Generalization of Variants Identified by Genome-wide Association Studies for Electrocardiographic Traits in African Americans

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SUMMARY

Electrocardiographic (ECG) measurements vary by ancestry. Genome-wide association studies (GWAS) have identified loci that contribute to ECG measurements; however most are performed in Europeans collected from population-based cohorts or surveys. The strongest associations reported are in *NOS1AP* with QT interval and *SCN10A* with PR and QRS durations. The extent to which these associations can be generalized to African Americans has yet to be determined. Using electronic medical records, PR and QT intervals, QRS duration, and heart rate were determined in 455 African Americans as part of the Vanderbilt Genome-Electronic Records Project and Northwestern University NUgene Project. We tested for an association between these ECG traits and >930K SNPs. We identified a total 36 novel associations with PR interval, QRS duration, QT interval, and heart rate at p< 1.0 ×10^{-6}. Using published GWAS data, we compared our results

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with those previously identified in other populations. Five associations originally identified in other populations generalized with respect to statistical significance and direction of effect. A total of 43 associations have a consistent direction of effect with European and/or Asian populations. This work provides a catalogue of generalized versus non-generalized associations, a necessary step in prioritizing GWAS-identified regions for further fine-mapping in diverse populations.

Keywords

Electrocardiography; African Americans; GWAS; Generalization; Electronic Medical Records

INTRODUCTION

Candidate gene studies have identified several genes that affect cardiac depolarization and conduction measured by ECG traits. One set of candidates consists of genes that encode voltage gated potassium and sodium channels, which also play an important role in the pathophysiology of long QT syndrome (Lai et al. 1994; Splawski et al. 2002; Wang et al. 1996; Wang et al. 1995a; Wang et al. 1995b). These associations have been confirmed by molecular genetic studies, and, in the past five years, GWAS have also identified these associations with various ECG phenotypes in European and Asian-descent populations (Chambers et al. 2010; Newton-Cheh et al. 2009; Smith et al. 2009). These GWAS have not only implicated common variation in congenital long QT syndrome genes, but also have identified associations between genes not previously implicated in cardiac electrophysiology and ECG traits, such as *NOS1AP* with QT interval (Arking et al. 2006; Post et al. 2007). Genome-wide association studies for ECG traits have also revealed pleiotropy: for example, variants in the cardiac sodium channel gene *SCN5A,* has been associated with across multiple ECG traits (Holm et al. 2010; Jeff et al. 2011; Marroni et al. 2009; Newton-Cheh et al. 2007; Smith et al. 2009). Variants in *SCN10A,* a gene previously known to play a role in the action potentials in nociceptive nerve fibers (Abrahamsen et al. 2008; Akopian et al. 1999; Zimmermann et al. 2007), have been identified by GWAS for an association with PR and QRS interval (Chambers et al. 2010; Denny et al. 2010; Holm et al. 2010; Pfeufer et al. 2010; Sotoodehnia et al. 2010).

As of October 2011, there were 127 unique trait-SNP associations reported in the National Human Genome Research Institute's (NHGRI) GWAS catalog for electrocardiographic (ECG) traits (http://www.genome.gov/gwastudies/). Most of these studies were limited to European (118 associations) or Asian (9 associations)-descent populations, and it is unclear if these GWAS-identified variants generalize across populations, particularly the extent to which these associations generalize to African Americans. There is considerable variability in ECG traits across populations. African Americans have a shorter QRS duration, QTc interval, and a longer PR interval compared to Europeans (Ramirez et al. 2011). From a genetic standpoint, there are also significant differences in allele frequencies and linkage disequilibrium patterns between Africans and Europeans. For example, rs7626962 (S1103Y) in *SCN5A* is rare in European and Asian-descent populations but is common in African Americans and has been linked to arrhythmia susceptibility (Jeff et al. 2011; Splawski et al. 2002). Expanding genetic association studies to diverse populations has been of recent

interest to many investigators in the field. To date there has been one GWAS published for ECG traits in African Americans on PR interval and one fine-mapping study for QT interval in African Americans (Avery et al. 2012; Smith et al. 2011). Missing from the current literature is a comprehensive study of multiple ECG traits that explain the generalizability or lack thereof across populations. Furthermore, to date there are no GWAS reported for heart rate in African Americans.

Assessing the utility of electronic medical records (EMRs) systems coupled to DNA repositories as a tool for genome science is one of the primary objectives for the National Human Genome Research Institute's electronic MEdical Records and GEnomics (eMERGE) Network (McCarty et al. 2011). Studies from eMERGE, including those on PR interval, have demonstrated that EMR-based genetic studies replicate existing findings and discover new ones (Crosslin et al. 2011; Denny et al. 2010; Denny et al. 2011; Turner et al. 2011). Here we performed a GWAS of ECG measurements to identify novel genetic associations and describe the extent to which previous associations generalize in African Americans within the eMERGE network. We also examine reasons for non-generalization of associations in our African American study population.

MATERIALS AND METHODS

Study population

African American subjects were collected from the Vanderbilt or Northwestern University biobanks. The Vanderbilt Genome-Electronic Records (VGER) accesses BioVU, the Vanderbilt biorepository of DNA extracted from blood collected for routine clinical care linked to de-identified electronic medical records (Roden et al. 2008). BioVU is a subset of the larger repository of de-identified EMRs known as the synthetic derivative. The Northwestern biobank, NUgene, combines DNA samples from consented participants with enrollment questionnaire and longitudinal data from the EMR (McCarty et al. 2011). Both biobanks were approved by Institutional Review Boards at their respective sites.

Study population demographics and characteristics are described in Table 1. Individuals with a normal ECG without evidence of cardiac disease before or within one month following the ECG, without concurrent use of medications that interfere with QRS duration, and who did not have abnormal electrolyte values at the time of the ECG were included. Using natural language processing combined with EMR (structured database queries) to query (specific to VGER), we excluded individuals with any of the following before or within one month of the ECG: indication of heart failure, arrhythmia, cardiomyopathy, cardiac conduction defect, or myocardial ischemia/infarct based on clinical notes, unstructured text, billing codes, and labs. VGER subjects were African American as indicated by observer reported ancestry, which is highly concordant with genetic ancestry (Dumitrescu et al. 2010). African American ancestry was self-reported for Northwestern subjects (McCarty et al. 2011), which is also known to be highly concordant with genetic ancestry. All ECGs had normal Bazett's corrected QT intervals (<450ms), heart rates (between 50–100 bpm), and QRS duration (65–120 ms).

Genotyping

Genotyping for the eMERGE network was performed by the Center for Inherited Disease Research (CIDR) and the Broad Institute. All individuals that met the inclusion criteria (n = 501) were genotyped for >1.1 million SNPs using the Illumina 1M BeadChip at the Broad Institute. Data were cleaned by the eMERGE QC pipeline (Zuvich et al. 2011). Individuals with cryptic relatedness, ancestry inconsistent with observer- or self-reported ancestry, anomalous X-chromosome heterozygosity or poor genotyping efficiency were removed from further analysis (n = 46). All markers that were intensity only probes that had technical failure, minor allele frequency 0.05, genotyping efficiency <99%, discordant calls with duplicates, and Mendelian errors >0 were removed. Tests of association were performed with and without SNP that deviated from Hardy Weinberg Equilibrium (p-value $<1.0 \times 10^{-4}$), and consistent findings were observed for both SNP sets (data not shown).

Statistical methods

Greater than 930K SNPs from the Illumina 1M BeadChip were tested for an association with PR interval, QRS duration, QTc interval, and heart rate using linear regression assuming an additive genetic model. Tests of association were performed unadjusted and adjusted for age, sex, PR/QT drug usage (for PR and QT interval only), and principal components (PCs; two to four PCs depending on the trait) using PLINK (Purcell et al. 2007). All results were plotted using Synthesis View, Haploview, or Locus Zoom (Barrett et al. 2005; Pendergrass et al. 2010; Pruim et al. 2010). Power calculations were performed using QUANTO (Gauderman & Morrison 2006) assuming genetic effect sizes based on the original published GWAS. The fixation index F_{ST}, a measure of population differentiation, was calculated using the Weir and Cockerham algorithm (Weir & Cockerham 1984). We calculated F_{ST} between European descent populations and our African American study population using the Platform for the Analysis, Translation, and Organization of large-scale data (PLATO) (Grady et al. 2010). Pair-wise linkage disequilibrium was calculated (r^2) around the *SCN5A/SCN10A* and *NOS1AP* regions using the SeattleSNPs Genome Variation Server (gvs.gs.washington.edu/).

Generalization

Using the NHGRI GWAS catalog, we identified SNPs associated with PR interval, QTc interval, QRS duration, and heart rate at significance threshold of $p<10^{-6}$ from European or Asian -descent populations. We then examined the significance level and direction of effect for the same SNP-trait pair in this African American dataset.

RESULTS

Discovery

None of the SNPs tested for an association met genome-wide significance ($p<5.0 \times 10^{-8}$) with any ECG trait. Although we did not detect associations at genome-wide significance, we were able to detect novel associations at $p<10^{-6}$ (Table 2, Supplementary Fig. 1). Nine common variants were associated with increased heart rate, representing five independent disease loci. Three SNPs were in complete linkage disequilibrium with each other ($r^2 = 1.0$)

in *SERPINI1* on chromosome 3. Aside from SNPs associated with heart rate, nine associations at $p<10^{-6}$ were observed for QT interval, QRS duration, and PR interval, separately (27 associations total). Collectively, these potentially novel associations represent 17 candidate genes throughout the genome associated with these traits. None of these associations have been reported by previously published GWAS for ECG traits in any population.

Generalization

In European-descent populations, 118 GWAS-identified SNPs have been reported for ECG traits in the NHGRI GWAS catalog as of October 2011. We examined the reported European-descent SNP-trait association to determine if the association "generalized" to African Americans. We considered an association generalized if the observed association was significant at a liberal significance threshold ($p<0.05$) and had a direction of effect consistent with the original study. Of the 118 SNPs identified in the NHGRI GWAS catalog, 92 were also directly genotyped in our study population: 26, 14, 19, and 33 SNPs were previously associated with heart rate, PR interval, QRS duration, and QT interval, respectively.

Overall, there were five SNP-trait associations that generalized to African descent populations with respect to both level of significance ($p<0.05$) and direction of effect: for heart rate rs4352210 (intergenic, $\beta= -1.6$, $p= 0.03$), for QTc interval, rs1112795 (*SCN5A*, $\beta = -4.77$; $p=0.05$) and rs4725982 (*KCNH2*, $\beta = 4.79$; $p=0.03$), and for QRS duration, rs6795970 (*SCN10A*, $\beta = 2.43$; $p=0.01$) and rs11710077 (*SCN5A*, $\beta= 2.42$; $p=0.004$) (Table 3). No SNPs generalized for PR interval. There were six additional SNP-trait associations from the GWAS catalog that were significant (p-value <0.05) but trended in the opposite direction in African Americans compared with European-descent populations (after accounting for the coded allele): four for PR interval, three for heart rate, and one for QT interval (Supplementary Table 1).

An additional 40 SNP-trait associations failed to achieve the liberal threshold of significance ($p<0.05$) in African Americans but did have consistent directions of effect compared with European-descent populations (Supplementary Table 2, Fig. 1). Based solely on direction of effect, approximately 50% and 52% of the associations tested for PR and QT intervals, respectively, have a consistent direction of effect in African Americans compared with European descent populations. For QRS duration, 37% of the associations tested generalized in African Americans while 44% generalized for heart rate. Collectively, 44 out of 92 (47%) SNP-trait associations had a consistent direction effect regardless of significance in African Americans compared to previously identified associations in European-descent populations. The remaining 48/92 (52%) SNP-trait associations identified in European-descent populations did not generalize to African Americans with respect to either level of significance or direction of effect.

There were ten SNPs reported in the NHGRI catalog that are associated with ECG traits in Asian -descent populations. Of these, six SNPs were also genotyped in our study population. None of these SNPs generalized in African Americans with respect to significance and

direction of effect, although two of these associations had a consistent direction of effect compared with the original study population.

Power

SNP-trait associations that failed to achieve significance or failed to generalize to African Americans may represent lack of power or true differences in allelic architecture and/or linkage disequilibrium patterns between the two populations. To help distinguish between these two possibilities, we calculated the power to detect the mostly European-reported associations in this African American sample. Overall, 17 SNP-trait tests of association were adequately powered (>80%). Among the adequately powered tests of association, almost all (16/17) SNP-trait tests of association failed to generalize in African Americans with respect to level of significance anddirection of effect (Table 4).

Allele Frequencies

We calculated the coded allele frequencies for previously identified SNPs (from European descent populations) in African Americans (Supplementary Table 3). To measure population differences, we calculated F_{ST} for all SNPs previously identified by GWAS in European descent populations that report sample sizes and minor allele frequencies (85 SNPs). There were 20 SNPs with an F_{ST} value >0.15 (ranging from 0.15 to 0.85), which is indicative of significant population differentiation at these loci. We observed the largest F_{ST} value (F= 0.85) for rs789852 located in the intron region of the *TMEMFF* gene located on chromosome 3. This SNP was previously associated with QT interval in Europeans (β= 0.25, p=7.0×10^{-7}) (Marroni et al. 2009). This association did not generalize in African Americans and trended in the opposite direction compared to Europeans (β = −0.95, p =0.60).

DISCUSSION

Here we identified novel associations with heart rate, QT interval, QRS duration, and PR interval. We also characterized previously reported associations in our African American study population derived in a clinical based setting. To our knowledge we are the first to perform a genome-wide association study for heart rate in African Americans and to characterize GWAS-identified variants in European and Asian-descent populations to African Americans for heart rate, QT interval, and QRS duration.

Discovery

We have identified 36 novel associations in 17 candidate genes with the four ECG traits tested at p< 1.0×10^{-6}. While none of our associations met genome-wide significance, reporting these associations can provide insight to novel regions in the genome that effect ECG trait variability yet to be explored in African populations. Interestingly we were able to detect a novel region on chromosome 3 with three SNPs that are in high LD and are associated with increased heart rate in *SERPINI1* (Supplementary Fig. 1C). The *SERPINI1* gene encodes serine peptidase inhibitors secreted by axons in the brain and has been associated with familial encephalopathy (Davis et al. 1999).

We also identified a region on chromosome 9 within the *DAB2IP* gene encompassing two SNPs that were associated with increased heart rate. This gene encodes a GTPase-activating protein and is an inhibitor of cell growth and survival. *DAB2IP* has been identified by a GWAS for an association with prostate cancer in European and African descent populations (Gretarsdottir et al. 2010). Recently, a GWAS of individuals from Iceland and the Netherlands identified an association with *DAB2IP* with abdominal aortic aneurysms and other vascular diseases including early onset myocardial infarction (Gretarsdottir et al. 2010).

Generalization

Four of the five generalizations we identified in African Americans are located in voltage-gated channels (Table 3). For PR interval, we compared the *SCN5A/SCN10* region association results in African Americans with previously identified European Americans (also ascertained from VGER; Supplementary Fig. 2)(Denny et al. 2010). Though not significant, the index SNP identified in Europeans was different compared to African Americans. This is likely due to differences in linkage disequilibrium patterns between the two populations (Supplementary Figs. 2 and 3).

For QRS duration, two of these variants are within the *SCN5A/SCN10A* region and generalize in African Americans (Table 3). *SCN10A* variant rs97595970 originally associated with PR interval has been previously reported to have pleiotropic effects with QRS duration (Chambers et al. 2010; Holm et al. 2010; Sotoodehnia et al. 2010). This association for QRS duration generalized to African Americans ($\beta = 2.43$, p= 0.01). There were a total of three associations that generalized in African Americans for QT interval, two of which are in voltage gated channels *KCNH2* and *SCN5A* (Table 3). The third association, rs12143842, is located in *NOS1AP*, which has been consistently associated with prolonged QT interval (Arking et al. 2006). The effect of this variant accounts for more 1.5% of the trait variability in Europeans (Arking et al. 2006) and 1.3% in our African Americans. For PR interval, two previously identified associations in the *SCN10A* gene have consistent directions of effect with African Americans (Fig. 1, Supplementary Table 2). Non-synonymous variant rs6795970 (in the *SCN10A* gene) has been recently reported to have an association with increased PR interval in Asian and European-descent populations (Holm et al. 2010; Pfeufer et al. 2010). In African Americans the magnitude of this effect (β= 3.67) is consistent with Europeans (β= 5.17) (Fig. 1, Supplementary Table 2).

There were 48 associations that did not generalize to African Americans with respect to direction of effect and statistical significance. GWAS associations identified in European descent populations may not generalize in African Americans for several reasons. More often than not, this is due to discordant minor allele frequency differences and linkage disequilibrium (LD) patterns, both of which impact statistical power. On average for SNPs that do not generalize, the MAF in the original population was significantly different compared to the MAF in our study population (p   0.01). The MAF was lower in African Americans compared to the original study population for 60% of the SNPs that do not generalize (Fig. 1). Low minor allele frequency is directly correlated with power in genetic

association studies. We also noticed this correlation in our analysis; 13/79 inadequately powered tests of association had a minor allele frequency < 0.09.

Replication of published GWAS in African Americans

As previously mentioned, there have been one recent GWAS and one fine-mapping study performed in African Americans for ECG traits (Avery et al. 2012; Smith et al. 2011). The first GWAS in African Americans for PR interval described an association between *SCN5A* intronic rs3922844 and increased PR interval (Smith et al. 2011). This association was also identified in an independent candidate gene study of *SCN5A* in African Americans (Jeff et al. 2011). In the present study, rs3922844 was associated with PR interval at p = 0.01 and a consistent direction of effect ($\beta = 3.06$) compared with the published reports (Supplementary Table 4). To date rs3922844 has only been identified in African descent populations and thus was not included in this generalization analysis. Although not statistically significant, we observed similar results for the other SNPs published by Smith et al (2011) (Supplementary Table 4). Despite the lack of power, these data collectively suggest and confirm previous reports that *SCN5A* has pleiotropic effects and is associated with multiple ECG traits in African Americans (Supplementary Table 4) (Jeff et al. 2011).

In the second study, GWAS regions identified for the QT interval in European and Asian populations were further fine-mapped in >8,000 African Americans (Avery et al. 2012). Approximately 40% of the associations reported in European or Asian populations generalized in the African American study population, which is consistent with this present study's generalization results, despite differences in sample size. Three novel associations with QT interval specific to African Americans were also reported; of these, two of the reported SNPs were not on the Illumina 1M BeadChip used for this present study, and one SNP (rs12061601) did not replicate in our African American study population (Supplementary Table 5). The fine-mapping effort also highlighted differences in the index SNP associated with QT interval between African Americans and Europeans. We compared the index SNPs reported in African Americans from the fine-mapping study to our study population (Supplementary Table 5). Of the fifteen index SNPs reported, only six SNPs were directly genotyped in our study of which only two, rs1805120 and rs735951, trended towards significance (Supplementary Table 5).

The Effects of Linkage Disequilibrium

Linkage disequilibrium (LD) is often used in genetic association studies to select tagSNPs for genotyping that represent a region in the genome. While this method is cost effective, identifying an association with a tagSNP does not necessarily identify the true functional variant given that the un-assayed functional variant is most likely in LD with the assayed variant. TagSNPs are also population specific; therefore, associations identified in one population may not necessary generalize to another population if only the index variant is genotyped. Our observations in this African American population compared with European descent populations for ECG trait associations are consistent with known properties of tagSNPs. That is, there are differences in LD between African Americans and Europeans for known loci associated with PR interval, QRS duration, and QT interval. For the *SCN10A/ SCN5A* and *NOS1AP* regions, we calculated pair-wise LD (r^2) for each SNP pair. As

expected, there is less linkage disequilibrium in African descent populations compared to European populations (Supplementary Figs. 3 and 4) (Rosenberg et al. 2010). This lack of LD could account for the non-generalization of associations in African Americans originally identified in European descent populations.

LD is often described as a "double-edged" sword: strong LD can be advantageous to identifying associations, but is it not useful when searching for the functional variants. Using populations with low amounts of LD can help fine map the functional variant (Rosenberg et al. 2010). Therefore, index associations that robustly associate with ECG traits in European descent populations but do not generalize to African descent populations could be prioritized for fine-mapping studies to identify the functional variant. Also, further large discovery and fine-mapping studies should be performed in African descent populations to identify additional ECG-trait associated loci not found in other populations.

Limitations and Strengths

There were several factors that limited our ability to detect novel associations at the GWAS level (at $p < 1.0 \times 10^{-8}$) with ECG traits. Our study population compared to recently published GWAS for ECG traits is relatively small and underpowered. Specifically, we were underpowered (<80%) to detect effects that explain less than 10% of the trait variability at $p < 1.0 \times 10^{-8}$ even for common variants (MAF >0.05). Power also limited our ability to generalize European/Asian identified associations to African Americans. As previously mentioned power is directly correlated to allele frequencies. Most GWAS fixed-content products are biased to common variation and based on LD patterns of European populations (Spencer et al. 2009). Therefore, the SNPs previously identified may only be common in Europeans and may be rare in other populations such as African Americans, limiting our power to generalize these variants. It is important to note the power calculations we report in our generalization analysis were limited to the effect sizes detected in the original study. These effect sizes could be subject to the "winner's curse" and may over estimate the true effect size (Xiao & Boehnke 2009; Zhong & Prentice 2010). Using these potentially overestimated effect sizes in our power calculations could consequently over estimate our power to detect these effects.

Another limitation to both the discovery and the generalization analyses was our liberal significance threshold. For discovery, a conservative Bonferroni threshold to correct for multiple testing is the generally accepted 5.0×10^{-8}. Given our small sample size and this conservative threshold, we had sufficient power to detect large genetic effect sizes; however, these effects are not realistic given previously reported candidate gene and GWAS findings for these traits. To address this limitation, we arbitrarily choose a significance threshold of 1.0×10^{-6} to identify possible real associations that would be missed by the conservative significance threshold. For generalization, we declared a generalization as having a consistent direction of effect and meeting a liberal significance threshold of $p < 0.05$. Given that the generalization analysis was limited to only a subset of loci that was previously identified, a genome-wide correction for multiple testing was not necessary.

Here we confirm the ability to use electronic medical records (EMRs) linked to DNA to identify genotype-phenotype relationships. We identified several potentially novel

associations across the genome for heart rate, PR interval, QT interval, and QRS duration. Additionally, we generalized several associations identified by GWAS in European and Asian -descent populations to African Americans. Most importantly, we extensively characterized European and Asian identified associations in African Americans by reporting population specific information such as allele frequency and linkage disequilibrium differences, which may be important in both research and clinic-based settings.

We successfully assessed the generalizability of European identified genetic associations for ECG traits in African Americans derived from an electronic medical record. Additionally, we report novel associations for ECG traits in African Americans. Replication of these findings in an independent African American population is needed to confirm these associations. Indeed, in the future, replication may be possible within the eMERGE network given that the network has expanded with respect to study sites and sample size. Most of the associations identified in European and Asian -descent populations failed to generalize due to power (as a consequence of sample size and low minor allele frequencies). However, there were several adequately powered associations that did not generalize to African Americans. These data suggest that the functional variant has yet to be identified for these traits by GWAS and highlight the need for future fine mapping studies in a large African-descent population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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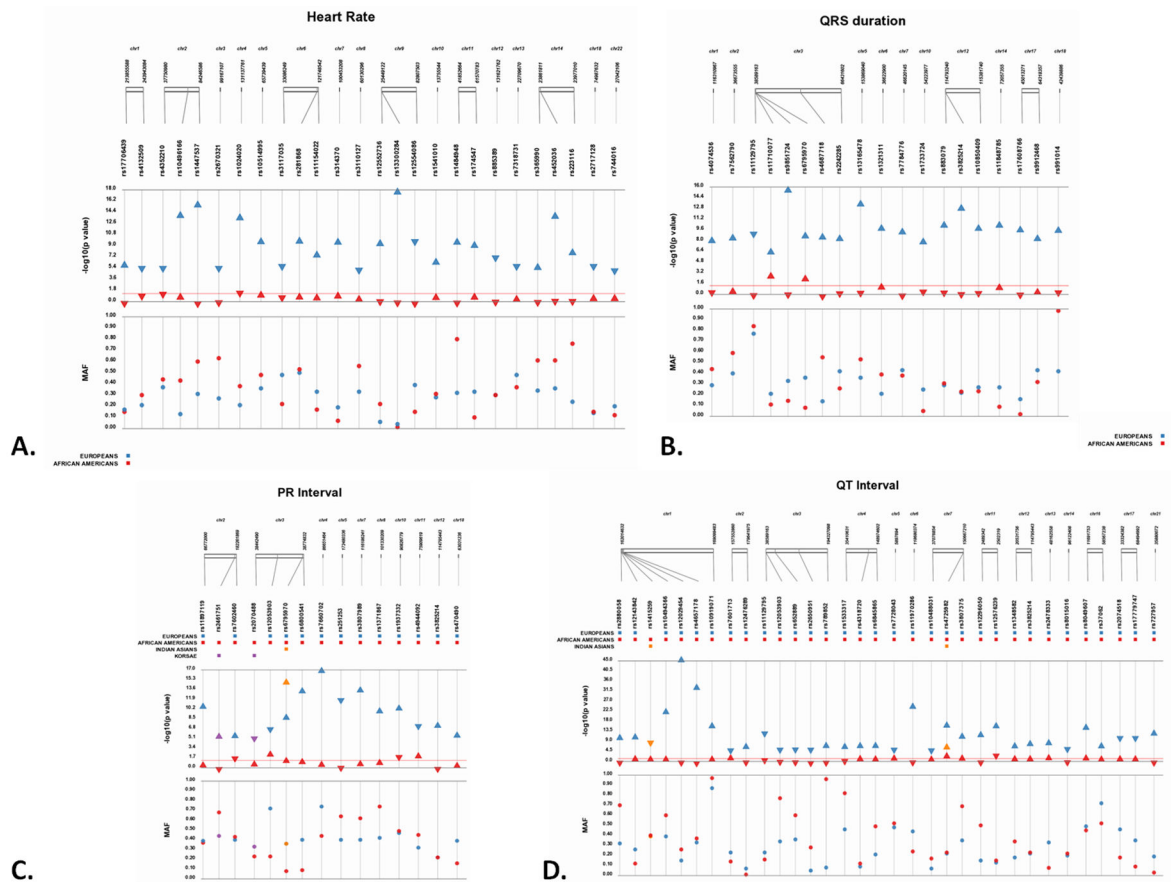
Figure 1. (A–D). SNP-trait association comparison between European or Asian -descent and African American populations across ECG traits

Each SNP was tested for an association with each ECG trait assuming an additive genetic model adjusted for age and sex. P-values are −log10 transformed along the y-axis and corresponding location for each SNP is located on the x-axis. Each point represents a p-value for each population indicated by color (see legend). The direction of the arrows corresponds to the direction of the effect (measured by beta coefficient). The significance threshold is indicated by the red bar at p= 0.05. The bottom panel displays the minor allele frequency comparisons for both populations for each SNP.

Table 1

Descriptive statistics of the study population

Means and standard deviations were calculated in the final study population for all covariates and ECG traits unless otherwise noted.

Study Population (n= 455)		
Variable	**Mean /%**	**SD**
Female	77%	--
Age (yr)	46	15
PR duration (msec)	159	21
QRS duration (msec)	82	8
QTc duration (msec)	410	21
Heart Rate (msec)	74	11
On QT drug	10%	--
On PR drug	21%	--

Table 2

Most significant genome-wide association study (GWAS) results in African Americans for heart rate, QT interval, QRS duration, and PR interval

We performed single SNP tests of association between >930 SNPs and ECG traits using linear regression assuming an additive genetic model in African Americans (n=455). All tests of association were adjusted by age, sex, and principal components. Associations at p $\leq$ 10^{-6} are shown, and for each association, chromosome, rs number, nearest gene, coded allele, beta coefficient, and p-value are given.

Heart Rate

CHR	SNP	LOCATION	CODED ALLELE	BETA	P
8	rs1015003	Intergenic	G	3.94	1.21E-06
8	rs6468401	Intergenic	A	3.93	1.55E-06
5	rs816475	Intergenic	T	3.69	2.83E-06
3	rs13090836	*SERPINI1* (intron)	T	3.58	6.86E-06
3	rs9815034	*SERPINI1* (intron)	A	3.59	7.26E-06
3	rs1473511	*SERPINI1* (intron)	T	3.59	7.26E-06
12	rs1282498l	*TMEM132D* (intron)	T	4.56	8.90E-06
9	rs35061590	*DAB2IP* (intron)	T	16.03	9.45E-06
9	rs13290547	*DAB2IP* (intron)	T	16.03	9.45E-06

QT Interval

CHR	SNP	LOCATION	CODED ALLELE	BETA	P
5	rs6894385	Intergenic	C	−9.92	1.03E-06
6	rs9342616	Intergenic	A	−6.92	1.04E-06
7	rs12666280	*DPP6* (intron)	C	8.93	1.66E-06
20	rs237450	Intergenic	A	6.86	5.36E-06
4	rs6819013	Intergenic	A	6.06	5.50E-06
4	rs4698433	*FGFBP2* (near 5′ region)	T	7.23	5.53E-06
4	rs1483012	*LDB2* (intron)	G	6.02	7.19E-06
16	rs8045405	Intergenic	G	−11.38	9.44E-06
15	rs17237606	*UNC13C* (intron)	G	−8.91	9.92E-06

QRS Duration

CHR	SNP	LOCATION	CODED ALLELE	BETA	P

Heart Rate				
CHR	**SNP**	**LOCATION**	**CODED ALLELE**	**BETA**	**P**
14	rs1867082	Intergenic	A	2.82	1.46E-06
6	rs504008	*NKAIN2* (intron)	C	2.70	2.58E-06
5	rs6861497	Intergenic	A	2.34	4.73E-06
11	rs308309	Intergenic	C	4.39	4.95E-06
6	rs12194062	*C6orf190* (intron)	T	5.16	5.10E-06
4	rs6820368	*ADH6* (intron)	C	9.90	5.57E-06
12	rs10784762	Intergenic	T	−2.38	6.31E-06
16	rs17444745	Intergenic	A	−6.40	6.96E-06
1	rs13375391	*HMCN1* (intron)	A	5.82	9.37E-06

PR Interval				
CHR	**SNP**	**LOCATION**	**CODED ALLELE**	**BETA**	**P**
11	rs1994318	*MICAL2* (intron)	A	−6.79	1.52E-06
6	rs10447419	Intergenic	A	−8.65	1.95E-06
10	rs16926523	*MYO3A* (intron)	A	9.55	4.23E-06
2	rs7604827	*VWC2L* (intron)	C	6.54	4.52E-06
3	rs3733017	*BCL6* (intron)	G	−10.07	5.55E-06
15	rs746265	Intergenic	C	−6.27	7.92E-06
3	rs1524976	*MAGI1* (intron)	A	8.00	7.96E-06
1	rs3103778	*MFSD2* (intron)	G	6.30	8.67E-06
15	rs12595668	Intergenic	G	−6.26	9.01E-06

Table 3

Association results for genome-wide association study (GWAS)-identified associations that generalize in African Americans

We compared GWAS-identified association results originally identified in European or Asian-descent populations to 455 African Americans from VGER and NUgene in the eMERGE network. We declared a generalization as having a consistent direction of genetic effect (expressed as a beta coefficient) and p-value <0.05. Abbreviations: CAF= coded allele frequency.

Trait	SNP	Coded Allele	Gene	Original Study				African Americans		
				Population	P-value	Effect	CAF	P-value	Effect	CAF
QT interval	rs11129795	A	*SCN5A*	European	5.0E-14	−1.27	0.23	0.05	−4.77	0.16
QT interval	rs4725982	T	*KCNH2*	European and Asian-descent	5.0E-16	1.58	0.22	0.03	4.79	0.23
QRS duration	rs6795970	A	*SCN10A*	European and Asian-descent	4.0E-09	5.17	0.36	0.01	2.43	0.08
QRS duration	rs11710077	T	*SCN5A*	European	1.0E-06	0.44	0.21	0.004	2.42	0.11
Heart rate	rs4352210	A	Intergenic	European	2.00E-06	−0.14	0.37	0.03	−1.6	0.44

Table 4

Association results for adequately powered genome-wide association study (GWAS)-identified SNPs that do not generalize in African Americans

Using the effect size, mean, and standard deviations reported in the published study, we calculated our power to detect the same effect given our sample size and minor allele frequency in African Americans. CAF= coded allele frequency.

SNP	Trait	Gene	Coded Allele	Original Study			African Americans			
				CAF	P-value	Beta	CAF	P-value	Beta	Power
rs10494366	QT Interval	NOS1AP	G	0.39	5.00E-22	12.2	0.60	0.88	0.28	0.99
rs11129795	QRS duration	SCN5A	G	0.77	5.00E-10	−8.24	0.84	0.73	−0.25	0.99
rs12296050	QT Interval	KCNQ1	T	0.15	1.00E-11	13.16	0.50	0.52	−1.20	0.99
rs3807989	PR interval	CAV1	A	0.40	7.00E-13	6.40	0.62	0.46	0.94	0.95
rs3825214	QRS duration	TBX5	G	0.22	3.00E-13	7.35	0.23	0.52	−0.41	0.99
rs3825214	PR interval	TBX5	G	0.22	1.00E-07	5.88	0.22	0.79	−0.40	0.81
rs1321311	QRS duration	CDKN1A	T	0.21	3.00E-10	6.52	0.39	0.17	0.77	0.99
rs174547	Heart Rate	FADS1	C	0.33	2.00E-09	6.20	0.10	0.43	1.028	0.99
rs223116	Heart Rate	MYH7, NDNG	A	0.24	3.00E-08	7.40	0.76	0.44	−0.635	0.99
rs2461751	PR interval	Intergenic	G	0.44	8.00E-06	4.54	0.68	0.83	−0.30	0.80
rs281868	Heart Rate	SLC35F1	G	0.50	4.00E-10	6.30	0.53	0.41	0.64	0.99
rs314370	Heart Rate	SLC12A9	C	0.19	6.00E-10	7.60	0.07	0.28	1.58	0.99
rs365990	HR	MYH6	G	0.34	7.00E-06	5.25	0.61	0.61	−0.41	0.99
rs3807375	QT Interval	KCNH2	T	0.35	5.00E-11	11.95	0.69	0.32	1.95	0.99
rs452036	Heart Rate	MYH6	A	0.36	4.00E-14	7.80	0.61	0.41	−0.68	0.99
rs7660702	PR interval	ARHGAP24	T	0.74	3.00E-17	8.46	0.44	0.60	0.65	0.99