

UCSF

UC San Francisco Previously Published Works

Title

A Common SCN5A Variant Is Associated with PR Interval and Atrial Fibrillation Among African Americans

Permalink

<https://escholarship.org/uc/item/0hz0666p>

Journal

Journal of Cardiovascular Electrophysiology, 25(11)

ISSN

1045-3873

Authors

ILKHANOFF, LEONARD
ARKING, DAN E
LEMAITRE, ROZENN N
[et al.](#)

Publication Date

2014-11-01

DOI

10.1111/jce.12483

Peer reviewed



Published in final edited form as:

J Cardiovasc Electrophysiol. 2014 November ; 25(11): 1150–1157. doi:10.1111/jce.12483.

A Common *SCN5A* Variant is Associated with PR Interval and Atrial Fibrillation among African Americans

Leonard Ilkhanoff, MD, MS¹, Dan E. Arking, PhD², Rozenn N. Lemaitre, PhD, MPH³, Alvaro Alonso, MD, PhD⁴, Lin Y. Chen, MBBS, MS⁵, Peter Durda, BS⁶, Stephanie E. Hesselton, PhD⁷, Kathleen F. Kerr, PhD⁸, Jared W. Magnani, MD, MSc⁹, Gregory M. Marcus, MD, MAS¹⁰, Renate B. Schnabel, MD, MSc^{9,11}, J. Gustav Smith, MD, PhD^{12,13}, Elsayed Z. Soliman, MD, MSc, MS¹⁴, Alexander P. Reiner, MD, MSc¹⁵, and Nona Sotoodehnia, MD, MPH^{3,16} on behalf of the Candidate-gene Association Resource (CARE) Consortium and the Cardiac Arrest Blood Study (CABS) Investigators

¹Northwestern University; Department of Medicine, Division of Cardiology, Section of Electrophysiology, Chicago, IL

²McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD

³Cardiovascular Health Research Unit, Department of Medicine, University of Washington, Seattle, WA

⁴Division of Epidemiology & Community Health, School of Public Health, University of Minnesota, Minneapolis, MN

⁵Cardiac Arrhythmia Center, Cardiovascular Division, Department of Medicine, University of Minnesota Medical School, Minneapolis, MN

⁶Department of Pathology, College of Medicine, University of Vermont, Burlington, VT

⁷Cardiovascular Research Institute, University of California, San Francisco, San Francisco, CA, and Diabetes and Obesity Division, The Garvan Institute of Medical Research, Sydney, NSW 2010, Australia

⁸Department of Biostatistics, School of Public Health, University of Washington, Seattle, WA

⁹Boston University and NHLBI's Framingham Heart Study, Framingham, MA

¹⁰Division of Cardiology, Electrophysiology Section, University of California, San Francisco, CA

¹¹Department of General and Interventional Cardiology, University Heart Center Hamburg-Eppendorf, Germany

¹²Broad Institute of Harvard & Massachusetts Institute of Technology, Cambridge, MA

¹³Department of Cardiology, Faculty of Medicine, Lund University, Lund, Sweden

Corresponding author: Nona Sotoodehnia, MD, MPH, John and Cookie Laughlin Endowed Professor of Cardiology, Cardiovascular Health Research Unit, University of Washington, Seattle, Washington, USA, nsotoo@u.washington.edu, phone - 206-287-2777, fax - 206-287-2666.

No disclosures.

¹⁴Epidemiological Cardiology Research Center (EPICARE), Wake Forest University School of Medicine, Winston Salem, NC

¹⁵Department of Epidemiology, University of Washington, and Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, WA

¹⁶Division of Cardiology, Department of Medicine, University of Washington, Seattle, WA

Abstract

Objective—We examined the association of rs7626962 (S1103Y) or rs7629265, a variant in high linkage disequilibrium with S1103Y ($r^2=0.87-1$), with sudden cardiac death (SCD) and atrial fibrillation (AF) among African Americans.

Background—The *SCN5A* missense variant S1103Y has been associated with SCD among African Americans in small case-control studies, but larger population-based studies are needed to validate these findings. The association of this variant with AF has not been fully explored.

Methods—Using genotyping data on over 7000 African Americans from five cohorts (ARIC, CFS, JHS, MESA, CHS), we examined the association of rs7629265 with electrocardiographic PR, QRS and QT intervals, and with incident AF and SCD. We examined association of S1103Y (rs7626962) with SCD using a population-based case-control study of SCD (CABS).

Results—Meta-analyses across five cohorts demonstrated that rs7629265 was significantly associated with PR duration ($\beta = -4.1\text{ms}$, $p = 2.2 \times 10^{-6}$), but not significantly associated with QRS or QT intervals. In meta-analyses of prospectively-followed ARIC and CHS participants ($n = 3656$), rs7629265 was associated with increased AF risk ($n = 299$ AF cases; $\text{HR} = 1.74$, $p = 1.9 \times 10^{-4}$). By contrast, rs7629265 was not significantly associated with SCD risk in ARIC ($n = 83$ SCD cases, $p = 0.30$) or CHS ($n = 54$ SCD cases; $p = 0.47$). Similarly, S1103Y was not significantly associated with SCD risk in CABS ($n = 225$ SCD cases; $p = 0.29$).

Conclusion—The common *SCN5A* variant, rs7629265, is associated with increased AF risk and shorter PR interval among African Americans. In contrast to prior reports, we found no evidence of association of rs7629265 or rs7626962 (S1103Y) with SCD risk in the general population.

Keywords

atrial fibrillation; sudden death; electrocardiogram; genetics; PR interval

INTRODUCTION

Sudden cardiac death (SCD) is a major public health concern, particularly among African Americans where risk of cardiac arrest is higher than in the general population, and survival is poor. Three small case-control studies have identified a missense variant of the *SCN5A* cardiac sodium channel gene (rs7626962, C->A, S1103Y), common among African Americans (allele frequency 6.8%) but absent among those of European descent, to be associated with arrhythmia susceptibility and SCD risk (1–3). Splawski et al found an 8-fold increase in risk of arrhythmias, syncope, and sudden death among 23 patients who were heterozygous or homozygous for the variant allele (referred to as S1102Y in their study) (1). Computational modeling suggested that Y1103 increases the likelihood of QT prolongation

in the setting of drugs or hypokalemia that inhibit cardiac repolarization (1). Whether the S1103Y variant is associated with SCD in the general population, or in the setting of specific risk factors, such as hypokalemia or diuretic medications, has not been validated in larger population-based studies. Furthermore, whether S1103Y is associated with risk of atrial fibrillation (AF), the most common sustained cardiac arrhythmia, has not been fully explored.

We, therefore, sought to investigate whether rs7629265 (C->T), an intronic variant in high linkage disequilibrium (LD), with S1103Y (rs7626962), is associated with risk of SCD and AF in the general population by examining two large African-American cohorts followed prospectively. We further examined association of SCD directly with S1103Y (rs7626962) in a large population-based case-control study of the determinants of SCD. Using the National Heart Lung and Blood Institute's (NHLBI) Candidate-gene Association Resource (CARE) Consortium, we also examined the association of the intronic variant rs7629265 with electrocardiographic (ECG) parameters of PR, QRS and QT intervals -- intermediary electrophysiologic measures that influence AF or SCD risk.

METHODS

CARE Study samples

Individuals of self-reported African-American ancestry from five cohort studies (the Atherosclerosis Risk in Communities (ARIC) study, the Cleveland Family Study (CFS), the Cardiovascular Health Study (CHS), the Jackson Heart Study (JHS), and the Multi-Ethnic Study of Atherosclerosis (MESA) study) were genotyped as part of the CARE Consortium. Descriptions of these cohorts are detailed in the supplemental section and have been published previously (4). The Institutional Review Board at all participating institutions approved the study. Only individuals who provided informed consent to genetic testing were included.

CARE Genotyping and Quality Control

DNA samples and phenotype information from the CARE cohorts were shipped to the Broad Institute of Massachusetts Institute of Technology (MIT) and Harvard, and harmonized across studies (<http://www.cdisc.org/models/sds/v3.1/index.html>). Genotype quality control procedures were performed separately for each cohort. We used a cardiovascular 50K SNP IBC array (ITMAT, Broad, and CARE) to type samples at the Broad Institute (MIT, Cambridge, MA). While the rs7626962 (S1103Y) variant was not directly measured in CARE, a surrogate, rs7620265, which is in strong LD with rs7626962, was typed.

TaqMan Genotyping of rs7626962 (S1103Y) in CHS

In CHS, in addition to genotyping with the IBC array described above, direct genotyping of rs7626962 (S1103Y) was performed after PCR amplification using a high-throughput TaqMan assay (Applied Biosystems, Foster City, CA). The PCR product was sequenced using big dye terminator chemistry and an ABI310 DNA sequencer.

CARe ECG Recordings and Phenotype Definition

Twelve-lead ECGs with standard lead placements were recorded during 10 seconds in all cohorts at baseline using Marquette MAC PC, MAC6 or MAC1200 machines (GE Healthcare, Chalfont St Giles, UK). For our ECG parameters analysis, PR, QRS, and QT intervals were measured electronically using either the Marquette 12SL algorithm or the MC MEANS algorithm. We excluded from all ECG analyses individuals with missing covariates, or who were <18 years of age, or pregnant.

For the PR interval analysis, participants were excluded for prevalent AF on ECG; pacemaker in place; ventricular preexcitation; second or third degree heart block; history of myocardial infarction or heart failure; and for extreme PR trait values of 80 ms or 320 ms. Consistent with prior studies assessing common genetic variation (9;20), PR duration cutoffs were chosen to exclude extreme values. For the QRS analysis, participants were excluded for prevalent AF on ECG; pacemaker in place; ventricular preexcitation; second or third degree heart block; history of myocardial infarction or heart failure; and QRS 120 ms. For the QT analysis, participants were excluded for prevalent AF on ECG; pacemaker in place; QRS 120 msec. A clinical definition of hypokalemia was used (K^+ level <3.7 milliequivalents per liter (mEq/L)), obtained on baseline blood draw. Diuretic use was defined by use of loop (furosemide) or thiazide (hydrochlorothiazide) diuretic at baseline evaluation.

ARIC and CHS Event Ascertainment: Atrial Fibrillation

Two of the five cohorts (ARIC and CHS) have systematically ascertained AF and SCD events, and were included in the analyses of these phenotypes. AF in both cohorts was limited to incident cases. In ARIC, AF was ascertained from three different sources: ECGs, hospitalizations, and death certificates. Study participants underwent 12-lead ECG at baseline and at each follow-up exam (3 exams; one exam every 3 years). All ECG recordings coded as AF by machine recording were visually rechecked by a cardiologist to confirm the diagnosis. Trained abstractors obtained and recorded all ICD-9 hospital discharge diagnoses from a participant's hospitalizations reported in annual follow-up interviews and from surveillance of local hospitals. AF was defined as the presence of ICD-9 code 427.31 or 427.32 in the discharge codes or at clinic follow-up visits. In addition, ARIC participants were classified as AF cases if AF was listed as one of the diagnoses in the death certificate (5). AF has been reported to be accurately ascertained from ICD-9 codes and death certificates with high validity (6). In CHS, the diagnosis of AF was made if AF or atrial flutter was present on an annual clinic visit ECG between 1989 and 1999, or when a hospital discharge ICD-9 code for AF or atrial flutter was present. The date of incident AF was taken as the earlier of the date of the clinic visit for AF identified on clinic ECG, or the date of hospital admission for AF identified from hospital discharge diagnosis. In both CHS and ARIC, AF that occurred during the same hospital stay as coronary artery bypass surgery or valve surgery was not included as an AF event.

ARIC and CHS Event Ascertainment: Sudden Cardiac Death

Both ARIC and CHS classified all cases of fatal cardiovascular death according to standard protocols, and causes of death were adjudicated by respective ARIC and CHS events

committees. To identify cases of SCD in ARIC and CHS for the present study, all cases of fatal cardiovascular death that occurred by July 31, 2006, in CHS and by December 31, 2001, in ARIC were reviewed and adjudicated by physicians. SCD was similarly defined in both ARIC and CHS as a sudden pulseless condition presumed due to a ventricular tachyarrhythmia in a previously stable individual without evidence of a non-cardiac cause of cardiac arrest. *We a priori* sought to exclude cases with nonarrhythmic characteristics, including those with evidence of progressive hypotension or advanced decompensated congestive heart failure before death. All SCD events in this analysis occurred out of the hospital or in the emergency room. Available data from death certificates, informant interviews, physician questionnaires, coroner reports, and hospital discharge summaries were reviewed, in addition to circumstances surrounding the event, to help classify whether the subject had experienced SCD. For unwitnessed deaths, the participant must have been seen within 24 hours of the arrest in a stable condition and without evidence of a noncardiac cause of cardiac arrest.

In ARIC, each event was adjudicated independently by 2 investigators, and classified as “definite sudden arrhythmic death,” “possible sudden arrhythmic death,” “definite nonsudden death,” or “unclassifiable.” If disagreement existed between the first 2 reviewers, a third investigator independently reviewed the event to provide final classification. In CHS, each event was adjudicated by a cardiologist’s record review, and classified as “definite sudden cardiac death,” “probable sudden cardiac death,” and “not sudden cardiac death or unclassifiable.” A blinded second physician review of a random sample of 70 of these death records showed an 88% inter-reviewer agreement and $\kappa=0.74$ for SCD. Both of these physicians also participated on the ARIC SCD review panel, to ensure consistency of phenotype across studies.

For the present analysis, SCD was defined as deaths that were definite or probable/possible sudden deaths. Participants were censored at time of loss to follow-up or death if the cause of death was other than SCD. The administrative censoring date was July 31, 2006, for CHS and December 31, 2001, for ARIC, based on the study’s adjudication schedules.

Cardiac Arrest Blood Study – Population

We examined a third population-based study of SCD risk determinants in order to directly examine the association of rs7626962 (S1103Y) with SCD incidence. Cases were selected from the Cardiac Arrest Blood Study Repository (CABS), a large population-based repository of data and specimens from adult out-of-hospital cardiac arrest patients who were attended by paramedics in Seattle and King county, Washington. SCD was defined as a sudden pulseless condition in an otherwise stable person in the absence of a non-cardiac cause of arrest. The records of 6003 persons identified by paramedics to suffer cardiac arrest were reviewed and classified as definite, probable, possible, or non-SCD based on initial rhythm (e.g., VF vs. asystole vs. pulseless electrical activity), circumstances (e.g., witnessed vs. unwitnessed) and possible contribution of comorbidities to the event. We excluded nursing home residents to avoid misclassification as to the cause of death. For the current analysis, we restricted our case population to those of African descent with a cardiac arrest classified as definite or probable SCD. We excluded individuals with a presenting rhythm of

pulseless electrical activity as these cases often have a different underlying pathophysiology than those with VF. We restricted the analysis to African Americans using the following two-step algorithm. First, only cases and controls were genotyped that were identified by paramedics (cases) as “African American / Black” or self-identified (controls) as “African American / Black.” Second, we excluded 1 ethnic outlier using principal components analysis.

We identified 225 SCD cases between the years of 1988 and 2007 that met these criteria. Controls (n=198) were identified from two sources (1) random digit dialing in the community and (2) random selection from enrollees of Group Health, a large Health Maintenance Organization in Western Washington State. The combined controls were frequency-matched to cases on age and gender. The Human Subject Review Committees of the University of Washington and Group Health Cooperative approved the study.

Cardiac Arrest Blood Study – Genotyping

Genotyping was performed using Affymetrix Axiom panel. Exclusion criteria at the sample level were call rates <90%, gender mismatches or non-African descent by ancestry informative markers. Exclusion criteria at the single nucleotide polymorphism (SNP) level were call rate <95%, out of Hardy-Weinberg equilibrium ($p < 0.01$). The rs7626962 (S1103Y) was directly genotyped on the Axiom panel.

Statistical Analysis – ECG Phenotypes

Hardy-Weinberg equilibrium was assessed by chi-squared test. For continuous ECG phenotypes, linear regression using an additive model was performed in each cohort, adjusted for age, gender, ancestry using 10 principal components, and study site. Additional adjustments for the PR and QRS analyses included body mass index, height, and systolic blood pressure. Consistent with prior studies evaluating these ECG variables, QT and PR analyses were also adjusted for RR interval (7–10). The Jackson Heart Study contains a family-based subcohort. We accounted for family structure using mixed linear models with a random effect term for pedigree. Cohort-specific results were combined using fixed effects meta-analyses with inverse variance weights.

Statistical Analysis – Atrial Fibrillation and Sudden Cardiac Death

For the analyses of SCD and AF, participants with missing covariate or genotype data at baseline were excluded. For analyses of incident AF, participants with prevalent AF at baseline (7 from ARIC and 12 from CHS) were excluded. Loss to follow-up was a censoring event. Because few study participants were homozygous for the minor allele, we used a dominant model for the outcomes of AF and SCD. Cox proportional hazards regression using a dominant model was employed, adjusting for age, gender, ancestry using 10 principal components, and study site in each cohort. Sensitivity analyses were performed using an additive model. For the incident AF analysis, the outcome was time to AF (or censor) from baseline. For the SCD analysis, the outcome was time to SCD (or censor) from baseline. We used a fixed effects meta-analytic approach with inverse variance weights to combine the regression parameter estimates from CHS and ARIC.

For the case-control analyses of SCD in the CABS study, associations of genotype with SCD risk were assessed using logistic regression with robust or 'sandwich' standard errors to obtain odds ratios (OR) and their 95% confidence intervals. These regressions were adjusted for age, gender, and 10 principal components derived from ancestry informative markers to control for potential residual population stratification.

Significance and Secondary Analyses

A p-value of less than $0.01=0.05/5$ (for the number of outcomes examined in this manuscript) was deemed statistically significant for all primary analyses (ECG phenotypes, AF, and SCD). In exploratory secondary analyses, we examined whether these associations were modified by diuretic use (loop or thiazide diuretics), hypokalemia, or gender in ARIC and CHS. We tested for interaction of the genotype-phenotype association by diuretic use (diuretic users vs. nonusers), hypokalemia ($K^+ < 3.7$ mEq/L) vs. normokalemia, or gender, using multiplicative models.

RESULTS

Baseline characteristics by cohort are shown in Table 1. The mean age of the study participants across the five cohorts examined ranged from 37 to 73 years. Overall, approximately 40% of the participants were male. Minor allele frequencies (MAF) for rs7629265 were similar across cohorts, and there was no decline in allele frequency in older cohorts. The variant examined in the CARE study participants, rs7629265, was in high LD ($r^2 = 0.88$) with S1103Y, rs7626962, in CHS where both variants were directly genotyped. The average age of CABS study participants was 62 years and 38% were male. In CABS, MAF of S1103Y was 0.072.

Association of rs7629265 with ECG Parameters

Approximately 7000 study participants were examined for each ECG phenotype at baseline across the 5 cohorts, after exclusion criteria were applied. rs7629265 was significantly associated with shortening of the PR interval by 4.1 msec for each copy of the minor (T) allele (Table 2; 95% confidence interval (CI)= -5.9 to -2.3 msec; meta-analysis $p=2.2 \times 10^{-6}$). rs7629265 was nominally associated with QRS shortening (beta=-0.7 msec; 95% CI= -1.3 to -0.1 msec; meta-analysis $p=0.021$) and QT lengthening (beta=1.6 msec, 95% CI= 0.2 to 3.0 msec; meta-analysis $p=0.019$), Table 2, but these associations were not significant after adjustment for multiple testing.

Association of rs7629265 with Incident Atrial Fibrillation

Among 2866 ARIC and 790 CHS participants, 169 (5.9%) and 130 (16.5%) incident AF cases were identified during follow-up, respectively. The higher incidence of AF in CHS compared with ARIC is consistent with the older age of the CHS cohort participants. In meta-analyses, ARIC and CHS participants heterozygous or homozygous for the rs7629265 variant (T) allele had a significantly higher risk of AF (meta-analysis HR=1.74; 95% CI=1.30-2.33; $p=1.9 \times 10^{-4}$; Table 3) than those homozygous for the C allele. In sensitivity analyses, results for the additive model minimally differed from those for the dominant model, due to the very few individuals homozygous for the variant allele.

Association with Sudden Cardiac Death

During follow-up, 83 (2.9%) and 54 (6.8%) SCD cases were identified in ARIC and CHS, respectively. There was no evidence of association of the rs7629265 variant allele with SCD risk in these two large African-American cohorts followed prospectively ($p>0.30$, Table 4). To further examine association with SCD risk among African Americans, we examined a large population-based case-control study ($n=225$ cases, $n=198$ controls) where rs7626962 (S1103Y) was directly genotyped, and similarly found no evidence of an association with SCD risk ($p=0.29$, Table 4).

Secondary Analyses

In secondary analyses in ARIC and CHS, where information on drug use and potassium levels were available, there was a suggestion that the rs7629265 variant allele was associated with increased risk of SCD among diuretic users ($n=1035$ total, 42 SCD cases; $HR=2.05$; 95% $CI=0.95-4.47$; $p=0.07$), and a decrease in risk of SCD among diuretic non-users ($n=2604$ total, 95 SCD cases; $HR=0.33$; 95% $CI=0.13-0.81$; $p=0.02$), meta-analysis interaction $p=0.006$. A similar difference in risk was not seen among those with and without hypokalemia ($K^+< 3.7$ mEq/L) at baseline. Furthermore, there was no interaction of diuretic use or hypokalemia on the outcomes of AF, or ECG parameters of PR interval duration, QRS duration, or QT interval. There was also no evidence of an interaction with gender.

In CHS, where both variants (rs7626962, S1103Y; and rs7629265) were directly genotyped, findings for all ECG parameters (PR, QRS, QT intervals) and outcomes (AF and SCD) examined were similar for both variants, as would be expected by their high LD.

DISCUSSION

Examining several large population-based cohorts, we found that a common cardiac sodium channel gene (*SCN5A*) variant, rs7629265 is associated with a 74% increase in risk of AF and shortening of the PR interval among African Americans. In contrast to prior reports examining S1103Y (1–3), the two variants examined in this study, rs7629265 and rs7626962 (S1103Y), were not associated with risk of SCD among African Americans in three large population-based studies of SCD. Our findings lend support to the contribution of genetic factors to AF among African Americans, and, importantly, temper prior reports suggesting a strong association of S1103Y with SCD.

AF, the most common sustained cardiac arrhythmia, increases risk of stroke and overall mortality. A number of tools for prediction of AF have been developed, primarily among those of European descent (11–13), which to date do not include genetic markers. It is noteworthy that a 74% increase in risk is one of the largest common single risk markers, with its effect estimate being greater than or comparable to that of tobacco use, prior myocardial infarction, hypertension, and diabetes (14). It remains to be investigated whether including this genetic marker in risk models may help better identify African Americans at high risk of AF and could lead to preventive measures that decrease the health-related and financial burden of AF (15).

While the burden of risk factors associated with AF, such as diabetes and hypertension, is higher among African Americans than among those of European descent, the prevalence of AF is paradoxically lower among African Americans (16–18).

Our finding of a variant found commonly among African Americans and absent among European Americans that increases risk of AF, adds to this paradox, and supports the hypothesis that African Americans may have different underlying mechanisms for arrhythmogenesis than those of European ancestry (19). Our findings of an association of this variant with shortened PR interval and increased risk of AF is consistent with prior reports examining the effect of variation in the *SCN5A* gene on atrial conduction and arrhythmias (8–10,20). Investigating the physiologic foundations for this discordant PR-atrial fibrillation relationship could be particularly informative in elucidating the mechanisms by which *SCN5A* influences atrioventricular conduction and atrial arrhythmia risk.

Importantly, despite initial small case-control studies that implicated S1103Y with ventricular arrhythmias and SCD (1–3), our findings from three large population-based studies (n=362 SCD total cases) did not reveal an association of SCD with either rs7629265 or rs7626962 (S1103Y), highlighting the importance of validating findings in larger and prospective studies. Our discrepant results with prior reports may be due to the differing populations and outcomes examined. While Splawski examined 23 cases with arrhythmia-related phenotypes and found an eight-fold increase risk with the S1103Y variant, only 10 of those cases were adults (1). Whereas we examined SCD among adults in the general population, most of the 10 adults examined in the Splawski study had significant cardiomyopathy and were taking a repolarization influencing medication such as amiodarone. Furthermore, the case phenotype definition in the Splawski report included syncope and QT prolongation, and not just SCD, as outcomes (1). A report by Sun et al examined African-American patients with heart failure with defibrillator implantation, and found that the S1103Y variant was more common among the 23 cases who received an appropriate defibrillatory shock therapy compared with the 89 controls who did not (35% versus 13%, respectively; p=0.03), but there was no association with mortality (3). In contrast to these two reports examining a small number of cases with structural heart disease, a larger study by Burke and colleagues found no association between the S1103Y variant and SCD risk among 117 cases with structural heart disease compared with 107 non-SCD controls, but did find increased risk in subgroups without any heart disease on autopsy examination (n=25), or with only mild cardiomegaly (n=40) (2).

Ours is the largest study to examine SCD outcomes among African Americans in the general population (n=392 SCD cases across three studies). The three studies examined in this report were population-based: two (CHS and ARIC) were cohorts followed prospectively and one (CABS) was a population-based case-control study of SCD. Furthermore, using ARIC and CHS African-American participants, we examined the conclusions by Splawski et al that the Y1103 allele may be associated with ventricular arrhythmias in the setting of additional acquired risk factors, such as medications or hypokalemia (1). Whereas there was no overall association with SCD in our study, in secondary analyses, we did find an interaction between the rs7629265 allele and use of diuretic medications on the outcome of sudden

death. This finding, although intriguing, needs to be replicated. Taken together, these findings do not provide compelling evidence for a large effect of S1103Y (rs7626962) or rs7629265 on SCD risk in the general population. Whether the S1103Y variant is associated with more modest risk of SCD, and in what clinical populations, deserves further investigation.

The mechanism by which either of the two *SCN5A* variants examined in our study, rs7629265 and rs7626962 (S1103Y), influence PR interval or AF incidence is unknown. *SCN5A* encodes the alpha-subunit of the voltage-gated cardiac sodium channel responsible for initiating the cardiac action potential (21). Common and rare variation in this gene influence cardiac conduction, repolarization, and arrhythmia risk (22–25). The two variants examined in our study, rs7629265 and rs7626962 (S1103Y), 28 kb apart, are in complete LD ($r^2 = 1.0$) among African Americans in HapMap3 (American South Western population) and in strong LD in CHS African Americans ($r^2 = 0.88$), where both variants were directly genotyped. No other SNP in HapMap3 or in 1000 Genomes is in moderate or high LD ($r^2 > 0.35$) with S1103Y (rs7626962). Which of these two variants is likely to be the functional allele in relation to PR interval and AF is unknown, although there is functional support for the missense SNP S1103Y (rs7626962). Electrophysiologic studies have shown that the S1103Y variant undergoes minimal kinetic shifts at baseline, but when exposed to other factors, such as cellular acidosis, late I_{Na} current is increased (26). By contrast, rs7629265 is a SNP in intron 8, and examination of the RegulomeDB database, which catalogues annotations from the Encyclopedia of DNA Elements (ENCODE) project, provides no compelling evidence for a functional regulatory role for rs7629265 (27). Additional functional studies are needed to further elucidate the mechanism of action of the functional variant.

Several limitations should be considered. First, AF cases were captured through annual ECGs and medical records. Asymptomatic paroxysmal AF would have been missed by these surveillance methods. Moreover, although ours is the largest study of SCD among African Americans, we were underpowered to identify modest associations. Larger studies are needed, with a particular focus on interactions with medications.

In conclusion, we found a 74% increase in risk of AF with an intronic variant in *SCN5A*, rs7629265, which is in strong LD with a missense variant (S1103Y, rs7626962) found commonly among African Americans. Including this genetic factor in risk models of AF among African Americans may help better identify those at elevated risk for developing AF and could lead to preventive measures that decrease the health-related and financial burden of this disease. Larger scale, prospective studies are needed to address these questions. Importantly, in contrast to previous small case-control studies examining S1103Y, we also found no strong association between rs7629265 or rs7626962 (S1103Y) with SCD risk (1). Taken together, our findings underscore the importance of prospective replication, and evaluation of potential genetic markers of arrhythmia susceptibility in larger studies to better understand and refine their role in arrhythmia risk prediction.

Acknowledgments

Funding Sources:

Cardiac Arrest Blood Study (CABS): The CABS research was supported by R01 HL111089, R01 HL092111-01, R01 HL088456, R01 HL116747, R01 HL091244, the John L. Locke Charitable Trust, and the Sandra Daugherty Foundation. **Atherosclerosis Risk in Communities (ARIC):** The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C). The authors thank the staff and participants of the ARIC study for their important contributions. **Cleveland Family Study (CFS):** Case Western Reserve University (NIH HL 46380, M01RR00080); **Jackson Heart Study (JHS):** Jackson State University (N01-HC-95170), University of Mississippi (N01-HC-95171), Tougaloo College (N01-HC-95172); **Multi-Ethnic Study of Atherosclerosis (MESA):** University of Washington (N01-HC-95159), Regents of the University of California (N01-HC-95160), Columbia University (N01-HC-95161), Johns Hopkins University (N01-HC-95162, N01-HC-95168), University of Minnesota (N01-HC-95163), Northwestern University (N01-HC-95164), Wake Forest University (N01-HC-95165), University of Vermont (N01-HC-95166), New England Medical Center (N01-HC-95167), Harbor-UCLA Research and Education Institute (N01-HC-95169), Cedars-Sinai Medical Center (R01-HL-071205), University of Virginia (subcontract to R01-HL-071205). **Framingham Health Study (FHS):** This FHS research was supported by 1R01HL092577; 1R01HL101056; 1R01HL102214; N01-HC 25195. **Cardiovascular Health Study (CHS):** This CHS research was supported by contracts HHSN268201200036C, HHSN268200800007C, N01 HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086, and grant HL080295 from the National Heart, Lung, and Blood Institute (NHLBI), with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was provided by AG023629 from the National Institute on Aging (NIA). A full list of principal CHS investigators and institutions can be found at <http://www.chs-nhlbi.org/PI.htm>. DNA handling and genotyping was supported in part by National Center for Research Resources grant M01-RR00425 to the Cedars-Sinai General Clinical Research Center Genotyping core and National Institute of Diabetes and Digestive and Kidney Diseases grant DK063491 to the Southern California Diabetes Endocrinology Research Center.

The Candidate gene Association Resource (CARE) wishes to acknowledge the support of the National Heart, Lung and Blood Institute and the contributions of the research institutions, study investigators, field staff and study participants in creating this resource for biomedical research (NHLBI contract number HHSN268200960009C). The following eight parent studies have contributed parent study data, ancillary study data, and DNA samples through the Broad Institute (N01-HC-65226) to create this genotype/phenotype database for wide dissemination to the biomedical research community: the Atherosclerosis Risk in Communities (ARIC) study, the Cardiovascular Health Study (CHS), the Cleveland Family Study (CFS), the Coronary Artery Risk Development in Young Adults (CARDIA) study, the Framingham Heart Study (FHS), the Jackson Heart Study (JHS), the Multi-Ethnic Study of Atherosclerosis (MESA), and the Sleep Heart Health Study (SHHS). Of the aforementioned, five parent studies have contributed electrocardiographic and other phenotype data on African-American study participants for genotype/phenotype analyses (ARIC, CHS, CFS, JHS, and MESA). Funding attributions for the individual cohorts whose data were used in the current analysis are presented.

Abbreviations

AF	atrial fibrillation
SCD	sudden cardiac death
ECG	electrocardiogram
LD	linkage disequilibrium
MI	myocardial infarction
HF	heart failure
PEA	pulseless electrical activity
VF	ventricular fibrillation
K+	potassium

References

1. 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. [PubMed: 12193783]
2. 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. [PubMed: 16061744]
3. 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;163–168. [PubMed: 21498565]
4. Musunuru K, Lettre G, Young T, Farlow DN, Pirruccello JP, Ejebe KG, Keating BJ, Yang Q, Chen MH, Lapchuk N, Crenshaw A, Ziaugra L, Rachupka A, Benjamin EJ, Cupples LA, Fornage M, Fox ER, Heckbert SR, Hirschhorn JN, Newton-Cheh C, Nizzari MM, Paltoo DN, Papanicolaou GJ, Patel SR, Psaty BM, Rader DJ, Redline S, Rich SS, Rotter JI, Taylor HA Jr, Tracy RP, Vasani RS, Wilson JG, Kathiresan S, Fabsitz RR, Boerwinkle E, Gabriel SB. NHLBI Candidate Gene Association Resource. Candidate gene association resource (CARE): design, methods, and proof of concept. *Circ Cardiovasc Genet*. 2010; 3:267–275. [PubMed: 20400780]
5. Chamberlain AM, Agarwal SK, Ambrose M, Folsom AR, Soliman EZ, Alonso A. Metabolic syndrome and incidence of atrial fibrillation among blacks and whites in the Atherosclerosis Risk in Communities (ARIC) Study. *Am Heart J*. 2010; 159:850–856. [PubMed: 20435195]
6. Smith JG, Platonov PG, Hedblad B, Engstrom G, Melander O. Atrial fibrillation in the Malmo Diet and Cancer study: a study of occurrence, risk factors and diagnostic validity. *Eur J Epidemiol*. 2010; 25:95–102. [PubMed: 19936945]
7. Soliman EZ, Rautaharju PM. Heart rate adjustment of PR interval in middle aged and older adults. *J Electrocardiol*. 2012; 45:66–69. [PubMed: 21784432]
8. Smith JG, Avery CL, Evans DS, Nalls MA, Meng YA, Smith EN, Palmer C, Tanaka T, Mehra R, Butler AM, Young T, Buxbaum SG, Kerr KF, Berenson GS, Schnabel RB, Li G, Ellinor PT, Magnani JW, Chen W, Bis JC, Curb JD, Hsueh WC, Rotter JI, Liu Y, Newman AB, Limacher MC, North KE, Reiner AP, Quibrera PM, Schork NJ, Singleton AB, Psaty BM, Soliman EZ, Solomon AJ, Srinivasan SR, Alonso A, Wallace R, Redline S, Zhang ZM, Post WS, Zonderman AB, Taylor HA, Murray SS, Ferrucci L, Arking DE, Evans MK, Fox ER, Sotoodehnia N, Heckbert SR, Whitsett EA, Newton-Cheh C. CARE and COGENT consortia. Impact of ancestry and common genetic variants on QT interval in African Americans. *Circ Cardiovasc Genet*. 2012; 5:647–655. [PubMed: 23166209]
9. Smith JG, Magnani JW, Palmer C, Meng YA, Soliman EZ, Musani SK, Kerr KF, Schnabel RB, Lubitz SA, Sotoodehnia N, Redline S, Pfeuffer A, Müller M, Evans DS, Nalls MA, Liu Y, Newman AB, Zonderman AB, Evans MK, Deo R, Ellinor PT, Paltoo DN, Newton-Cheh C, Benjamin EJ, Mehra R, Alonso A, Heckbert SR, Fox ER. Candidate-gene Association Resource (CARE) Consortium. Genome-wide association studies of the PR interval in African Americans. *PLoS Genet*. 2011; 7 (2):e1001304. [PubMed: 21347284]
10. Smith JG, Lowe JK, Kovvali S, Maller JB, Salit J, Daly MJ, Stoffel M, Altshuler DM, Friedman JM, Breslow JL, Newton-Cheh C. Genome-wide association study of electrocardiographic conduction measures in an isolated founder population: Kosrae. *Heart Rhythm*. 2009; 6:634–641. [PubMed: 19389651]
11. Schnabel RB, Sullivan LM, Levy D, Pencina MJ, Massaro JM, D'Agostino RB Sr, Newton-Cheh C, Yamamoto JF, Magnani JW, Tadros TM, Kannel WB, Wang TJ, Ellinor PT, Wolf PA, Vasani RS, Benjamin EJ. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. *Lancet*. 2009; 373:739–745. [PubMed: 19249635]
12. Chamberlain AM, Agarwal SK, Folsom AR, Soliman EZ, Chambless LE, Crow R, Ambrose M, Alonso A. A clinical risk score for atrial fibrillation in a biracial prospective cohort (from the Atherosclerosis Risk in Communities [ARIC] study). *Am J Cardiol*. 2011; 107:85–91. [PubMed: 21146692]

13. Alonso A, Krijthe BP, Aspelund T, Stepas KA, Pencina MJ, Moser CB, Sinner MF, Sotoodehnia N, Fontes JD, Janssens AC, Kronmal RA, Magnani JW, Witteman JC, Chamberlain AM, Lubitz SA, Schnabel RB, Agarwal SK, McManus DD, Ellinor PT, Larson MG, Burke GL, Launer LJ, Hofman A, Levy D, Gottdiener JS, Kääh S, Couper D, Harris TB, Soliman EZ, Stricker BH, Gudnason V, Heckbert SR, Benjamin EJ. Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF consortium. *J Am Heart Assoc.* 2013; 2:e000102.10.1161/JAHA.112.000102 [PubMed: 23537808]
14. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA.* 1994; 271:840–844. [PubMed: 8114238]
15. Benjamin EJ, Chen PS, Bild DE, Mascette AM, Albert CM, Alonso A, Calkins H, Connolly SJ, Curtis AB, Darbar D, Ellinor PT, Go AS, Goldschlager NF, Heckbert SR, Jalife J, Kerr CR, Levy D, Lloyd-Jones DM, Massie BM, Nattel S, Olgin JE, Packer DL, Po SS, Tsang TS, Van Wagoner DR, Waldo AL, Wyse DG. Prevention of atrial fibrillation: report from a National Heart, Lung, and Blood Institute workshop. *Circulation.* 2009; 119:606–618. [PubMed: 19188521]
16. Borzecki AM, Bridgers DK, Liebschutz JM, Kader B, Kazis LE, Berlowitz DR. Racial differences in the prevalence of atrial fibrillation among males. *J Natl Med Assoc.* 2008; 100:237–245. [PubMed: 18300541]
17. Bush D, Martin LW, Leman R, Chandler M, Haywood LJ. NHLBI AFFIRM Investigators. Atrial fibrillation among African Americans, Hispanics and Caucasians: clinical features and outcomes from the AFFIRM trial. *J Natl Med Assoc.* 2006; 98:330–339. [PubMed: 16573295]
18. Alonso A, Agarwal SK, Soliman EZ, Ambrose M, Chamberlain AM, Prineas RJ, Folsom AR. Incidence of atrial fibrillation in whites and African Americans: the Atherosclerosis Risk in Communities (ARIC) study. *Am Heart J.* 2009; 158:111–117. [PubMed: 19540400]
19. Marcus GM, Alonso A, Peralta CA, Lettre G, Vittinghoff E, Lubitz SA, Fox ER, Levitzky YS, Mehra R, Kerr KF, Deo R, Sotoodehnia N, Akylbekova M, Ellinor PT, Paltoo DN, Soliman EZ, Benjamin EJ, Heckbert SR. Candidate-Gene Association Resource (CARE) Study. European ancestry as a risk factor for atrial fibrillation in African Americans. *Circulation.* 2010; 122:2009–2011. [PubMed: 21098467]
20. Pfeufer A, van Noord C, Marcianti KD, Arking DE, Larson MG, Smith AV, Tarasov KV, Müller M, Sotoodehnia N, Sinner MF, Verwoert GC, Li M, Kao WH, Köttgen A, Coresh J, Bis JC, Psaty BM, Rice K, Rotter JI, Rivadeneira F, Hofman A, Kors JA, Stricker BH, Uitterlinden AG, van Duijn CM, Beckmann BM, Sauter W, Gieger C, Lubitz SA, Newton-Cheh C, Wang TJ, Magnani JW, Schnabel RB, Chung MK, Barnard J, Smith JD, Van Wagoner DR, Vasani RS, Aspelund T, Eiriksdottir G, Harris TB, Launer LJ, Najjar SS, Lakatta E, Schlessinger D, Uda M, Abecasis GR, Müller-Miyhok B, Ehret GB, Boerwinkle E, Chakravarti A, Soliman EZ, Lunetta KL, Perz S, Wichmann HE, Meitinger T, Levy D, Gudnason V, Ellinor PT, Sanna S, Kääh S, Witteman JC, Alonso A, Benjamin EJ, Heckbert SR. Genome-wide association study of PR interval. *Nat Genet.* 2010; 42:153–159. [PubMed: 20062060]
21. George A Jr. Inherited disorders of voltage gated sodium channels. *J Clin Invest.* 2005; 115:1990–1999. [PubMed: 16075039]
22. 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. [PubMed: 7889574]
23. Rook MB, Bezzina Alshinawi C, Groenewegen WA, van Gelder IC, van Ginneken AC, Jongsma HJ, Mannens MM, Wilde AA. Human SCN5A gene mutations alter cardiac sodium channel kinetics and are associated with the Brugada syndrome. *Cardiovasc Res.* 1999; 44:507–517. [PubMed: 10690282]
24. Sotoodehnia N, Isaacs A, de Bakker PI, Dörr M, Newton-Cheh C, Nolte IM, van der Harst P, Müller M, Eijgelsheim M, Alonso A, Hicks AA, Padmanabhan S, Hayward C, Smith AV, Polasek O, Giovannone S, Fu J, Magnani JW, Marcianti KD, Pfeufer A, Gharib SA, Teumer A, Li M, Bis JC, Rivadeneira F, Aspelund T, Köttgen A, Johnson T, Rice K, Sie MP, Wang YA, Klopp N, Fuchsberger C, Wild SH, Mateo Leach I, Estrada K, Völker U, Wright AF, Asselbergs FW, Qu J, Chakravarti A, Sinner MF, Kors JA, Petersmann A, Harris TB, Soliman EZ, Munroe PB, Psaty BM, Oostra BA, Cupples LA, Perz S, de Boer RA, Uitterlinden AG, Völzke H, Spector TD, Liu

FY, Boerwinkle E, Dominiczak AF, Rotter JI, van Herpen G, Levy D, Wichmann HE, van Gilst WH, Witteman JC, Kroemer HK, Kao WH, Heckbert SR, Meitinger T, Hofman A, Campbell H, Folsom AR, van Veldhuisen DJ, Schwienbacher C, O'Donnell CJ, Volpato CB, Caulfield MJ, Connell JM, Launer L, Lu X, Franke L, Fehrmann RS, te Meerman G, Groen HJ, Weersma RK, van den Berg LH, Wijmenga C, Ophoff RA, Navis G, Rudan I, Snieder H, Wilson JF, Pramstaller PP, Siscovick DS, Wang TJ, Gudnason V, van Duijn CM, Felix SB, Fishman GI, Jamshidi Y, Stricker BH, Samani NJ, Kääh S, Arking DE. Common variants in 22 loci are associated with QRS duration and cardiac ventricular conduction. *Nat Genet.* 2010; 42:1068–1076. [PubMed: 21076409]

25. Jeff JM, Brown-Gentry K, Buxbaum SG, Sarpong DF, Taylor HA, George AL Jr, Roden DM, Crawford DC. SCN5A variation is associated with electrocardiographic traits in the Jackson Heart Study. *Circ Cardiovasc Genet.* 2011; 4:139–144. [PubMed: 21325150]
26. Plant LD, Bowers PN, Liu Q, Morgan T, Zhang T, State MW, 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. [PubMed: 16453024]
27. Boyle AP, Hong EL, Hariharan M, Cheng Y, Schaub MA, Kasowski M, Karczewski KJ, Park J, Hitz BC, Weng S, Cherry JM, Snyder M. Annotation of functional variation in personal genomes using RegulomeDB. *Genome Res.* 2012; 22:1790–1797. [PubMed: 22955989]

APPENDIX

Additional authors below made significant contributions to the manuscript:

Ermeg L. Akyzbekova, MS, MStat¹⁷; Traci M. Bartz, MS^{3,8}; Emelia J. Benjamin, MD, ScM^{9,18,19}; Jennifer Brody, BA³; Rajat Deo, MD, MTR²⁰; Patrick T. Ellinor, MD, PhD^{21–22}; Susan R. Heckbert, MD, PhD^{3,23}; Catherine O. Johnson, PhD, MPH³; Pui-Yan Kwok, MD, PhD⁷; Go Li, MS³; Steven A. Lubitz, MD, MPH²²; Angel C.Y. Mak, PhD⁷; Reena Mehra, MD²⁴; Christopher Newton-Cheh, MD, MPH^{12,25}; Peter A. Noseworthy, MD²⁶; George J. Papanicolaou, PhD²⁷; Ronald Prineas, MD, PhD²⁸; Jerome I. Rotter, MD²⁹; David S. Siscovick, MD, MPH^{3,23}; Russell P. Tracy, PhD³⁰

¹⁷Jackson Heart Study, Jackson State University, Jackson, MS;

³Cardiovascular Health Research Unit, Department of Medicine, University of Washington, Seattle, WA;

⁹Boston University and NHLBI's Framingham Heart Study, Framingham, MA;

¹⁸Department of Epidemiology, Boston University School of Public Health, Boston, MA

¹⁹Section of Cardiovascular Medicine, Boston University School of Medicine, Boston, MA;

²⁰Division of Cardiology, Electrophysiology Section, University of Pennsylvania, Philadelphia, PA;

²¹Cardiovascular Research Center and Center for Human Genetic Research, Massachusetts General Hospital, Harvard Medical School, Boston, MA;

²²Cardiac Arrhythmia Service, Massachusetts General Hospital, Boston, MA;

²³Department of Epidemiology, University of Washington, Seattle, WA;

⁷Cardiovascular Research Institute, University of California, San Francisco, San Francisco, CA;

²⁴Sleep Disorders Center, Neurologic Institute, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH;

¹²Broad Institute of Harvard & Massachusetts Institute of Technology, Cambridge, MA;

²⁵Cardiology Division, Massachusetts General Hospital, Boston, MA;

²⁶Mayo Clinic College of Medicine, Division of Cardiovascular Diseases, Cardiac Electrophysiology, Mayo Clinic, Rochester, MN;

²⁷Division of Cardiovascular Sciences, National Heart, Lung and Blood Institute, Bethesda, MD;

²⁸Department of Epidemiology, Division of Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, NC;

²⁹Institute for Translational Genomics and Population Sciences Los Angeles Biomedical Research Institute and Department of Pediatrics, Harbor-UCLA Medical Center, Torrance, CA;

³⁰Departments of Pathology and Biochemistry, College of Medicine, University of Vermont, Burlington, VT

Table 1

Baseline characteristics of African Americans by cohort

	ARIC	CFS	CHS	JHS	MESA
Total Number	2874	632	822	2232	1754
Age in yrs (SD)	53 (6)	37 (19)	73 (6)	50 (12)	62 (10)
Male (%)	37	43	37	39	45
MAF of rs7629265	0.074	0.064	0.076	0.076	0.070
PR in msec (SD)	171.8 (28)	169.0 (26)	170.5 (30)	170.6 (26)	170.8 (26)
QRS in msec (SD)	90.0 (10)	89.4 (10)	87.5 (11)	91.9 (10)	91 (10)
QT in msec (SD)	400.2 (31)	397.5 (30)	408.4 (35)	413.0 (31)	410.3 (32)

Abbreviations: yrs = years; SD = standard deviation; MAF = minor allele frequency; SCD: sudden cardiac death; msec: milliseconds; SD: standard deviation.

Table 2

Association of rs7629265 and ECG parameters by cohort

	ARIC	CFS	CHS	JHS	MESA	Meta	Meta-Analysis P value
Number of participants in PR analysis	2146	264	612	1985	1549	6556	2.2×10 ⁻⁶
Beta PR in msec (SE)	-1.6 (1.5)	-9.9 (5.0)	-1.8 (3.2)	-5.9 (1.5)	-4.7 (1.8)	-4.1 (0.9)	
Number of participants in QRS analysis	2487	360	613	1912	1655	7027	0.021
Beta QRS in msec (SE)	-0.4 (0.5)	-0.5 (1.4)	-1.1 (1.1)	-0.6 (0.6)	-1.4 (0.7)	-0.7 (0.3)	
Number of participants in QT analysis	1947	340	601	2021	1527	6436	0.019
Beta QT in msec (SE)	0.4 (1.3)	3.3 (2.7)	2.6 (2.5)	-0.05 (1.2)	4.0 (1.3)	1.6 (0.7)	

Abbreviations: msec: milliseconds; SE: standard error. Coded allele (T); referent allele (C)

Table 3

Association of rs7629265 with incident atrial fibrillation

Cohort	rs7629265 CC AF/Total	rs7629265 CT or TT AF/Total	HR (95% CI)	P-value
CHS	108 / 689	22 / 101	1.65 (1.03–2.64)	0.038
ARIC	133 / 2455	36 / 411	1.80 (1.24–2.61)	0.002
Meta-analysis	241 / 3144	58 / 512	1.74 (1.30–2.33)	1.9×10^{-4}

Abbreviations: AF: atrial fibrillation

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 4

Association of rs7629265 with sudden cardiac death

Cohort Study	rs7629265 CC SCD/Total	rs7629265 CT or TT SCD/Total	HR (95% CI)	P-value
CHS	49 / 698	5 / 104	0.71 (0.28 – 1.79)	0.47
ARIC	74 / 2433	9 / 407	0.69 (0.34 – 1.40)	0.30
Case-control Study	rs7626962 S1103/S1103 Cases / Controls	rs7626962 Y1103/S1103 or Y1103/Y1103 Cases / Controls	OR (95% CI)	P-value
CABS	190 / 175	35 / 23	1.37 (0.77–2.43)	0.29

Abbreviations: SCD: sudden cardiac death

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript