

# The impact of ancestry and common genetic variants on QT interval in African Americans

## Supplemental material

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**Supplementary Methods.** Cohort descriptions.

Genome-wide association analyses were performed in the following population-based cohorts as part of the Continental Origins and Genetic Epidemiology Network (COGENT) and Candidate-gene Association Resource (CARE) consortia.

Atherosclerosis Risk in Communities Study (ARIC): The ARIC study is an ongoing, prospective population-based cohort designed to examine the etiology of cardiovascular and pulmonary disease, patterns of medical care, and disease variation over time.<sup>1</sup> The study includes 15,792 participants (4,314 African-Americans) selected using probability sampling from four United States communities (Forsyth County NC, Jackson MS, suburban Minneapolis MN, and Washington County MD). Between 1987 and 1989, the study enrolled participants aged 45–64 years. Standardized physical examinations and interviewer-administered questionnaires were conducted at baseline, and at three triennial follow-up examinations. Electrocardiographic recordings used in the present study were performed at baseline examinations between 1987–1989. Blood was drawn for DNA extraction at baseline or later visits and participants consented to genetic testing. This study was approved by the institutional review board at each field center and all subjects provided written informed consent. This analysis was approved by the University of North Carolina at Chapel Hill School of Public Health Institutional Review Board.

Baltimore Longitudinal Study on Aging (BLSA): The BLSA study is a population-based study aimed to evaluate contributors of healthy aging in the older population

Smith et al, Cardiac repolarization in African Americans: Supplemental material residing predominantly in the Baltimore-Washington DC area.<sup>2, 3</sup> Starting in 1958, participants were examined every one to four years, depending on their age, during visits to the NIA's Gerontology Research Center in Baltimore. Currently there are approximately 1,100 active participants enrolled in the study. Each man received an extensive interim medical and psychological history and physical examination at each visit. Electrocardiographic recordings used in the present study were performed at follow-up examinations between 2003–2009. Blood samples were collected for DNA extraction, and genome-wide genotyping was completed for 1,231 participants. The BLSA has continuing approval from the Institutional Review Board (IRB) of the Johns Hopkins Bayview Medical Center, the Gerontology Research Center, and Medstar Research Institute. Informed consent was obtained from all participants.

Bogalusa Heart Study (BHS): The BHS is a long-term epidemiologic study of cardiovascular risk factors from birth through the age of 38 years in a biracial population with whites and African Americans. Between 1973 and 2008, nine cross-sectional surveys of children aged 4-17 years and 10 cross-sectional surveys of adults aged 18-48 years, who had been previously examined as children, were conducted for cardiovascular disease risk factor examinations in Bogalusa, Louisiana.<sup>4</sup> Electrocardiographic recordings used in the present study were performed at a follow-up visit between 2000–2002. In the ongoing Longitudinal Aging Study funded by NIH and NIA since 2000, there are 1,202 Caucasian and African American participants who have been examined 4-14 times from childhood to adulthood with DNA available for genotyping. Study protocols were approved by the

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Institutional Review Board of the Tulane University Medical Center. Informed consent was obtained from all participants.

Cardiovascular Health Study (CHS): The CHS is a population-based, longitudinal cohort designed to study risk factors for cardiovascular disease in the elderly.<sup>5</sup>

Starting in 1989, 244 African American adults aged 65 years or older were sampled from four United States communities (Forsyth County, North Carolina; Pittsburgh, Pennsylvania; Sacramento County, California; and Washington County, Maryland).

Between 1992 and 1993, a second cohort of 687 African Americans was enrolled.

Extensive physical and laboratory evaluations were performed at baseline to identify the presence and severity of CVD risk factors such as hypertension,

hypercholesterolemia and glucose intolerance; subclinical disease such as carotid artery atherosclerosis, left ventricular enlargement, and transient ischemia; and

clinically overt CVD. Electrocardiographic recordings used in the present study were

performed at the baseline examination. In 2010, genotyping was performed for 844

African-American participants who consented to genetic testing and had available

DNA. The institutional review board at each of the study sites approved the study

protocols, and written informed consent was obtained from all participants.

Cleveland Family Study (CFS): The CFS is a family-based longitudinal study

designed to study the risk factors for sleep apnea.<sup>6</sup> Participants include first-degree

or selected second-degree relatives of a proband with either laboratory diagnosed

obstructive sleep apnea or neighborhood control of an affected proband. ECG

recordings used for the present study were performed at the final exam cycle

conducted in a Clinical Research Unit between 2001 and 2006. Families were

Smith et al, Cardiac repolarization in African Americans: Supplemental material selected for genotyping on the basis of genetic informativity, including multigenerational data or individuals from the extremes of the distribution of apnea phenotype.<sup>7, 8</sup> The 632 African Americans with available DNA were genotyped as part of CARE. The institutional review board approved the study, and written informed consent was obtained from all participants.

The Health, Aging and Body Composition Study (HABC): The Health ABC Study is a longitudinal study of the factors that contribute to incident disability and the decline in function of healthier older persons, with a particular emphasis on changes in body composition in old age.<sup>9, 10</sup> Between 1997 and 1998, 3075 adults aged 70-79 years were recruited using mass mailings with telephone follow-up. White individuals were identified through a random sample of Medicare-eligible residents and African American individuals were identified from two clinical centers in Pittsburgh, Pennsylvania, and Memphis, Tennessee. Participants had no reported difficulty in walking a quarter of a mile, climbing 10 steps without resting, or performing mobility-related activities of daily living. Exclusion criteria were any life-threatening condition, participation in any research study involving medications or modification of eating or exercise habits, plans to move from the geographical area within 3 years and difficulty in communicating with the study personnel or cognitive impairment. The key components of Health ABC included a baseline exam with blood specimen collection, annual follow-up clinical exams, and phone contacts every 6 months to identify major health events and document functional status between clinic visits. The institutional review boards at both clinical centers approved the study, and written informed consent was obtained from all participants.

The Healthy Aging in Neighborhoods of Diversity across the Life Span Study

(HANDLS): HANDLS is an interdisciplinary, community-based, prospective longitudinal epidemiologic study examining the influences of race and socioeconomic status (SES) on the development of age-related health disparities in overall longevity, cardiovascular disease, and cognitive decline among socioeconomically diverse African Americans and whites in Baltimore.<sup>11</sup> A total of 3,722 (2200 African American and 1522 Caucasian) participants between 30 and 64 years of age were recruited as a fixed cohort of participants by household screenings from an area probability sample of Baltimore based on the 2000 Census. Data were collected in two separate phases. Phase 1 consisted of screening, recruitment, a household interview (assessing sociodemographic information and physiological and psychological chronic exposure) and a first 24 hour recall; phase 2 consisted of an in-depth examination in a mobile medical research vehicle (MRV) and included a second dietary assessment with a 24 hour recall, psychometric measures (e.g. for depressive symptoms and cognitive function), anthropometric and body composition measurements. Electrocardiographic recordings used in the present study were performed at baseline examinations over the course of one year. Genotyping was performed for 1,024 participants who self-report as African Americans. The study protocol was approved by the human subjects review boards at both MedStar Research Institute and the University of Delaware. All participants provided written informed consent.

Jackson Heart Study (JHS): The JHS is a prospective population-based study of the causes of the high prevalence of common complex diseases among African Americans in the Jackson, Mississippi metropolitan area, including cardiovascular

Smith et al, Cardiac repolarization in African Americans: Supplemental material disease, type-2 diabetes, obesity, chronic kidney disease, and stroke.<sup>12</sup> Between 2000 and 2004, 5,302 adult African American residents of a tri-county area near Jackson, Mississippi (Hinds County, Rankin County and Madison County) were recruited from four sources, including (1) randomly sampled households from a commercial listing; (2) ARIC participants; (3) a structured volunteer sample that was designed to mirror the eligible population; and (4) a nested family cohort. Unrelated participants were between 35 and 84 years old, and members of the family cohort were  $\geq 21$  years old when consent for genetic testing was obtained and blood was drawn for DNA extraction. ECG recordings and DNA extraction were performed at the baseline examination. Based on DNA availability, appropriate informed consent, and genotyping results that met quality control procedures, genotype data were available for 3,030 individuals, including 885 who were also ARIC participants. In the current study, JHS participants who were also enrolled in the ARIC study were analyzed with the ARIC dataset. The institutional review board approved the study protocol, and written informed consent was obtained from all participants.

Multi-Ethnic Study of Atherosclerosis (MESA): MESA is a multicenter, population-based cohort initiated to investigate subclinical cardiovascular disease and the risk factors that predict progression to clinically overt cardiovascular disease.<sup>13</sup> Between 2000 and 2002, the study enrolled 6,814 asymptomatic males and females aged 45–84 from six US field centers (Baltimore, MD; Chicago, IL; Los Angeles, CA; New York, NY; St. Paul, MN; Winston-Salem, NC). Those with a history of CVD (defined as physician-diagnosed myocardial infarction, angina, heart failure, stroke, transient ischemic attack or history of invasive procedure for CVD) were excluded from participation. Approximately 28% of the sample was African American participants.

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ECG recordings and blood for DNA extraction were obtained at the baseline examination. This study was approved by the institutional review boards of each study site, and written informed consent was obtained from all participants.

Women's Health Initiative (WHI): The WHI is a large and complex clinical investigation of strategies for the prevention and control of some of the most common causes of morbidity and mortality among postmenopausal women, including cancer, cardiovascular disease, and osteoporotic fractures. The WHI comprises both randomized clinical trials (CT) and an observational study (OS). This study is limited to WHI CT participants, as ECGs were not available for WHI OS participants. The WHI clinical trials were designed to allow randomized, controlled evaluation of estrogen with or without progestin treatment, calcium/vitamin D supplementation, and dietary modification on the risk of breast and colorectal cancer, cardiovascular disease, and bone fractures.<sup>14</sup> Between 1993 and 1998, the trials enrolled 68,132 postmenopausal women aged 50–79 years who were followed at one of 75 US examination sites (including satellites, remote sites, and their changes in location). Women were ineligible if they had medical conditions predictive of survival time less than 3 years, if they were known to have conditions inconsistent with study participation and adherence, or if they were active participants in another randomized, controlled trial. Those who remained eligible and interested were invited to follow-up examinations at 1, 3, 6, and 9 years. Electrocardiographic recordings used in the present study were performed at baseline examinations between 1994–1998. Of the CT and OS minority participants enrolled in WHI, the WHI SNP Health Association Resource (SHARe) GWA study project includes 12,157 (8,515 self-identified African American and 3,642 self-identified Hispanic) women who consented



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to genetic research. DNA was extracted by the Specimen Processing Laboratory at the Fred Hutchinson Cancer research Center (FHCRC) using specimens that were collected at enrollment. Specimens were stored at -80°C. Study protocols and consent forms were approved by the Institutional Review Boards at all participating institutions.

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**Supplementary Table 1.** Genotyping characteristics for the genome-wide association analyses of ten studies in the meta-analysis.

Study	Genotyping array	Genotype calling algorithm	Sample call rate filter	SNP call rate filter	SNP MAF filter <sup>a</sup>	HWE p-value filter <sup>b</sup>	Imputation software <sup>c</sup>	GWAS statistical analysis software	No. of autosomal SNPs passing QC
ARIC	Affymetrix 6.0	Birdseed	<95%	<90%	<1%	NA	MACH v1.16	PLINK	796,384
BLSA	Illumina 550K	BeadStudio	≤98.5%	<99%	<1%	≤10 <sup>-4</sup>	MACH 1.0	Merlin	501,704
BHS	Illumina Human610 BeadChip, HumanCVD BeadChip	BeadStudio	<99%	<90%	NA	NA	MACH v1.0.16	PLINK	608,756
CFS	Affymetrix 6.0	Birdseed	<95%	<90%	<1%	NA	MACH v1.16	R	867,495
CHS	Illumina HumanOmni1-Quad_v1 BeadChip system	Illumina GenomeStudio	<95%	≤97%	NA	<10 <sup>-5</sup>	BEAGLE version 3.2.1	R	963,248
HABC	Illumina 1M	BeadStudio	<97%	<97%	<1%	<10 <sup>-6</sup>	MACH v1.16	R	1,007,948
HANDLS	Illumina 1M <sup>d</sup>	BeadStudio	≤95%	≤95%	≤1%	≤10 <sup>-7</sup>	MACH v1.16	R, MACH2QTL	907,763
JHS	Affymetrix 6.0	Birdseed	<95%	<90%	<1%	NA	MACH v1.16	PLINK	868,969
MESA	Affymetrix 6.0	Birdseed	<95%	<90%	<1%	NA	MACH v1.16	PLINK	881,666
WHI	Affymetrix 6.0	Birdseed	<95%	<95%	<1%	<10 <sup>-6</sup>	MACH v1.0.16	PLINK, ProbABEL	829,370

<sup>a</sup>SNP MAF filter applied pre-imputation.

<sup>b</sup>Genotyped SNP results used to replace imputed SNP results were not filtered by HWE P-value.

<sup>c</sup>All studies used HapMap phase 2 release 22 build 36 and the HapMap Reference panel 1:1 CEU:YRI phase II.

<sup>d</sup>1024 HANDLS participants were successfully genotyped at the equivalent of Illumina 1M SNP coverage (709 samples using Illumina 1M and 1Mduo arrays, the remainder using a combination of 550K, 370K, 510S and 240S to equate the million SNP level of coverage).

ARIC, Atherosclerosis Risk in Communities; BLSA, Baltimore Longitudinal Study on Aging; BHS, Bogalusa Heart Study; CFS, Cleveland Family Study; CHS, Cardiovascular Health Study; HABC, The Health, Aging, and Body Composition Study; HANDLS, The Healthy Aging in Neighborhoods of Diversity across the Life Span Study; JHS, Jackson Heart Study; MESA, Multi-Ethnic Study of Atherosclerosis; WHI, Women's Health Initiative.

**Supplementary Table 2.** Samples sizes after hierarchical exclusions.

<b>Exclusion</b>	<b>ARIC</b>	<b>BHS</b>	<b>BLSA</b>	<b>CFS</b>	<b>CHS</b>	<b>HABC</b>	<b>HANDLS</b>	<b>JHS</b>	<b>MESA</b>
<b>Total</b>	3388	199	282	391	812	1139	1024	3597	1754
<b>QT interval not available</b>	3283	193	171	391	806	1138	971	3583	1744
<b>RR interval not available</b>	3276	193	171	391	806	1138	971	3583	1744
<b>LBBB/RBBB</b>	3229	190	171	377	793	1095	957	3490	1689
<b>IVCD</b>	3187	190	171	367	789	1082	957	3478	1658
<b>QRS<math>\geq</math>120 ms</b>	3161	188	163	365	682	1052	957	3426	1658
<b>Pacemaker</b>	3161	188	157	365	677	1052	957	3426	1658
<b>Atrial fibrillation/flutter</b>	3145	188	153	364	667	1038	957	3411	1658
<b>Participants in both ARIC and JHS</b>	2176	188	153	364	667	1038	957	3411	1658

**Supplementary Table 3.** Cohort-specific results for genome-wide significant SNPs.

SNP	ARIC	BHS	BLSA	CFS	CHS	HABC	HANDLS	JHS	MESA	WHI
rs12143842	-2,30 (1,19)	-2,94 (3,10)	-5,66 (2,79)	-4,16 (2,20)	-2,46 (1,49)	-2,60 (1,53)	-4,73 (1,58)	-4,24 (1,08)	-0,56 (1,07)	-3,68 (0,64)
rs16847548	0,14 (0,97)	-1,00 (2,85)	5,36 (2,62)	5,10 (1,91)	0,33 (1,23)	3,42 (1,38)	1,29 (1,30)	2,12 (0,92)	2,29 (0,90)	2,87 (0,56)
rs1320976	-3,27 (0,84)	N/A	N/A	-2,64 (1,53)	-1,14 (1,27)	N/A	N/A	-2,00 (0,76)	-1,12 (0,78)	-2,13 (0,50)
rs12061601	-2,99 (0,86)	-0,48(2,41)	-1,41 (2,29)	-2,51 (1,60)	-1,15 (1,27)	0,14 (1,22)	-2,73 (1,20)	-2,07 (0,78)	-1,13 (0,80)	-2,07 (0,51)
rs4657175	1,06 (0,79)	-0,94(2,30)	-0,65 (2,34)	1,52 (1,42)	-0,15 (1,09)	3,87 (1,11)	3,78 (1,15)	1,18 (0,73)	1,26 (0,73)	2,29 (0,48)
rs4391647	-1,01 (0,79)	1,07(2,30)	0,55 (2,33)	-1,52 (1,42)	0,20 (1,10)	-4,00 (1,12)	-3,72 (1,14)	-1,25 (0,73)	-1,18 (0,74)	-2,31 (0,48)
rs6692381	-1,09 (0,79)	0,52(2,23)	0,73 (2,36)	-1,09 (1,41)	-0,06 (1,08)	-4,19 (1,11)	-3,74 (1,14)	-1,17 (0,72)	-1,13 (0,73)	-2,20 (0,48)
rs12123267	-1,14 (0,80)	0,82(2,29)	0,68 (2,35)	-1,40 (1,45)	-0,13 (1,08)	-4,00 (1,11)	-3,63 (1,13)	-1,02 (0,73)	-1,11 (0,73)	-2,24 (0,48)
rs12567315	1,08 (0,79)	-0,52(2,23)	-0,73 (2,36)	1,10 (1,45)	-0,21 (1,10)	4,20 (1,11)	3,74 (1,14)	1,17 (0,72)	1,14 (0,73)	2,19 (0,48)
rs6667431	1,09 (0,79)	-0,52(2,23)	-0,73 (2,36)	1,09 (1,44)	-0,22 (1,10)	4,19 (1,11)	3,74 (1,14)	1,17 (0,72)	1,13 (0,73)	2,19 (0,48)
rs3934467	-1,25 (0,79)	1,06(2,28)	0,87 (2,36)	-1,08 (1,45)	0,16 (1,10)	-4,16 (1,12)	-3,62 (1,14)	-1,11 (0,73)	-1,17 (0,74)	-2,17 (0,48)
rs7534004	0,93 (0,82)	-1,21(2,36)	-0,96 (2,47)	0,98 (1,52)	-0,21 (1,12)	5,03 (1,14)	3,38 (1,15)	0,83 (0,76)	1,41 (0,75)	2,33 (0,50)
rs12027785	1,25 (0,79)	-0,98(2,28)	-0,94 (2,35)	1,01 (1,45)	-0,18 (1,10)	4,19 (1,12)	3,58 (1,14)	1,03 (0,73)	1,19 (0,74)	2,16 (0,48)
rs12116744	1,24 (0,79)	-0,97(2,28)	-0,95 (2,35)	1,00 (1,45)	-0,19 (1,09)	4,23 (1,12)	3,58 (1,14)	1,03 (0,73)	1,20 (0,74)	2,16 (0,48)
rs4480335	-1,43 (0,80)	0,94(2,30)	0,95 (2,35)	-1,03 (1,42)	0,20 (1,10)	-4,39 (1,12)	-3,51 (1,14)	-1,03 (0,73)	-1,19 (0,74)	-2,06 (0,49)
rs12029454	0,89 (0,84)	-1,54(2,39)	-0,85 (2,47)	1,03 (1,53)	-0,27 (1,12)	4,92 (1,14)	3,32 (1,14)	0,77 (0,76)	1,53 (0,77)	2,34 (0,50)
rs10800352	-1,23 (0,79)	0,93(2,30)	0,95 (2,35)	-1,03 (1,45)	0,21 (1,10)	-4,44 (1,12)	-3,51 (1,14)	-0,94 (0,73)	-1,19 (0,74)	-2,14(0,48)
rs4306106	1,22 (0,79)	-0,93(2,30)	-0,95 (2,35)	1,03 (1,45)	-0,21 (1,10)	4,39 (1,12)	3,51 (1,134)	0,94 (0,73)	1,19 (0,74)	2,14 (0,48)
rs10127719	0,92 (0,81)	-0,95(2,33)	-0,93 (2,41)	0,66 (1,51)	0,11 (1,14)	4,84 (1,14)	3,12 (1,16)	0,95 (0,76)	1,06 (0,75)	2,22 (0,50)

**Supplementary Table 4.** Results for SNPs with  $p < 10^{-5}$ .

The table shows the location, allele frequency, beta coefficient with standard error and p-value for all SNPs with  $p < 10^{-5}$  in the meta-analysis. CAF refers to the allele frequency for the coded allele (A1).

SNP	CHR	POSITION	A1	A2	CAF	Beta	SE	P-VALUE
rs12143842	1	160300514	C	T	0.80	-3.14	0.39	$1.79^{-15}$
rs16847548	1	160301898	C	T	0.22	2.17	0.33	$1.84^{-10}$
rs1320976	1	167339970	A	G	0.25	-2.06	0.32	$2.01^{-10}$
rs12061601	1	167337074	C	T	0.29	-1.89	0.30	$5.88^{-10}$
rs4657175	1	160462362	G	T	0.33	1.74	0.28	$7.24^{-10}$
rs4391647	1	160453555	A	G	0.67	-1.74	0.27	$7.73^{-10}$
rs6692381	1	160434508	C	T	0.66	-1.71	0.28	$1.23^{-09}$
rs12123267	1	160465975	C	T	0.66	-1.70	0.28	$1.67^{-09}$
rs12567315	1	160433270	A	G	0.33	1.69	0.28	$1.82^{-09}$
rs6667431	1	160434545	A	G	0.33	1.69	0.28	$1.85^{-09}$
rs3934467	1	160449301	C	T	0.66	-1.69	0.28	$2.58^{-09}$
rs7534004	1	160413333	A	G	0.31	1.73	0.29	$3.11^{-09}$
rs12027785	1	160447769	A	T	0.33	1.67	0.28	$3.45^{-09}$
rs12116744	1	160447080	A	G	0.33	1.67	0.28	$3.56^{-09}$
rs4480335	1	160440001	A	C	0.67	-1.67	0.28	$4.32^{-09}$
rs12029454	1	160399741	A	G	0.31	1.73	0.29	$4.37^{-09}$
rs10800352	1	160439313	A	G	0.67	-1.66	0.28	$4.69^{-09}$
rs4306106	1	160438618	A	G	0.33	1.66	0.28	$5.07^{-09}$
rs10127719	1	160422794	C	T	0.32	1.64	0.29	$1.75^{-08}$
rs12036340	1	160282364	A	G	0.77	-1.84	0.33	$4.12^{-08}$
rs10918602	1	160304324	C	T	0.16	2.32	0.42	$4.97^{-08}$
rs6664702	1	160471531	C	T	0.41	1.47	0.27	$5.46^{-08}$
rs1380181	17	15133781	A	G	0.20	-1.97	0.38	$2.92^{-07}$
rs4657173	1	160452170	G	T	0.69	-1.54	0.30	$4.60^{-07}$
rs2204037	13	62334801	A	G	0.39	1.38	0.27	$5.16^{-07}$
rs8049607	16	11599254	C	T	0.52	-1.63	0.33	$7.37^{-07}$
rs6873793	5	3145192	C	T	0.40	1.47	0.30	$1.10^{-06}$
rs2579330	4	72345753	C	T	0.38	1.36	0.28	$1.34^{-06}$
rs7729539	5	64453434	C	T	0.20	-2.59	0.53	$1.36^{-06}$
rs17879755	3	3122981	C	T	0.91	5.64	1.16	$1.71^{-06}$
rs1546498	5	126060863	C	T	0.61	7.69	1.59	$1.85^{-06}$
rs11752626	6	118895345	G	T	0.74	-1.56	0.32	$1.91^{-06}$
rs3757458	7	100668123	A	G	0.01	-8.00	1.65	$1.95^{-06}$
rs17825393	6	118879276	C	T	0.23	1.60	0.33	$1.99^{-06}$
rs2414059	15	48660636	A	T	0.51	1.24	0.26	$2.24^{-06}$
rs231906	11	2709185	A	G	0.64	1.51	0.32	$2.28^{-06}$
rs16928297	11	2442696	G	T	0.51	1.25	0.26	$2.28^{-06}$
rs1079974	17	15127062	G	T	0.21	-1.78	0.37	$2.96^{-06}$
rs2323653	17	15126774	A	G	0.21	-1.77	0.37	$3.06^{-06}$
rs7580640	2	178956666	C	T	0.80	3.64	0.77	$3.09^{-06}$

rs17878749	3	3125573	G	T	0.59	-5.51	1.16	3.13 <sup>-06</sup>
rs3778872	7	150300909	C	G	0.64	-1.77	0.37	3.17 <sup>-06</sup>
rs3778873	7	150300800	C	G	0.64	-1.76	0.37	3.24 <sup>-06</sup>
rs4307206	6	118920013	A	C	0.25	1.51	0.32	3.34 <sup>-06</sup>
rs1817143	4	72278359	A	C	0.29	1.39	0.30	3.58 <sup>-06</sup>
rs7672316	4	72251809	C	T	0.29	1.39	0.30	3.61 <sup>-06</sup>
rs11968176	6	119007633	A	C	0.25	1.50	0.32	3.92 <sup>-06</sup>
rs12661338	6	118901383	A	C	0.25	1.49	0.32	3.99 <sup>-06</sup>
rs16845974	4	72280878	A	G	0.30	1.40	0.30	4.04 <sup>-06</sup>
rs4557101	3	73623308	C	T	0.22	1.72	0.37	4.11 <sup>-06</sup>
rs1138486	1	167368559	C	T	0.82	1.78	0.38	4.23 <sup>-06</sup>
rs16845938	4	72245400	A	C	0.70	-1.41	0.30	4.25 <sup>-06</sup>
rs17226667	6	118828321	A	G	0.73	-1.51	0.32	4.33 <sup>-06</sup>
rs12505704	4	72286060	C	T	0.70	-1.39	0.30	4.38 <sup>-06</sup>
rs2198341	4	72281908	A	G	0.29	1.39	0.30	4.73 <sup>-06</sup>
rs4694092	4	72279083	A	G	0.26	1.50	0.32	4.84 <sup>-06</sup>
rs873955	4	72251193	A	G	0.70	-1.39	0.30	4.86 <sup>-06</sup>
rs9984896	21	36857539	A	C	0.85	-2.85	0.62	5.35 <sup>-06</sup>
rs735951	16	11601037	A	G	0.44	-1.44	0.31	5.55 <sup>-06</sup>
rs7502492	17	15126210	A	G	0.22	-1.67	0.36	5.74 <sup>-06</sup>
rs10027628	4	95862980	C	T	0.26	-1.81	0.39	5.98 <sup>-06</sup>
rs7616330	3	71198441	A	C	0.22	1.72	0.37	5.98 <sup>-06</sup>
rs1380179	17	15136862	A	G	0.71	1.65	0.36	6.12 <sup>-06</sup>
rs539383	15	48665770	A	G	0.53	1.20	0.26	6.45 <sup>-06</sup>
rs7122937	11	2443126	C	T	0.52	-1.35	0.29	6.74 <sup>-06</sup>
rs11641991	16	11612317	A	G	0.17	1.94	0.42	6.75 <sup>-06</sup>
rs12087800	1	160428564	A	G	0.53	1.21	0.26	7.03 <sup>-06</sup>
rs17155315	5	102787557	G	A	0.63	4.73	1.04	7.17 <sup>-06</sup>
rs9866825	3	8225790	A	C	0.41	1.18	0.26	7.54 <sup>-06</sup>
rs6751349	2	46030466	A	C	0.36	-1.22	0.27	7.85 <sup>-06</sup>
rs872712	16	11631856	A	G	0.24	1.89	0.42	7.85 <sup>-06</sup>
rs1426063	4	76249945	A	G	0.55	-1.18	0.26	7.91 <sup>-06</sup>
rs13228494	7	150268027	A	G	0.60	-1.71	0.38	8.04 <sup>-06</sup>
rs9557754	13	101351249	G	T	0.62	-1.23	0.27	8.07 <sup>-06</sup>
rs13149020	4	26803169	A	C	0.45	10.69	2.36	8.14 <sup>-06</sup>
rs4725982	7	150268796	C	T	0.66	-1.71	0.38	8.51 <sup>-06</sup>
rs16878969	4	26803641	C	T	0.55	-10.64	2.36	8.66 <sup>-06</sup>
rs11008099	10	30874638	A	G	0.11	2.74	0.61	8.88 <sup>-06</sup>
rs170745	17	15146746	A	G	0.12	-1.91	0.42	8.92 <sup>-06</sup>
rs11663697	18	72864123	G	T	0.74	-13.71	3.04	8.98 <sup>-06</sup>
rs758887	7	150265381	C	T	0.67	-1.70	0.38	9.38 <sup>-06</sup>
rs7699444	4	95857514	A	G	0.73	1.79	0.40	9.45 <sup>-06</sup>
rs11242260	5	135049856	G	T	0.75	-1.43	0.32	9.80 <sup>-06</sup>
rs1508002	17	49599985	A	T	0.42	2.11	0.47	9.83 <sup>-06</sup>
rs1200164	1	167393519	C	T	0.80	-1.19	0.26	9.84 <sup>-06</sup>
rs11112867	12	105020976	C	T	0.22	2.28	0.51	9.85 <sup>-06</sup>

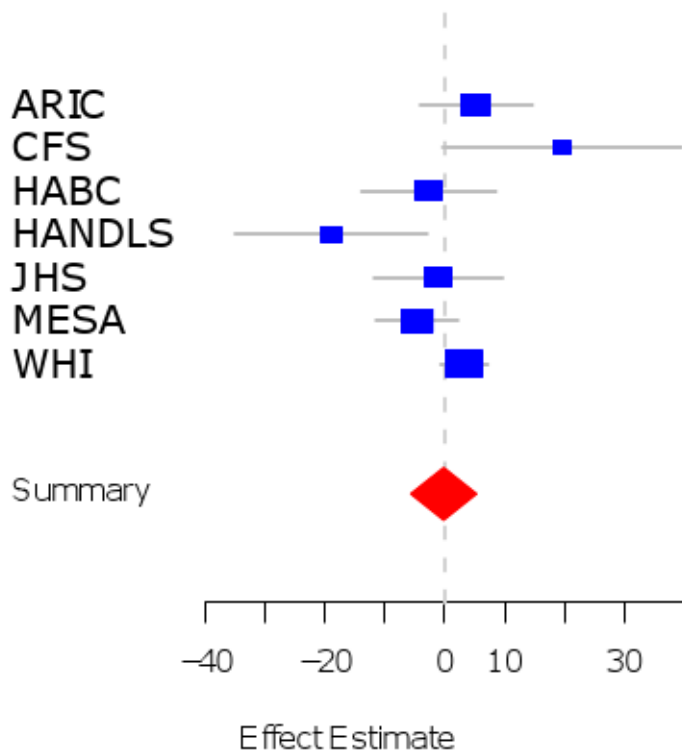
**Supplementary Table 5.** Results for SNPs from GWA studies in individuals of European ancestry.

The table shows the location, allele frequency and p-value for the most significant SNP at each locus with genome-wide significance and independent replication from studies in individuals of European ancestry. Positions refer to NCBI35. CAF refers to the allele frequency for the coded allele (A1).  $N_{\text{eff}}$  refers to the effective sample size in the meta-analysis, defined as  $N \times R^2$ , and reflects the loss of power with poor imputation compared to the total sample size. Effects are milliseconds / coded allele copy with standard error within parentheses. Effects with concordant directionality to the original finding in individuals of European ancestry are indicated with a positive sign. CAF EURO refers to the frequency of the coded allele in the original study.

SNP	CHR	POSITION	A1	A2	CAF	$N_{\text{eff}}$	QT effect	P-VALUE	LOCUS	Concordant effect	ORIGINAL STUDY	CAF EURO
rs10494366	1	160352309	G	T	0.59	13121.6	0.83 (0.26)	0.002	NOS1AP	+	Arking	0.36
rs12143842	1	160300514	C	T	0.80	12811.7	-3.14 (0.39)	$2 \times 10^{-15}$	NOS1AP	+	QTGEN,QTSCD	0.26/0.24
rs12029454	1	160399741	A	G	0.31	12674.6	1.73 (0.29)	$4 \times 10^{-9}$	NOS1AP	+	QTGEN	0.15
rs16857031	1	160379534	C	G	0.68	12207.1	-0.80 (0.29)	0.008	NOS1AP	+	QTGEN	0.14
rs846111	1	6201957	C	G	0.17	8242.9	0.65 (0.55)	0.25	RNF207	+	QTGEN,QTSCD	0.28/0.29
rs10919071	1	167366107	A	G	0.97	6455.1	2.08 (1.13)	0.07	ATP1B1	+	QTSCD	0.87
rs12053903	3	38568397	C	T	0.72	12128.3	-0.41 (0.34)	0.23	SCN5A	-	QTGEN	0.34
rs11129795	3	38564167	A	G	0.24	12194.1	-0.01 (0.34)	0.98	SCN5A	+	QTSCD	0.23
rs11756438	6	119100325	A	C	0.40	12579.4	0.08 (0.27)	0.77	PLN	+	QTGEN	0.47
rs11970286	6	118787067	C	T	0.70	11376.5	-0.56 (0.32)	0.09	PLN	+	QTSCD	0.44
rs11153730	6	118774215	C	T	0.32	12798.5	0.57 (0.29)	0.05	PLN	+	Nolte	0.48
rs4725982	7	150268796	C	T	0.66	7598.9	-1.71 (0.38)	$9 \times 10^{-6}$	KCNH2	+	QTGEN	0.22
rs2968864	7	150253095	C	T	0.25	8013.4	-0.33 (0.83)	0.69	KCNH2	+	QTGEN	0.25
rs2968863	7	150254070	C	T	0.83	9089.3	1.77 (0.64)	0.006	KCNH2	+	QTSCD	0.29
rs2074238	11	2441379	C	T	0.51	1504.4	3.11 (3.48)	0.38	KCNQ1	+	QTGEN	0.06
rs12576239	11	2458895	C	T	0.75	9752.6	-0.59 (0.39)	0.14	KCNQ1	+	QTGEN	0.13
rs12296050	11	2445918	C	T	0.52	1662.4	0.76 (0.78)	0.34	KCNQ1	-	QTSCD	0.20
rs37062	16	-	-	-	-	-	-	-	CNOT1	-	QTGEN	0.24
rs7188697	16	57179679	A	G	0.74	11007.4	1.44 (0.35)	$4 \times 10^{-5}$	CNOT1	+	QTSCD	0.74
rs8049607	16	11599254	C	T	0.52	8275.2	-1.63 (0.33)	$7 \times 10^{-7}$	LITAF	+	QTGEN,QTSCD	0.49/0.71
rs2074518	17	30348495	C	T	0.76	12781.1	0.66 (0.36)	0.07	LIG3	+	QTGEN	0.46
rs17779747	17	66006587	G	T	0.82	12606.4	0.35 (0.44)	0.43	KCNJ2	+	QTSCD	0.35
rs1805128	21	34743550	T	C	0.85	490.8	14.20 (6.54)	0.03	KCNE1	+	QTGEN	0.01



**Supplementary Figure 1.** Genetic ancestry and QT interval.



Effect estimates are presented as beta coefficients, represented by blue boxes with 95% confidence intervals. The random-effects weighted overall effect is presented as a red diamond.