

Impact of Ancestry and Common Genetic Variants on QT Interval in African Americans

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Background—Ethnic differences in cardiac arrhythmia incidence have been reported, with a particularly high incidence of sudden cardiac death and low incidence of atrial fibrillation in individuals of African ancestry. We tested the hypotheses that African ancestry and common genetic variants are associated with prolonged duration of cardiac repolarization, a central pathophysiological determinant of arrhythmia, as measured by the electrocardiographic QT interval.

Methods and Results—First, individual estimates of African and European ancestry were inferred from genome-wide single-nucleotide polymorphism (SNP) data in 7 population-based cohorts of African Americans (n=12097) and regressed on measured QT interval from ECGs. Second, imputation was performed for 2.8 million SNPs, and a genome-wide association study of QT interval was performed in 10 cohorts (n=13 105). There was no evidence of association between genetic ancestry and QT interval ($P=0.94$). Genome-wide significant associations ($P<2.5\times 10^{-8}$) were identified with SNPs at 2 loci, upstream of the genes *NOS1AP* (rs12143842, $P=2\times 10^{-15}$) and *ATP1B1* (rs1320976, $P=2\times 10^{-10}$). The most significant SNP in *NOS1AP* was the same as the strongest SNP previously associated with QT interval in individuals of European ancestry. Low probability values ($P<10^{-5}$) were observed for SNPs at several other loci previously identified in genome-wide association studies in individuals of European ancestry, including *KCNQ1*, *KCNH2*, *LITAF*, and *PLN*.

Conclusions—We observed no difference in duration of cardiac repolarization with global genetic indices of African American ancestry. In addition, our genome-wide association study extends the association of polymorphisms at several loci associated with repolarization in individuals of European ancestry to include individuals of Afr. (*Circ Cardiovasc Genet.* 2013;5:647-655.)

Key Words: electrocardiography ■ electrophysiology ■ genome-wide association studies ■ ion channels ■ repolarization

Ethnic differences in cardiac arrhythmia incidence have been reported, with higher incidence of sudden cardiac death and lower incidence of atrial fibrillation in African Americans compared with Americans of European ancestry.¹⁻³ These differences have been independent of measured environmental and behavioral factors and therefore attributed to differences in genetic makeup, although the specific genetic

determinants have not been identified.^{3,4} Rare nonsynonymous genetic variants in cardiac ion channel genes have been found more often in African Americans than in European Americans,⁵ some of which have been associated with arrhythmia risk and myocardial electrophysiological characteristics.⁶

Clinical Perspective on p 655

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With regard to myocardial electrophysiological characteristics, myocardial repolarization time has been established to be of particular importance for arrhythmia risk. Prolongation of the myocardial repolarization time, as measured by the electrocardiographic QT interval, confers increased risk of sudden cardiac death,⁷ whereas shortening of the atrial repolarization time has been associated with atrial fibrillation.⁸ Furthermore, QT interval has been shown to be highly heritable in individuals of both European⁹ and African ancestry,¹⁰ resulting from genetic determination by rare variants, common genetic variants, or both. Thus, ancestral differences in repolarization time might account for the observed pattern of ethnic differences in arrhythmia incidence. We therefore formed a consortium of African American cohorts with information on QT interval duration and genome-wide single-nucleotide polymorphism (SNP) data. Two hypotheses—first whether genetic ancestry is associated with QT interval and second whether common genetic variants are associated with QT interval duration in African Americans—were tested in a genome-wide association (GWA) study.

Material and Methods

Study Samples

The study included 10 cohorts of self-reported African ancestry with genome-wide SNP data as part of the Continental Origins and Genetic Epidemiology Network, the Candidate-Gene Association Resource consortium, and the Women's Health Initiative (WHI) SNP Health Association Resource. The 4 cohorts genotyped as part of the Candidate-Gene Association Resource consortium—Atherosclerosis Risk in Communities study,¹¹ Cleveland Family Study,¹² Jackson Heart Study,¹³ and Multi-Ethnic Study of Atherosclerosis¹⁴—have been described previously,¹⁵ as have the Continental Origins and Genetic Epidemiology Network cohorts: Bogalusa Heart Study,¹⁶ Baltimore Longitudinal Study of Aging,^{17,18} Cardiovascular Health Study,¹⁹ Health, Aging and Body Composition Study (Health ABC),^{20,21} Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS),²² and the WHI.²³ Additional cohort descriptions are available in the online-only Data Supplement Methods. Genotyping, quality control, calculation of eigenvectors, and imputation in the 4 cohorts of the Candidate-Gene Association Resource consortium have been detailed previously^{15,24} and are summarized along with other cohorts in online-only Data Supplement Table I. The study protocol was approved by the Institutional Review Boards of participating institutions. Only individuals who provided informed consent for genetic testing were included. The authors had full access to the data and take responsibility for their integrity. All authors have read and agreed to the article as written.

Electrocardiographic Measurements

Twelve-lead ECGs with standard electrode placements were recorded with a paper speed of 25 mm per second during 10 seconds in all cohorts using either MAC PC, MAC6 (Cleveland Family Study), MAC5000 (Baltimore Longitudinal Study of Aging), MAC5500 (HANDLS), or MAC1200 (Multi-Ethnic Study of Atherosclerosis) machines (GE Healthcare, Milwaukee, WI). QT and RR interval durations were measured electronically using either the Marquette 12SL algorithm or the MC MEANS algorithm (Jackson Heart Study).

Phenotype Modeling

We excluded individuals on the basis of missing measurements of QT or RR interval duration, atrial fibrillation or flutter, left or right

bundle-branch block, QRS duration ≥ 120 ms, intraventricular conduction delay, or a pacemaker implant. In both ancestry and GWA analyses, adjustment was performed for age, sex, RR interval, and study site in multicenter cohorts (Atherosclerosis Risk in Communities, Cardiovascular Heart Study, Health ABC, Multi-Ethnic Study of Atherosclerosis, and WHI) in linear regression models.

Ancestry Analysis

In the 4 Candidate-Gene Association Resource cohorts, individual estimates of the proportion of African relative to European ancestry was calculated from 3192 independent ancestry informative markers included on the Affymetrix 6.0 array using the Markov Chain Monte Carlo algorithm implemented in ANCESTRYMAP²⁵ as in previous studies.^{3,15} Ancestry estimates were calculated from 656852 autosomal markers using the maximum likelihood algorithm implemented in frappe²⁶ (which has been demonstrated to be robust to linkage disequilibrium [LD]) in WHI and the model-based clustering algorithm of STRUCTURE²⁷ in Health ABC and HANDLS, including 1335 independent ancestry informative markers²⁸ and 279967 markers after LD-based pruning ($r^2 < 0.5$) from the Illumina 1 mol/L array, respectively. To test the association of this measure of continental ancestry with QT interval, QT interval was regressed linearly on ancestry estimates with adjustment for the covariates listed above and association tested using likelihood-ratio or Wald tests. Heterogeneity was assessed across cohorts and results combined using the rmeta package for R (R Foundation for Statistical Computing, Vienna, Austria).

GWA Analysis

Genetic association analyses were performed in each cohort using multiple linear regression models under an additive genetic model, using various statistical software packages as shown in online-only Data Supplement Table I. Directly genotyped SNPs were tested where available; otherwise imputed genotypes were used to achieve a common set of SNPs across cohorts for the combined analysis and to improve coverage. For the family-based Cleveland Family Study, association was assessed using linear mixed-effects models as implemented in the GWAF package for R.¹⁵ Pedigrees were confirmed using identity by state or identity by descent estimates. The Jackson Heart Study contains a family-based subcohort, but use of family-based methods had minimal effects on inflation in preliminary analyses for a set of traits, so linear regression was used as in previous studies.¹⁵ Adjustment for the first 10 or 2 (Health ABC) eigenvectors of genetic variation was performed in study-specific regression models to account for population substructure. Eigenvectors were calculated individually in each cohort using PLINK (HANDLS) or EIGENSTRAT (all other cohorts). Cohort-specific GWA results were combined using fixed-effects meta-analysis with inverse variance weights. Genomic control was applied to results from each cohort before meta-analysis and in the combined results. A genome-wide significance threshold of 2.5×10^{-8} was prespecified based on a Bonferroni-adjusted threshold of $P < 0.05$, assuming 2 million independent common variant tests in genomes of individuals of African ancestry as previously suggested.^{15,29} Effect heterogeneity across cohorts was assessed by Cochran's χ^2 test of heterogeneity and the I^2 test.^{30,31}

To identify multiple, independent signals within the same region, LD pruning was performed, whereby independent signals were defined as at least 2 genome-wide significant SNPs in low LD ($r^2 < 0.05$) in the same 1000 kb region. Starting with the index SNP, defined as the most significant result, all surrounding genome-wide significant SNPs within 1000 kb with a pairwise $r^2 \geq 0.05$ were placed into a bin with the index SNP using LD patterns from a 1:1 ratio of the HapMap European CEU sample and the Yoruba YRI sample. The

procedure was repeated until all genome-wide SNPs were assigned membership into a bin.

Results

Baseline characteristics of the 10 study cohorts are shown in Table 1. Hierarchical exclusions are shown in online-only Data Supplement Table II. Participants were predominantly middle aged and with a higher proportion of women. The proportion of variation in QT interval (r^2) explained by basic covariates (age, sex, RR interval) was relatively high, largely attributable to RR interval, ranging from 0.44 to 0.67 as shown in Table 1.

Genetic Ancestry and QT Interval

Ancestry estimates were available in 7 cohorts, including 12097 individuals. The distribution of estimated proportion of African ancestry relative to European ancestry was roughly similar across cohorts as shown in Table 2. Significant heterogeneity of effects was detected across cohorts (P for heterogeneity = 0.03), as shown in online-only Data Supplement Figure I, and hence cohorts were combined using random-effects meta-analysis. Overall, there was no association of continental ancestry with QT interval in the combined sample ($P=0.94$).

GWA Study

A meta-analysis of the 10 GWA studies was performed, including 13 105 individuals with typed or imputed genotypes for 2.8 million SNPs. Mild inflation of test statistics was observed with an overall genomic inflation factor (λ_{GC}) estimate of 1.03. After genomic control, there was a slight excess of low probability values (Figure 1). A total of 19 SNPs passed genome-wide significance ($P<2.5\times 10^{-8}$), as shown in Table 3 and Figure 2. No evidence of significant heterogeneity was observed, after accounting for 19 tests ($P>0.0026$), as shown in Table 3. Cohort-specific results are shown in online-only Data Supplement Table III. All 19 SNPs were noncoding and located on chromosome 1 at 2 loci separated by 7 megabases; 17 SNPs upstream of the *NOS1AP* gene and 2 SNPs upstream of *ATP1B1*.

With LD clustering of the 17 genome-wide significant SNPs upstream of *NOS1AP*, we identified 2 separate signals that were in very low LD ($r^2 < 0.05$) in Yoruban (YRI) and

European (CEU) HapMap samples; 1 signal marked by rs12143842, (minor allele frequency = 0.20), which was also the strongest SNP in GWA studies in individuals of European ancestry and with a similar effect,³²⁻³⁴ and a second signal marked by rs4657175 (minor allele frequency = 0.33, r^2 to rs12143842 < 0.01 in YRI). rs4657175 was also strongly correlated with an independent signal previously reported in the QTGEN study³² (rs12029454, $r^2=0.81$ in YRI), which also reached genome-wide significance in our study. Both SNPs were directly genotyped or imputed with high accuracy in all cohorts (observed/expected variance > 0.9). No effect heterogeneity was observed for rs12143842 ($I^2=0.32$, $P=0.21$), and nominally significant heterogeneity was observed for rs4657175 ($I^2=0.51$, $P=0.05$).

The 2 genome-wide significant SNPs upstream of *ATP1B1* were in very strong LD (r^2 in YRI: 1.0) but were not correlated with the *ATP1B1* variant previously identified in the QTSCD study,³³ rs10919071 ($r^2=0.02$ in CEU, monomorphic in YRI). Indeed, rs10919071 was not significantly associated with QT interval in African Americans (minor allele frequency = 0.03, $P=0.07$), although it had a similar effect estimate in the same direction (β coefficient = 2.08 ms per minor allele). The most significant SNP at the locus in the current study, rs1320976, showed no evidence of effect heterogeneity ($I^2=0$, $P=0.71$) and was directly genotyped in all cohorts, except in 4 of the smaller cohorts (Bogalusa Heart Study, Baltimore Longitudinal Study of Aging, Health ABC, and HANDLS).

Several additional SNPs at loci identified in GWA studies in individuals of European ancestry also reached low P values ($P<10^{-5}$) in African Americans, including SNPs near *LITAF* (rs8049607), *PLN* (rs11752626), *KCNQ1* (rs231906), and *KCNH2* (rs3778872), as shown in online-only Data Supplement Table IV. The same SNP near *LITAF* showed the most significant association at the locus in blacks ($P=7\times 10^{-7}$), whereas SNPs near *PLN* ($P=2\times 10^{-6}$), *KCNQ1* ($P=2\times 10^{-6}$), and *KCNH2* ($P=3\times 10^{-6}$) showed strong-to-moderate correlation with the most significant SNPs at these loci in studies of individuals with European ancestry.³²⁻³⁴ Results in African Americans for top SNPs at each of the 12 loci from GWA studies in individuals of European ancestry are shown in online-only Data Supplement Table V.

Table 1. Sample Characteristics

	ARIC (n=1808)	BHS (n=188)	BLSA (n=153)	CFS (n=316)	CHS (n=667)	Health ABC (n=1038)	HANDLS (n=957)	JHS (n=2057)	MESA (n=1556)	WHI (n=4365)
Age, y	53.7 (5.9)	35.6 (4.8)	64.2 (11.3)	44.3 (15.2)	72.7 (5.6)	73.4 (2.9)	48.4 (8.9)	54.6 (12.7)	61.9 (10.1)	61.6 (6.8)
Male sex, %	36.3	32.4	36.9	39.3	33.9	42.0	44.2	36.7	44.7	0
QT interval, ms	409.2 (30.8)	389.8 (30.5)	413.6 (25.7)	397.5 (30.0)	404.0 (35.6)	410.7 (35.1)	407.4 (32.1)	413.0 (30.9)	410.3 (31.8)	400.7 (34.0)
Heart rate, bpm	67.5 (11.3)	68.9 (11.0)	63.1 (13.4)	68.1 (9.8)	67.3 (11.5)	66.1 (11.2)	68.0 (11.4)	64.6 (10.5)	63.0 (10.3)	67.3 (10.9)
r^2	0.52	0.57	0.53	0.51	0.67	0.56	0.44	0.52	0.65	0.65
λ_{GC}	1.02	1.00	1.00	1.05	1.07	1.00	1.00	1.05	1.01	1.03

ARIC indicates Atherosclerosis Risk in Communities study; BHS, Bogalusa Heart Study; BLSA, Baltimore Longitudinal Study of Aging; CFS, Cleveland Family Study; CHS, Cardiovascular Heart Study; Health ABC, Health, Aging, and Body Composition Study; HANDLS, Healthy Aging in Neighborhoods of Diversity across the Life Span; JHS, Jackson Heart Study; MESA, Multi-Ethnic Study of Atherosclerosis; WHI, Women's Health Initiative; r^2 , coefficient of determination for a clinical model with age, sex, and RR interval; and λ_{GC} , genomic inflation factor.

Mean and SD are reported for continuous variables and percentage of cases for dichotomous traits.

Table 2. Genetic Ancestry and QT Interval

Cohort	Effect*	P	African Ancestry†
ARIC	5.3 (4.8)	0.27	0.85 (0.78–0.89)
CFS	19.6 (10.2)	0.06	0.82 (0.74–0.87)
Health ABC	–2.7 (5.7)	0.64	0.81 (0.72–0.88)
HANDLS	–19.0 (8.2)	0.02	0.84 (0.78–0.89)
JHS	–1.1 (5.5)	0.84	0.84 (0.79–0.88)
MESA	–4.7 (3.5)	0.19	0.81 (0.70–0.88)
WHI	3.2 (2.0)	0.10	0.79 (0.69–0.87)
Overall	–0.2 (–5.7, 5.3)	0.94	

ARIC indicates Atherosclerosis Risk in Communities Study; CFS, Cleveland Family Study; Health ABC, Health, Aging, and Body Composition Study; HANDLS, Healthy Aging in Neighborhoods of Diversity across the Life Span; JHS, Jackson Heart Study; MESA, Multi-Ethnic Study of Atherosclerosis; and WHI, Women's Health Initiative.

*Effect estimates are given as β coefficients with SEs for individual cohorts, with an overall effect estimate with 95% confidence interval. β coefficients refer to milliseconds with complete African ancestry compared with European ancestry.

†African ancestry refers to the proportion of African compared with European ancestry, presented as median and interquartile range.

Discussion

This study examined the association of genetically inferred continental ancestry and genetic polymorphisms on cardiac repolarization, as measured by the electrocardiographic QT interval, in several large cohorts of African Americans. We observed no overall evidence of association for QT interval with proportion of individual African ancestry inferred from genome-wide data. In a GWA study including 13 105 blacks, we observed genome-wide significant associations with SNPs at 2 loci (*NOS1AP*, *ATP1B1*) and consistent associations ($P < 10^{-5}$) for SNPs at 4 additional loci (*LITAF*, *PLN*, *KCNQ1*, and *KCNH2*) previously associated with QT interval in individuals of European ancestry.^{32–34} Although the P values for association were modest, the direction of effect for the top SNP at each of the 12 previously reported loci was the same, consistent with modest power to detect mostly true underlying effects. The most significant association in *NOS1AP*, rs12143842, was the same SNP reported by 3 previous GWA studies of QT in populations of European descent.^{32–34} Furthermore, the variant we identified in the *ATP1B1* locus was independent from the previously reported SNP,³³ consistent with a second signal of association.

Genetic Ancestry

In contrast to our findings, a shorter average QT interval in individuals of self-reported African ancestry compared with self-reported European ancestry was observed in a small subset of the ARIC study³⁵ and in a large cohort of inpatients and outpatients from the electronic medical records of the Vanderbilt University Medical Center.³⁶ Both studies accounted for differences in heart rate using Bazett formula, which is explicitly discouraged in current guidelines for ECG interpretation³⁷ and can under- or overcorrect the influence of heart rate on QT interval.³⁸ A previous study from the WHI adjusting for heart rate using linear regression did not observe differences

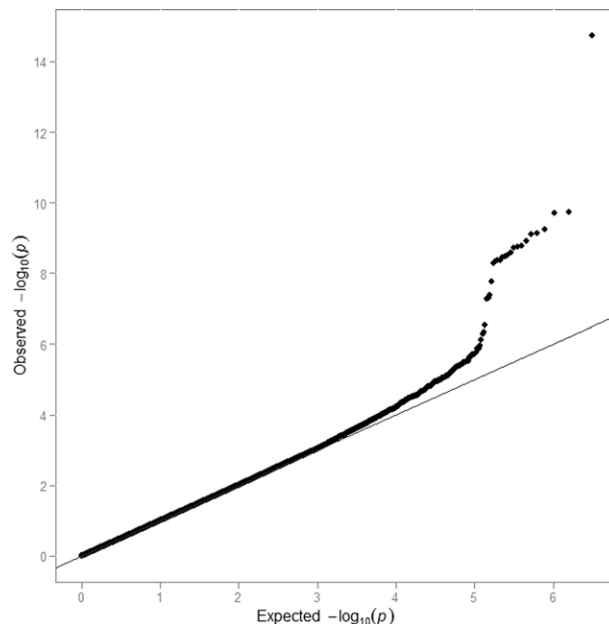


Figure 1. Quantile–quantile plot of genome-wide association (GWA) analysis of QT interval. Plotted are expected versus observed $-\log_{10}$ of all P values after genomic control from QT interval GWA study. The measure of overdispersion of the test statistics, λ_{GC} , was 1.03 before genomic control and, by definition, was 1.0 after genomic control.

in QT interval by self-reported ancestry.³⁹ Our study has some advantages over these previous studies. First, our derivation of ancestry from genome-wide genetic data reduced bias resulting from the ambiguity of self-reported ancestry and allowed treatment of ancestry as a continuous variable. Second, our use of multiple population-based cohorts reduced bias resulting from ethnic differences in access and utilization of health care and allowed consistency in methodology used for ascertainment and measurement of QT interval. Third, our meta-analysis of several large cohorts allowed adequate power to detect strong or modest ancestral effects. Fourth, our use of continuous ECG measurements of QT and RR intervals allowed adjustment for heart rate using regression modeling techniques, which are well known to be more stable across the entire range of QT interval than Bazett formula.³⁷ Thus, our findings from several large population cohorts that QT interval adjusted for major covariates is not associated with the proportion of African ancestry based on whole-genome SNP suggest that observations in the 2 previous studies might reflect chance, selection bias, measurement bias, or other confounding influences that contribute to between-race comparisons rather than within-race proportion genetic ancestry analyses. However, our findings do not rule out a small effect.

Common Genetic Variants and QT Interval

GWA studies in samples of European ancestry have to date reported 12 loci associated with QT interval (online-only Data Supplement Table V), with multiple independent signals at least at 1 locus (*NOS1AP*).^{32–34,40} Our findings establish with genome-wide significance that SNPs at 2 of these loci on chromosome 1–*ATP1B1* and 2 signals at

Table 3. Results From GWA Analysis of QT Interval With $P < 2.5 \times 10^{-8}$

SNP	Position on Chromosome 1	Alleles	CAF	N_{eff}	QT effect (SE)	P	Q	I^2	Locus
rs12143842	160300514	T/C	0.20	12812	3.14 (0.39)	1.79×10^{-15}	0.21	0.32	NOS1AP
rs16847548	160301898	C/T	0.22	12629	2.17 (0.33)	1.84×10^{-10}	0.02	0.58	NOS1AP
rs1320976	167339970	A/G	0.25	10767	-2.06 (0.32)	2.00×10^{-10}	0.71	0	ATP1B1
rs12061601	167337074	C/T	0.29	12608	-1.89 (0.30)	5.88×10^{-10}	0.65	0	ATP1B1
rs4657175	160462362	G/T	0.33	13077	1.74 (0.28)	7.24×10^{-10}	0.05	0.51	NOS1AP
rs4391647	160453555	G/A	0.33	13077	-1.74 (0.28)	7.73×10^{-10}	0.04	0.53	NOS1AP
rs6692381	160434508	T/C	0.34	13093	-1.71 (0.28)	1.23×10^{-10}	0.05	0.51	NOS1AP
rs12123267	160465975	T/C	0.34	13115	-1.70 (0.28)	1.67×10^{-09}	0.06	0.49	NOS1AP
rs12567315	160433270	A/G	0.33	13202	1.69 (0.28)	1.82×10^{-09}	0.04	0.53	NOS1AP
rs6667431	160434545	A/G	0.33	13232	1.69 (0.28)	1.85×10^{-09}	0.04	0.53	NOS1AP
rs3934467	160449301	T/C	0.34	13170	-1.69 (0.28)	2.58×10^{-09}	0.03	0.54	NOS1AP
rs7534004	160413333	A/G	0.31	12902	1.73 (0.29)	3.11×10^{-09}	0.006	0.64	NOS1AP
rs12027785	160447769	A/T	0.33	13203	1.67 (0.28)	3.45×10^{-09}	0.03	0.55	NOS1AP
rs12116744	160447080	A/G	0.33	13220	1.67 (0.28)	3.56×10^{-09}	0.03	0.55	NOS1AP
rs4480335	160440001	C/A	0.33	13104	-1.67 (0.28)	4.32×10^{-09}	0.03	0.55	NOS1AP
rs12029454	160399741	A/G	0.31	12675	1.73 (0.29)	4.37×10^{-09}	0.005	0.64	NOS1AP
rs10800352	160439313	G/A	0.33	13272	-1.66 (0.28)	4.70×10^{-09}	0.02	0.57	NOS1AP
rs4306106	160438618	A/G	0.33	13270	1.66 (0.28)	5.07×10^{-09}	0.02	0.56	NOS1AP
rs10127719	160422794	C/T	0.32	12746	1.64 (0.29)	1.75×10^{-08}	0.02	0.58	NOS1AP

GWA indicates genome-wide association; SNP, single-nucleotide polymorphism; and CAF, coded allele frequency.

All SNPs are noncoding. Positions are on the forward strand from the reference sequence in National Center for Biotechnology Information (NCBI) build 35. SNP IDs refer to dbSNP. All SNPs are on chromosome 1. Alleles are shown as coded/noncoded. CAF refers to coded allele frequency. N_{eff} refers to the effective sample size in the meta-analysis, defined as $N \times R^2$ and reflects the loss of power with poor imputation compared with the total sample size. Effects are milliseconds/coded allele copy with SE within parentheses. Results of heterogeneity tests are presented as the probability value for Cochran's Q test (Q) and the I^2 statistic.

NOS1AP—associate with QT interval in African Americans as well, with the strongest association for the same SNP upstream of *NOS1AP* conferring a similar QT prolongation as in previous studies (≈ 3 ms per minor allele copy). Furthermore, we observed low P -values ($P < 10^{-5}$) for SNPs at 4 additional loci previously reported in populations of European descent. These observations provide additional support for a similar genetic architecture for myocardial repolarization time in individuals of African and European ancestry.

For *NOS1AP* and *LITAF*, the identical SNP showed the strongest association, whereas top SNPs near *PLN*, *KCNQ1*, and *KCNH2* were correlated with top SNPs from studies in individuals of European ancestry. In contrast, the 2 SNPs upstream of *ATP1B1* of genome-wide significance were not correlated with the SNP from studies in individuals of European ancestry, which itself was not associated with QT interval in African Americans. This finding could reflect ancestry-specific association signals at the locus or different degrees of LD across ancestries with a true, ungenotyped causal variant. In addition, this could also reflect the modest power to detect common variant associations of weak effect. The current study is similar in size to the QTGEN and QTSCD studies, and it is perhaps not unexpected that different equally powered studies will identify different common variants when multiple variants exist at a locus, as has now been observed in many large-scale genetic association studies. Additional studies are needed to identify the causal variants and genes. Although the most significant associations were observed with

SNPs in potential regulatory regions upstream of *NOS1AP* and *ATP1B1* (<http://genome.ucsc.edu/ENCODE/>), associations could be mediated by causal variants in longer-range LD blocks or located in regulatory motifs influencing more distant genes. However, *NOS1AP* and *ATP1B1* are strong candidate genes; *NOS1AP* encodes a protein that may interact with neuronal nitric oxide synthase to accelerate cardiac repolarization by inhibition of L-type calcium channels,⁴¹ whereas *ATP1B1* encodes the cardiac β -subunit of the membrane-bound Na, K-ATPase that is essential in the maintenance of the myocardial resting membrane potential, for which the α -subunit is targeted by digoxin.⁴²

Potential Clinical Implications

QT interval is a strong determinant of arrhythmia risk. Substantial heritability estimates (h^2) have been reported for QT interval in individuals of both European and African ancestry, ranging from 0.35 in individuals of European ancestry⁹ to 0.41 in African Americans,¹⁰ after adjustment for basic covariates including age, sex, and RR interval. A large proportion of QT variability has been shown to be explained by genetic factors, up to 40%, and about half of this was recently shown to be explained by common genetic variants.⁴³ In the present and previous studies,¹⁵ we have shown that electrocardiographic markers of conduction and repolarization are not associated with genetic ancestry. These findings suggest that the reported ethnic differences in risk of cardiac arrhythmia

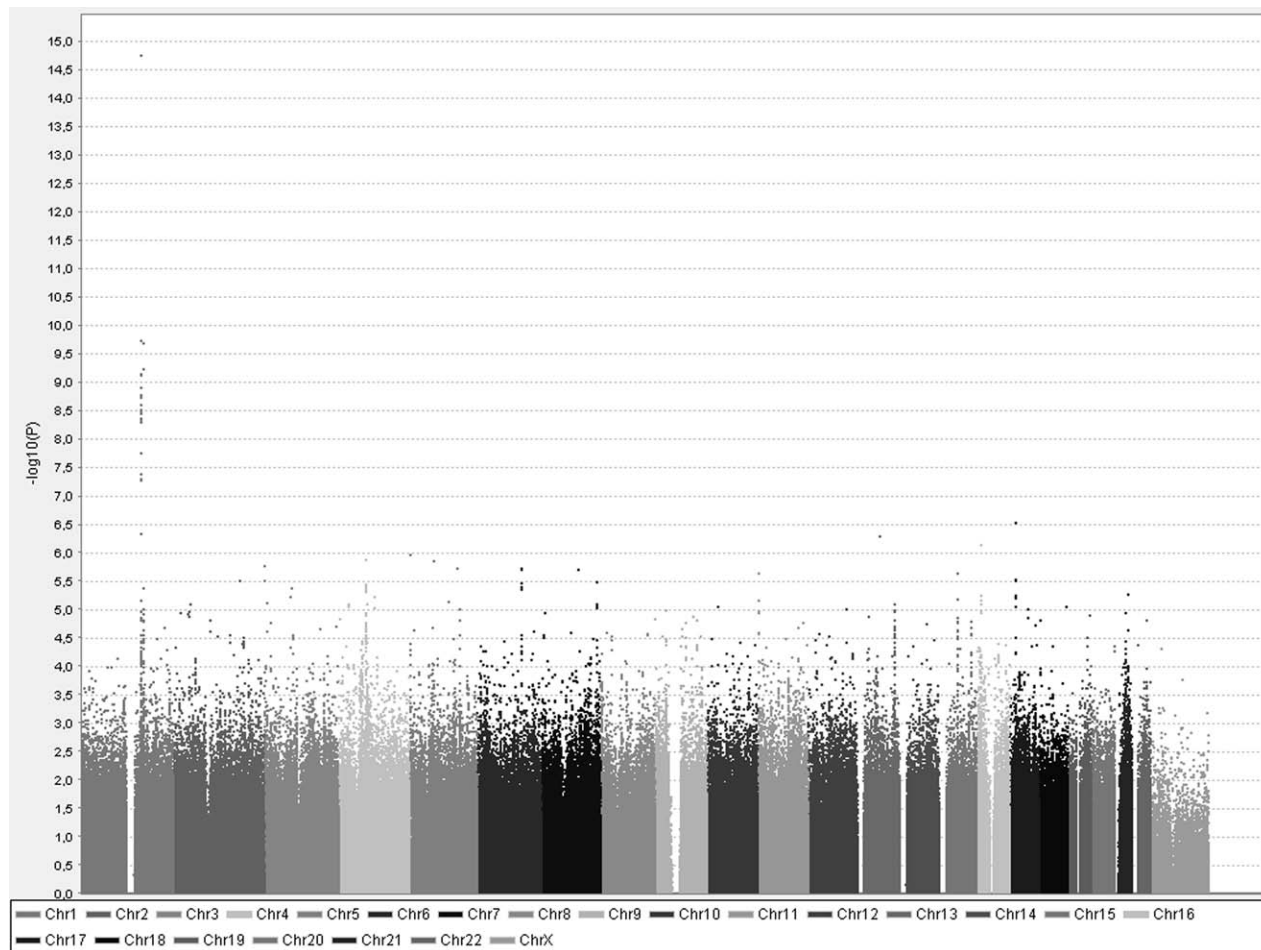


Figure 2. Results of genome-wide association analysis of QT interval. Each dot represents 1 SNP. On the y-axis is $-\log_{10}$ probability value and on the x-axis physical position by chromosome.

may not be explained by an excess of common or rare variants influencing cardiac repolarization, but this has not been systematically tested. Indeed, in GWA studies, we identify many of the same genetic associations with QT interval in individuals of African ancestry as have been found among individuals of European ancestry. Ancestral differences in arrhythmia risk might therefore be mediated by differences that do not impact electrophysiological properties of global repolarization or conduction.

Single polymorphisms have limited predictive ability individually and are unlikely to individually have clinical use. However, each novel locus can provide novel insights into pathophysiology and potentially therapeutic targets. Our analysis only found 2 genome-wide significant loci even though our sample size was similar to 2 previous studies in individuals of European ancestry, which identified 10 loci each.^{32,33} Such a discrepancy could reflect the greater heterogeneity in populations of African ancestry or that admixed populations have lower effective sample sizes if locus-specific ancestry is associated with differing LD patterns. Individuals of African ancestry have been shown to exhibit greater heterozygosity with more rare variants, lower proportion of common variants, and shorter-range LD patterns,^{44,45} resulting in lower coverage and power of GWA approaches compared with European-derived populations.

Strengths and Limitations

In forming a consortium of large, population-based cohort studies of African American participants, our study was well powered to detect substantial ancestral and genetic effects and allowed linear modeling of ancestry on QT interval with adjustment for major covariates. Furthermore, our use of multiple African American population cohorts collected at several different locations makes our study likely to provide a broader coverage of African American populations.

Our study also has limitations that merit consideration. First, our results cannot rule out a smaller effect of ancestry on QT interval duration. Second, participants with extreme repolarization abnormalities may not have survived to the baseline visit of the cohorts studied. This limitation is likely to be of small impact, as participants of most cohorts were in the early middle age. Third, we did not have information on several clinical factors that are known to influence QT interval, including concurrent medications, myocardial ischemia, heart failure, and time point on the day of ECG recording, which potentially explain a large proportion of QT variation. Although such factors are unlikely to be determined by genotypic effects and thus unlikely to bias our observations, they could potentially dilute the effect of genetic associations.

In conclusion, our results establish that QT interval does not differ substantially by ancestry and extended the association

of genetic polymorphisms at several loci including *NOS1AP* and *ATP1B1* to populations of African ancestry. Future studies aimed at identifying mediators of excess genetic arrhythmia risk in African Americans should focus on factors other than cardiac conduction and repolarization.

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Appendix

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CLINICAL PERSPECTIVE

Ethnic differences in cardiac arrhythmia incidence have been reported, with a particularly high incidence of ventricular fibrillation and sudden cardiac death and a low incidence of atrial fibrillation in African Americans compared with Americans of European ancestry. However, it remains unknown whether such differences result from differences in inherited myocardial electrophysiological properties. Previous studies have shown inconsistent results regarding ethnic differences in electrocardiographic QT interval, a measure of myocardial repolarization time, and a central pathophysiological determinant of arrhythmia known to have a strong genetic component. In the present study, we therefore studied whether African compared with European ancestry inferred from genome-wide genotype data were associated with QT interval in 12 000 African Americans from 7 population-based studies. We observed no difference in duration of QT interval with African compared with European ancestry, arguing against important differences in myocardial repolarization time across these ethnicities. We also performed a genome-wide association study to identify common genetic variants associated with electrocardiographic QT interval in 13 000 blacks from 10 cohorts and observed association with QT interval for several loci previously identified as genetic determinants of QT interval in individuals of European ancestry, including SNPs at genetic loci harboring the genes *NOS1AP*, *ATP1B1*, *KCNQ1*, *KCNH2*, *LITAF*, and *PLN*.