Original Investigation

Genetic Investigation Into the Differential Risk of Atrial Fibrillation Among Black and White Individuals

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IMPORTANCE White persons have a higher risk of atrial fibrillation (AF) compared with black individuals despite a lower prevalence of risk factors. This difference may be due, at least in part, to genetic factors.

OBJECTIVES To determine whether 9 single-nucleotide polymorphisms (SNPs) associated with AF account for this paradoxical differential racial risk for AF and to use admixture mapping to search genome-wide for loci that may account for this phenomenon.

DESIGN, SETTING, AND PARTICIPANTS Genome-wide admixture analysis and candidate SNP study involving 3 population-based cohort studies that were initiated between 1987 and 1997, including the Cardiovascular Health Study (CHS) (n = 4173), the Atherosclerosis Risk in Communities (ARIC) (n = 12 341) study, and the Health, Aging, and Body Composition (Health ABC) (n = 1015) study. In all 3 studies, race was self-identified. Cox proportional hazards regression models and the proportion of treatment effect method were used to determine the impact of 9 AF-risk SNPs among participants from CHS and the ARIC study. The present study began July 1, 2012, and was completed in 2015.

MAIN OUTCOMES AND MEASURES Incident AF systematically ascertained using clinic visit electrocardiograms, hospital discharge diagnosis codes, death certificates, and Medicare claims data.

RESULTS A single SNP, rs10824026 (chromosome 10; position 73661450), was found to significantly mediate the higher risk for AF in white participants compared with black participants in CHS (11.4%; 95% CI, 2.9%-29.9%) and ARIC (31.7%; 95% CI, 16.0%-53.0%). Admixture mapping was performed in a meta-analysis of black participants within CHS (n = 811), ARIC (n = 3112), and Health ABC (n = 1015). No loci that reached the prespecified statistical threshold for genome-wide significance were identified.

CONCLUSIONS AND RELEVANCE The rs10824026 SNP on chromosome 10q22 mediates a modest proportion of the increased risk of AF among white individuals compared with black individuals, potentially through an effect on gene expression levels of MYOZ1. No additional genetic variants accounting for a significant portion of the differential racial risk of AF were identified with genome-wide admixture mapping, suggesting that additional genetic or environmental influences beyond single SNPs in isolation may account for the paradoxical racial risk of AF among white individuals and black individuals.
Atrial fibrillation (AF), the most common sustained cardiac arrhythmia, is a rapidly growing health epidemic associated with increased risks of heart failure, stroke, and death.\(^1\)\(^-\)\(^4\) White persons have an increased risk of AF compared with black individuals despite a lower prevalence of well-established clinical risk factors.\(^4\)\(^-\)\(^7\) The paradoxical differential racial risk of AF among white and black individuals may be secondary to genetic factors. Black persons in the United States are an admixed population with both African and European ancestry. A greater percentage of European ancestry among black persons has been associated\(^8\) with an increased risk of AF. This finding supports the possibility of genetic factors contributing to the increased risk of AF among white individuals; however, the potential genetic culprits accounting for this association remain unknown.

To explore the genetics underlying the differential racial risk of the arrhythmia, we evaluated the impact of 9 single-nucleotide polymorphisms (SNPs) previously associated with AF risk.\(^9\)\(^-\)\(^13\) We also sought to identify novel genetic loci associated with the arrhythmia through the use of admixture mapping. Admixture mapping is a modified form of a genome-wide association study that can be used to uncover genetic loci in populations of mixed ancestry when there is a differential ancestral risk of disease (a more detailed description of admixture mapping is provided in the eMethods in the Supplement) and has been used to map loci and genetic variants for end-stage renal disease, prostate cancer, and ethnic neutropenia among African American individuals; breast cancer risk in Latina individuals; and other traits.\(^15\)\(^-\)\(^21\) Thus, we used genome-wide admixture mapping in the African American populations in the Cardiovascular Health Study (CHS), the Atherosclerosis Risk in Communities (ARIC) study, and the Health, Aging, and Body Composition (Health ABC) study cohorts to search for novel loci that may contribute to AF risk.

### Methods

Our investigation was conducted using large population-based cohort studies comprising black and white individuals that had systematically ascertained incident AF in participants who had undergone genome-wide analysis of SNPs using DNA microarrays. The design, recruitment, baseline characterization, and outcome ascertainment procedures for these cohorts have been previously described in detail\(^22\)\(^-\)\(^25\); brief summaries are provided below. The present study received approval via a certificate of confidentiality from the University of California, San Francisco, Committee on Human Research to perform these deidentified analyses. The present study began July 1, 2012, and was completed in 2015.

### Study Cohorts

**Cardiovascular Health Study**

The CHS enrolled 5201 participants 65 years or older who were recruited in 1989-1990 from Medicare eligibility lists in 4 US communities: Forsyth County, North Carolina; Washington County, Maryland; Sacramento County, California; and Pittsburgh, Pennsylvania. An additional 687 black participants were recruited into the study in 1992-1993. Race was self-identified, and participants underwent comprehensive examinations at study entry to document baseline demographics and medical comorbidities. Methods for ascertaining prevalent hypertension, diabetes mellitus, heart failure, and coronary artery disease have been described.\(^23\) Subsequent follow-up was performed with alternating clinic visits and telephone calls every 6 months until 1999, with semiannual telephone calls thereafter. Resting 12-lead electrocardiograms (ECGs) were performed at each clinic visit. Prevalent AF at baseline was documented using the baseline ECG, and incident AF was ascertained on the basis of clinic visit ECGs and hospital discharge diagnosis codes that were supplemented with Medicare inpatient and outpatient claims data.\(^26\)

**Atherosclerosis Risk in Communities**

ARIC enrolled 15 792 adults aged 45 to 64 years between 1987 and 1989 from 4 US communities: the northwest suburbs of Minneapolis, Minnesota; Washington County, Maryland; Jackson, Mississippi; and Forsyth County, North Carolina. Comprehensive baseline evaluations were performed followed by annual telephone interviews and 3 subsequent examinations spaced approximately 3 years apart. Methods for ascertaining baseline comorbidities, including hypertension, diabetes, heart failure, and coronary artery disease, have been documented\(^24\); race was self-identified. Standard resting 12-lead ECGs were performed at each visit. Prevalent AF was identified from the baseline ECG, and incident AF was identified from study visit ECGs, hospital discharge diagnoses, and death certificates.\(^5\)

**Health ABC**

Health ABC enrolled 3075 adults aged 70 to 79 years between 1997 and 1998 from 2 US communities: Pittsburgh, Pennsylvania, and Memphis, Tennessee. Participants underwent a comprehensive baseline examination followed by clinic visits at 2, 3, 4, 5, 6, 8, and 10 years with alternating biannual telephone calls. The telephone calls continued through year 15 of the study. Race was self-identified, and methods for ascertaining prevalent hypertension, diabetes, heart failure, and coronary artery disease have been described.\(^25\) Standard resting 12-lead ECGs were performed at the baseline and 4-year

### Key Points

**Question**
Do genetic variants account for the paradoxical differential risk of atrial fibrillation (AF) among white and black individuals?

**Findings**
In this genetic study involving 17 325 participants, the rs10824026 single-nucleotide polymorphism (SNP) mediated between 11% and 32% of the increased risk of AF among white individuals relative to black individuals. No additional SNPs were identified with genome-wide admixture mapping.

**Meaning**
The rs10824026 SNP mediates a modest proportion of the increased risk of AF among white individuals compared with black individuals; our inability to identify additional sources suggests that influences beyond single SNPs in isolation may be operative.
visits. Prevalent AF was identified using the baseline ECG and Medicare claims data. Incident AF was identified from the fourth-year ECG, hospital discharge diagnoses, or Medicare claims data.27

Genotyping, SNP Selection, and Imputation
Genotyping of study participants was completed using DNA microarrays or chips that permit simultaneous analysis of hundreds of thousands of SNPs present throughout the genome. CHS performed whole-genome SNP analysis using the Illumina 370 CNV and HumanOmni-Quad_v1 BeadChip system in white and black participants, respectively (Illumina), and DNA analysis in Health ABC was performed using the Illumina Human IM-Duo microarray. Variant calling for both studies was performed using the Illumina BeadStudio algorithm. Genotyping within ARIC was performed on the Affymetrix 6.0 DNA microarray (Affymetrix) and analyzed with the Birdseed variant-calling algorithm.13 Although different genotyping platforms were used in the different cohorts, comparison of measures of associations between cohorts was still considered valid, consistent with the approach used in other genetic studies.13

Quality control criteria were subsequently used to filter SNPs containing possible errors. Single-nucleotide polymorphisms were excluded from analysis based on previously established thresholds within each cohort for SNP call rates, Hardy-Weinberg P values, and minor allele frequencies. Individuals with either known or cryptic relatedness were also excluded.

Analysis of the 9 AF-risk SNPs was performed in both the CHS and ARIC cohorts. Three of the 9 SNPs (rs2200733, rs3807989, and rs10824026) were directly genotyped in CHS; 2 (rs2200733 and rs2106261) were directly genotyped in ARIC. The remaining SNPs were imputed after phasing the data sets with SHAPEIT.28 Imputation serves as a highly accurate method to determine SNP carrier status when the SNPs are not directly genotyped as part of genome-wide SNP analysis. For each SNP, a surrounding 1-megabase region was selected and imputed using IMPUTE2 with the full 1000 Genomes data set (phase 1, version 3) as the reference.19 For each of the SNPs, we checked the imputation quality and found it to be high in all of the data sets (IMPUTE2 info score >0.95) when sufficient reference overlap was present to perform imputation.

Polygenic Risk Score
Polygenic risk scores based on the 9 AF-associated SNPs were calculated for white and black participants in the CHS and ARIC cohorts. The polygenic risk score was based on the odds ratio determined for each SNP in the prior AF genome-wide association study meta-analysis among white participants.13 The odds ratio for each SNP was exponentiated to the number of risk alleles carried by each participant, and the overall polygenic risk score was the product of these 9 values.30 This calculation assumes a multiplicative risk across loci with no interaction terms.

Locus-Specific Ancestry Estimation for Admixture Mapping
Locus-specific African ancestry across the genome in black participants was estimated with the program LAMPLD, version 1.0, using a 2-population model (African and European).31 Genotype data for Yoruba in Ibadan, Nigeria, and Utah residents with Northern and Western European ancestry from the International HapMap Project (http://www.hapmap.org) were used as ancestral reference data for the 2 ancestral populations. The use of Yoruban genotypes was based on previous work indicating that Yorubans serve as the best reflection of African ancestry among modern-day Africans. The mean of locus-specific African ancestry across the genome was calculated and used as the global African ancestry for each black individual. The analysis included 596464 markers from ARIC, 588058 markers from CHS, and 876739 markers from Health ABC.

Statistical Analysis
Normally distributed continuous variables are presented as means (SDs) and were compared using a paired, 2-tailed t test. Comparison of categorical values and minor allele frequencies for black and white participants was performed using the χ² test.

Time-to-event analyses using Cox proportional hazards regression models were used to evaluate for an association between each of the 9 SNPs and incident AF. Covariates included in these models were baseline age, sex, body mass index, hypertension, diabetes, heart failure, and coronary artery disease. Associations between polygenic risk scores and incident AF were also determined using Cox proportional hazards regression models after controlling for the aforementioned covariates. The proportion of treatment effect (PTE) method was applied to determine whether SNP carrier status mediated the association between race and AF through time-to-event analyses using adjusted Cox proportional hazards regression models and the previously specified covariates.33 Proportion of treatment effect evaluates the magnitude of effect of a putative mediator based on the proportional reduction in the regression coefficient of the predictor of interest when the putative mediator is included in the Cox proportional hazards regression model (a more detailed description of the PTE is provided in the eMethods in the Supplement). The impact of each SNP was examined in isolation, and a model containing all SNPs examined their cumulative effect. Bootstrap resampling with 1000 repetitions was used to obtain 95% CIs.

Cox proportional hazards regression models were also used to evaluate for an association between locus-specific African ancestry and incident AF in the admixture mapping component of the study. Locus-specific ancestry was coded as a continuous variable between 0 and 2, with 0 equivalent to having 0% probability of any African chromosomes and 2 equivalent to 100% probability of having 2 African chromosomes at a locus. To adjust for potential confounding, covariates added to these models included baseline age, sex, body mass index, hypertension, diabetes, left ventricular hypertrophy, prevalent heart failure, history of myocardial infarction, study site, and percentage of genome-wide African ancestry for each individual (percentage of European ancestry is accounted for by the percentage of African ancestry in the model since the two are, by definition of the model, forced to total 100%).
Given previous evidence\(^{12}\) that racial differences in AF may be most pronounced among individuals without conventional AF risk factors, the admixture mapping was performed using all AF as the primary outcome and AF in the absence of prespecified baseline risk factors as a secondary outcome. For the secondary analysis, participants with prevalent hypertension, diabetes, heart failure, and history of myocardial infarction at baseline were excluded. Covariates included in the multivariate Cox proportional hazards regression models were otherwise the same as above. Meta-analyses with inverse variance weighting were performed on the results from all 3 studies for both the overall cohorts and the lone AF analyses using the program METAL.\(^{34}\) The genome-wide significance threshold for admixture mapping was \(7 \times 10^{-6}\), which corresponds to a Bonferroni correction for testing 7000 independent ancestry blocks in the genome and was derived empirically based on permutations.\(^{35}\)

Admixture mapping was performed using the survival analysis package in R, version 3.0.2 (The R Foundation). The remainder of the statistical analyses were performed using Stata, version 12 (StataCorp). With the exception of the genome-wide admixture mapping analyses, 2-tailed values of \(P < .05\) were considered statistically significant.

### Results

#### Study Participants

**Cardiovascular Health Study**

A total of 4173 individuals (81.0%) from the CHS cohort had a self-reported race of white, and 811 were black. The baseline clinical characteristics of the cohort are summarized in Table 1. During a mean follow-up period of 11.2 years, 1023 individuals (30.4%) received a diagnosis of incident AF. Among the overall cohort, a subgroup of 589 participants (14.1%) were classified as having developed AF in the absence of the prespecified risk factors described above.

**Atherosclerosis Risk in Communities**

Within the ARIC cohort, 9229 (74.8%) and 3112 (25.2%) reported their race as white or black, respectively. Baseline clinical characteristics of the cohort are summarized in Table 1. Among 12 341 individuals, a total of 1341 (10.9%) received a diagnosis of incident AF during a mean follow-up period of 17.5 years, and a subgroup of 569 (42.4%) participants developed incident AF in the absence of the prespecified AF risk factors at baseline.

**Health ABC**

A total of 1078 individuals from the Health ABC cohort had a self-reported race of black and underwent genome-wide SNP analysis. Among this group, 63 individuals (5.8%) had prevalent AF and were excluded from the analysis. The remaining baseline clinical characteristics of the cohort are summarized in Table 1. During a mean follow-up period of 10.5 years during which time 63 individuals were excluded from analyses, a total of 237 individuals (23.3%) received a diagnosis of incident AF. Among the overall cohort, a subgroup of 24 participants (2.4%) developed incident AF in the absence of the baseline prespecified risk factors.

#### Association of AF-Risk SNPs With Differential Racial Risk

We found significant differences in the allele frequencies between races for each of the 9 SNPs (all \(P < .001\)) (Table 2). The direction and magnitude of the minor allele frequency differences between races were consistent in both cohorts. The 3 SNPs with the strongest associations with AF in prior studies (rs2200733, rs2106261, and rs6666258) had markedly greater risk allele frequencies among black compared with white participants (Table 2).

We evaluated the effect of each SNP on AF risk in both the CHS and ARIC cohorts for white and black participants. Findings were generally consistent between the cohorts, races, and previously reported results (eTable 1 in the Supplement). The polygenic risk scores indicated incident AF among white and black participants in both cohorts (eTable 2 in the Supplement).

We used the PTE to evaluate the effect of these SNPs on the differential racial risk of the arrhythmia. In an overall model containing each SNP, there was evidence of mediation of the race-AF relationship in ARIC (PTE, 24.8 [95% CI, 3.0 to 49.9]; \(P = .03\)); however, this association was not replicated in CHS (PTE, −12.4 [95% CI, −67.7 to 13.4]; \(P = .74\)). One SNP, rs10824026 (chromosome 10: position 73661450; intronic within SYNPO2L), appeared to be a mediator of the relationship in the anticipated direction consistent with a protective effect of the SNP on the risk of AF in both CHS and ARIC (Table 3). The rs10824026 SNP was estimated to account for
11.4% (95% CI, 2.9% to 29.9%; \( P = .01 \)) and 31.7% (95% CI, 16.0% to 53.0%; \( P < .01 \)) of the increased risk of the arrhythmia in white compared with black participants in CHS and ARIC, respectively. None of the remaining 8 SNPs exhibited statistically significant mediation effects in the anticipated direction in both cohorts (Table 3). The minor allele (G) previously shown\(^{13}\) to exhibit a protective effect against AF was more common among black participants than white participants in both CHS and ARIC (Table 2). The minor allele frequencies among black participants ranged from 37.7% to 37.8% in comparison with 15.5% to 16.4% among white individuals.

### Admixture Mapping

Because most of the risk difference between the groups was unexplained by the 9 known risk SNPs, we searched for new loci that may affect AF risk using admixture mapping. To enhance the power, data from a third cohort, Health ABC, were added.

### Meta-analysis

The results of admixture mapping from the 3 individual cohorts are provided in the eResults in the Supplement. Combined analysis of the 3 cohorts identified the peak for the locus-specific ancestry association at rs1977904 (chromosome 21: position 31589767) (Figure 1D). In contrast to the top loci in the individual cohorts, this locus conferred an increased risk of incident AF in association with African ancestry (hazard ratio [HR], 1.42 [95% CI, 1.20-1.67]; \( P = 2.40 \times 10^{-5} \)) for each additional African chromosome. Among the prespecified AF subgroup lacking baseline risk factors, the strongest locus-specific ancestry association was at rs4649274 (chromosome 1: position 230801857) (Figure 2D). Unlike in the overall meta-analysis, but consistent with the observed differential racial risk of the arrhythmia, African ancestry was associated with a reduced likelihood of incident AF within the prespecified AF subgroup (HR, 0.49 [95% CI, 0.35-0.69]; \( P = 4.44 \times 10^{-5} \)). The peak locus-specific ancestry associations in the meta-analyses for both the overall cohort and the prespecified AF subgroup failed to meet the threshold for genome-wide significance (\( P = 7 \times 10^{-6} \)).

### Admixture Mapping and rs10824026

The impact of the locus-specific ancestry associated with rs10824026, the SNP found to partially mediate the increased risk of AF among white relative to black participants in the initial analysis, was also examined in the admixture mapping

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Table 2. Minor Allele Frequencies of AF-Associated SNPs in CHS and ARIC

<table>
<thead>
<tr>
<th>SNP</th>
<th>Genetic Locus</th>
<th>Nearest Gene</th>
<th>Effect of Minor Allele on AF Risk</th>
<th>CHS, %a</th>
<th>ARIC Study, %a</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2200733</td>
<td>4q25</td>
<td>PITX2</td>
<td>Increased</td>
<td>13.7</td>
<td>11.5</td>
</tr>
<tr>
<td>rs2106261</td>
<td>16q22</td>
<td>ZFHX3</td>
<td>Increased</td>
<td>16.4</td>
<td>17.0</td>
</tr>
<tr>
<td>rs6666258</td>
<td>1q21</td>
<td>KCNN3</td>
<td>Increased</td>
<td>28.7</td>
<td>30.3</td>
</tr>
<tr>
<td>rs3903239</td>
<td>1q24</td>
<td>PRRX1</td>
<td>Increased</td>
<td>46.2</td>
<td>43.8</td>
</tr>
<tr>
<td>rs3807989</td>
<td>7q31</td>
<td>CAV1</td>
<td>Protective</td>
<td>40.3</td>
<td>40.8</td>
</tr>
<tr>
<td>rs10821415</td>
<td>9q22</td>
<td>C9orf3</td>
<td>Increased</td>
<td>42.4</td>
<td>42.2</td>
</tr>
<tr>
<td>rs10824026</td>
<td>10q22</td>
<td>SYNPO2L</td>
<td>Protective</td>
<td>16.4</td>
<td>15.5</td>
</tr>
<tr>
<td>rs1152591</td>
<td>14q23</td>
<td>SYNE2</td>
<td>Increased</td>
<td>45.6</td>
<td>48.1</td>
</tr>
<tr>
<td>rs7164883</td>
<td>15q24</td>
<td>HCN4</td>
<td>Increased</td>
<td>16.9</td>
<td>15.6</td>
</tr>
</tbody>
</table>

Abbreviations: AF, atrial fibrillation; ARIC, Atherosclerosis Risk in Communities; CHS, Cardiovascular Health Study; SNP, single-nucleotide polymorphism.

a Differences significant at \( P < .001 \) except for rs3807989 in the CHS cohort (\( P = .08 \)).

Table 3. Proportion of Treatment Effect of AF-Associated SNPs on the Differential Risk in Races

<table>
<thead>
<tr>
<th>SNP</th>
<th>Genetic Locus</th>
<th>Nearest Gene</th>
<th>CHS PTE (95% CI)</th>
<th>P Value</th>
<th>ARIC Study PTE (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2200733</td>
<td>4q25</td>
<td>PITX2</td>
<td>−4.58 (−16.82 to −0.78)</td>
<td>.03</td>
<td>−11.7 (−18.24 to −6.35)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>rs2106261</td>
<td>16q22</td>
<td>ZFHX3</td>
<td>−0.84 (−5.24 to 1.28)</td>
<td>.54</td>
<td>−4.91 (−8.36 to −1.72)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>rs6666258</td>
<td>1q21</td>
<td>KCNN3</td>
<td>−3.14 (−14.19 to 0.98)</td>
<td>.14</td>
<td>−2.60 (−5.05 to −0.68)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>rs3903239</td>
<td>1q24</td>
<td>PRRX1</td>
<td>−1.70 (−7.73 to 2.18)</td>
<td>.34</td>
<td>6.73 (0.46 to 13.52)</td>
<td>.03</td>
</tr>
<tr>
<td>rs3807989</td>
<td>7q31</td>
<td>CAV1</td>
<td>−1.61 (−7.11 to 1.00)</td>
<td>.31</td>
<td>−2.36 (−8.19 to 2.95)</td>
<td>.38</td>
</tr>
<tr>
<td>rs10821415</td>
<td>9q22</td>
<td>C9orf3</td>
<td>−4.52 (−16.22 to 2.44)</td>
<td>.21</td>
<td>5.14 (−1.52 to 11.27)</td>
<td>.11</td>
</tr>
<tr>
<td>rs10824026</td>
<td>10q22</td>
<td>SYNPO2L</td>
<td>11.40 (2.90 to 20.87)</td>
<td>.01</td>
<td>31.7 (10.0 to 53.0)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>rs1152591</td>
<td>14q23</td>
<td>SYNE2</td>
<td>9.17 (−0.09 to 20.35)</td>
<td>.07</td>
<td>12.99 (2.96 to 24.54)</td>
<td>&lt;.01</td>
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<tr>
<td>rs7164883</td>
<td>15q24</td>
<td>HCN4</td>
<td>−4.52 (−14.98 to 0.81)</td>
<td>.11</td>
<td>−8.03 (−14.78 to −3.00)</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

Abbreviations: AF, atrial fibrillation; ARIC, Atherosclerosis Risk in Communities; CHS, Cardiovascular Health Study; PTE, proportion of treatment effect; SNP, single-nucleotide polymorphism.
Because it was not directly genotyped, the SNP in greatest linkage disequilibrium with rs10824026 (rs12570126; \( r^2 = 0.935, D' = 1.00 \)) was used as a proxy to estimate its locus-specific ancestry association. In the overall meta-analysis, the locus-specific ancestry associated with the rs12570126 SNP exhibited a nonsignificantly lower risk of AF among black participants (HR, 0.78 [95% CI, 0.54-1.12]; \( P = .174 \)).

Discussion

Our investigation into the genetics underlying the differential racial risk of AF suggests that one of the SNPs with an established association with AF, rs10824026, may partially mediate the increased risk of the arrhythmia among white compared with black individuals. The minor allele of the SNP is known to be protective against AF and is significantly more common among black than white persons. Our study suggests that the rs10824026 SNP may account for 11.4% to 31.7% of the reduced risk of AF observed among black persons compared with white individuals. The admixture mapping component of our study involving 3 large population-based cohorts failed to identify a novel genetic variant that reached genome-wide significance on meta-analysis; this finding emphasizes that a single SNP in isolation is unlikely to account for the paradoxical differential racial risk of AF. However, within the subgroup analysis of individuals who developed AF in the absence of prespecified baseline risk factors, the top locus with nonsignificant association by admixture mapping conferred an increased risk of incident AF in association with European ancestry consistent with the known epidemiology.

The rs10824026 SNP, present within the 10q22 genetic locus, is located 5 and 20 kb upstream of the SYNPO2L (Gene ID 79933) and MYOZ1 (Gene ID 58529) genes, respectively. Both of these genes are expressed within cardiac tissue; however, their precise functions are unknown. The SYNPO2L gene encodes the synaptopodin 2–like protein, which, as suggested, has structural similarities with the SYNPO2 gene, whose name is derived from its presence within renal podocytes and postsynaptic densities and dendritic spines. Review of the Expression Quantitative Trait Loci (eQTL) Genotype-Tissue Expression (GTEx) database (http://www.gtexportal.org/home/) suggested that, although the SNP is in closer proximity to SYNPO2L, its biological effect is actually mediated through altered expression levels of MYOZ1. GTEx is an eQTL database that possesses genome-wide SNP and RNA transcript data that permits evaluation of SNP status in relation to transcript levels of nearby genes in specific tissues. In analyses restricted to atrial
tissue, the rs10824026 SNP was associated with a significant change in transcript levels of a single gene, MYOZ1 (effect size, −1.1; \(P = 4.0 \times 10^{-16}\)). The myozenin 1 protein, encoded by MYOZ1, appears to influence calcineurin signaling and interacts with proteins at the Z-disc of the cardiac sarcomere, including α-actinin and γ-filamin. These eQTL findings are consistent with previous work suggesting that the AF risk residing in the chromosome 10q22 locus is secondary to MYOZ1.

The finding that the rs10824026 SNP mediates the reduced risk of AF observed among black individuals compared with white persons is consistent with the minor allele being protective against AF and more common in black persons. In contrast, the minor allele frequencies of the 3 SNPs with the strongest associations with AF (rs2200733, rs2106261, and rs6666258) are markedly more common in black individuals (Table 2). This finding is especially surprising given that the minor allele of each of these 3 SNPs is associated with an increased risk of the arrhythmia among both races and hence would be anticipated to be more common among white individuals. Although an explanation for these observations is not immediately clear, the lower risk of the arrhythmia within black persons is likely secondary to additional genetic and/or environmental factors that serve to at least partially counteract the effect of these SNPs.

Within the admixture mapping component of the study, there were no loci that met the prespecified threshold for genome-wide significance. In contrast to the overall meta-analysis, the top hit within the subgroup analysis involving individuals who developed AF in the absence of the prespecified risk factors was associated in the anticipated direction, consistent with a reduced risk of the arrhythmia among black compared with white participants. The SNP with the strongest locus-specific ancestry association in this subgroup analysis (rs4649274) is intronic within SIPA1L2, a gene located on chromosome 1 that encodes the signal-induced, proliferation-associated 1-like-2 protein. The function of SIPA1L2 is unclear; however, it is expressed in the heart and could potentially exert a role in AF pathophysiology. The gene from which it derives its name, SIPA1, encodes a mitogen-induced guanosine triphosphatase–activating protein.

Our inability to identify SNPs responsible for the differential racial risk of AF with admixture mapping highlights the increasing difficulty of uncovering novel genetic variants that predispose to the arrhythmia. Most of the heritability of the arrhythmia remains unexplained and may be secondary to multiple weak signals that fall below our current level of detection, gene–gene and gene-environmental interactions, and/or environmental exposures in isolation. It is also
possible that the heritability of the arrhythmia is primarily mediated by rare variants, and large-scale whole exome and genome initiatives will be required to uncover the remaining genetic culprits.

Our study has several potential limitations. As discussed, the failure to identify a statistically significant genetic variant with admixture mapping may be secondary to inadequate power given that our study comprised only 4938 black participants in the overall meta-analysis. However, these are the 3 largest population-based cohort studies involving black individuals that have undergone genome-wide association study analysis; consequently, our study leverages the most extensive data available. Second, these cohorts, particularly CHS and Health ABC, are predominantly made up of older individuals. The effect of genetics on AF risk is generally more modest in older age groups; therefore, our results may not be generalizable to younger populations. In addition, we did not adjust for multiple hypothesis testing in the analysis of the 9 previously established AF-associated SNPs. Although increasing the possibility of a spurious association, the involvement of these 9 SNPs with AF has been firmly established, and they were identified a priori for this analysis. In addition, we further minimized the possibility of a type 1 error through replication in a second cohort. Multiple SNPs in our candidate SNP analysis were not directly genotyped but instead were imputed (each with high probability: >0.95). Although imputation may introduce some error, it is anticipated to be random. Any resulting bias would be expected to occur toward the null and therefore should not lead to spurious false-positive associations. Finally, there have been 5 additional SNPs found to be associated with AF beyond the 9 evaluated in this study. To try to minimize the impact of multiple hypothesis testing, we did not examine for a role of these additional SNPs; however, their potential involvement as mediators should be evaluated in future studies.

Conclusions

Our investigation into the genetic determinants accounting for the paradoxical differential racial risk of AF among white and black individuals suggests that a previously known AF-associated SNP (rs10824026) may be a partial mediator of this association. The admixture mapping component of our analysis failed to identify any novel genetic variants. Taken together, these findings demonstrate that additional genetic or environmental influences beyond single SNPs in isolation are likely operational. Given the consistent observations that race is a powerful risk factor for AF that can supersede conventional risk factors, our data suggest that this phenomenon is primarily driven by polygenic influences, gene-environment interactions, or environmental influences in isolation.
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REFERENCES


