cell nucleus, and promote fibrogenesis and adipogenesis.[90] ARVC is more prominent in Italy and Europe in general.[91] Its incidence in AA/Black subjects or other racial or ethnic groups in the United States is unknown.

ROLE OF EPIGENETICS IN ION CHANNELOPATHIES, DISPARITIES, AND SCD

Genetic mutations have contributed to pathological conditions affecting ion channel function, or its constituent membrane proteins thus manifest as channelopathies with increased risk of SCD. However, the presence of genetic mutations may not be associated with a clinical phenotype, and the absence of genetic mutations has been recognized in cases where a clinical disease phenotype is present.[92] These findings have led to the postulation that disease manifestation in the presence of genetic mutations may have incomplete penetrance or, conversely, that in the absence of a genetic mutation, phenotypic expression of disease may be modulated by mechanisms that do not require alterations in the DNA sequence. Epigenetics refers to changes in gene expression unrelated to alterations in the DNA sequence but representing modifications in the translation of genetic information. Since the initial description of epigenetics over 80 years ago, there has been growing interest in understanding processes, mechanisms, and environmental factors involved.[93] The term "genotype-negative" phenotype has been ascribed to conditions in which clinical disease is evident in the absence of a positive genetic test; however, the environmental factors responsible for disease manifestation have not been elucidated. Epigenetic activity has been documented to occur via DNA methylation at

cytosine preceding guanosine (CpG island) dinucleotide sites mediated by DNA methyltransferases, acetylation, or methylation of histone proteins, and metabolic processes involving microRNAs.[94] The consequences of these epigenetic processes may result in gene silencing, via inhibitory activity in the promoter region of the gene during transcription, enhanced genetic expression with histone protein acetylation, or blocking of gene expression via microRNA modification. Activation or repression of gene expression may occur with each process, but details of the interplay with a specific gene are complex and beyond the scope of this review. The role of transcriptional and epigenetic effects on BrS and ARVC substrates during early development and pathological remodeling is noted in a recent publication.[95]

Given the racial or ethnic disparities in CVD manifestation and outcomes and the disproportionate burden of comorbidities in AA/Black subjects, the impact of sociocultural, environmental, and psychosocial stressors on gene expression has been explored as a potential contributor to CVD morbidity and mortality.[8,96,97] Conceptually, psychosocial factors, such as economic hardship, discrimination, low social status, and neighborhood violence, are postulated to have biological effects and contribute to elevation in circulating proinflammatory cytokines and endothelial dysfunction, thus playing a role in mediating stress-induced vascular inflammation and atherogenesis.[98–100] These factors, considered social determinants of health, are thought to provide an epigenetic signature that may impact normal or variant genes. More specific description of social determinants of health involves assessment of data in relation to where one was born, was raised, works, or lives or the impact of pollution on cardiovascular health. The contribution of epigenetic factors to disease phenotypes is further enhanced when one considers that research studies repeatedly affirmed that between-group genetic differences have been shown to be small when compared with genetic variations within geographical regions and groups.[101,102] Monozygotic twin studies revealed that a low-birth-weight twin has an elevated risk for diabetes and hypertension when compared with the normal birth weight twin, thus demonstrating epigenetic influences on the same genetic substrate but with different outcomes.[103,104] Whether these epigenetic effects have a durable life course or transgenerational effects on the propensity for SCD is under investigation. Furthermore, documented differences in DNA methylation between AA/Black and White subjects in relation to age, sex, and poverty level suggest the need to pursue additional studies to understand the contribution of these epigenetic factors on the biological milieu impacting diseases associated with arrhythmic risk for SCD.[105]

Genetic testing continues to play an important role in disease management, classification of channelopathies, and heritable conditions associated with SCD. The sensitivity and specificity of genetic test results are insufficient to give it primacy among the diagnostic armamentarium; nevertheless, it remains an essential component in the evaluation of patients when the index of suspicion is high, or in cascade screening and shared decision-making.[92] Data from 2467 patients enrolled in the SHaRe (Sarcomeric Human Cardiomyopathy Registry) revealed that among the 8% of AA/Black subjects included, AA/Black subjects were less likely to undergo genetic testing, less likely to be referred to a subspecialist for care, and less likely to have sarcomeric mutations.[106] AA/Black subjects were more likely to have New York Heart Association class III or IV heart failure and hypertension. In another study of patients undergoing evaluation for HCM, misclassification of AA/Black subjects undergoing genetic testing was reported when benign variants were unrecognized as such because of the lack of diversity in the sampled control data set.[75] In a reported first publication, a case series of 5 Africans with strict clinical phenotype for BrS and genotype negative for the disease was documented when no prior occurrence of this disease in AA/Black subjects was known.[52] The association of the *SCN5A* gene–*Y1102* allele with sudden infant death syndrome in AA/Black subjects has been documented, and arrhythmic risk in adults appears enhanced, although may require perturbations, such as hypokalemia or contribution from epigenetic factors, to manifest clinically.[107–109]

Confirmation that specific epigenetic factors are influential in disease manifestation requires that future studies apply strategies to integrate psychosocial, socioeconomic, and environmental factors, and racial makeup in assessing health equity. Identification of epigenetic mechanisms may provide a novel target for therapeutic intervention.

UNDERUSE OF ICD THERAPY IN THE BLACK POPULATION

The ICD was introduced by Mirowski et al, and the first human implant was in 1980. Since then, this therapy has revolutionized the approach and treatment of patients at risk for SCD.[110] The ICD has been shown to decrease total mortality and death attributable to SCA in at-risk patients.[31,111–113] Initial reports of benefit from ICD therapy were derived from several major trials but to the exclusion of sufficient numbers of racial or ethnic groups; thus, the salutary effects in these groups were not immediately conferred in those initial trials.[31,112,113] However, data from the SCD-HEFT (Sudden Cardiac Death in Heart Failure Trial) supported the use of the

ICD as primary prevention therapy in all patients, including AA/Black subjects.[113]

Despite proven efficacy of the ICD in primary and secondary prevention, Thomas et al reported that AA/Black subjects were significantly less likely to receive ICDs than White subjects.[114] Other data showed that although AA/Black and White subjects benefit equally from ICD implantation following a cardiac arrest, for unclear reasons, AA/Black subjects were less likely to undergo this potentially life-saving therapy.[115]

Several landmark trials have demonstrated that ICD use decreases total mortality and SCD in at-risk patients.[111,113,116] However, the effectiveness in AA/Black subjects was not widely known, as a concurrent era comparative study in a cohort of 1232 patients (8% AA/Black subjects) revealed that total mortality, cardiac death, and SCD benefits were only observed in White subjects.[31] SCD was 1.7-fold greater in AA/Black compared with White subjects. It is likely that the small sample size precluded sufficient statistical power to avoid a type 1 error. This disparity was noted although no known biological differences were recognized as causal factors. Other major trials did not enroll sufficient numbers of AA/Black subjects to refute those findings. Thomas et al reported that AA/Black subjects were significantly less likely than White subjects to receive the ICD as primary prevention therapy, even after adjusting for demographics, clinical characteristics, and socioeconomic factors.[114,115]

Bardy et al later reported efficacy in the use of ICDs as primary prevention therapy in all patients, including AA/Black subjects.[113] In the largest cohort of patients with heart failure treated with cardiac resynchronization therapy, Fontaine et al have demonstrated that AA/Black subjects derived the same benefits from this therapy as White subjects, but disparities in use persist today despite long-term support from published guidelines.[117] Explorations to ascertain the reason for these disparities are warranted.

DISPARITIES IN PREVENTION OF ARRHYTHMIC SCD

The discovery that echocardiographic evidence of left ventricular hypertrophy (LVH) is a marker of risk for SCD was published by Savage et al as they recognized this risk marker in patients with hypertension who were enrolled as part of the Framingham cohort.[118] Those data and the investigation of others led to the recognition and targeting of patients with hypertension for more aggressive therapy, as regression of LVH was feasible, and better control of hypertension became a major therapeutic objective. The FHS (Framingham Heart Study) examined the correlation of ventricular arrhythmias with LVH in 6218 subjects.[118] LVH defined by ECG was present in 171 participants, and echocardiographic evidence of hypertrophy was present in 869; both were associated with higher risk for ventricular
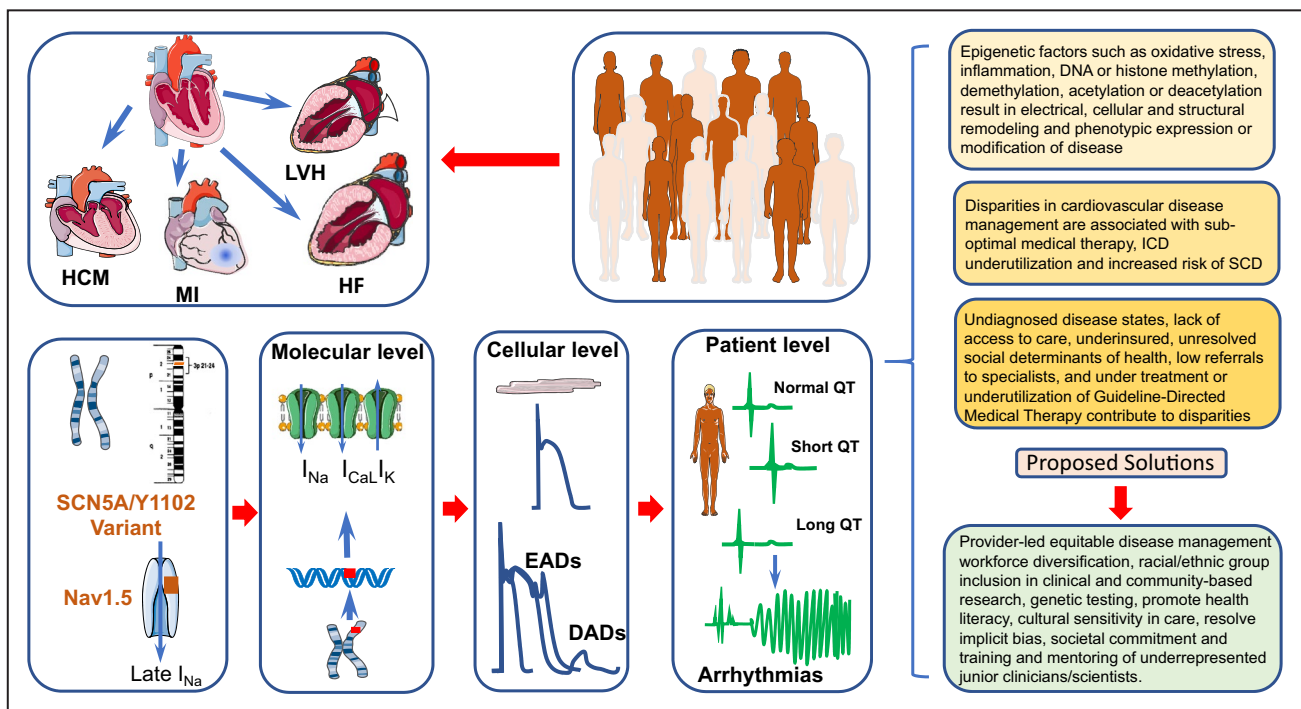

Figure 5. Racial or ethnic disparities in cardiovascular diseases: genetic, epigenetic, and socioeconomic contributors.
DAD indicates delayed after depolarization; EAD, early after depolarization; HCM, hypertrophic cardiomyopathy; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVH, left ventricular hypertrophy; MI, myocardial infarction; and SCD, sudden cardiac death.

arrhythmias in men and women. The association of echocardiographic and not ECG LVH with ventricular arrhythmia continued to be significant after adjustment for age, sex, and baseline clinical characteristics.

AA/Black subjects have a greater burden of cardiovascular risk factors, including hypertension and LVH, than White subjects, and heart failure often manifests at a younger age than in their non-Hispanic White counterparts.[8,119,120] Racial or ethnic groups have been consistently less likely to receive evidence-based cardiovascular therapies (including cardiac catheterization and coronary artery bypass graft surgery) than their non-Hispanic White counterparts and have higher morbidity and mortality associated with these procedures.[8,119–121] AA/Black subjects have a greater propensity to be admitted to lower-quality hospitals for acute myocardial infarction than non-Hispanic White subjects. Racial or ethnic groups are more likely to live in neighborhoods with less access to healthy foods, recreational activities, and adverse living conditions. In fact, AA/Black subjects, Hispanic subjects, and individuals who reside in poor neighborhoods are less likely to receive bystander CPR and have lower rates of survival from a cardiac arrest than White subjects or those who live in affluent neighborhoods.[16,122,123] Both in-hospital and OHCA survival from SCA are lower for AA/Black subjects than non-Hispanic White subjects.

CONCLUSIONS

Despite the important progress made in elucidating race and ethnic disparities in the pathogenesis of SCD associated with cardiac channelopathies and other inherited cardiovascular disorders, significant proactive efforts are still needed to reach equity in clinical enrollment of racial or ethnic groups in translational research and funding of biomedical and behavioral studies focusing on the molecular genetic aspects of these disparities. The inclusion of different racial and ethnic groups in such studies will have a significant impact on SCD burden and associated risk factors, with major public health implications for prevention and implementing new therapeutic management of SCD. Device underuse in the management of SCD and risk thereof need to be rectified with the appropriate approach to shared decision-making, the understanding
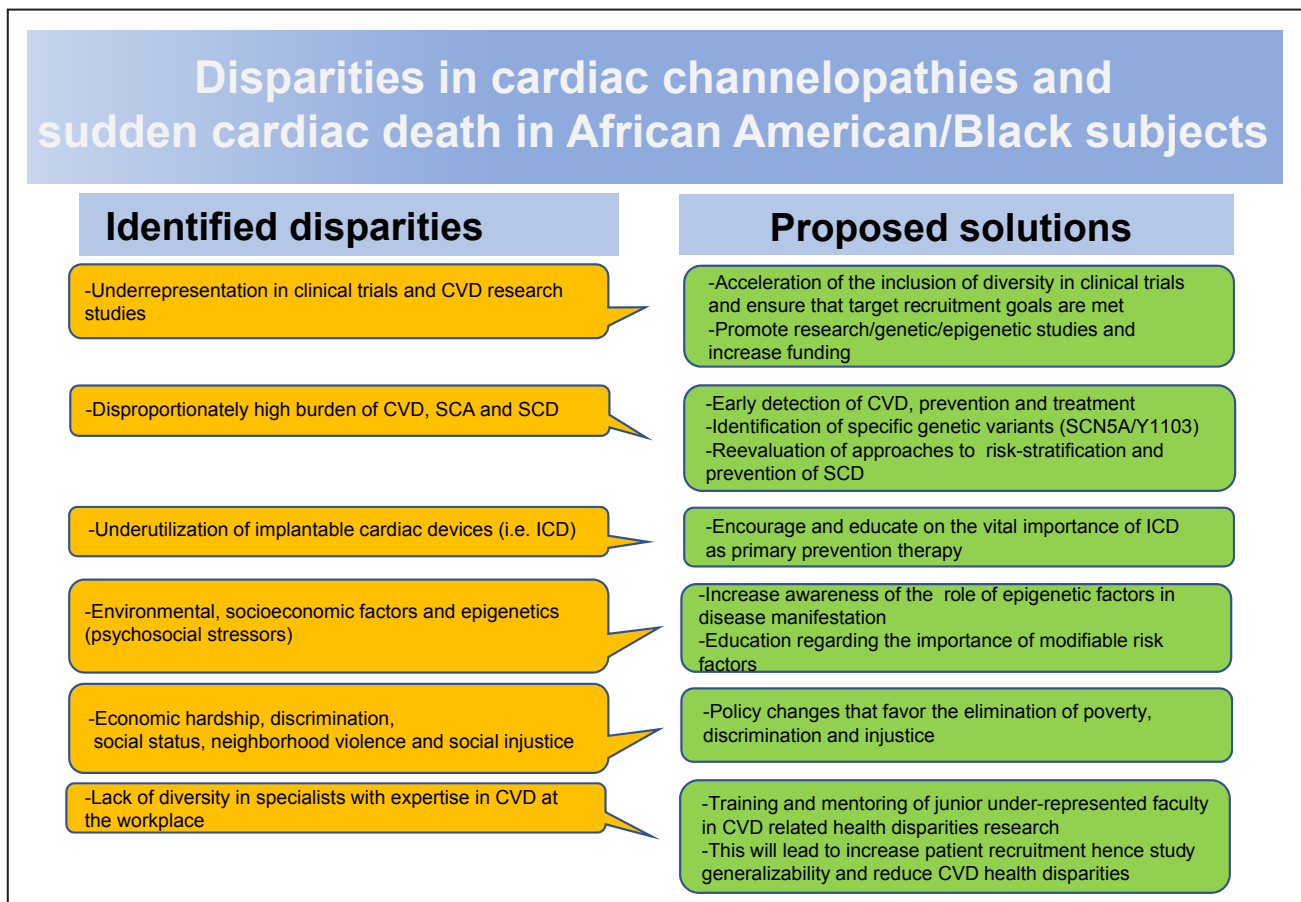

Figure 6. **Summary of disparities and proposed solutions.**
CVD indicates cardiovascular disease; ICD, implantable cardioverter-defibrillator; SCA, sudden cardiac arrest; and SCD, sudden cardiac death.

of goals of therapy, health-literacy interventions, and resource allocation to communities in need. The training and mentoring of junior faculty, both clinicians and scientists, from underrepresented backgrounds in CVD-related health disparities research is another key factor to reducing/eliminating CVD health disparities by increasing diversity at the workplace and promoting research focused on CVD[124,125] (Figure 5). The interplay of the various contributing factors superimposed on biological and genetic substrates manifesting as CVD and proposed solutions are illustrated in Figure 6.

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REFERENCES

1. Flanagin A, Frey T, Christiansen SL, Bauchner H. The reporting of race and ethnicity in medical and science journals: comments invited. *JAMA*. 2021;325:1049–1052. doi: 10.1001/jama.2021.2104
2. Estes NA III. Predicting and preventing sudden cardiac death. *Circulation*. 2011;124:651–656. doi: 10.1161/CIRCULATIONAHA.110.974170
3. Deo R, Albert CM. Epidemiology and genetics of sudden cardiac death. *Circulation*. 2012;125:620–637. doi: 10.1161/CIRCULATIONAHA.111.023838
4. El-Sherif N, Boutjdir M, Turitto G. Sudden cardiac death in ischemic heart disease: pathophysiology and risk stratification. *Card Electrophysiol Clin*. 2017;9:681–691. doi: 10.1016/j.ccep.2017.08.003
5. Zheng ZJ, Croft JB, Giles WH, Mensah GA. Sudden cardiac death in the United States, 1989 to 1998. *Circulation*. 2001;104:2158–2163. doi: 10.1161/hc4301.098254
6. Institute of Medicine. *Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care*. National Academies Press; 2003.
7. Lillie-Blanton M, Maddox TM, Rushing O, Mensah GA. Disparities in cardiac care: rising to the challenge of healthy people 2010. *J Am Coll Cardiol*. 2004;44:503–508. doi: 10.1016/j.jacc.2004.04.043
8. Mensah GA. Eliminating disparities in cardiovascular health: six strategic imperatives and a framework for action. *Circulation*. 2005;111:1332–1336. doi: 10.1161/01.CIR.0000158134.24860.91
9. McNally B, Robb R, Mehta M, Vellano K, Valderrama AL, Yoon PW, Sasson C, Crouch A, Perez AB, Merritt R, et al. Out-of-hospital cardiac arrest surveillance – cardiac arrest registry to enhance survival (CARES), United States, October 1, 2005–December 31, 2010. *MMWR Surveill Summ*. 2011;60:1545–8636.
10. Sawyer KN, Camp-Rogers TR, Kotini-Shah P, Del Rios M, Gossip MR, Moitra VK, Haywood KL, Dougherty CM, Lubitz SA, Rabinstein AA, et al. Sudden cardiac arrest survivorship: a scientific statement from the American Heart Association. *Circulation*. 2020;141:e654–e685. doi: 10.1161/CIR.0000000000000747
11. Nichol G, Rumsfeld J, Eigel B, Abella BS, Labarthe D, Hong Y, O'Connor RE, Mosesso VN, Berg RA, Leeper B", et al. Essential features of designating out-of-hospital cardiac arrest as a reportable event: a scientific statement from the American Heart Association Emergency Cardiovascular Care Committee; council on cardiopulmonary, perioperative, and critical care; council on cardiovascular nursing; council on clinical cardiology; and quality of care and outcomes research interdisciplinary working group. *Circulation*. 2008;117:2299–2308. doi: 10.1161/CIRCULATIONAHA.107.189472
12. Rea TD, Fahrenbruch C, Culley L, Donohoe RT, Hambly C, Innes J, Bloomingdale M, Subido C, Romines S, Eisenberg MS. CPR with chest compression alone or with rescue breathing. *N Engl J Med*. 2010;363:423–433. doi: 10.1056/NEJMoa0908993
13. Chugh SS, Jui J, Gunson K, Stecker EC, John BT, Thompson B, Ilias N, Vickers C, Dogra V, Daya M, 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. doi: 10.1016/j.jacc.2004.06.029
14. Kong MH, Fonarow GC, Peterson ED, Curtis AB, Hernandez AF, Sanders GD, Thomas KL, Hayes DL, Al-Khatib SM. Systematic review of the incidence of sudden cardiac death in the United States. *J Am Coll Cardiol*. 2011;57:794–801. doi: 10.1016/j.jacc.2010.09.064
15. Tomaselli GF. Introduction to a compendium on sudden cardiac death: epidemiology, mechanisms, and management. *Circ Res*. 2015;116:1883–1886. doi: 10.1161/CIRCRESAHA.115.306515
16. Shah KS, Shah AS, Bhopal R. Systematic review and meta-analysis of out-of-hospital cardiac arrest and race or ethnicity: Black US populations fare worse. *Eur J Prev Cardiol*. 2014;21:619–638. doi: 10.1177/2047487312451815
17. Reinier K, Nichols GA, Huertas-Vazquez A, Uy-Evanado A, Teodorescu C, Stecker EC, Gunson K, Jui J, Chugh SS. Distinctive clinical profile of blacks versus whites presenting with sudden cardiac arrest. *Circulation*. 2015;132:380–387. doi: 10.1161/CIRCULATIONAHA.115.015673
18. Sasson C, Magid DJ, Chan P, Root ED, McNally BF, Kellermann AL, Haukoos JS. Association of neighborhood characteristics with bystander-initiated CPR. *N Engl J Med*. 2012;367:1607–1615. doi: 10.1056/NEJMoa1110700
19. Nichol G, Thomas E, Callaway CW, Hedges J, Powell JL, Aufderheide TP, Rea T, Lowe R, Brown T, Dreyer J, et al. Regional variation in out-of-hospital cardiac arrest incidence and outcome. *JAMA*. 2008;300:1423–1431. doi: 10.1001/jama.300.12.1423
20. Shojania KG, Burton EC. The vanishing nonforensic autopsy. *N Engl J Med*. 2008;358:873–875. doi: 10.1056/NEJMp0707996
21. Chernomordik F, Jons C, Klein HU, Kutyifa V, Nof E, Zareba W, Daubert JP, Greenberg H, Glikson M, Goldenberg I, et al. Death with an implantable cardioverter-defibrillator: a MADIT-II substudy. *Europace*. 2019;21:1843–1850. doi: 10.1093/europace/euz263
22. Hinkle LE Jr, Thaler HT. Clinical classification of cardiac deaths. *Circulation*. 1982;65:457–464. doi: 10.1161/01.CIR.65.3.457
23. Organization Sudden Cardiac Death. World Health Organization Thenical Report Series 726. 1985. Available at: https://apps.who.int/iris/handle/10665/39554. Accessed September 2, 2021.
24. Tseng ZH, Olgin JE, Vittinghoff E, Ursell PC, Kim AS, Sporer K, Yeh C, Colburn B, Clark NM, Khan R, et al. Prospective countywide surveillance and autopsy characterization of sudden cardiac death: post SCD study. *Circulation*. 2018;137:2689–2700. doi: 10.1161/CIRCULATIONAHA.117.033427
25. Tseng ZH, Ramakrishna S, Salazar JW, Vittinghoff E, Olgin JE, Moffatt E. Sex and racial differences in autopsy-defined causes of presumed sudden cardiac death. *Circ Arrhythm Electrophysiol*. 2021;14:e009393. doi: 10.1161/CIRCEP.120.009393
26. Tseng ZH, Hayward RM, Clark NM, Mulvanny CG, Colburn BJ, Ursell PC, Olgin JE, Hart AP, Moffatt E. Sudden death in patients with cardiac implantable electronic devices. *JAMA Intern Med*. 2015;175:1342–1350. doi: 10.1001/jamainternmed.2015.2641

27. Ricceri S, Salazar JW, Vu AA, Vittinghoff E, Moffatt E, Tseng ZH. Factors predisposing to survival after resuscitation for sudden cardiac arrest. *J Am Coll Cardiol*. 2021;77:2353–2362. doi: 10.1016/j.jacc.2021.03.299

28. Hayashi M, Shimizu W, Albert CM. The spectrum of epidemiology underlying sudden cardiac death. *Circ Res*. 2015;116:1887–1906. doi: 10.1161/CIRCRESAHA.116.304521

29. Groeneveld PW, Heidenreich PA, Garber AM. Racial disparity in cardiac procedures and mortality among long-term survivors of cardiac arrest. *Circulation*. 2003;108:286–291. doi: 10.1161/01.CIR.0000079164.95019.5A

30. Bardy GH, Lee KL, Mark DB, Poole JE, Toff WD, Tonkin AM, Smith W, Dorian P, Packer DL, White RD, et al. Home use of automated external defibrillators for sudden cardiac arrest. *N Engl J Med*. 2008;358:1793–1804. doi: 10.1056/NEJMoa0801651

31. Vorobiof G, Goldenberg I, Moss AJ, Zareba W, McNitt S. Effectiveness of the implantable cardioverter defibrillator in blacks versus whites (from MADIT-II). *Am J Cardiol*. 2006;98:1383–1386. doi: 10.1016/j.amjcard.2006.04.036

32. Wang D, Shah KR, Um SY, Eng LS, Zhou BO, Lin Y, Mitchell AA, Nicaj L, Prinz M, McDonald TV, et al. Cardiac channelopathy testing in 274 ethnically diverse sudden unexplained deaths. *Forensic Sci Int*. 2014;237:90–99. doi: 10.1016/j.forsciint.2014.01.014

33. Lin Y, Williams N, Wang D, Coetzee W, Zhou BO, Eng LS, Um SY, Bao R, Devinsky O, McDonald TV, et al. Applying high-resolution variant classification to cardiac arrhythmogenic gene testing in a demographically diverse cohort of sudden unexplained deaths. *Circ Cardiovasc Genet*. 2017;10:e001839. doi: 10.1161/CIRCGENETICS.117.001839

34. Kong T, Feulefack J, Ruether K, Shen F, Zheng W, Chen XZ, Sergi C. Ethnic differences in genetic ion channelopathies associated with sudden cardiac death: a systematic review and meta-analysis. *Ann Clin Lab Sci*. 2017;47:481–490.

35. Voegele LD, Gross A, Prioleau WH Jr, Hairston P. The use of shunts in patients undergoing bilateral carotid endarterectomies: help or hindrance. *Am Surg*. 1983;49:234–237.

36. Hua W, Zhang L-F, Wu Y-F, Liu X-Q, Guo D-S, Zhou H-L, Gou Z-P, Zhao L-C, Niu H-X, Chen K-P, et al. Incidence of sudden cardiac death in China: analysis of 4 regional populations. *J Am Coll Cardiol*. 2009;54:1110–1118. doi: 10.1016/j.jacc.2009.06.016

37. Tokashiki T, Muratani A, Kimura Y, Muratani H, Fukiyama K. Sudden death in the general population in Okinawa: incidence and causes of death. *Jpn Circ J*. 1999;63:37–42. doi: 10.1253/jcj.63.37

38. Williams N, Manderski E, Stewart S, Bao R, Tang Y. Lessons learned from testing cardiac channelopathy and cardiomyopathy genes in individuals who died suddenly: a two-year prospective study in a large medical examiner's office with an in-house molecular genetics laboratory and genetic counseling services. *J Genet Couns*. 2020;29:293–302. doi: 10.1002/jgc4.1157

39. Guo L, Torii S, Fernandez R, Braumann RE, Fuller DT, Paek K-H, Gadhoke NV, Maloney KA, Harris K, Mayhew CM, et al. Genetic variants associated with unexplained sudden cardiac death in adult white and African American individuals. *JAMA Cardiol*. 2021;6:1013–1022. doi: 10.1001/jamacardio.2021.1573

40. El-Sherif N, Turitto G, Boutjdir M. Congenital long QT syndrome and torsade de pointes. *Ann Noninvasive Electrocardiol*. 2017;22:e12481. doi: 10.1111/anec.12481

41. Itoh T, Tanaka T, Nagai R, Kamiya T, Sawayama T, Nakayama T, Tomoike H, Sakurada H, Yazaki Y, Nakamura Y. Genomic organization and mutational analysis of *herg*, a gene responsible for familial long QT syndrome. *Hum Genet*. 1998;102:435–439.

42. Splawski I, Timothy KW, Tateyama M, Clancy CE, Malhotra A, Beggs AH, Cappuccio FP, Sagnella GA, Kass RS, Keating MT. Variant of SCN5A sodium channel implicated in risk of cardiac arrhythmia. *Science*. 2002;297:1333–1336. doi: 10.1126/science.1073569

43. Ackerman MJ, Splawski I, Makielski JC, Tester DJ, Will ML, Timothy KW, Keating MT, Jones G, Chadha M, Burrow CR, et al. Spectrum and prevalence of cardiac sodium channel variants among black, white, Asian, and Hispanic individuals: implications for arrhythmogenic susceptibility and Brugada/long QT syndrome genetic testing. *Heart Rhythm*. 2004;1:600–607. doi: 10.1016/j.hrthm.2004.07.013

44. Ackerman MJ, Tester DJ, Jones GS, Will ML, Burrow CR, Curran ME. Ethnic differences in cardiac potassium channel variants: implications for genetic susceptibility to sudden cardiac death and genetic testing

for congenital long QT syndrome. *Mayo Clin Proc*. 2003;78:1479–1487. doi: 10.4065/78.12.1479

45. Lu Y, Mahaut-Smith MP, Huang CL, Vandenberg JI. Mutant MIRP1 subunits modulate HERG K+ channel gating: a mechanism for proarrhythmia in long QT syndrome type 6. *J Physiol*. 2003;551:253–262. doi: 10.1113/jphysiol.2003.046045

46. Abbott GW, Sesti F, Splawski I, Buck ME, Lehmann MH, Timothy KW, Keating MT, Goldstein SA. MIRP1 forms I_{kr} potassium channels with HERG and is associated with cardiac arrhythmia. *Cell*. 1999;97:175–187. doi: 10.1016/S0092-8674(00)80728-X

47. Wang Q, Shen J, Splawski I, Atkinson D, Li Z, Robinson JL, Moss AJ, Towbin JA, Keating MT. SCN5A mutations associated with an inherited cardiac arrhythmia, long QT syndrome. *Cell*. 1995;80:805–811. doi: 10.1016/0092-8674(95)90359-3

48. Fugate T II, Moss AJ, Jons C, McNitt S, Mullally J, Ouellet G, Goldenberg I, Zareba W, Robinson JL. Long QT syndrome in African-Americans. *Ann Noninvasive Electrocardiol*. 2010;15:73–76. doi: 10.1111/j.1542-474X.2009.00342.x

49. Chen S, Chung MK, Martin D, Rozich R, Tchou PJ, Wang Q. SNP S1103Y in the cardiac sodium channel gene SCN5A is associated with cardiac arrhythmias and sudden death in a white family. *J Med Genet*. 2002;39:913–915. doi: 10.1136/jmg.39.12.913

50. Sun AY, Koontz JI, Shah SH, Piccini JP, Nilsson KR Jr, Craig D, Haynes C, Gregory SG, Hranitzky PM, Pitt GS. The S1103Y cardiac sodium channel variant is associated with implantable cardioverter-defibrillator events in blacks with heart failure and reduced ejection fraction. *Circ Cardiovasc Genet*. 2011;4:163–168. doi: 10.1161/CIRCGENETICS.110.958652

51. Mongkhonsiri P, Tong-Un T, Wyss JM, Roysommuti S. Blunted nighttime sympathetic nervous system response to stress among Thai men with positive family history of sudden unexplained nocturnal death syndrome. *Int Heart J*. 2019;60:55–62. doi: 10.1536/ihj.18-061

52. Bonny A, Tonet J, Fontaine G, Lacotte J, Coignard E, Duthoit G, Hidden-Lucet F, Charron P, Brugada P, Frank R. Brugada syndrome in pure black Africans. *J Cardiovasc Electrophysiol*. 2008;19:421–426. doi: 10.1111/j.1540-8167.2007.01041.x

53. Shogade TT, Akpabio AA, Markson FE, Sogade FO. An unusual case of Brugada syndrome in an 82-year old black hypertensive man. *J Integr Cardiol Open Access*. 2020;3:2–3. doi: 10.31487/j.JICOA.2020.03.07

54. Gaita F, Giustetto C, Bianchi F, Wolpert C, Schimpf R, Riccardi R, Grossi S, Richiardi E, Borggrefe M. Short QT syndrome: a familial cause of sudden death. *Circulation*. 2003;108:965–970. doi: 10.1161/01.CIR.0000085071.28695.C4

55. Iribarren C, Round AD, Peng JA, Lu M, Klatsky AL, Zaroff JG, Holve TJ, Prasad A, Stang P. Short QT in a cohort of 1.7 million persons: prevalence, correlates, and prognosis. *Ann Noninvasive Electrocardiol*. 2014;19:490–500. doi: 10.1111/anec.12157

56. Priori SG, Pandit SV, Rivolta I, Berenfeld O, Ronchetti E, Dhamoon A, Napolitano C, Anumonwo J, di Barletta MR, Gudapakkam S, et al. A novel form of short QT syndrome (SQT3) is caused by a mutation in the KCNJ2 gene. *Circ Res*. 2005;96:800–807.

57. Cordeiro JM, Brugada R, Wu YS, Hong K, Dumaine R. Modulation of I(KR) inactivation by mutation n588k in KCNH2: a link to arrhythmogenesis in short QT syndrome. *Cardiovasc Res*. 2005;67:498–509.

58. Hong K, Piper DR, Diaz-Valdecantos A, Brugada J, Oliva A, Burashnikov E, Santos-de-Soto J, Grueso-Montero J, Diaz-Enfante E, Brugada P, et al. De novo KCNQ1 mutation responsible for atrial fibrillation and short QT syndrome in utero. *Cardiovasc Res*. 2005;68:433–440. doi: 10.1016/j.cardiores.2005.06.023

59. Antzelevitch C, Yan GX, Ackerman MJ, Borggrefe M, Corrado D, Guo J, Gussak I, Hasdemir C, Horie M, Huikuri H, et al. J-wave syndromes expert consensus conference report: emerging concepts and gaps in knowledge. *Europace*. 2017;19:665–694.

60. Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, Blom N, Brugada J, Chiang C-E, Huikuri H, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. *Heart Rhythm*. 2013;10:1932–1963. doi: 10.1016/j.hrthm.2013.05.014

61. Bonny A, Noah DN, Amougou SN, Saka C. Prevalence and significance of early repolarisation in a black African population: data of 246 individuals with cardiovascular morbidity. *Cardiovasc J Afr*. 2013;24:280–285.

62. Roukoz H, Wang K. ST elevation and inverted t wave as another normal variant mimicking acute myocardial infarction: the prevalence, age, gender, and racial distribution. *Ann Noninvasive Electrocardiol*. 2011;16:64–69. doi: 10.1111/j.1542-474X.2010.00410.x

63. Crouse SF, Meade T, Hansen BE, Green JS, Martin SE. Electrocardiograms of collegiate football athletes. *Clin Cardiol*. 2009;32:37–42. doi: 10.1002/clc.20452

64. Thomas J, Harris E, Lassiter G. Observations on the T wave and S-T segment changes in the precordial electro-cardiogram of 320 young Negro adults. *Am J Cardiol*. 1960;5:468–472. doi: 10.1016/0002-9149(60)90102-8

65. Swan H, Piippo K, Viitasalo M, Heikkilä P, Paavonen T, Kainulainen K, Kere J, Keto P, Kontula K, Toivonen L. Arrhythmic disorder mapped to chromosome 1q42-q43 causes malignant polymorphic ventricular tachycardia in structurally normal hearts. *J Am Coll Cardiol*. 1999;34:2035–2042. doi: 10.1016/S0735-1097(99)00461-1

66. Priori SG, Napolitano C, Tiso N, Memmi M, Vignati G, Bloise R, Sorrentino V, Danieli GA. Mutations in the cardiac ryanodine receptor gene (HRYR2) underlie catecholaminergic polymorphic ventricular tachycardia. *Circulation*. 2001;103:196–200.

67. Laitinen PJ, Brown KM, Piippo K, Swan H, Devaney JM, Brahmbhatt B, Donarum EA, Marino M, Tiso N, Viitasalo M, et al. Mutations of the cardiac ryanodine receptor (RYR2) gene in familial polymorphic ventricular tachycardia. *Circulation*. 2001;103:485–490. doi: 10.1161/01.CIR.103.4.485

68. Lahat H, Eldar M, Levy-Nissenbaum E, Bahan T, Friedman E, Khoury A, Lorber A, Kastner DL, Goldman B, Pras E. Autosomal recessive catecholamine- or exercise-induced polymorphic ventricular tachycardia: clinical features and assignment of the disease gene to chromosome 1p13-21. *Circulation*. 2001;103:2822–2827. doi: 10.1161/01.CIR.103.23.2822

69. Postma AV, Denjoy I, Hoorntje TM, Lupoglazoff JM, Da Costa A, Sebillon P, Mannens MM, Wilde AA, Guicheney P. Absence of calsequestrin 2 causes severe forms of catecholaminergic polymorphic ventricular tachycardia. *Circ Res*. 2002;91:e21–e26. doi: 10.1161/01.RES.0000038886.18992.6B

70. Roston TM, Guo W, Krahn AD, Wang R, Van Petegem F, Sanatani S, Chen SR, Lehman A. A novel RYR2 loss-of-function mutation (I4855M) is associated with left ventricular non-compaction and atypical catecholaminergic polymorphic ventricular tachycardia. *J Electrocardiol*. 2017;50:227–233. doi: 10.1016/j.jelectrocard.2016.09.006

71. Javed A, Zalawadiya S, Kottam A, Afonso L. New mutation in casequestrin gene: a major discovery in catecholaminergic polymorphic ventricular tachycardia. *J Am Coll Cardiol*. 2014;63:A651. doi: 10.1016/S0735-1097(14)60651-3

72. Maron BJ, Maron MS, Semsarian C. Genetics of hypertrophic cardiomyopathy after 20 years: clinical perspectives. *J Am Coll Cardiol*. 2012;60:705–715. doi: 10.1016/j.jacc.2012.02.068

73. Maron BJ, Maron MS, Maron BA, Loscalzo J. Moving beyond the sarcomere to explain heterogeneity in hypertrophic cardiomyopathy: JACC review topic of the week. *J Am Coll Cardiol*. 2019;73:1978–1986. doi: 10.1016/j.jacc.2019.01.061

74. Maron MS, Olivotto I, Harrigan C, Appelbaum E, Gibson CM, Lesser JR, Haas TS, Udelson JE, Manning WJ, Maron BJ. Mitral valve abnormalities identified by cardiovascular magnetic resonance represent a primary phenotypic expression of hypertrophic cardiomyopathy. *Circulation*. 2011;124:40–47. doi: 10.1161/CIRCULATIONAHA.110.985812

75. Manrai AK, Funke BH, Rehm HL, Olesen MS, Maron BA, Szolovits P, Margulies DM, Loscalzo J, Kohane IS. Genetic misdiagnoses and the potential for health disparities. *N Engl J Med*. 2016;375:655–665. doi: 10.1056/NEJMsa1507092

76. Exome Variant Server, NHLBI GO Exome Sequencing Project (ESP), Seattle, WA. Available at: http://evs.gs.washington.edu/EVS/. Accessed September 9, 2021.

77. Andreasen C, Nielsen JB, Refsgaard L, Holst AG, Christensen AH, Andreasen L, Sajadieh A, Haunsø S, Svendsen JH, Olesen MS. New population-based exome data are questioning the pathogenicity of previously cardiomyopathy-associated genetic variants. *Eur J Hum Genet*. 2013;21:918–928. doi: 10.1038/ejhg.2012.283

78. Stenson PD, Mort M, Ball EV, Howells K, Phillips AD, Thomas NS, Cooper DN. The human gene mutation database: 2008 update. *Genome Med*. 2009;1:13. doi: 10.1186/gm13

79. Genomes Project Consortium. An integrated map of genetic variation from 1,092 human genomes. *Nature*. 2012;491:56–65.

80. Li JZ, Absher DM, Tang H, Southwick AM, Casto AM, Ramachandran S, Cann HM, Barsh GS, Feldman M, Cavalli-Sforza LL, et al. Worldwide human relationships inferred from genome-wide patterns of variation. *Science*. 2008;319:1100–1104. doi: 10.1126/science.1153717

81. Bick A, Flannick J, Ito K, Cheng S, Vasan R, Parfenov M, Herman D, DePalma S, Gupta N, Gabriel S, et al. Burden of rare sarcomere gene variants in the Framingham and Jackson Heart Study Cohorts. *Am J Hum Genet*. 2012;91:513–519. doi: 10.1016/j.ajhg.2012.07.017

82. Maron BJ. Clinical course and management of hypertrophic cardiomyopathy. *N Engl J Med*. 2018;379:655–668. doi: 10.1056/NEJMra1710575

83. Corrado D, Link MS, Calkins H. Arrhythmogenic right ventricular cardiomyopathy. *N Engl J Med*. 2017;376:61–72. doi: 10.1056/NEJMra1509267

84. Moreau A, Gosselin-Badaroudine P, Boutjdir M, Chahine M. Mutations in the voltage sensors of domains I and II of Nav1.5 that are associated with arrhythmias and dilated cardiomyopathy generate gating pore currents. *Front Pharmacol*. 2015;6:301. doi: 10.3389/fphar.2015.00301

85. McNair WP, Ku L, Taylor MR, Fain PR, Dao D, Wolfel E, Mestroni L. SCN5A mutation associated with dilated cardiomyopathy, conduction disorder, and arrhythmia. *Circulation*. 2004;110:2163–2167.

86. Te Riele AS, Agullo-Pascual E, James CA, Leo-Macias A, Cerrone M, Zhang M, Lin X, Lin B, Sobreira NL, Amat-Alarcon N, et al. Multilevel analyses of scn5a mutations in arrhythmogenic right ventricular dysplasia/cardiomyopathy suggest non-canonical mechanisms for disease pathogenesis. *Cardiovasc Res*. 2017;113:102–111.

87. Sato PY, Coombs W, Lin X, Nekrasova O, Green KJ, Isom LL, Taffet SM, Delmar M. Interactions between ankyrin-g, plakophilin-2, and connexin43 at the cardiac intercalated disc. *Circ Res*. 2011;109:193–201. doi: 10.1161/CIRCRESAHA.111.247023

88. Fressart V, Duthoit G, Donal E, Probst V, Deharo J-C, Chevalier P, Klug D, Dubourg O, Delacretaz E, Cosnay P, et al. Desmosomal gene analysis in arrhythmogenic right ventricular dysplasia/cardiomyopathy: spectrum of mutations and clinical impact in practice. *Europace*. 2010;12:861–868. doi: 10.1093/europace/euq104

89. Dadson K, Hauck L, Billia F. Molecular mechanisms in cardiomyopathy. *Clin Sci*. 2017;131:1375–1392. doi: 10.1042/CS20160170

90. Awad MM, Calkins H, Judge DP. Mechanisms of disease: molecular genetics of arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Nat Clin Pract Cardiovasc Med*. 2008;5:258–267. doi: 10.1038/ncpcardio1182

91. van Lint FHM, Murray B, Tichnell C, Zwart R, Amat N, Lekanne Deprez RH, Dittmann S, Stallmeyer B, Calkins H, van der Smagt JJ, et al. Arrhythmogenic right ventricular cardiomyopathy-associated desmosomal variants are rarely de novo. *Circ Genom Precis Med*. 2019;12:e002467. doi: 10.1161/CIRCGEN.119.002467

92. Musunuru K, Hershberger RE, Day SM, Klinedinst NJ, Landstrom AP, Parikh VN, Prakash S, Semsarian C, Sturm AC. Genetic testing for inherited cardiovascular diseases: a scientific statement from the American Heart Association. *Circ Genom Precis Med*. 2020;13:e000067. doi: 10.1161/HCG.0000000000000067

93. Waddington CH. The epigenotype: 1942. *Int J Epidemiol*. 2012;41:10–13.

94. Ordovás JM, Smith CE. Epigenetics and cardiovascular disease. *Nat Rev Cardiol*. 2010;7:510–519. doi: 10.1038/nrcardio.2010.104

95. Jimenez J, Rentschler SL. Transcriptional and epigenetic regulation of cardiac electrophysiology. *Pediatr Cardiol*. 2019;40:1325–1330. doi: 10.1007/s00246-019-02160-w

96. Mensah GA, Jaquish C, Srinivas P, Papanicolaou GJ, Wei GS, Redmond N, Roberts MC, Nelson C, Aviles-Santa L, Puggal M, et al. Emerging concepts in precision medicine and cardiovascular diseases in racial and ethnic minority populations. *Circ Res*. 2019;125:7–13. doi: 10.1161/CIRCRESAHA.119.314970

97. Yusuf S, Hawken S, Ôunpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364:937–952. doi: 10.1016/S0140-6736(04)17018-9

98. Lu XT, Zhao YX, Zhang Y, Jiang F. Psychological stress, vascular inflammation, and atherogenesis: potential roles of circulating cytokines. *J Cardiovasc Pharmacol*. 2013;62:6–12. doi: 10.1097/FJC.0b013e3182858fac

99. Toda N, Nakanishi-Toda M. How mental stress affects endothelial function. *Pflugers Arch*. 2011;462:779–794. doi: 10.1007/s00424-011-1022-6

100. Saban KL, Mathews HL, DeVon HA, Janusek LW. Epigenetics and social context: implications for disparity in cardiovascular disease. *Aging Dis*. 2014;5:346–355. doi: 10.14336/ad.2014.0500346

101. Goodman AH. Why genes don't count (for racial differences in health). *Am J Public Health*. 2000;90:1699–1702.

102. Jorde LB, Wooding SP. Genetic variation, classification and "race." *Nat Genet*. 2004;36:S28–S33. doi: 10.1038/ng1435

103. Bo S, Cavallo-Perin P, Scaglione L, Ciccone G, Pagano G. Low birthweight and metabolic abnormalities in twins with increased susceptibility to type 2 diabetes mellitus. *Diabetic Med*. 2000;17:365–370. doi: 10.1046/j.1464-5491.2000.00288.x

104. Iliadou A, Cnattingius S, Lichtenstein P. Low birthweight and type 2 diabetes: a study on 11 162 Swedish twins. *Int J Epidemiol*. 2004;33:948–953. doi: 10.1093/ije/dyh117

105. Chitrala KN, Hernandez DG, Nalls MA, Mode NA, Zonderman AB, Ezike N, Evans MK. Race-specific alterations in DNA methylation among middle-aged African Americans and Whites with metabolic syndrome. *Epigenetics*. 2020;15:462–482. doi: 10.1080/15592 294.2019.1695340

106. Eberly LA, Day SM, Ashley EA, Jacoby DL, Jefferies JL, Colan SD, Rossano JW, Semsarian C, Pereira AC, Olivotto I, et al. Association of race with disease expression and clinical outcomes among patients with hypertrophic cardiomyopathy. *JAMA Cardiol*. 2020;5:83–91. doi: 10.1001/jamacardio.2019.4638

107. Ackerman MJ, Siu BL, Sturner WQ, Tester DJ, Valdivia CR, Makielski JC, Towbin JA. Postmortem molecular analysis of *SCN5A* defects in sudden infant death syndrome. *JAMA*. 2001;286:2264–2269.

108. Burke A, Creighton W, Mont E, Li L, Hogan S, Kutys R, Fowler D, Virmani R. Role of scn5a y1102 polymorphism in sudden cardiac death in blacks. *Circulation*. 2005;112:798–802. doi: 10.1161/CIRCU LATIONAHA.104.482760

109. Plant LD, Bowers PN, Liu Q, Morgan T, Zhang T, Chen W, Kittles RA, Goldstein SA. A common cardiac sodium channel variant associated with sudden infant death in African Americans, SCN5A S1103Y. *J Clin Invest*. 2006;116:430–435. doi: 10.1172/JCI25618

110. Mirowski M, Reid PR, Mower MM, Watkins L, Gott VL, Schauble JF, Langer A, Heilman MS, Kolenik SA, Fischell RE, et al. Termination of malignant ventricular arrhythmias with an implanted automatic defibrillator in human beings. *N Engl J Med*. 1980;303:322–324.

111. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med*. 2002;346:877–883. doi: 10.1056/NEJMoa013474

112. Lane RE, Cowie MR, Chow AW. Prediction and prevention of sudden cardiac death in heart failure. *Heart*. 2005;91:674–680. doi: 10.1136/hrt.2003.025254

113. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med*. 2005;352:225–237. doi: 10.1056/NEJMoa043399

114. Thomas KL, Al-Khatib SM, Kelsey RC II, Bush H, Brosius L, Velazquez EJ, Peterson ED, Gilliam FR. Racial disparity in the utilization of implantable-cardioverter defibrillators among patients with prior myocardial infarction and an ejection fraction of <or=35%. *Am J Cardiol*. 2007;100:924–929.

115. Hernandez AF, Fonarow GC, Liang L, Al-Khatib SM, Curtis LH, LaBresh KA, Yancy CW, Albert NM, Peterson ED. Sex and racial differences in the use of implantable cardioverter-defibrillators among patients hospitalized with heart failure. *JAMA*. 2007;298:1525–1532. doi: 10.1001/jama.298.13.1525

116. Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med*. 1997;337:1576–1583.

117. Fontaine JM, Franklin SM, Essilfie G, Ahiable LE. Cardiac resynchronization therapy: a comparative analysis of mortality in African Americans and Caucasians. *Pacing Clin Electrophysiol*. 2018;41:536–545. doi: 10.1111/pace.13326

118. Levy D, Anderson KM, Savage DD, Balkus SA, Kannel WB, Castelli WP. Risk of ventricular arrhythmias in left ventricular hypertrophy: the Framingham Heart study. *Am J Cardiol*. 1987;60:560–565. doi: 10.1016/0002-9149(87)90305-5

119. Bonow RO, Grant AO, Jacobs AK. The cardiovascular state of the union: confronting healthcare disparities. *Circulation*. 2005;111:1205–1207. doi: 10.1161/01.CIR.0000160705.97642.92

120. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, Carnethon MR, Dai S, de Simone G, Ford ES, et al. Heart disease and stroke statistics–2011 update: a report from the American Heart Association. *Circulation*. 2011;123:e18–e209.

121. Kaul P, Lytle BL, Spertus JA, DeLong ER, Peterson ED. Influence of racial disparities in procedure use on functional status outcomes among patients with coronary artery disease. *Circulation*. 2005;111:1284–1290. doi: 10.1161/01.CIR.0000157731.66268.E1

122. Ghobrial J, Heckbert SR, Bartz TM, Lovasi G, Wallace E, Lemaitre RN, Mohanty AF, Rea TD, Siscovick DS, Yee J, et al. Ethnic differences in sudden cardiac arrest resuscitation. *Heart*. 2016;102:1363–1370. doi: 10.1136/heartjnl-2015-308384

123. Starks MA, Schmicker RH, Peterson ED, May S, Buick JE, Kudenchuk PJ, Drennan IR, Herren H, Jasti J, Sayre M, et al. Association of neighborhood demographics with out-of-hospital cardiac arrest treatment and outcomes: where you live may matter. *JAMA Cardiol*. 2017;2:1110–1118. doi: 10.1001/jamacardio.2017.2671

124. Diallo AF, Alabi O, Groves A, Johnson AE, Okoro F, Ramos SR, Nelson RK, Boutjdir M. Training underrepresented early-career faculty in cardiovascular health research during COVID-19: structural inequities and health disparity. *Ethn Dis*. 2021;31:411–416. doi: 10.18865/ed.31.3.411

125. Boutjdir M, Aromolaran AS, de Las FL, Boyington JEA, Arteaga SS, Jobe J, Jeffe DB, Rao DC, Rice TK, Davila-Roman VG. Research education and mentoring program in cardiovascular diseases for underrepresented junior faculty from NHLBI SIPID/PRIDE. *J Am Coll Cardiol*. 2019;73:1861–1865. doi: 10.1016/j.jacc.2019.01.042