Fine mapping of QT interval regions in global populations refines previously identified QT interval loci and identifies signals unique to African and Hispanic descent populations

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BACKGROUND The electrocardiographically measured QT interval (QT) is heritable and its prolongation is an established risk factor for several cardiovascular diseases. Yet, most QT genetic studies have been performed in European ancestral populations, possibly reducing their global relevance.

OBJECTIVE To leverage diversity and improve biological insight, we fine mapped 16 of the 35 previously identified QT loci (46%) in populations of African American (n = 12,410) and Hispanic/Latino (n = 14,837) ancestry.

METHODS Racial/ethnic-specific multiple linear regression analyses adjusted for heart rate and clinical covariates were examined separately and in combination after inverse-variance weighted trans-ethnic meta-analysis.

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RESULTS The 16 fine-mapped QT loci included on the Illumina Metabochip represented 21 independent signals, of which 16 (76%) were significantly (P-value $\leq 9.1\times10^{-5}$) associated with QT. Through sequential conditional analysis we also identified three trans-ethnic novel SNPs at *ATP1B1, SCN5A-SCN10A*, and *KCNQ1* and three Hispanic/Latino-specific novel SNPs at *NOS1AP* and *SCN5A-SCN10A* (two novel SNPs) with evidence of associations with QT independent of previous identified GWAS lead SNPs. Linkage disequilibrium patterns helped to narrow the region likely to contain the functional variants at several loci, including *NOS1AP, USP50-TRPM7*, and *PRKCA*, although intervals surrounding *SLC35F1-PLN* and *CNOT1* remained broad in size (>100 kb). Finally, bioinformatics-based functional characterization suggested a regulatory function in cardiac tissues for the majority of independent signals that generalized and the novel SNPs.

CONCLUSION Our findings suggest that a majority of identified SNPs implicate gene regulatory dysfunction in QT prolongation, that the same loci influence variation in QT across global populations, and that additional, novel, population-specific QT signals exist.

KEYWORDS Hispanic/Latino; African American; QT interval; Fine mapping; Electrocardiography

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Introduction

The role of QT interval (QT) prolongation in the etiology of ventricular arrhythmias that predispose to sudden cardiac death (SCD), a leading cause of mortality,[1] was recognized as early as 1957 upon the identification of a congenital long QT syndrome.[2] Sixty years later, population-based research has demonstrated the potential for studies of QT prolongation to enhance mechanistic understanding of SCD[3–5] as well as coronary heart disease[6] and stroke.[7] Drug-induced QT prolongation has also attracted regulatory scrutiny as the most common cause of the withdrawal or restricted marketing of pharmaceuticals.[4,5] Yet, identification of populations at increased risk of SCD following innate or acquired QT prolongation remains difficult, necessitating a better understanding of underlying molecular mechanisms.[8]

Genome-wide association studies (GWAS) have identified 35 QT loci,[9–18] predominantly in large (n ~ 100,000) populations of European descent,[9–15] providing new insights into mechanisms underlying ventricular conduction.[19] QT GWAS in Indian Asian,[15] East Asian,[16,17] and African American[18] populations have been performed, but identified fewer loci than GWAS in European descent populations, likely reflecting smaller sample sizes (n = 2,994-12,097), lower genotyping array coverage,[15,17,18] or imputation to suboptimal reference panels.[18] The global relevance of previously identified QT loci and whether population-specific single nucleotide polymorphism (SNP) influencing QT exists therefore remain largely unknown. Furthermore, several populations not yet included in QT GWAS, including Hispanics/Latinos, trace their recent origins to Europe, Africa, and the Americas,[20] presenting exceptional yet underutilized opportunities for fine mapping, particularly when combined with data from African Americans. Here, we extend our previous QT fine-mapping study of 8644 African American participants and 11 QT loci densely genotyped on the Illumina Metabochip (San Diego, CA) array[21] by including 3766 additional African American and 14,837 Hispanic/Latino participants and evaluating 4 additional loci.

Methods

Study populations

The Population Architecture Using Genomics and Epidemiology consortium is a National Human Genome Research Institute–funded effort examining the epidemiologic architecture of genetic variants associated with human diseases and traits across diverse populations. Six Population Architecture Using Genomics and Epidemiology studies,[22] in addition to the Multi-Ethnic Study of Atherosclerosis, contributed data to this study (Online Supplemental Methods). For all populations, race/ethnicity was defined by self-report; ancestral outliers were identified principal component analysis and excluded. All procedures performed in studies of human participants were approval by local institutional review boards.

Genotype platforms

The Metabochip is a custom Illumina iSELECT array designed to support large-scale follow-up of cardiovascular and metabolic loci, including QT.[23] Sixteen QT loci (46% of QT loci identified as of October 2016) were represented on the Metabochip

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(Table 1; Online Supplement). Index SNPs, that is, locus-specific SNPs with the lowest *P* value reported by previous GWAS, that were not directly genotyped on the Metabochip were, when possible, represented by SNPs in high linkage disequilibrium (LD; $r^2 \geq 0.80$) with the index SNP in the ancestral population in which the association was first reported.

Statistical analysis

To interpret fine-mapping results, LD was calculated in 500 kb sliding windows using PLINK[24] and African American, Hispanic/Latino, and transethnic (ie, combined African American and Hispanic/Latino) data, the latter in proportion to racial/ethnic-specific (ie, each race/ethnicity separately) sample sizes. Metabochip LD and allele frequency information for a European population was provided for 2143 Malmö Diet and Cancer Study control participants.[25]

Racial/ethnic-stratified linear regression (Atherosclerosis Risk in Communities Study [ARIC] Epidemiologic Architecture using Genomics and Epidemiology Vanderbilt University Biobank [EAGLE BioVU] Coronary Artery Risk Development in Young Adults [CARDIA] Cardiovascular Health Study [CHS] Multi-Ethnic Study of Atherosclerosis [MESA], and Women's Health Initiative [WHI]; implemented in PLINK[24]) or a weighted version of generalized estimating equations (The Hispanic Community Health Study/Study of Latinos [HCHS/SOL]; implemented in SUGEN)[26] were used to evaluate the association between QT and a maximum of 7239 SNPs (racial/ethnic-specific minor allele frequency [MAF] ≥0.01) from 16 previously identified QT loci assuming an additive genetic model and including age, sex, study center/region, ancestry principal components, and heart rate as covariates. Racial/ethnic-stratified and transethnic estimates were combined via inverse variance meta-analysis using METAL.[27]

Generalization

We first evaluated whether loci identified in European populations generalized to African American and Hispanic/Latino populations by identifying all common and low-frequency (MAF ≥1%) index SNPs, and all SNPs correlated with the index SNPs ($r^2 \geq 0.20$) using Malmö Diet and Cancer Study LD estimates; these are the only SNPs evaluated for generalization. For loci with multiple index SNPs, SNPs with $r^2 < 0.20$ were considered independent signals. The generalization significance criterion was defined as $\alpha_a = 9.1 \times 10^{-5}$, calculated using the number of tag SNPs in African Americans ($r^2 \geq 0.80$; determined using African American LD patterns) that captured all SNPs that were correlated with the index SNPs ($r^2 \geq 0.20$; determined using Malmö Diet and Cancer Study LD patterns). Index SNPs rs10919070 (*ATP1B1*), rs11756438 (*SLC35F1-PLN*), rs2072413 (*KCNH2*), rs7122937 (*KCNQ1*), and rs2074238 (*KCNQ1*) did not pass quality control, and no proxy was available for rs2968864 (*KCNH2*). For *KCNJ2*, all SNPs correlated with the index SNPs either did not pass quality control or had MAF <0.01.

Novel SNP identification

To identify novel SNPs, we selected all SNPs at the 16 QT loci that were uncorrelated with the index SNPs ($r^2 < 0.20$ in the Malmö Diet and Cancer Study), which potentially represent genetic associations not previously reported for QT. Sequential conditional analyses were then performed adjusting for significant lead SNPs, that is, the most significant transethnic or racial/ethnic SNP at each locus, until no significant SNPs remained. If a statistically significant SNP was identified, defined as 0.05 divided by the number of SNPs in African Americans with MAF ≥ 0.01 that were uncorrelated with the index SNPs (n = 6082; $\alpha_b = 8.22 \times 10^{-6}$), the SNP was identified as novel and added to the adjustment set.

Bioinformatics categorization of QT loci

Functional annotation was performed for all significant lead SNPs, novel SNPs, and correlated SNPs ($r^2 \geq 0.80$; identified in the appropriate 1000 Genomes reference populations) in relevant cardiac tissues. Specifically, using HaploReg v2 (http://www.broadinstitute.org/mammals/haploreg/haploreg.php), all SNPs in each LD block were characterized with putative functional roles including conservation; promoter and/or enhancer epigenetic markers, derived from the Roadmap Epigenomics Project and ENCODE; DNAse hypersensitive sites; and transcription factor binding motifs.

Results

Participants were drawn from 7 studies (Online Supplement), which contributed 12,410 African American and 14,837 Hispanic/Latino participants (Online Supplemental Table S1). The majority of participants were women (19,345 [71%]), and the mean age ranged from 39 to 73 years. Estimates of mean QT and heart rate were generally consistent across studies (weighted mean 408 ms), but were expectedly lower in EAGLE BioVU given exclusion criteria (Online Supplement).

We examined a maximum of 7239 SNPs at 16 previously identified QT loci represented on the Metabochip. In African Americans, the number of SNPs at each locus ranged from 42 to 1195 (mean number of SNPs per locus 451; Online Supplemental Table S2). Among Hispanics/Latinos, the number of SNPs per locus was slightly lower and ranged from 33 to 97 (mean number of SNPs per locus 361).

Generalization

A total of 39 QT index SNPs across 21 independent signals were identified, with the *NOS1AP*, *ATP1B1*, *SLC35F1-PLN*, and *KCNH2* loci harboring multiple independent signals (Table 1). Sixteen (76%) independent signals generalized to the transethnic population, encompassing 12 QT loci (Table 1; Online Supplemental Tables S3 and S4). Among these 16 independent signals, 6 lead SNPs were identical to previously reported index SNPs (rs846111 [*RNF207*], rs12143842 [*NOS1AP*], rs2968863 [*KCNH2*], rs12296050 [*KCNQ1*], rs735951 [*LITAF*], and rs2074518 [*LIG3*]), 6 lead SNPs were equivalent to previously reported index SNPs (ie, *P* values within ~1 order of magnitude), and 4 lead SNPs had

Table 1 Association results examining evidence of generalization for trans-ethnic lead SNPs at 21 independent signals at 16 QT loci to n=12,410 African Americans and n=14,837 Hispanic/Latinos.

Genome-wide Significant Published Index SNPs						Trans-Ethnic Population								African Americans				Hispanic/Latino			
Locus	Ind. Signal	Index SNP[c]	A1/A2	Race/Ethnicity	Beta	SE	CAF	Lead SNP	A1/A2	Beta	SE	*P*-value		Beta	SE	*P*-value	CAF	Beta	SE	*P*-value	CAF
RNF207	1	rs846111	C/G	EA	1.73	0.13	0.28	rs846111	C/G	1.73	0.29	1.4×10^{-9}		0.39	0.62	0.54	0.056	2.09	0.32	8.4×10^{-11}	0.17
NOS1AP	1	rs12143842	T/C	EA	3.50	0.11	0.24	rs12143842	T/C	2.86	0.23	1.1×10^{-35}		2.40	0.37	6.9×10^{-11}	0.12	3.15	0.29	6.3×10^{-27}	0.22
		rs2880058	G/A	EA	0.19[d]	0.06[d]	0.32														
		rs1572498[a]	G/T	EA	4.90	1.0	0.39														
		rs10494365	NR	AS	NR	NR	0.39														
	2	rs4657178	G/T	EA	2.19	0.26	0.33	rs12123267	T/C	1.89	0.19	1.9×10^{-23}		1.60	0.27	2.0×10^{-9}	0.30	2.18	0.27	4.8×10^{-16}	0.28
		rs12029454	A/G	EA	3.00	0.18	0.15														
		rs10800352[a]	NR	AS	1.71	NR	NR														
	3	rs16857031	G/C	EA	3.32	0.35	0.14	rs885148	T/C	1.29	0.21	6.6×10^{-10}		1.26	0.37	8.1×10^{-4}	0.14	1.30	0.25	2.1×10^{-7}	0.46
ATP1B1	1	rs10919071	A/G	EA	2.05	0.29	0.87	rs72706963	C/T	2.46	0.29	2.7×10^{-17}		2.03	0.78	9.0×10^{-3}	0.97	2.53	0.31	7.2×10^{-16}	0.82
		rs10919070	C/A	EA	−1.68	0.14	0.13														
	2	rs12061601[a]	C/T	AA	−1.89	0.30	0.29	rs12061601	C/T	−2.01	0.22	3.4×10^{-19}		−1.91	0.28	8.4×10^{-12}	0.26	−2.19	0.38	5.8×10^{-9}	0.12
SCN5A-SCN10A	1	rs6793245	A/G	EA	−1.12	0.10	0.32	rs62241188	G/C	−1.64	0.30	3.2×10^{-8}		0.87	0.54	0.11	0.05	1.96	0.35	2.8×10^{-8}	0.13
		rs12053903	C/T	EA	−1.40	0.18	0.34														
		rs11129795	A/G	EA	−1.27	0.23	0.23														
SLC35F1-PLN	1	rs11153730	T/C	EA	−1.65	0.10	0.50	rs763254	T/C	−1.58	0.20	2.1×10^{-15}		−1.12	0.28	7.3×10^{-5}	0.75	−2.03	0.28	4.6×10^{-13}	0.74
		rs11970286	T/C	EA	1.64	0.20	0.44														
		rs11756438	A/C	EA	1.58	0.18	0.47														
	2	rs12210810	C/G	EA	−3.13	0.43	0.06	rs3901856	G/A	−0.90	0.25	2.9×10^{-4}		−0.28	0.35	0.41	0.15	−1.55	0.36	1.4×10^{-5}	0.13
CAV1	1	rs9920	C/T	EA	0.79	0.14	0.09	rs6978354	A/G	−0.67	0.19	3.1×10^{-4}		−0.71	0.28	0.012	0.47	−0.64	0.25	9.3×10^{-3}	0.48
KCNH2	1	rs2968863	T/C	EA	−1.35	0.23	0.29	rs2968863	T/C	−1.74	0.29	2.9×10^{-9}		−1.40	0.56	0.012	0.046	−1.86	0.34	5.9×10^{-8}	0.14
		rs2968864	C/T	EA	−1.40	0.35	0.25														
		rs2072413	T/C	EA	−1.68	0.11	0.27														
	2	rs4725982	T/C	EA	1.60	0.35	0.22	rs3815459	T/C	1.09	0.20	3.7×10^{-8}		0.88	0.30	3.9×10^{-3}	0.31	1.24	0.26	1.8×10^{-6}	0.35
KCNQ1	1	rs12296050	T/C	EA	1.93	0.12	0.19	rs12296050	T/C	1.13	0.18	1.9×10^{-10}		0.94	0.25	1.3×10^{-4}	0.48	1.33	0.26	1.8×10^{-7}	0.35
		rs12576239	T/C	EA	2.10	0.35	0.13														
ATP2A2	1	rs3026445	C/T	EA	0.62	0.09	0.36	rs4630352	A/G	0.52	0.17	0.0028		0.43	0.25	0.086	0.59	0.61	0.24	0.012	0.43
USP50-TRPM7	1	rs3105593	T/C	EA	0.66	0.10	0.45	rs3109882	A/G	0.82	0.18	2.9×10^{-6}		0.96	0.25	1.2×10^{-4}	0.38	0.69	0.25	5.6×10^{-3}	0.47
LITAF	1	rs735951	A/G	EA	−1.15	0.10	0.46	rs735951	A/G	−1.33	0.17	1.5×10^{-14}		−0.85	0.25	5.7×10^{-4}	0.44	−1.80	0.24	1.3×10^{-13}	0.41
		rs8049607	T/C	EA	1.25	0.22	0.46														
CNOT1	1	rs246196	C/T	EA	−1.73	0.11	0.26	rs9926577	T/C	−1.99	0.21	2.7×10^{-21}		−1.46	0.32	1.5×10^{-5}	0.84	−2.32	0.27	4.8×10^{-18}	0.66
		rs37060[b]	A/G	EA	1.66	0.23	0.74														
		rs37062	G/A	EA	−2.10	0.35	0.24														
LIG3	1	rs2074518	T/C	EA	−1.23	0.18	0.46	rs2074518	T/C	−0.71	0.20	3.4×10^{-4}		−0.73	0.32	0.024	0.17	−0.71	0.25	4.8×10^{-3}	0.38
		rs1052536	C/T	EA	0.98	0.10	0.53														
PRKCA	1	rs9892651	C/T	EA	−0.74	0.10	0.43	rs56152251	A/G	−1.00	0.17	8.5×10^{-9}		−0.67	0.24	3.4×10^{-4}	0.48	−1.34	0.25	6.3×10^{-8}	0.45
KCNJ2	1	rs1396515[a]	C/G	EA	−0.98	0.09	0.52	rs189495613	T/C	0.72	0.18	5.1×10^{-5}		0.49	0.24	3.4×10^{-4}	0.57	0.99	0.26	1.6×10^{-4}	0.69
		rs17779747	T/G	EA	−1.16	0.21	0.35														
KCNE1	1	rs1805128	T/C	EA	7.42	0.85	0.01	N/a[b]													

A = adenine; A1/A2 = coded/non-coded allele; AA = African American; AS = East Asian ancestry; C = cytosine; CAF = coded allele frequency; EA = European ancestry; G = guanine; Ind = independent; N/a = not applicable; NR = not reported; SE = standard error; T = thymine.

aProxy substituted.

bNo SNPs with minor allele frequency ≥0.01.

cIf SNP reported by multiple studies, effect from largest study reported.

dRank transformation applied.

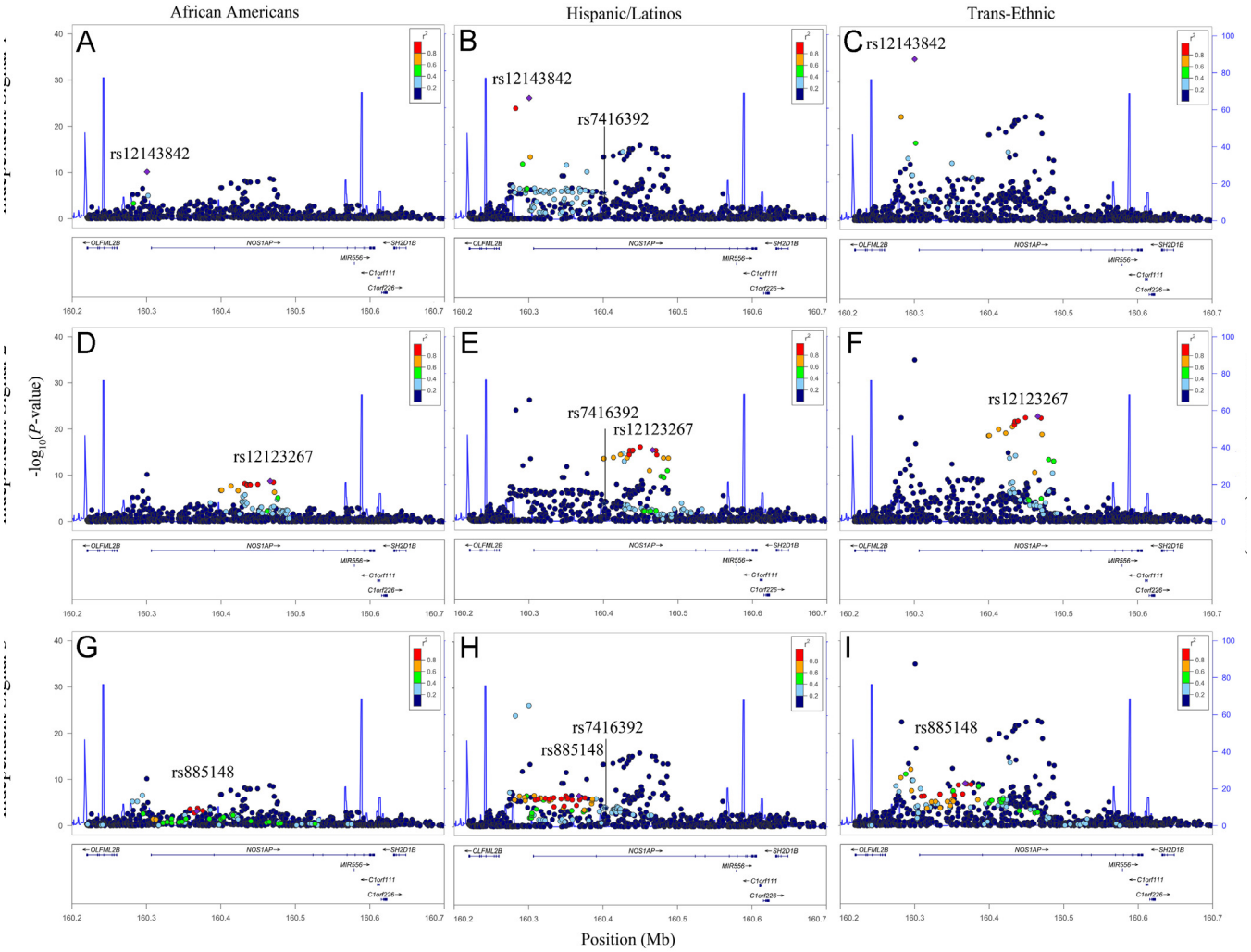

Figure 1 Racial/ethnic-specific and transethnic regional association plots for *NOS1AP* independent signals 1 (**A–C**), 2 (**D–F**), and 3 (**G–I**). Population-specific $\log_{10}(P$ values) (left y axis) are plotted against the SNP genomic position (National Center for Biotechnology Information Build 36 [NCBI Build 36], x axis); the estimated recombination rate from the 1000 Genomes Project is shown in blue on the right y axis. Lead SNPs are denoted with a purple diamond. SNPs are colored to reflect population-specific r^2 with the lead SNP. Novel SNPs are denoted by vertical lines and stars. SNP = single nucleotide polymorphism.

P values at least 2 orders of magnitude farther from the null than index SNP *P* values (Online Supplemental Table S3). For example, the *SCN5A-SCN10A* index SNP *P* values were ~5 times lower in magnitude (index SNP *P*-value range 0.0015–0.024; Online Supplemental Table S3) than the transethnic lead SNP *P* value of 3.2×10^{-8} (Table 1). Effect sizes also were consistently lower in African Americans than in Hispanics/Latinos.

The transethnic lead SNP was also identical to the racial/ethnic-specific lead SNP for 11 of the 16 independent signals in African Americans and 10 of the 16 independent signals in Hispanics/Latinos (Online Supplemental Table S5), and effect sizes were again consistently of smaller magnitude in African Americans. For the remaining independent signals, *P* values for the racial/ethnic-specific lead SNPs were equivalent to (ie, within ~1 order of magnitude) those for the transethnic lead SNP, with the exception of 1 lead SNP in African Americans (*RNF207*) and 2 lead SNPs in Hispanics/Latinos (*NOS1AP* independent signal 3 and *KCNH2* independent signal 1) (Online Supplemental Table S3).

Among the 5 independent signals that did not generalize to the transethnic population (*SLC35F1-PLN* independent signal 2, *CAV1*, *ATP2A2*, *LIG3*, and *KCNE1*), effect estimates for all but *KCNE1* were directionally consistent with effects estimated in European ancestral populations, but of considerably smaller magnitude, particularly in African Americans (Online Supplemental Table S4). For the *KCNE1* independent signal, no SNPs with MAF >1% were identified, although rs1805128, the *KCNE1* index SNP, was significant in Hispanics/Latinos (MAF 0.0053; $P = 1.4 \times 10^{-7}$) (Online Supplemental Table S3).

Finally, varied generalization success was observed for racial/ethnic-specific analyses. For example, only 5 independent signals generalized to African Americans, whereas 15 independent signals generalized to Hispanics/Latinos. Other notable observations include the consistently lower estimated effects in African Americans than in Hispanics/Latinos (Online Supplemental Table S3).

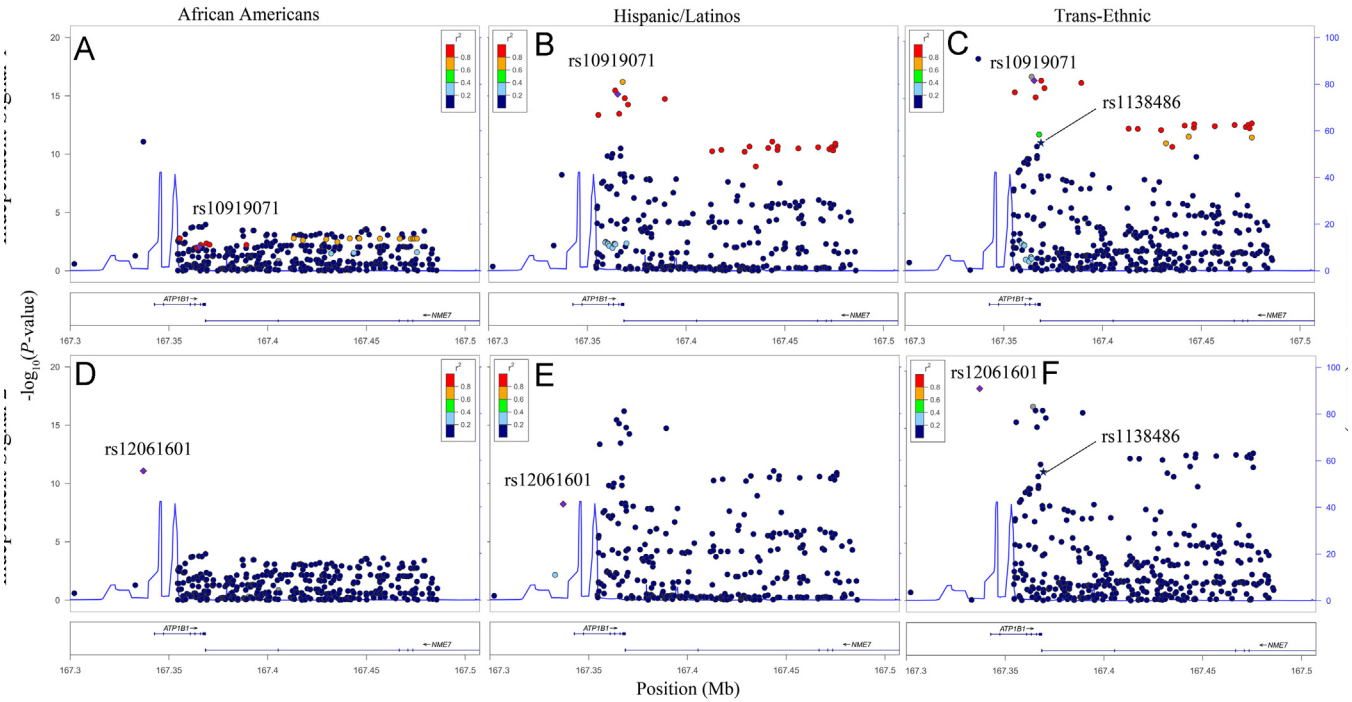

Figure 2 Racial/ethnic-specific and transethnic regional association plots for *ATP1B1* independent signals 1 (**A–C**) and 2 (**D–F**). Population-specific $\log_{10}(P$ values) (left y axis) are plotted against the SNP genomic position (NCBI Build 36, x axis); the estimated recombination rate from the 1000 Genomes Project is shown in blue on the right y axis. Lead SNPs are denoted with a purple diamond. SNPs are colored to reflect population-specific r^2 with the lead SNP. Novel SNPs are denoted by vertical lines and stars. SNP = single nucleotide polymorphism.

Locus refinement

We then examined the degree to which LD patterns assisted with the narrowing of independent signals that generalized (Online Supplemental Table S6, Figures 1–4, and Online Supplemental Figures S1–S8). On average, African American LD patterns were associated with the fewest number of SNPs correlated with the lead SNP and the smallest interval size. However, transethnic LD patterns produced slightly smaller interval sizes when restricted to independent signals that generalized to African Americans and Hispanics/Latinos separately.

Novel signals

We identified 3 transethnic novel SNPs at *ATP1B1*, *SCN5A-SCN10A*, and *KCNQ1* and 3 Hispanic/Latino-specific novel SNPs at *NOS1AP* and *SCN5A-SCN10A* (2 SNPs) (Tables 2 and 3 and Figures 1–4). Notably, the 3 *SCN5A-SCN10A* novel SNPs were uncorrelated when examining African American ($r^2 < 0.038$), European ($r^2 < 0.052$), and Hispanic/Latino ($r^2 < 0.095$) LD patterns. Effect estimates for novel Hispanic/Latino SNPs (β range −1.17 to −2.34) also were almost twice as large as effects estimated in African Americans (β range −0.62 to −1.22; Table 2).

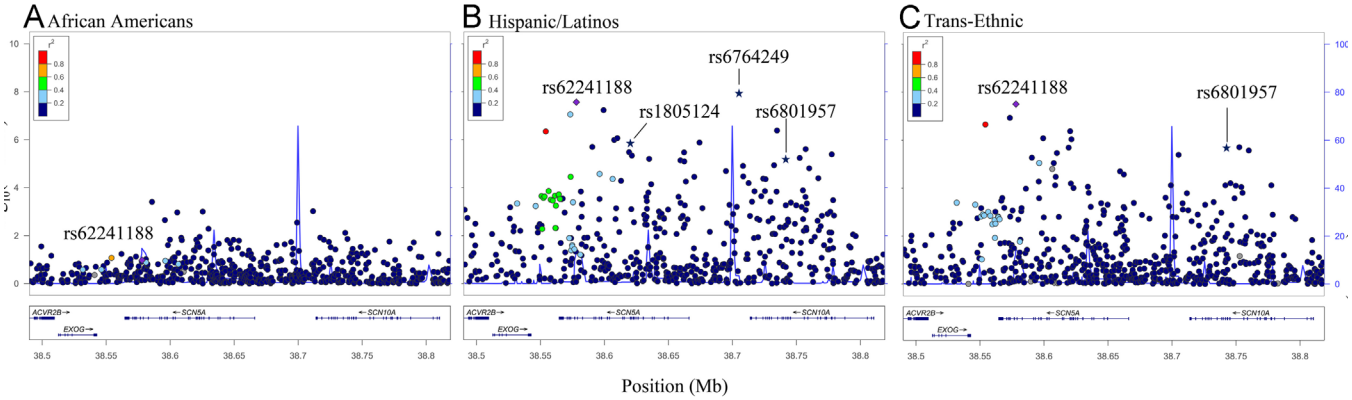

Figure 3 Racial/ethnic-specific and transethnic regional association plots for *SCN5A/SCN10A*. Population-specific $\log_{10}(P$ values) (left y axis) are plotted against the SNP genomic position (NCBI Build 36, x axis); the estimated recombination rate from the 1000 Genomes Project is shown in blue on the right y axis. Lead SNPs are denoted with a purple diamond. SNPs are colored to reflect population-specific r^2 with the lead SNP. Novel SNPs are denoted by vertical lines and stars. SNP = single nucleotide polymorphism.

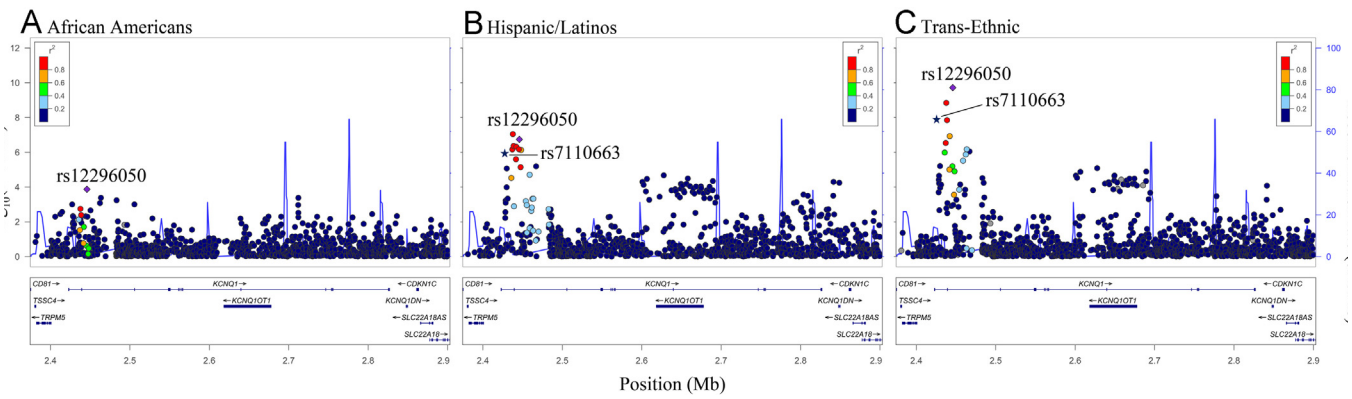

Figure 4 Racial/ethnic-specific and transethnic regional association plots for *KCNQ1*. Population-specific $\log_{10}(P$ values) (left y axis) are plotted against the SNP genomic position (NCBI Build 36, x axis); the estimated recombination rate from the 1000 Genomes Project is shown in blue on the right y axis. Lead SNPs are denoted with a purple diamond. SNPs are colored to reflect population-specific r^2 with the lead SNP. Novel SNPs are denoted by vertical lines and stars. SNP = single nucleotide polymorphism.

Bioinformatics characterization

Bioinformatics characterization identified 3 nonsynonymous coding SNPs, for which in silico prediction algorithms indicated that the amino acid changes were tolerated (Online Supplemental Tables S7 and S8). With the exception of 4 SNPs in Hispanics/Latinos and 2 SNPs in African Americans, all independent signals contained at least 1 SNP with evidence for a regulatory function in ≥1 relevant tissues.

Discussion

Here, we conducted the largest and most racially/ethnically diverse fine-mapping study of QT to date. We demonstrated allelic heterogeneity through the identification of multiple independent signals, refined the location of previously known QT loci by reducing the number of potential causal variants for future interrogation, and identified racial/ethnic-specific signals. These efforts enhance our understanding of the genetic architecture of QT in previously underrepresented populations.

One notable observation was our success generalizing QT loci transethnically, suggesting that previously identified independent signals are relevant across global populations. However, we had different degrees of success generalizing QT loci to each population separately. Although we increased our sample size by ~50%,[21] we still generalized only a handful (~24%) of independent signals to African Americans, for whom effect sizes were consistently of smaller magnitude than for Hispanic/Latino or European populations. In contrast, 71% of independent signals successfully generalized to Hispanics/Latinos, despite approximately equivalent effective sample sizes between the 2 study populations. These distinctions may reflect greater average European ancestry in Hispanics/Latinos than in African Americans[28] and a higher proportion of shared functional variants. The LD structure in Hispanic/Latino and European ancestral populations also may be more similar to each other than to African populations, thus enabling the detection of functional variants. In addition, the Metabochip was developed using an early release of the 1000 Genomes Project and therefore incompletely captured African-specific variation,[23] despite low LD and high genetic heterogeneity that make African populations ideal for fine mapping.[29]

The need to further expand fine-mapping efforts is underscored by findings for *NOS1AP* independent signal 1 that harbors rs12143842. rs12143842 is the most commonly reported QT index SNP identified to date and was also identified by our transethnic and racial/ethnic-specific meta-analyses. Yet, functional studies of *NOS1AP* identified rs7539120, not rs12143842, as the functional variant,[19] although rs7539120 was not genotyped on the Metabochip. Inconsistencies between prior GWAS and *NOS1AP* functional studies likely reflect both the HapMap2 platform to which the majority of prior GWAS were imputed, which did not include rs7539120, and the decreased imputation accuracy for rs7539120 compared to rs12143842 that lowered estimated effects for rs7539120 in contrast to rs12143842. Interestingly, rs12143842 and rs7539120 are weakly correlated in the 1000 Genomes Americans of African Ancestry in

Table 2 Novel SNPs at three previously identified QT loci in n=12,410 African Americans and n=14,837 Hispanic/Latinos.

		Trans-Ethnic Population				African Americans				Hispanic/Latinos			
Locus	Lead SNP	Beta	SE	*P*-value	CA	Beta	SE	*P*-value	CAF	Beta	SE	*P*-value	CAF
ATP1B1	rs1138486	−1.79	0.25	2.0×10^{-12}	T	−1.12	0.34	9.9×10^{-4}	0.16	−2.34	0.38	1.0×10^{-9}	0.15
SCN5A-SCN10A	rs6801957	−0.97	0.21	3.7×10^{-6}	A	−0.62	0.34	0.073	0.16	−1.17	0.26	8.5×10^{-6}	0.38
KCNQ1	rs7110663	−1.49	0.25	6.5×10^{-11}	T	−1.22	0.29	2.6×10^{-5}	0.34	−1.92	0.37	1.8×10^{-7}	0.33

A = adenine; CA = coded allele; CAF = coded allele frequency; SE = standard error; T = thymine.

Table 3 Novel SNPs at 2 previously identified QT loci in 14,837 Hispanics/Latinos

						Coded allele frequency			
Locus	Lead SNP	β	SE	*P*	CA	EU*	AF†	HL‡	ASN§
NOS1AP	rs7416392	−1.76	0.38	5.0×10^{-6}	T	0.32	0.57	0.42	0.50
SCN5A-SCN10A	rs6764249	1.70	0.31	3.8×10^{-8}	G	0.15	0.22	0.24	0.35
SCN5A-SCN10A	rs1805124	1.35	0.29	4.3×10^{-6}	G	0.21	0.29	0.22	0.10

AF = African American; ASN = East Asian; CA = coded allele; EU = European; HL = Hispanic/Latino; QT = QT interval; SE = standard error; SNP = *single nucleotide polymorphism*.

*Calculated in the Malmö Diet and Cancer Study.

†Calculated in the Atherosclerosis Risk in Communities Study.

‡Calculated in the Hispanic Community Health Study/Study of Latinos.

§Calculated in the 1000 Genomes ASN population.

SW USA population ($r^2 = 0.16$), but moderately correlated in the European ($r^2 = 0.54$) and admixed American ($r^2 = 0.38$) populations. These findings suggest that fine mapping in African American populations, enabled by denser genotyping or high-quality imputation, may have negated the targeted saturation sequencing of *NOS1AP* in European ancestral populations that was required to pinpoint the causal variant.

We also reported varied success in narrowing intervals surrounding previously identified GWAS index SNPs. For several loci, including *RNF207*, *NOS1AP*, *ATP1B1*, *SCN5A-SCN10A*, and *KCNQ1*, we identified a limited number of SNPs for future interrogation. Indeed, recent functional studies have identified *RNF207* as an important regulator of cardiac excitation, although few studies have been performed to pinpoint the exact causal SNPs.[30] *RNF207* also was the only locus for which bioinformatics characterization identified a nonsynonymous SNP, rs846111, although in silico prediction suggested that the amino acid change was tolerated. Yet, transethnic and racial/ethnic-specific LD patterns did not identify any SNPs in high LD with rs846111. Additional work examining a denser panel of SNPs at this locus is likely warranted.

Despite success for several independent signals, substantial narrowing of intervals was not achieved for other independent signals, including *CNOT1* and *SLC35F1-PLN* independent signal 1, possibly reflecting LD block size and the extent of LD differences with the causal variant between ancestral populations. Expansion of fine-mapping efforts to include other global populations may offer improved locus refinement. For example, wide variation in the number of SNPs correlated with *SLC35F1-PLN* index SNP rs11153730 in 1000 Genomes populations was observed, ranging from 61 in the Han Chinese in Beijing to 134 in the African Ancestry in SW USA population. Future studies should evaluate the extent to which East Asian populations can be used to further narrow the *SCL35F1-PLN* locus.

Study limitations

There are several limitations of the present study. First, although the Metabochip included dense genotyping of 16 QT loci, the majority of recently discovered QT loci were excluded.[12] Second, it is possible that the causative variants were not included on the Metabochip, necessitating future sequencing studies or studies for which high imputation accuracy is possible, both of which are outside the scope of the current effort. Finally, the implications of conducting a QT GWAS in predominantly female populations shouldering higher burdens of QT-prolonging risk factors than in the original discovery populations, for example, obesity and diabetes, also deserve examination, including the degree to which variation in known QT correlates modify reported genetic associations and underlying pathways.[31,32]

Conclusion

Our findings suggest that the same genes influence variation in QT across ancestral populations and that additional, novel, and possibly population-specific signals exist, which together implicate gene regulatory dysfunction. Additional characterization of QT loci through whole-genome sequencing or large-scale genotyping combined with imputation panels that capture population genetic content may further illuminate the genetic and molecular mechanisms underlying QT.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.hrthm.2016.12.021.

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