

Evidence of Heterogeneity by Race/Ethnicity in Genetic Determinants of QT Interval

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Background: QT interval (QT) prolongation is an established risk factor for ventricular tachyarrhythmia and sudden cardiac death. Previous genome-wide association studies in populations of the European descent have identified multiple genetic loci that influence QT, but few have examined these loci in ethnically diverse populations.

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Methods: Here, we examine the direction, magnitude, and precision of effect sizes for 21 previously reported SNPs from 12 QT loci, in populations of European (n = 16,398), African (n = 5,437), American Indian (n = 5,032), Hispanic (n = 1,143), and Asian (n = 932) descent as part of the Population Architecture using Genomics and Epidemiology (PAGE) study. Estimates obtained from linear regression models stratified by race/ethnicity were combined using inverse-variance weighted meta-analysis. Heterogeneity was evaluated using Cochran's Q test.

Results: Of 21 SNPs, 7 showed consistent direction of effect across all 5 populations, and an additional 9 had estimated effects that were consistent across 4 populations. Despite consistent direction of effect, 9 of 16 SNPs had evidence ($P < 0.05$) of heterogeneity by race/ethnicity. For these 9 SNPs, linkage disequilibrium plots often indicated substantial variation in linkage disequilibrium patterns among the various racial/ethnic groups, as well as possible allelic heterogeneity.

Conclusions: These results emphasize the importance of analyzing racial/ethnic groups separately in genetic studies. Furthermore, they underscore the possible utility of trans-ethnic studies to pinpoint underlying causal variants influencing heritable traits such as QT.

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Studies of the QT interval (QT), a measurement of ventricular depolarization and repolarization obtained from the electrocardiogram (ECG), have shown that QT prolongation is an established risk factor for ventricular tachyarrhythmias,¹ coronary heart disease,² sudden cardiovascular death, and all-cause mortality.² Several correlates of QT prolongation have been identified, including structural heart disease,³ sex,⁴ and age.⁵ QT is also heritable, with estimates ranging from 35% to 40%.⁶

Early family-based linkage studies have identified rare and highly penetrant mutations associated with long- and short-QT syndromes.⁷ Recent genome-wide association studies (GWAS) in large population-based studies of European descent populations also have identified several common single nucleotide polymorphisms (SNPs) associated with modest increases in QT, including *NOS1AP*, *KCNQ1*, and *SCN5A*,^{8–10} which together account for approximately 10% of the variance in QT.¹¹ However, much of the variation in QT remains unexplained.

To date, the majority of published GWAS of QT have been conducted in populations of European descent.^{8–10} Few studies have examined the relevance of GWAS-identified QT SNPs in multiethnic populations,^{12,13} although such studies are needed to fully understand the genetic architecture underlying QT. Therefore, we examined evidence of generalizability for 21 SNPs associated with QT in previous GWAS^{8–10} across populations of African, American Indian, Hispanic, and Asian descent from the Population Architecture using Genomics and Epidemiology (PAGE) Study.

METHODS

Study Populations

The PAGE study is a collaboration of 4 large, multiethnic, and deeply phenotyped consortia.¹⁴ Using the ethnically diverse populations of the participating studies, the goal of PAGE is to better understand the epidemiologic architecture of well-replicated genetic variants associated with complex disease in global populations. Three PAGE consortia contributed the following studies to this research: the National Health and Nutrition Examination Surveys (NHANES) through the Epidemiologic Architecture for Genes Linked to Environment study,¹⁵ the Women's Health Initiative Clinical Trial through the Women's Health Initiative,¹⁶ and the Causal Variants Across the Life Course Consortium which included the Atherosclerosis Risk in Communities study,¹⁷ the Cardiovascular Health Study,¹⁸ the Strong Heart Study,¹⁹ and the Strong Heart Family Study.²⁰ Each study was approved by the Institutional Review Board at the respective sites and all participants provided written consent. Further details on each study are available in eAppendix (<http://links.lww.com/EDE/A825>).

A total of 42,525 participants from the above studies were genotyped in PAGE. Of these, 10,051 were excluded according to the following hierarchical criteria (eTable 1, <http://links.lww.com/EDE/A825>): QT information unavailable ($n = 5,286$); poor ECG quality (grade = 5, $n = 1,654$); major conduction defects, including left- or right-bundle branch block and intraventricular conduction delay ($n = 1,197$); QRS interval ≥ 120 ms ($n = 662$); pacemaker or defibrillator implants ($n = 20$); atrial fibrillation or atrial flutter on baseline ECG ($n = 44$); participants under 18 years of age ($n = 334$); and genetic ancestry data unavailable ($n = 854$).

QT Interval Measurement

In each study, certified technicians recorded at baseline, resting, supine (or semirecumbent), standard 12-lead ECGs using either Marquette MAC 12 or MAC PC machines (GE Healthcare, Milwaukee, WI, USA). Comparable procedures were used for preparing participants, placing electrodes, recording, transmitting, processing, and controlling quality of ECGs. The QT interval was measured electronically using Marquette 12SL algorithm. ECGs from Atherosclerosis Risk in Communities study, Cardiovascular Health Study, and Women's Health Initiative were processed by the central

Epidemiological Cardiology Research Center at Wake Forest University, Winston-Salem, NC. Epidemiologic Architecture for Genes Linked to Environment study, Strong Heart Study, and Strong Heart Family Study ECGs were read at independent ECG reading centers using comparable protocols (eTable 2, <http://links.lww.com/EDE/A825>).

SNP Selection and Genotyping

The 21 SNPs examined in this study were reported by previously published QT GWAS (as of January 2010). The SNPs represent 12 genetic loci, with multiple SNPs reported for *NOS1AP* (4 SNPs), *KCNH2* (3 SNPs), *KCNQ1* (3 SNPs), *PLN* (2 SNPs), and *SCN5A* (2 SNPs). The 21 SNPs examined here were either targeted for genotyping by the PAGE study or were available on previous GWAS chips. Genotyping was done separately by each study (eAppendix, <http://links.lww.com/EDE/A825>). Cross-study quality control was performed centrally by the PAGE Coordinating Center using 360 samples from the International HapMap Project that were genotyped by each participating study.

Statistical Analysis

Study- and race-stratified tests of association between each SNP and QT (in milliseconds [ms]) were performed using linear regression models, and assuming an additive genetic mode of inheritance. We included the following confounders: study site (where appropriate), sex, age (continuous in years), RR interval (ms), or heart rate (beats per minute) when RR interval was not measured directly, and ancestral principal components that assessed global ancestry among study participants. Results were combined by inverse-variance weighted meta-analysis using METAL,²¹ and heterogeneity was evaluated using Cochran's Q statistic.²² *P* values were 2-sided.

Generalizability of SNPs originally identified in European descent populations was assessed by examining the direction, precision, and magnitude of estimated effects across racial/ethnic groups. SNPs were considered directionally consistent if their direction of effect was the same across populations. For each non-European descent population, we categorized SNPs as stronger than, weaker than, or equal (within 0.05 ms) to the estimates from the European descent population, based on the absolute value of the estimated effect sizes. Precision was gauged using the 95% confidence limit difference (CLD).

Haplotype Block Analysis

Given the potential for variation in linkage disequilibrium patterns between SNPs across racial/ethnic groups,²³ haplotype blocks were examined using HapMap III data.²⁴ Briefly, we calculated pairwise measures of linkage disequilibrium using Hedrick's multiallelic D' , and we generated linkage disequilibrium plots using Haploview 4.2²⁵ and dense genotype data from 5 International HapMap III populations: African Americans from the southwest U.S., Utah residents of northern and western European ancestry, Han Chinese from

Beijing, China, Japanese from Tokyo, Japan, and a Mexican American population from Los Angeles, CA. In accordance with convention, data from the Chinese and Japanese populations were pooled before analysis and referred to as “Asian.”

RESULTS

Study Population Characteristics

A total of 32,474 participants from the PAGE consortium were included in this analysis with the following breakdown by race/ethnicity: European American (n = 18,802), African American (n = 6,132), American Indian (n = 5,465), Hispanic (n = 1,143), and Asian (n = 932) (Table 1). All studies contributed approximately equal proportions of male and female participants, with the exception of the Women’s Health Initiative Clinical Trial, which enrolled only female participants. Notably, the Women’s Health Initiative Clinical Trial was the only study contributing participants of Asian descent. Estimated mean age varied slightly by race/ethnicity, with the highest mean age observed among European Americans (63.8 years) and the lowest among American Indians (59.1 years). Mean QT was consistent across race/ethnicity (range = 403–405 ms).

Evidence of variation in allele frequency by race/ethnicity was observed for a majority of GWAS-identified QT SNPs (Table 2). For example, we observed mean allele frequency differences between populations greater than 20% for thirteen SNPs. The 2 most striking differences were for rs12053903 and rs4725982, both of which had a difference of 44% between the lowest and highest frequency; for rs12053903, this difference translated to a coded allele frequency of 33% in European Americans and 77% in African American, whereas for rs4725982, the largest difference was between European Americans (22%) and Asians (66%).

Summary Results Among European Descent Populations

After meta-analysis, 20 of 21 SNPs (95%) representing all 12 genetic loci were associated with QT in European Americans, with little evidence of study heterogeneity (eTables 3 and 4, <http://links.lww.com/EDE/A825>). The only European ancestry-identified SNP that was not associated with QT was rs12053903 (intronic to *SCN5A*), which had an estimated effect size of -0.21 (95% confidence interval [CI] = -0.86 to 0.45). For the remaining 20 SNPs, the estimated direction and magnitude of effects were consistent with previously published results.

Generalizability of GWAS-Identified QT SNPs to Populations of Non-European Descent

Direction and Precision of Effect

Seven of the 21 previously reported QT SNPs (33%) had a consistent direction of effect across all populations (Figure 1). These 7 SNPs (rs12143842, rs12029454, rs11129795, rs2074238, rs37062, rs2074518, and rs1805128) represented

TABLE 1. Descriptive Characteristics of PAGE Study Populations by Race/Ethnicity and Study

Study	No.	Female (%)	Age (years) ^a Mean (SD)	QT Interval (ms) ^a Mean (SD)
European American				
Total	18,802	65	64 (3)	405 (15)
ARIC	10,926	53	54 (6)	399 (29)
CHS	2,508	64	72 (5)	413 (32)
EAGLE	1,291	60	63 (14)	409 (33)
WHI CT	4,077	100	63 (7)	402 (29)
African American				
Total	6,132	69	62 (3)	403 (17)
ARIC	4,020	63	54 (6)	400 (33)
CHS	492	67	72 (6)	405 (34)
EAGLE	578	56	55 (12)	406 (33)
WHI CT	1,042	100	60 (7)	401 (34)
American Indian				
Total	5,465	65	59 (5)	404 (18)
SHS	2,200	64	63 (8)	408 (33)
SHFS	3,086	64	42 (16)	408 (33)
WHI CT	179	100	59 (6)	398 (29)
Hispanic				
Total	1,143	71	60 (6)	405 (21)
EAGLE	655	50	56 (12)	405 (30)
WHI CT	488	100	61 (7)	404 (30)
Asian				
WHI CT	932	100	62 (7)	405 (33)

^aOverall mean calculated using inverse-variance weighted method.

ARIC indicates Atherosclerosis Risk in Communities; CHS, Cardiovascular Health Study; EAGLE, Epidemiologic Architecture for Genes Linked to Environment study; WHI CT, Women’s Health Initiative Clinical Trial; SHS, Strong Heart Study; SHFS, Strong Heart Family Study.

6 genetic loci (*NOS1AP*, *SCN5A*, *KCNQ1*, *NDRG4*, *LIG3*, and *KCNE1*). Results were noticeably less precise for rs2074238 and rs1805128 (imprecise in all 4 non-European populations) than for the other 5 SNPs, which were precise in all 5 populations. Estimated imprecision for these 2 SNPs likely reflects the low estimated minor allele frequency across race/ethnicity (0.02 – 0.08 frequency for rs2074238; 0.002 – 0.01 for rs1805128) and a smaller sample size for rs2074238. Additionally, rs12143842, rs37062, and rs1805128 showed heterogeneity within at least 1 race/ethnicity (eTables 5–7, <http://links.lww.com/EDE/A825>).

Nine SNPs (43%) showed a consistent direction of effect in 4 of the 5 populations (Figure 1). These 9 SNPs (rs17779747, rs12053903, rs11756438, rs4725982, rs2968864, rs2968863, rs10919071, rs10494366, and rs12296050) represented 7 loci (*KCNJ2*, *SCN5A*, *PLN*, *KCNH2*, *ATP1B1*, *NOS1AP*, and *KCNQ1*). There was no race/ethnicity identified as an outlier across these 9 SNPs: the directionally inconsistent effect estimate was observed in the African American, Asian, and American Indian populations 4, 3, and 2 times, respectively. Of these 9 SNPs, imprecision was noted among Hispanic and

TABLE 2. GWAS-Identified QT SNP Characteristics and Allele Frequencies from 32,474 Eligible Participants from PAGE Study

SNP	Nearest Gene	Chr	Base Pair ^a	CA	NCA	Coded Allele Frequency					Function
						European American	African American	American Indian	Hispanic	Asian	
rs846111	<i>RNF207</i>	1	6279370	G	C	0.27	0.05	0.15	0.18	0.25	Missense
rs12143842	<i>NOS1AP</i>	1	162033890	T	C	0.25	0.13	0.20	0.24	0.38	Intergenic
rs10494366	<i>NOS1AP</i>	1	162085685	T	G	0.63	0.41	0.57	0.57	0.32	Intronic
rs16857031	<i>NOS1AP</i>	1	162112910	G	C	0.14	0.29	0.06	0.15	0.15	Intronic
rs12029454	<i>NOS1AP</i>	1	162133117	A	G	0.15	0.26	0.13	0.24	0.39	Intronic
rs10919071	<i>ATP1B1</i>	1	169099483	G	A	0.13	0.03	0.32	0.19	0.04	Intronic
rs11129795	<i>SCN5A</i>	3	38589163	A	G	0.24	0.17	0.14	NA	NA	Near Gene-3 ^b
rs12053903	<i>SCN5A</i>	3	38593393	C	T	0.33	0.77	0.55	0.45	0.51	Intronic
rs12210810	<i>PLN</i>	6	118653204	C	G	0.05	0.01	0.02	0.02	0.0005	Intergenic
rs11756438	<i>PLN</i>	6	118993632	A	C	0.48	0.40	0.19	0.31	0.26	Intronic
rs2968864	<i>KCNH2</i>	7	150622162	G	A	0.24	0.05	0.07	0.15	0.05	Intergenic
rs2968863	<i>KCNH2</i>	7	150623137	A	G	0.23	0.05	0.07	0.17	0.05	Intergenic
rs4725982	<i>KCNH2</i>	7	150637863	T	C	0.22	0.25	0.46	0.33	0.66	Intergenic
rs2074238	<i>KCNQ1</i>	11	2484803	T	C	0.08	0.02	0.06	0.04	0.04	Intronic
rs12296050	<i>KCNQ1</i>	11	2489342	T	C	0.20	0.52	0.29	0.30	0.35	Intronic
rs12576239	<i>KCNQ1</i>	11	2502319	T	C	0.14	0.18	0.15	0.14	0.10	Intronic
rs8049607	<i>LITAF</i>	16	11691753	T	C	0.51	0.46	0.64	0.57	0.50	Intergenic
rs37062	<i>NDRG4</i>	16	58567238	G	A	0.25	0.16	0.48	0.37	0.38	Intronic
rs2074518	<i>LIG3, RFFL</i>	17	33324382	A	G	0.45	0.17	0.53	0.40	0.24	Intronic
rs17779747	<i>KCNJ2</i>	17	68494992	T	G	0.33	0.10	0.19	0.28	0.12	Intergenic
rs1805128	<i>KCNE1</i>	21	35821680	A	G	0.01	0.002	0.01	0.004	0.01	Missense

^aBase pair based on genome build 37.

^bIntergenic within 2,000 basepairs of the 3' end of the gene.

Chr indicates chromosome; CA, Coded Allele, based on allele reported in previous genome-wide association studies; NCA, noncoded allele.

Asian subpopulations for rs10919071 and rs2968863 and in Asians alone for rs2968864 and rs17779747; these groups had smaller sample sizes than the other race/ethnic groups. Additionally, 2 SNPs (rs4725982 and rs12296050) in African Americans and 5 SNPs (rs2968864, rs2968863, rs4725982, rs12296050, and rs17779747) in American Indians showed within-population heterogeneity in American Indians (eTables 5–7, <http://links.lww.com/EDE/A825>).

The remaining 5 SNPs (24%: rs12210810, rs16857031, rs846111, rs12576239, and rs8049607) showed considerable variation in direction of effect across race/ethnicity, with notable variation in precision.

Magnitude of Effect

In general, populations of non-European descent were more likely to have weaker estimated effect sizes than the European American population, although we found some variation in precision, particularly for Hispanic and Asian populations (eTable 3, <http://links.lww.com/EDE/A825>). Evidence of effect attenuation was particularly apparent among African American participants (18 of 21 SNPs with effects closer to the null). Notably, Hispanics were equally likely to have weaker or stronger effects compared with European descent populations.

Heterogeneity of Estimated Effects Across Race/Ethnicity

Overall, evidence of heterogeneity was observed for 12 of the 21 examined SNPs (57%). Of the 7 directionally consistent SNPs, heterogeneity of $P < 0.05$ among racial/ethnic groups was observed for 2 *NOS1AP* SNPs (rs12143842 [$P = 2 \times 10^{-3}$] and rs12029454 [$P = 2 \times 10^{-5}$]) (Figure 1, eTable 8, <http://links.lww.com/EDE/A825>). Among the 9 SNPs showing a consistent direction of effect in 4 populations, 7 demonstrated notable heterogeneity among groups: rs10919071, rs111756438, rs10494366, rs4725982, rs12296050, rs2968863, and rs2968864. For SNPs with an inconsistent direction of effect, heterogeneity of $P < .05$ was observed for 3 of these 5 SNPs (rs8049607 [$P = 1 \times 10^{-8}$], rs12576239 [$P = 2 \times 10^{-4}$], and rs846111 [$P = 0.04$]).

Haplotype Structure

Given the substantial evidence of among-race heterogeneity, we examined linkage disequilibrium patterns using data from 5 HapMap 3 populations to determine whether the observed heterogeneity of effect could be attributed to differences in linkage disequilibrium among racial/ethnic groups. For example, a large haplotype block surrounded rs12143842 (test for heterogeneity among racial/ethnic groups, $P = 0.002$)

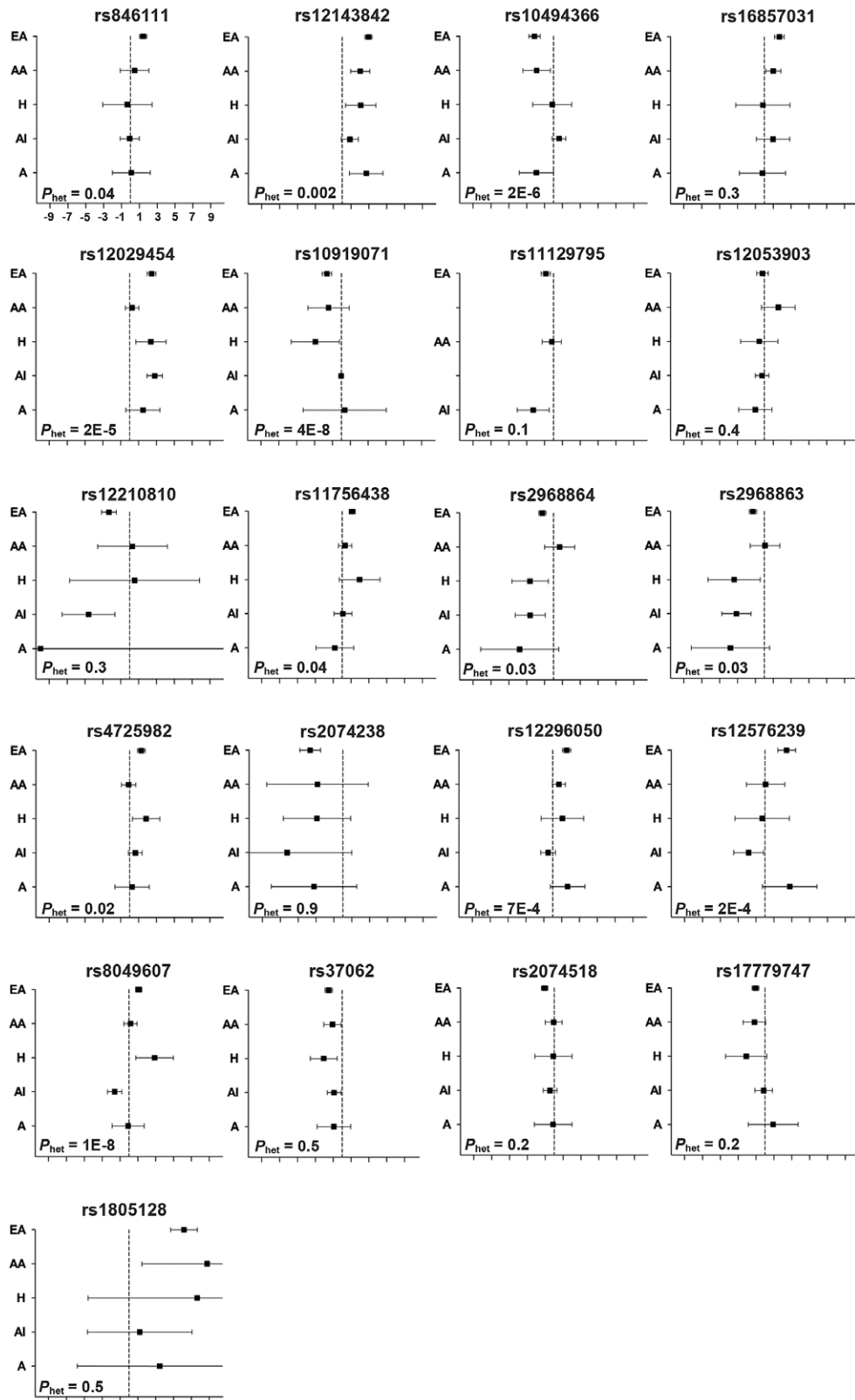


FIGURE 1. Forest plots of risk variants effect sizes (95% confidence interval) for a race/ethnicity-stratified meta-analysis of 32,474 participants from 6 participating PAGE studies. A, Asian; AA, African American; AI, American Indian; EA, European American; H, Hispanic; P_{het} , 2-sided P value for test of heterogeneity across populations.

in the European ancestry (24 kilobases [kb]), Asian ancestry (14kb), and Hispanic ancestry (10kb) populations (Figure 2). However, for African Americans, the haplotype block containing rs12143842 was much smaller (4kb) and did not contain any SNPs downstream of rs12143842. Another example of population-specific linkage disequilibrium patterns that may help explain the observed heterogeneity was provided by rs2968864 (test for heterogeneity, $P = 0.03$), which exhibited marked variation in effect size and haplotype block structure by race/ethnicity. Conversely, rs17779747, which did not exhibit among-race heterogeneity ($P = 0.2$), showed very similar linkage disequilibrium patterns across HapMap populations.

DISCUSSION

In this study, we evaluated evidence of generalizability for 21 index QT SNPs identified by prior GWAS of European descent populations in multiethnic populations from the PAGE study. Evidence of heterogeneity of effect across race/ethnicity was observed for a majority of SNPs, including SNPs from *NOS1AP*, the most commonly identified QT locus.^{8–10,12,13} Analyses of HapMap 3 populations suggested that variation in estimated effect by race/ethnicity may reflect underlying variation in linkage disequilibrium among race/ethnicity. Variation in linkage disequilibrium patterns as a cause for estimated effect size variation is further supported by the weaker effects seen in African Americans, where linkage disequilibrium blocks are smaller, which suggests that the causal SNPs may not be as effectively tagged as in European Americans.

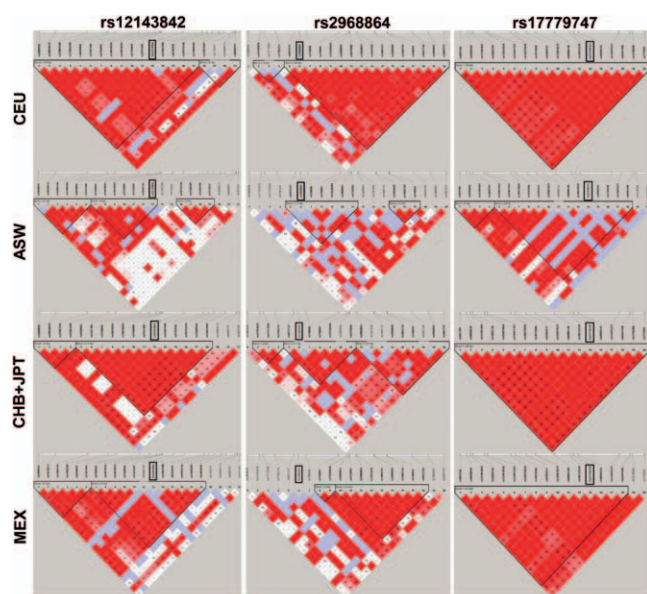


FIGURE 2. Linkage disequilibrium plots (D') from haplotype view for selected risk variants across 4 global populations. All populations come from International HapMap III populations. ASW, Samples of African American Ancestry; CEU, Samples of European Ancestry; CHB+JPT, Samples of Asian Ancestry; MEX, Samples of Hispanic Ancestry.

Heterogeneity of effect by race/ethnicity can reflect several phenomena, including variation in linkage disequilibrium among populations,²³ allelic heterogeneity (ie, the same locus but different causal variants influencing a trait across populations),²⁶ or gene-gene and gene-environment interaction.²⁷ Variation in linkage disequilibrium by race is a plausible source of the observed heterogeneity, given that several PAGE populations, particularly African Americans and Hispanics, have smaller linkage disequilibrium blocks than populations of European descent.²³ For this reason, the index SNPs identified in European American populations may not tag the underlying causal SNP in populations of African or Hispanic descent because it resides in a different linkage disequilibrium block.

Another potential cause of heterogeneity of effect across race/ethnicity is allelic heterogeneity, which has been demonstrated by studies of other ECG traits, particularly the PR interval.²⁸ In addition to the potential for race/ethnicity-specific alleles influencing QT, allelic heterogeneity is complicated by the potential for rare causal variants that can create “synthetic” signals. GWAS-identified index SNPs, including QT index SNPs, could simply represent a collection of rare causal variants, which would likely differ among populations – rather than a single causal SNP.²⁹ As the number of rare variants increases, so too does the potential for these synthetic associations to be found.²⁹ Thus, estimated effects would be expected to differ among racial/ethnic groups, as the SNPs evaluated above are representative of a diverse collection of rare variants.

Furthermore, heterogeneity of effect could be caused by underlying gene-gene or gene-environment interaction, especially if potential modifiers vary among populations. Previous studies have shown interaction between genetic variants and QT-altering pharmaceuticals, although only a single SNP examined in this study (rs1805128) was previously identified as a potential modifier in a large pharmacogenomics effort examining QT.³⁰ Additionally, lifestyle factors (including physical activity, rest/sleep, and emotional stimuli) may also interact with genetic variants associated with long-QT syndromes,³¹ although few studies have evaluated these potential modifiers in large population-based samples. Gene-gene interactions also are biologically plausible causes of heterogeneity, given evidence of population-specific variants influencing QT.³² However, very few studies have examined the influence of gene-gene interactions with QT, given the immensity of the task of testing interactions among millions of GWAS variants.

Regardless of the source of heterogeneity, these results, as well as studies of other heritable traits including type 2 diabetes³³ and obesity,³⁴ suggest that genomic studies of ancestrally diverse populations should analyze racial/ethnic groups separately, unless strong evidence of homogeneity is observed. However, the pooling of results across these groups is common in genetic epidemiology studies, particularly when there are small samples of non-European populations.^{35,36} A similar practice is the meta-analysis of summary

results across racial/ethnic background,^{37,38} although for common variants this approach is equivalent to pooling.³⁹ Therefore, strategies that pool or meta-analyze results across race implicitly assume that the index SNP tags the causal variant across all populations; they also assume the absence of allelic heterogeneity and among-race gene-gene or gene-environment interactions. Instead, to fully understand the genetic architecture underlying disease in diverse populations, studies should allow for these potential differences across distantly related populations and analyze them independently.

Although a hurdle for researchers who wish to combine results, genetic heterogeneity can be leveraged to identify novel genes and narrow intervals flanking index SNPs.²³ For example, fine-mapping studies are particularly relevant among admixed populations such as African Americans, Hispanics/Latinos, and American Indians. For QT, fine mapping has been conducted in African Americans³² to refine the region of association surrounding several genes and identify novel *NOS1AP* and *ATP1B1* SNPs specific to African Americans. The evidence of heterogeneity identified by our study further underscores the potential utility of fine-mapping studies in other populations, which could harness among-population differences in linkage disequilibrium to refine regions of association and identify additional SNPs influencing QT.

This study had several notable limitations. First, sample sizes in non-European American populations were modest, especially for Asian Americans, and thus produced less precise estimates. Nonetheless, few studies to date have examined associations between genetic variants and QT across 5 distinct racial/ethnic groups. Second, SNPs were selected in 2010 and therefore did not reflect more recent publications.¹² However, since SNP selection, only 1 new genetic locus (*SLC8A1*) has been identified for QT,¹² ensuring that our results remain contemporary. Additionally, we did not account for potential comorbidities in our primary analysis, as was done in previous GWAS. However, our results were robust to the exclusion of participants with prevalent stroke and prevalent ischemic heart disease (eTable 9, <http://links.lww.com/EDE/A825>). Furthermore, variations in ECG machines, sampling rates (250 Hz vs. 500 Hz), and reading software between studies (eTable 2, <http://links.lww.com/EDE/A825>) could have accounted for a portion of the heterogeneity observed among studies. A sensitivity analysis comparing results using 2 reading algorithms and sampling rates (Dalhousie at 250 Hz, Marquette 12SL at 500 Hz) among Women's Health Initiative participants showed little change in the effect estimates between the 2 methods and no change in the overall conclusions, indicating that differences in ECG methods likely had little effect on the results (eTable 10, <http://links.lww.com/EDE/A825>). Finally, we estimated effects of small magnitude that likely explained only a small fraction of the variation in QT. However, these results have

potential clinical and regulatory relevance. The Food and Drug Administration's standard for regulating QT-prolonging pharmaceuticals is a change of QT interval of 5 ms,⁴⁰ a threshold that is easily met when considering combinations of SNPs. Furthermore, our results suggest that the 21 SNPs are likely tag SNPs, which are expected to have smaller effects when compared with the underlying causal SNP.

In conclusion, our findings suggest the presence of considerable heterogeneity among racial/ethnic groups for previously identified QT index SNPs that may reflect several phenomena, including population-specific linkage disequilibrium patterns. More broadly, our results underscore the utility of examining heterogeneity by race/ethnicity in genetic association studies. Further characterization of these loci across multiethnic populations, including large-scale genotyping, is needed to provide additional insights into the genetic architecture of QT.

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