ExomeChip-Wide Analysis of 95 626 Individuals Identifies 10 Novel Loci Associated With QT and JT Intervals

See Editorial by Bos and Pereira

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BACKGROUND: QT interval, measured through a standard ECG, captures the time it takes for the cardiac ventricles to depolarize and repolarize. JT interval is the component of the QT interval that reflects ventricular repolarization alone. Prolonged QT interval has been linked to higher risk of sudden cardiac arrest.

METHODS AND RESULTS: We performed an ExomeChip-wide analysis for both QT and JT intervals, including 209 449 variants, both common and rare, in 17 341 genes from the Illumina Infinium HumanExome BeadChip. We identified 10 loci that modulate QT and JT interval duration that have not been previously reported in the literature using single-variant statistical models in a meta-analysis of 95 626 individuals from 23 cohorts (comprised 83 884 European ancestry individuals, 9610 blacks, 1382 Hispanics, and 750 Asians). This brings the total number of ventricular repolarization associated loci to 45. In addition, our approach of using coding variants has highlighted the role of 17 specific genes for involvement in ventricular repolarization, 7 of which are in novel loci.

CONCLUSIONS: Our analyses show a role for myocyte internal structure and interconnections in modulating QT interval duration, adding to previous known roles of potassium, sodium, and calcium ion regulation, as well as autonomic control. We anticipate that these discoveries will open new paths to the goal of making novel remedies for the prevention of lethal ventricular arrhythmias and sudden cardiac arrest.

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Clinical Perspective

Prolonged QT interval has been associated with increased risk of sudden cardiac arrest, a major cause of mortality, with between 180 000 and 450 000 cases of sudden cardiac arrest in the United States of America annually. Because the vast majority of sudden cardiac arrest occurs in the absence of clinical features that would bring a victim to medical attention, identifying additional risk factors and dissecting the pathogenesis of disease are of high importance. In this study, we conduct ExomeChip-wide analyses in 95 626 population-based multiethnic individuals to interrogate the role of a largely unstudied class of variation on ventricular repolarization in the population—coding single nucleotide variants. These variants fill in the gap between the extremely rare large-effect coding variants that result in the Mendelian long- and short-QT syndromes and the common small-effect largely noncoding variation identified through genome-wide association studies. The focus on exons and coding variants has an added benefit of directly implicating genes. Our approach of focusing on coding variants and both QT and JT intervals measures has identified 10 novel loci associated with ventricular repolarization and has implicated 17 specific genes, 7 of which are in novel loci. Our analyses show a role for myocyte internal structure and interconnections in modulating QT interval duration, adding to previous known roles of potassium, sodium, and calcium ion regulation, as well as autonomic control. We anticipate that these discoveries will open new paths to the goal of making novel remedies for the prevention of lethal ventricular arrhythmias and sudden cardiac arrest.

Prolonged QT interval has been associated with increased risk of sudden cardiac arrest (SCA), a major cause of mortality, with between 180 000 and 450 000 cases of SCA in the United States of America annually.[1] Because the vast majority of SCA occurs in the absence of clinical features that would bring a victim to medical attention,[2] identifying additional risk factors and dissecting the pathogenesis of disease are of high importance.

Heritability estimates of QT interval are between 30% and 40%, indicating that genetic variants play a large role in modulating QT interval in the general population.[3] Mendelian syndromes of QT interval (long- and short-QT syndrome), which lead to increased risk of cardiac arrhythmias and SCA, occur in ≈1 in 2000 individuals and are caused by variants in ion channels or their interacting proteins.[4] Previous candidate gene and genome-wide association studies (GWAS), largely screening common noncoding variants, have identified 35 loci containing variants that modestly influence QT interval, the largest of these studies, the QT Interval International GWAS Consortium (QT-IGC),[5] included a discovery population of 76 061 European ancestry individuals.

In this study, we conduct ExomeChip-wide analyses in population-based samples to interrogate the role of a largely unstudied class of variation on ventricular repolarization in the population—coding single nucleotide variants (SNVs). These variants fill in the gap between the extremely rare large-effect coding variants that result in the Mendelian long- and short-QT syndromes and the common small-effect largely noncoding variation identified through GWAS. The focus on exons and coding variants has an added benefit of directly implicating genes. By contrast, noncoding variation typically implicates a region of the genome, often containing multiple genes, and therefore requiring extensive functional experiments to implicate a specific gene. Furthermore, in this study, we examine both QT and JT interval to more comprehensively examine ventricular repolarization. We have previously observed that variation in specific loci can influence ventricular depolarization and repolarization in a concordant fashion.[5,6]

We performed a meta-analysis of 23 cohorts including 95 626 multiethnic individuals comprised 83 884 European ancestry individuals, 9610 blacks, 1382 Hispanics, and 750 Asian individuals (Table I in the in the Data Supplement). Each individual was genotyped for 191 740 coding SNVs in 17 341 genes using the Illumina Infinium HumanExome BeadChip (ExomeChip), along with 17 709 noncoding SNVs of known importance from previous GWAS and variants tiling across the genome. These variants were chosen by evaluating ≈12 000 exome sequences for coding variants that appeared in at least 3 individuals.

METHODS

The data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results, subject to Data Use/Sharing Agreements adopted by individual participating cohorts. GWAS summary results will be available through the CHARGE Consortium Summary Results webpage available at dbGaP (phs000930).

This study was approved by local institutional review boards, and all participating subjects gave informed consent (detailed ethics statements in the Data Supplement).

SNV Association Tests and Meta-Analysis

Detailed methods are provided in the Data Supplement. Briefly, all cohorts excluded individuals with QRS intervals ≥120 ms, heart rate <40 beats per minute or >120 beats per

minute , left or right bundle branch block, atrial fibrillation on baseline ECG, Wolff–Parkinson–White syndrome, pacemaker, use of class I or class III blocking medication, or pregnant. Clinical characteristics summary statistics for each cohort are provided in Table I in the Data Supplement.

SNV effect size estimates are calculated via standard inverse variance–weighted meta-analysis of results provided by each cohort from a linear association model with QT/JT as the dependent variable, including covariates age, sex, RR interval (inverse heart rate), height, body mass index, and cohort-specific adjustments (principal components, clinic, family structure). Significance is similarly calculated by inverse variance–weighted meta-analysis; however, instead of raw QT/JT as the dependent variable in the linear regression, an inverse rank normal transformation is performed (details in the Data Supplement). These 2 models are used in tandem to avoid *P* value inflation from the analysis of the rare variants on the ExomeChip while maintaining the easy interpretation of effect sizes in milliseconds. The main analysis included all ethnic groups meta-analyzed together. SNVs with minor allele count <10 were excluded from the meta-analysis. SNVs were considered statistically significant if they exceeded the Bonferroni correction threshold of $P<2\times10^{-7}$.

Use of Functional Variants to Implicate Individual Genes Using Genome-Wide Significance

Genome-wide significance (GwiS) uses a greedy forward selection algorithm to identify independent genetic effects within a given gene/locus.[7] A locus was defined by the SNV with the most significant association±1 megabase. GWiS was run on European-only summary statistics from 22 cohorts (QT, n=83 884; JT, n=80 330), with linkage disequilibrium (LD) estimated from the merged ExomeChip and HapMap-imputed Atherosclerosis Risk in Communities (ARIC) European ancestry data set (n=9537; Data Supplement). An attempt to replace GWiS identified noncoding variants with equivalent coding variants ($r^2>0.8$) did not yield any substitutions.

RESULTS

QT Interval ExomeChip Analysis Identifies 6 Novel Loci

Meta-analysis identified SNVs in 25 loci associated with QT interval at ExomeChip-wide significance ($P<2\times10^{-7}$; Figure I in the Data Supplement). Of these, 19 loci were previously associated with QT interval, and 6 loci were novel (Table 1). At 4 of these novel loci (*PM20D1*, *SLC4A3*, *CASR*, and *NRAP*), the top hit is a nonsynonymous variant. For the 2 novel loci where the index SNV is a noncoding variant, no genes in these loci harbored coding SNVs associated with QT interval. Analyses stratified by ethnicity found similar effect sizes between European ancestry individuals and blacks and same general direction of effects in the much smaller Hispanics (n=1382) and Chinese (n=750) cohorts (Table II and Figure II in the Data Supplement).

Nineteen of the 25 loci associated with QT interval at ExomeChip-wide significance in our study had been associated with QT interval in prior European ancestry GWAS studies (Table 2, **P* value). Table 2 detail the 35 known QT loci identified from prior GWAS of European ancestry individuals. Of the 14 previously identified loci for which the most significant SNV in our current study is a coding variant (Table 2, A), 3 loci reached ExomeChip-wide significance in our study (**P* value). Of the 21 previously identified loci for which the most significant SNV in our study is a noncoding variant not in LD ($r^2>0.8$) with a nearby coding variant, 16 loci exceeded the significance threshold in our study (Table 2, B, **P* value). For 5 of these 16 loci where the top signal was a noncoding SNV, they nonetheless harbored coding variants in ≥1 nearby genes that also reached ExomeChip-wide significance (Table II in the Data Supplement).

Table 1. Six Novel Loci Associated With QT Interval

Nearby Gene	SNV	Chr	Coded/ Noncoded Allele	CAF	Effect in ms (SE)	*P* Value	Function	Gene(s) With Independent Coding Variation	DEPICT Implicated Gene(s)	eQTL
PM20D1	rs1361754	1	G/A	0.511	0.47 (0.08)	1E-09	Nonsynonymous	*PM20D1*		*PM20D1,* NUCKS1, RAB7L1,* SLC41A1*
SLC4A3	rs55910611	2	A/G	0.006	–3.06 (0.61)	2E-07	Nonsynonymous	*SLC4A3*		
CASR	rs1801725	3	T/G	0.126	–0.58 (0.12)	4E-08	Nonsynonymous	*CASR*		*CSTA*
ZNF37A	rs4934956	10	T/C	0.497	0.58 (0.10)	2E-10	Intergenic			
NRAP	rs3189030	10	A/G	0.299	–0.48 (0.09)	4E-08	Nonsynonymous	*NRAP*	*NRAP*	*CASP7**
GOSR2	rs17608766	17	C/T	0.123	0.72 (0.12)	3E-09	UTR3			*RPRML*

Significance was determined from analysis of inverse rank normal transformed residuals to avoid *P* value inflation from the analysis of rare variants. Effect size estimates in milliseconds (ms) are reported from untransformed analyses. n=95 626 number of samples. DEPICT[9] genes pass FDR <5% cutoff. Expression quantitative trait loci (eQTL) genes are pulled from the Genotype-Tissue Expression portal[10,11] using the representative SNV and GWiS independent SNVs. CAF indicates coded allele frequency; DEPICT, Data-driven Expression-Prioritized Integration for Complex Traits; FDR, false discovery rate; GwiS, genome-wide significance; SNV, single-nucleotide variants; and UTR3, three prime untranslated region.

*Gene if the eQTL is in the left ventricle.

Table 2. Thirty-Five Loci Previously Associated With QT Interval

Nearby Gene	SNV	Chr	Coded/ Noncoded Allele	CAF	Effect in ms (SE)	*P* Value	Function	QT-IGC Implicated Gene(s)	Gene(s) With Independent Coding Variation	DEPICT Implicated Gene(s)	eQTL
A, Known QT loci with coding variant as top SNV											
RNF207	rs709209	1	G/A	0.379	1.23 (0.09)	1E-48*	Nonsynonymous	*RNF207(c)*	*RNF207*	*RNF207*	*GPR153*
SP3	rs1047640	2	C/T	0.120	0.60 (0.12)	3E-06	Nonsynonymous		*SP3*		
TTN-CCDC141	rs72648998	2	T/C	0.054	1.00 (0.18)	3E-09*	Nonsynonymous	*CCDC141(i), TTN(i)*	*TTN*		*FKBP7, PRKRA*
SPATS2L	rs192861441	2	A/G	0.004	−2.22 (0.67)	3E-04	Nonsynonymous	*SPATS2L(t), SGOL2(p)*			
C3ORF75	rs2276853	3	G/A	0.411	−0.36 (0.08)	2E-05	Nonsynonymous	*KLHL18(t), PTPN23(t), SCAP(t), SETD2(t), MYL3(i)*		*NBEAL2*	*NBEAL2, PTPN23, SCAP*
SMARCAD1	rs7439869	4	T/C	0.378	0.41 (0.08)	8E-07	Nonsynonymous		*SMARCAD1*		
GMPR	rs1042391	6	T/A	0.551	−0.42 (0.09)	3E-06	Nonsynonymous	*GMPR(c), ATXN1(tp)*	*GMPR*		*GMPR*
KCNH2	rs1805123	7	G/T	0.214	−1.47 (0.10)	7E-51*	Nonsynonymous	*KCNH2(p)*	*KCNH2*†		*KCNH2*
LAPTM4B	rs17831160	8	A/G	0.030	−0.64 (0.24)	3E-03	Nonsynonymous				
AZIN1	rs143025416	8	A/G	0.001	4.90 (1.55)	2E-03	Nonsynonymous				
GBF1	rs143226354	10	T/C	8.89E-05	14.18 (4.66)	4E-03	Splicing/ nonsynonymous	*ACTR1A(i)*			
ATP2A2	rs11068997	12	A/G	0.040	−0.94 (0.21)	4E-07	Nonsynonymous	*VPS29(t), GPN3(t), ARPC3(t), C12ORF24(t), ATP2A2(pi)*	*GIT2, TCTN1*	*ATP2A2, PPTC7*	
USP50-TRPM7	rs8042919	15	A/G	0.097	−0.57 (0.14)	4E-05	Nonsynonymous				*SPPL2A, AP4E1, USP50*
CREBBP	rs143903106	16	T/G	0.001	4.10 (1.46)	5E-03	Nonsynonymous	*TRAP1(i)*			
B, Known QT loci with noncoding variant as top SNV											
TCEA3	rs1077514	1	G/A	0.179	−0.58 (0.11)	4E-08*	Intronic	*TCEA3(t)*			*TCEA3,‡ ASAP3*
NOS1AP	rs12143842	1	T/C	0.240	3.18 (0.10)	3E-255*	Intergenic				
ATP1B1	rs10919071	1	G/A	0.115	−1.37 (0.13)	3E-30*	Intronic	*ATP1B1(ti), NME7(t)*			*NME7*
SLC8A1	rs2540226	2	T/G	0.482	0.24 (0.08)	2E-03	Intergenic	*SLC8A1(p)*			*THUMPD2*
SCN5A-SCN10A	rs12053903	3	C/T	0.379	−0.88 (0.09)	1E-26*	Intronic	*SCN5A(p)*	*SCN10A*	*SCN5A*	*SNORA6, SCN5A*§
SLC4A4	rs7689609	4	C/T	0.212	0.64 (0.12)	4E-08*	Intronic				
GFRA3	rs4835768	5	G/A	0.485	0.34 (0.08)	7E-05	Intergenic	*FAM13B(t), ETF1(p)*		*MYOT, FAM13B*	
SLC35F1-PLN	rs11153730	6	C/T	0.467	1.41 (0.08)	5E-74*	Intergenic	*PLN(i)*		*PLN*	*SSXP10*
CAV1	rs3807989	7	A/G	0.429	0.54 (0.08)	4E-12*	Intronic	*CAV1(pi), CAV2(pi)*			*AC002066.1*
NCOA2	rs2926707	8	G/T	0.348	0.31 (0.09)	3E-04	Intronic				
KCNQ1	rs2074238	11	T/C	0.074	−3.58 (0.16)	8E-130*	Intronic	*C11ORF21(t), PHEMX(t), TSPAN32(t), KCNQ1(p)*	*KCNQ1*	*KCNQ1*	
FEN1-FADS2	rs1535	11	G/A	0.325	−0.48 (0.09)	8E-10*	Intronic	*FADS1(t), FADS2(t), FADS3(t)*			*FAD2,‡ FADS1, TMEM258*
KLF12	rs1886512	13	A/T	0.381	0.57 (0.09)	2E-10*	Intronic	*KLF12(t)*			*KLF12*‡
ANKRD9	rs11704	14	C/G	0.291	0.35 (0.09)	7E-05	UTR3	*ANKRD9(t)*		*ANKRD9*	*ZNF839*

(*Continued*)

Table 2. Continued

Nearby Gene	SNV	Chr	Coded/ Noncoded Allele	CAF	Effect in ms (SE)	*P* Value	Function	QT-IGC Implicated Gene(s)	Gene(s) With Independent Coding Variation	DEPICT Implicated Gene(s)	eQTL
LITAF	rs8049607	16	T/C	0.503	1.05 (0.08)	8E-44*	Intergenic	*LITAF(t)*			*LITAF*‡
MKL2	rs30208	16	T/C	0.501	0.45 (0.08)	2E-09*	Intergenic				
CNOT1	rs7188697	16	G/A	0.247	−1.57 (0.10)	4E-63*	Intronic	*NDRG4(t), CNOT1(t), GOT2(i)*			*SETD6, NDRG4*
LIG3	rs2074518	17	A/G	0.428	−0.79 (0.08)	2E-21*	Intronic	*LIG3(t), CCT6B(t), UNC45B(i)*			*LIG3,‡ CCT6B, RFFL,‡ RP5-837J1.2*
PRKCA	rs9912468	17	G/C	0.417	−0.68 (0.08)	2E-15*	Intronic	*PRKCA(t)*			*PRKCA*‡
KCNJ2	rs17779747	17	T/G	0.304	−1.08 (0.09)	3E-37*	Intergenic				
KCNE1	rs727957	21	T/G	0.168	0.48 (0.11)	3E-05	Intronic	*KCNE1(cp)*			

A section lists the 14 (of 35) previously identified loci (QT-IGC study of European ancestry individuals[5]) for which the most significant SNV in our current study is a coding variant. Because of the design of the Exome Chip with a focus on coding variants, only select intronic or intergenic SNVs were interrogated, and therefore not all QT-IGC SNVs were examined. B section lists the 21 previously identified loci for which the most significant SNV in our study is a noncoding variant not in LD (r^2>0.8) with a nearby coding variant. Significance was determined from analysis of inverse rank normal transformed residuals to avoid *P* value inflation from the analysis of rare variants. Effect size estimates in milliseconds (ms) are reported from untransformed analyses. n=95 626 number of samples. Within the QT-IGC Implicated Gene(s) column, evidence for the gene is c, coding variant; t, eQTL transcript; p, in silico protein-protein interactor; i, immunoprecipitation interactor. DEPICT[9] genes pass FDR<5% cutoff. Expression quantitative trait loci (eQTL) genes are pulled from the Genotype-Tissue Expression portal[10,11] using the representative SNV and GWiS independent SNVs. CAF indicates coded allele frequency; DEPICT, Data-driven Expression-Prioritized Integration for Complex Traits; FDR, false discovery rate; GwiS, genome-wide significance; QT-IGC, QT Interval International GWAS Consortium, and SNV, single nucleotide variants.

**P* value if significantly associated after Bonferroni correction, $P<2\times10^{-7}$.

‡Gene if the eQTL is in the left ventricle.

§GWiS independent SNV rs9851724 used to identify eQTL.

†Conditional analyses in ARIC contradict this result, see text for details.

JT Interval Association Identifies 4 Novel Loci

Although ventricular depolarization and repolarization are often coregulated, this is not universally true. Therefore, to more specifically examine ventricular repolarization, we also investigated genetic associations with JT interval, defined mathematically by subtracting the QRS interval (ventricular depolarization and conduction) from the QT interval, which primarily reflects ventricular repolarization.[8] Among the 15 590 ARIC participants, the correlations (r^2) among the intervals were 0.84 for QT and JT; 0.02 for QRS and JT; and 0.08 for QT and QRS. We analyzed JT interval as described above for QT interval while adding QRS interval as an additional covariate to further remove the effect of ventricular depolarization on the analysis. Thirty coding variants in 14 loci were associated with JT interval (Table III and Figure III in the Data Supplement). Four of these 14 loci were not identified as QT interval loci (Table 3). Three of these 4 novel repolarization loci had index SNVs that were coding variants: *SENP2*, *SLC12A7*, and *NACA*. The SNV rs9470361 (near *CDKN1A*) has previously been associated with QRS interval with an effect size estimate in the opposite direction (Table 3). Indeed, for 3 of these loci (*SENP2*, *CDKN1A*, and *NACA*), where an association was found with JT but not with QT interval, the index SNVs were significantly associated with QRS duration but with effect estimates in the opposite direction (Table 3). Hence, at these loci, variants that prolong the QRS interval (depolarization) shorten the JT interval (repolarization). Analyses run stratified by ethnicity found similar effect sizes between European ancestry individuals and blacks (Table III in the Data Supplement).

Use of Coding Variants to Implicate Specific Genes

Leveraging information from nominally significant coding SNVs, we sought to implicate causative genes in each locus by demonstrating that putatively functional coding variants are associated with ventricular repolarization independently of noncoding SNVs. We have previously[5] shown that several QT loci contain multiple independent genetic effects, including some loci harboring multiple significant coding variants (Tables II and III in the Data Supplement). Thus, even if not the top hit at a locus, putative functional SNVs can still implicate a specific gene at a locus. We used the GWiS[7] algorithm to determine the number of independent effects in all 45 ventricular repolarization associated loci from Tables 1 through 3 and to identify the SNV that best represents each independent effect in European ancestry individuals (n=83 884; Table IV in the Data Supplement). The *SCN5A-SCN10A* locus is a particularly illustrative example of the use of this approach. Although coding variants in *DLEC1*, *SCN5A*, and *SCN10A* are each ExomeChip-wide significant, after using GWiS, the

Table 3. Four Novel Loci Associated With JT Interval

Nearby Gene	SNV	Chr	Coded/ Noncoded Allele	CAF	JT Effect in ms (SE)	JT *P* Value	QRS Effect in ms (SE)	QRS *P* Value	Function	Gene(s) With Independent Coding Variation	DEPICT Implicated Gene(s)	eQTL
SENP2	rs6762208	3	A/C	0.358	0.44 (0.08)	2E-07*	−0.31 (0.05)	3.45E-12*	Nonsynonymous	*SENP2*		
SLC12A7	rs737154	5	C/T	0.500	−0.40 (0.08)	2E-07*	0.07 (0.04)	8.84E-02	Splicing/ synonymous	*SLC12A7*		*NKD2*
CDKN1A	rs9470361	6	A/G	0.249	−0.76 (0.09)	2E-15*	0.84 (0.05)	1.21E-63*	Intergenic			
NACA	rs2926743	12	A/G	0.252	0.53 (0.09)	6E-08*	−0.32 (0.05)	9.40E-11*	Nonsynonymous	*NACA*	*RBMS2*	

Significance was determined from analysis of inverse rank normal transformed residuals to avoid *P* value inflation from the analysis of rare variants. Effect size estimates in milliseconds (ms) are reported from untransformed analyses. QRS interval association summary data for these 4 variants were contributed by our coauthors Drs Prins, Jamshidi, and Arking from ExomeChip analyses they are running as a part of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium Electrocardiogram (EKG) working group. n=95 626 samples for JT interval association and n=85 593 samples for QRS interval association. DEPICT[9] genes pass FDR<5% cutoff. Expression quantitative trait loci (eQTL) genes are pulled from the Genotype-Tissue Expression portal[10,11] using the representative SNV and GWiS independent SNVs. CAF indicates coded allele frequency; DEPICT, Data-driven Expression-Prioritized Integration for Complex Traits; FDR, false discovery rate; GwiS, genome-wide significance; and SNV, single nucleotide variants.

**P* value if significantly associated after Bonferroni correction, $P<2\times10^{-7}$.

†Gene if the eQTL is in the left ventricle.

signal coming from the coding variants in *DLEC1* and *SCN5A* is explained by noncoding variants, and only the *SCN10A* coding variant signal remains (Table V in the Data Supplement). In the Gene(s) with independent coding variation column in Tables 1 through 3, we list the 17 genes in 16 loci that have an independent effect represented by a coding variant.

For the loci listed in Table 2 B, such as the *SCN5A-SCN10A* locus, where intronic and intergenic variants were included in the analyses, the independent associations in coding SNVs identified by GWiS are independent of the noncoding variants in the region. This analysis implicates 2 genes for involvement in cardiac repolarization among those of European descent: *SCN10A* and *KCNQ1*. For the novel loci in Table 1 where a coding SNV is the most significant association in our study, it is unlikely that noncoding variants of importance are present in those loci because the loci were not found during the QT-IGC efforts, a study of similar sample size.

In contrast, for the 14 previously identified QT loci where the top SNV in our study was a coding variant (Table 2, A), the GWiS findings are less conclusive because intronic and intergenic SNVs were largely not examined in these regions. Therefore, to determine whether the associated coding variants are independently associated with QT interval and hence implicate a causal gene, or alternatively, are associated simply because of LD with a more strongly associated noncoding variant not genotyped with the ExomeChip, we performed additional analyses in a subset of the data set, ARIC, that includes both the QT-IGC top SNV, as well as the top SNV, from the current study. We performed conditional analyses at the 7 loci in Table 2, A where significant associations were identified by GWiS (the remaining 7 loci did not have any SNVs identified as significant by GWiS after accounting for multiple testing), by including both the QT-IGC and ExomeChip variants in the same regression model in the ARIC Europeans data set (n=9537; Table VI in the Data Supplement). Conditional analyses demonstrate that the coding variant in *SP3* is independent of the top noncoding SNV at this locus discovered from QT-IGC, implicating this gene in QT interval modulation. For *GMPR*, the coding variant is in almost perfect linkage disequilibrium with the noncoding QT-IGC variant (r^2=0.99 in ARIC), suggesting that the coding variant may be the causal variant explaining the QT-IGC signal. For a third locus, *RNF207,* although conditional analysis suggested that the QT-IGC SNV accounts for the association at this locus, both the top QT-IGC SNV as well as the top SNV from this study are coding variants in high LD, thus implicating the *RNF207* gene in myocardial repolarization. For the remaining 4 loci, 1 coding variant is associated because of the stronger noncoding QT-IGC signal (*KCNH2*); 2 were not properly tested because of no effect in ARIC of the ExomeChip variant (*ATP2A2*) or the QT-IGC variant (*TTN*), although there was low LD (r^2<0.04) between the coding and noncoding variants, suggesting independence; and 1 was unclear (*SMARCAD1*), as putting both SNVs in the model significantly altered the β estimates for both SNVs.

In Silico Analyses to Implicate Causal Genes

To further decode the role these loci might play in regulating ventricular repolarization, Data-driven Expression-Prioritized Integration for Complex Traits[9] was used to investigate whether identified loci contain genes from functional annotated gene sets/pathways. Included in Tables 1 through 3 in the DEPICT Implicated Gene(s) column is a list of genes with a false discovery rate <5%. Furthermore, we looked up each of the Tables 1 through 3 SNVs in the Genotype-Tissue Expression Portal to identify single-tissue expression quantitative trait loci[10,11] (left ventricle expression quantitative trait loci, represented by footnote symbols in tables). Findings for

Data-driven Expression-Prioritized Integration for Complex Traits and expression quantitative trait loci analyses are largely consistent with those genes identified because of harboring significant coding variants and help clarify the causative gene.

DISCUSSION

Our approach of focusing on coding variants and both QT and JT intervals has identified 10 novel loci associated with ventricular repolarization and has implicated 17 specific genes, 7 of which are in novel loci. Previous studies have implicated roles for potassium ion regulation, sodium ion regulation, calcium ion regulation, and autonomic control of QT interval,[12] and our results provide support for each of these pathways. *SLC12A7* (*KCC4*), which is highly expressed in the left ventricle,[10,11] is a potassium chloride cotransporter involved in potassium efflux.[13] *CASR* is a G protein–coupled receptor that maintains circulating calcium ion homeostasis via parathyroid hormone secretion in the parathyroid and kidney tubule ion handling.[14]

In addition to previously implicated pathways, our analyses highlight a role for genes involved in generating the physical force of contraction inside of cardiomyocytes and for conducting electric signal between cardiomyocytes across the heart. Pathway enrichment analyses using Data-driven Expression-Prioritized Integration for Complex Traits (detailed methods in the Data Supplement) identified the GO category GO:0005916, which comprised the genes that code for fascia adherens, the structure that links myofibrils between cardiomyocytes, and contains N-cadherin. *NRAP*, found to have a significant independent coding variant, likely anchors terminal actin filaments of myofibrils to other protein complexes beneath the sarcolemma[15,16] and is expressed exclusively in skeletal muscle and heart.[10,11] skNAC (skeletal *NACA*) knockout mice, a muscle-specific isoform of *NACA*, which was found to have a significant independent coding variant, die between embryonic days 10.5 and 12.5 because of cardiac defects, showing interventricular septal defects and a thin myocardial wall.[17] With these 3 points of evidence combined with the previously known locus and GWiS-implicated gene, *TTN*, a clear class of genes emerge that influence ventricular repolarization through their effect on myocyte structure.

It is important to note that the intercalated disc, which is the interface between cardiomyocytes, contains fascia adherens, desmosomes, and gap junctions, the last of which is known to play a role in ion-mediated relaying of action potentials between cardiomyocytes and, in combination with the gene *NOS1AP*, has been implicated as regulating QT interval.[18] In contrast, we implicate a nonion-dependent structural/mechanical interconnect between cardiomyocytes mediated by the fascia adherens.

By looking specifically at ventricular repolarization (JT interval) without the influence of depolarization (QRS interval), we detected additional loci related to ventricular repolarization while teasing apart the differential regulation of the various phases of ventricular conduction. Our current results are consistent with our prior findings that variation in some loci influence ventricular depolarization and repolarization in a concordant fashion, others influence depolarization and repolarization in a discordant fashion, and still other loci are associated with one phenotype and not the other.[5,6] Although ventricular depolarization and repolarization are often coregulated, the difference in genetic effect indicates this is not universally true. Several limitations should be noted. First, we did not have an additional sample to perform replication studies although results were consistent across the diverse cohorts included in our study (Figures IV–XIII in the Data Supplement). Second, correlation of effect sizes was weak between the European ancestry and Hispanic and Asian populations, limiting extrapolation of findings to these populations.

In summary, we have identified 10 loci newly associated with ventricular repolarization. This brings the total number of ventricular repolarization–associated loci to 45. In addition, we have directly implicated 17 specific genes contained in these loci as likely affecting ventricular repolarization and outlined a class of genes that mechanically control QT interval. These new discoveries will likely allow for the development of novel vectors for the prevention of lethal ventricular arrhythmias and SCA.

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FOOTNOTES

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ExomeChip-Wide Analysis of 95 626 Individuals Identifies 10 Novel Loci Associated With QT and JT Intervals

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SUPPLEMENTAL MATERIAL

21. **Supplemental Figure 9:** Forest Plot of rs55910611 Association with QT interval.

22. **Supplemental Figure 10:** Forest Plot of rs737154 Association with JT interval.

23. **Supplemental Figure 11:** Forest Plot of rs2926743 Association with JT interval.

24. **Supplemental Figure 12:** Forest Plot of rs6762208 Association with JT interval.

25. **Supplemental Figure 13:** Forest Plot of rs9470361 Association with JT interval.

Supplemental Methods

Genotyping and Quality Control

Genotyping and quality control followed ExomeChip best practices put out by the CHARGE Consortium[1].

SNV Association Tests and Meta-Analysis

SNV effect size estimates are calculated via standard inverse variance weighted (IVW) meta-analysis of results provided by each cohort from a linear association model with QT/JT as the dependent variable, including covariates age, sex, RR interval, height, body mass index (BMI), and cohort specific adjustments (principal components, clinic, family structure). Significance (*P* value) is determined by first inverse rank normal transforming residuals from a linear model with QT/JT as the outcome using covariates: Age, Sex, RR interval, Height, and BMI, then running a standard IVW meta-analysis on a linear association model with the transformed residuals as the outcome using cohort specific adjustments as covariates. These two models are used in tandem to avoid *P* value inflation from the analysis of the rare variants on the ExomeChip while maintaining the easy interpretation of effect sizes in milliseconds.

Representative SNVs have the lowest p-value in each locus. QT loci are considered discovered if passing a Bonferroni correction, $P<0.05 / 209{,}449$ SNVs (2E-07). JT loci are considered discovered if passing a Bonferroni correction, $P< 0.05 / 208{,}917$ SNVs (2E-07). The difference in the number of SNVs is due to the fact not all cohorts that contributed data to the QT analysis contributed data to the JT analysis. Cohorts contribute slightly different number of SNVs due to individual QC efforts. Variants with minor allele counts less than 10 were excluded from the meta-analysis.

LD Calculations and Conditional Analyses

LD calculations were performed in the merged ExomeChip and HapMap-imputed ARIC European-ancestry dataset with 9,537 samples. Conditional analyses were run only if the QT-IGC variant had a nominal association in ARIC ($P<0.05$) to ensure the effect size estimate was stable.

Utilization of Functional Variants to Implicate Individual Genes using GWiS

Gene-Wide Significance (GWiS) uses a greedy forward selection algorithm to identify independent genetic effects within a given gene/locus[2]. We defined each locus as the most significant SNV ±1 MB and ran on European-only summary statistics from 22 cohorts for a sample size of 83,884 in QT analyses and 80,330 in JT analyses. GWiS finds the number of independent effects in each locus along with a SNV that best represents each independent effect. This is important because even coding variants may be significant in the analysis due to LD with a causal non-coding variant. The LD information needed for the GWiS analysis was estimated in the ARIC Europeans dataset as described above. To ensure accurate estimates of LD, the GWiS analysis was limited to European-only because ARIC has a large number of European-ancestry individuals. An attempt to replace GWiS identified non-coding variants with equivalent coding variants ($r^2>0.8$) did not yield any substitutions.

SKAT Gene-based Tests

SKAT tests were performed using the R package "seqMeta" with rare variants (MAF ≤ 0.01) from each gene. Variants were filtered to those that alter protein coding: frame-shift, nonsynonymous, stop-gain, stop-loss, or splicing[1]. In a second analysis, the nonsynonymous variants were further filtered to those predicted to be damaging by at least two of the following prediction algorithms: Polyphen2, LRT, SIFT, Mutation Taster[1]. Genes with only a single variant were excluded. Bonferroni corrected ExomeChip-wide significance is $P<0.05$ divided by the number of genes tested in either of the variant filters: 29,368 for QT and 29,366 for JT.

Pathway Enrichment

To further decode the role whether QT/JT-associated loci might play in regulating ventricular repolarization, Data-driven Expression-Prioritized Integration for Complex Traits (DEPICT)[3] was used to investigate if

identified loci contain genes from functional annotated gene sets/pathways. The 45 SNVs from Tables 1, 2, and 3 were used to seed the algorithm, however, only 38 SNVs were able to be matched to DEPICT's internal database used by the algorithm (Date Supplement Table VII). Included in Tables 1, 2, and 3 in the "DEPICT Implicated Gene(s)" column is a list of genes with a false discovery rate (FDR) < 5%. Three gene sets passed the FDR cutoff of 5%: C1QA subnetwork (ENSG00000173372; p=1.97E-6), fascia adherens (GO:0005916; p=8.28E-6), and ACOT13 subnetwork (ENSG00000112304; p=9.02E-6). Three tissues also passed the FDR cutoff of 5%: Heart Ventricles (A07.541.560; p=9.56E-4), Heart (A07.541; p=9.74E-4), and Atrial Appendage (A07.541.358.100; p=0.003).

GTEx eQTL Lookup

We looked up each of the Tables 1, 2, and 3 representative SNVs and GWiS independent SNVs (60 SNVs) in the GTEx Portal to identify single-tissue expression quantitative trait loci (eQTL)[4,5]. All eQTLs passed FDR<5%. The results are presented in Tables 1, 2, and 3's "eQTL" column (left ventricle association noted in bold). Genes were excluded if the SNV was towards the bottom of an LD significance peak indicating the association is due to low-level LD with a stronger eQTL not associated with QT/JT interval: *ATP1B1*, *ANKRD9*, *BAZ2A* from the *NACA* locus. Interestingly, rs1361754 was found to be both an ExomeChip-wide significant coding variant in *PM20D1* and an eQTL for the same gene in left ventricle. Furthermore, for loci where there were no independent coding SNV associations to implicate a causal gene, eQTL analysis from left ventricular tissue, arguably the most relevant tissue to the phenotype of cardiac repolarization, identifies 7 additional genes potentially involved in myocardial repolarization (bolded genes in Table 2B).

Cohort Specific Methods

AGES

In anticipation of the sequencing of the human genome and description of the human proteome, the Age, Gene/Environment Susceptibility-Reykjavik Study (AGES-Reykjavik)[6] was initiated in 2002. AGES-Reykjavik was designed to examine risk factors, including genetic susceptibility and gene/environment interaction, in relation to disease and disability in old age. The study is multidisciplinary, providing detailed phenotypes related to the cardiovascular, neurocognitive (including sensory), and musculoskeletal systems, and to body composition and metabolic regulation. Relevant quantitative traits, subclinical indicators of disease, and medical diagnoses are identified by using biomarkers, imaging, and other physiologic indicators. The AGES-Reykjavik sample is drawn from an established population-based cohort, the Reykjavik Study. This cohort of men and women born between 1907 and 1935 has been followed in Iceland since 1967 by the Icelandic Heart Association. The AGES-Reykjavik cohort, with cardiovascular risk factor assessments earlier in life and detailed late-life phenotypes of quantitative traits, will create a comprehensive study of aging nested in a relatively genetically homogeneous older population. This approach should facilitate identification of genetic factors that contribute to healthy aging as well as the chronic conditions common in old age.

ARIC

The Atherosclerosis Risk in Communities study[7] (https://www2.cscc.unc.edu/aric/) includes 15,792 men and women from four communities in the United States (Jackson, Mississippi; Forsyth County, North Carolina; Washington County, Maryland; suburbs of Minneapolis, Minnesota) enrolled in 1987–1989 and prospectively followed. ECGs were recorded at baseline using MAC PC ECG machines (Marquette Electronics) and processed initially by the Dalhousie ECG program in a central laboratory at the EPICORE Center (University of Alberta). Processing was later repeated for the present study using the GE Marquette 12-SL program (2001 version) at the EPICARE Center (Wake Forest University). All ECGs were visually inspected for technical errors and inadequate quality.

BRIGHT

The BRIGHT study[8] includes 2000 unrelated white European hypertensive individuals. Twelve-lead ECG recordings (Siemens-Sicard 440; http://www.brightstudy.ac.uk/info/sop04.html) producing automated measurements of the JT and QT interval were available for all subjects. All data were subsequently transferred from each recruitment centre by electronic modem to electrophysiologists from the West of Scotland Primary Prevention Study (Professor Peter MacFarlane) for central reporting.

CAMP

The MGH Cardiology and Metabolic Patient (CAMP MGH) cohort comprises 3857 subjects recruited between 2008 and 2012. Two thirds of the subjects were drawn from patients who had appointments with a physician in the MGH Heart Center, whereas one third were recruited independent of any hospital visit. All subjects had plasma and serum samples collected, as well as blood for genomic DNA. ECG was performed on subjects who did not have a tracing within the past 6 months.

CHS

The Cardiovascular Health Study (CHS) is a population-based cohort study of risk factors for coronary heart disease and stroke in adults ≥65 years conducted across four field centers[9]. The original predominantly European ancestry cohort of 5,201 persons was recruited in 1989-1990 from random samples of the Medicare eligibility lists; subsequently, an additional predominantly African-American cohort of 687 persons were enrolled for a total sample of 5,888. CHS was approved by institutional review committees at each field center and individuals in the present analysis had available DNA and gave informed consent including consent to use of genetic information for the study of cardiovascular disease.

ERF

The Erasmus Rucphen Family study[10] is comprised of a family-based cohort embedded in the Genetic Research in Isolated Populations (GRIP) program in the southwest of the Netherlands. The aim of this program is to identify genetic risk factors for the development of complex disorders. In ERF, twenty-two families that had a large number of children baptized in the community church between 1850 and 1900 were identified with the help of detailed genealogical records. All living descendants of these couples, and their spouses, were invited to take part in the study. Comprehensive interviews, questionnaires, and examinations were completed at a research center in the area; approximately 3,200 individuals participated. Examinations included 12 lead ECG measurements. Electrocardiograms were recorded on ACTA electrocardiographs (ESAOTE, Florence, Italy) and digital measurements of the QT and JT intervals were made using the Modular ECG Analysis System (MEANS). Data collection started in June 2002 and was completed in February 2005. In the current analyses, 965 participants for whom complete phenotypic, genotypic and genealogical information was available were studied.

FHS

The objective of the Framingham Heart Study was to identify the common factors or characteristics that contribute to CVD by following its development over a long period of time in a large group of participants who had not yet developed overt symptoms of CVD or suffered a heart attack or stroke. The researchers recruited 5,209 men and women between the ages of 30 and 62 from the town of Framingham, Massachusetts, and began the first round of extensive physical examinations and lifestyle interviews that they would later analyze for common patterns related to CVD development. Since 1948, the subjects have continued to return to the study every two years for a detailed medical history, physical examination, and laboratory tests, and in 1971, the Study enrolled a second generation - 5,124 of the original participants' adult children and their spouses - to participate in similar examinations. In 1994, the need to establish a new study reflecting a more diverse community of Framingham was recognized, and the first Omni cohort of the Framingham Heart Study was enrolled. In April 2002 the Study entered a new phase, the enrollment of a third generation of participants, the grandchildren of the Original Cohort. In 2003, a second group of Omni participants was enrolled.

Generation Scotland

The Generation Scotland: Scottish Family Health Study (GS:SFHS)[11] is a collaboration between the Scottish Universities and the NHS, funded by the Chief Scientist Office of the Scottish Government. GS:SFHS is a family-based genetic epidemiology cohort with DNA, other biological samples (serum, urine and cryopreserved whole blood) and socio-demographic and clinical data from ~24,000 volunteers, aged 18-98 years, in ~7,000 family groups. Participants were recruited across Scotland, with some family members from further afield, from 2006 - 2011. Most (87%) participants were born in Scotland and 96% in the UK or Ireland. GS:SFHS operates under appropriate ethical approvals, and all participants gave written informed consent.

GOCHA

The Genetics of Cerebral Hemorrhage on Anticoagulation (GOCHA) study[12] is a multicenter study comprised of patients age >55 years presenting to participating hospitals with primary ICH. Controls were enrolled from ambulatory clinics in the same centers from which cases were recruited.

GRAPHIC

The GRAPHIC Study[13] comprises 2024 individuals from 520 nuclear families recruited from the general population in Leicestershire, UK between 2003-2005 for the purpose of investigating the genetic determinants of blood pressure and related cardiovascular traits. Families were included if both parents aged 40-60 years and two offspring ≥18 years wished to participate. A detailed medical history was obtained from study subjects by standardized questionnaires and clinical examination was performed by research nurses following standard

procedures. Measurements obtained included height, weight, waist-hip ratio, clinic and ambulatory blood pressure and a 12-lead ECG.

Inter99

The Inter99 study[14] carried out in 1999-2001 included invitation of 12934 persons aged 30-60 years drawn from an age- and sex-stratified random sample of the population. The baseline participation rate was 52.5%, and the study included 6784 persons. The Inter99 study was a population-based randomized controlled trial (CT00289237, ClinicalTrials.gov) and investigated the effects of lifestyle intervention on CVD. Here 5827 participants with information on lipids and exome chip were analysed. ECG information was obtained from the MUSE Cardiology Information System (GE Healthcare, Wauwatosa, Wisconsin) analysed by Marquette 12SL algorithm version 21.

JHS

The Jackson Heart Study[15] (https://www.jacksonheartstudy.org/) includes 5,306 African-American men and women from the three counties, Hinds, Madison, and Rankin, that comprise the Jackson, MS metropolitan area. Participants were enrolled in 2000-2004 and have been followed prospectively. A supine 12-lead digital electrocardiogram (ECG) was recorded with the Marquette MAC/PC digital ECG recorder (Marquette Electronics, Milwaukee, Wis), and with electrode placement that duplicates that of the ARIC study. The ECGs are analyzed in accordance with the Minnesota Code Classification system, via an extensively validated computer algorithm that was developed specifically for epidemiologic studies. In-hospital surveillance ECGs are read visually according to the Minnesota Code Classification system.

KORA

KORA (Kooperative Gesundheitsforschung in der Region Augsburg)[16,17] is a series of independent population-based epidemiological surveys and follow-up studies of participants living in the city of Augsburg, Southern Germany, or its two adjacent counties. All participants are residents of Germany and have been sampled in strata of age and sex from the local registries. In the baseline survey used in this study, KORA S4, 4,261 subjects have been examined. 3,080 subjects participated in a 7-year follow-up examination of S4 in 2006-2008. Illumina HumanExome BeadChip was measured in KORA F4 participants.

CROATIA-Korcula

The CROATIA-Korcula[18] study sampled Croatians from the Adriatic island of Korcula, between the ages of 18 and 88. The fieldwork was performed in 2007 in the eastern part of the island, targeting healthy volunteers from the town of Korčula and the villages of Lumbarda, Žrnovo and Račišće.

Lifelines

LifeLines[19] is a multi-disciplinary prospective population-based cohort study examining in a unique three-generation design the health and health-related behaviours of 165,000 persons living in the North East region of The Netherlands. It employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioral, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multimorbidity and complex genetics. Details of the protocol have been described elsewhere (https://www.lifelines.nl/lifelines-research/news). Standard 12-lead electrocardiograms were recorded with CardioPerfect equipment (Cardio Control; currently Welch Allyn, Delft, The Netherlands) and digital measurements of the QT intervals were extracted.

MESA

The Multi-Ethnic Study of Atherosclerosis (MESA)[1,20] is a study of the characteristics of subclinical cardiovascular disease (disease detected non-invasively before it has produced clinical signs and symptoms) and

the risk factors that predict progression to clinically overt cardiovascular disease or progression of the subclinical disease. The cohort is a diverse, population-based sample of 6,814 asymptomatic men and women aged 45-84. Approximately 38 percent of the recruited participants are white, 28 percent African-American, 22 percent Hispanic, and 12 percent Asian (predominantly of Chinese descent). Participants were recruited during 2000-2002 from 6 field centers across the U.S. (at Wake Forest University; Columbia University; Johns Hopkins University; the University of Minnesota; Northwestern University; and the University of California – Los Angeles). All underwent anthropomorphic measurement and extensive evaluation by questionnaires at baseline, followed by 4 subsequent examinations at intervals of approximately 2-4 years. Age and sex were self-reported. ECGs were recorded in the supine position after a period of rest. ECG data were collected using GE MAC 1200 electrocardiographs. Digitally collected ECGs were transferred via phone lines to the MESA ECG center (EPICARE). The ECGs were automatically processed by use of GE Marquette 12-SL software (2001 version), after visual inspection of the recordings for quality.

NEO

The Netherlands Epidemiology of Obesity (NEO) study[21]: The NEO was designed for extensive phenotyping to investigate pathways that lead to obesity-related diseases. The NEO study is a population-based, prospective cohort study that includes 6,671 individuals aged 45–65 years, with an oversampling of individuals with overweight or obesity. At baseline, information on demography, lifestyle, and medical history have been collected by questionnaires. In addition, samples of 24-h urine, fasting and postprandial blood plasma and serum, and DNA were collected. Genotyping was performed using the Illumina HumanCoreExome chip, which was subsequently imputed to the 1000 genome reference panel. Participants underwent an extensive physical examination, including anthropometry, electrocardiography, spirometry, and measurement of the carotid artery intima-media thickness by ultrasonography. In random subsamples of participants, magnetic resonance imaging of abdominal fat, pulse wave velocity of the aorta, heart, and brain, magnetic resonance spectroscopy of the liver, indirect calorimetry, dual energy X-ray absorptiometry, or accelerometry measurements were performed. The collection of data started in September 2008 and completed at the end of September 2012. Participants are currently being followed for the incidence of obesity-related diseases and mortality.

RS

The Rotterdam Study[22] is a prospective cohort study in the Ommoord district in the city of Rotterdam, the Netherlands. Following the pilot in 1989, recruitment started in January 1990. The main objectives of the Rotterdam Study were to investigate the risk factors of cardiovascular, neurological, ophthalmological and endocrine diseases in the elderly. Up to 2008, approximately 15,000 subjects aged 45 years or over have been recruited. Participants were interviewed at home and went through an extensive set of examinations, bone mineral densiometry, including sample collections for in-depth molecular and genetic analyses. Examinations were repeated every 3-4 years in potentially changing characteristics. Participants were followed for the most common diseases in the elderly, including coronary heart disease, heart failure and stroke, Parkinson's disease, Alzheimer's disease and other dementias, depression and anxiety disorders, macular degeneration and glaucoma, diabetes mellitus and osteoporosis.

SHIP

The Study of Health In Pomerania[23] is a prospective longitudinal population-based cohort study in Western Pomerania assessing the prevalence and incidence of common diseases and their risk factors. SHIP encompasses the two independent cohorts SHIP and SHIP-TREND. Participants aged 20 to 79 with German citizenship and principal residency in the study area were recruited from a random sample of residents living in the three local cities, 12 towns as well as 17 randomly selected smaller towns. Individuals were randomly selected stratified by age and sex in proportion to population size of the city, town or small towns, respectively. A total of 4,308 participants were recruited between 1997 and 2001 in the SHIP cohort. Between 2008 and 2012

a total of 4,420 participants were recruited in the SHIP-TREND cohort. Individuals were invited to the SHIP study centre for a computer-assisted personal interviews and extensive physical examinations.

TwinsUK

TwinsUK[24] is a nation-wide registry of volunteer twins in the United Kingdom, with about 12,000 registered twins (83% female, equal number of monozygotic and dizygotic twins, predominantly middle-aged and older). Over the last 20 years, questionnaire and blood/urine/tissue samples have been collected on over 7,000 subjects, as well as three comprehensive phenotyping assessments in the clinical facilities of the Department of Twin Research and Genetic Epidemiology, King's College London. The primary focus of study has been the genetic basis of healthy aging process and complex diseases, including cardiovascular, metabolic, musculoskeletal, and ophthalmologic disorders. Alongside the detailed clinical, biochemical, behavioral, and socio-economic characterization of the study population, the major strength of TwinsUK is availability of several 'omics' technologies for the participants. These include genome-wide scans of single nucleotide variants, next-generation sequencing, exome sequencing, epigenetic markers (MeDIP sequencing), gene expression arrays and RNA sequencing, telomere length measures, metabolomic profiles, and gut flora microbiomics.

UHP

The Utrecht Health Project (UHP)[25] is an ongoing dynamic population study initiated in a newly developed large residential area in Leidsche Rijn, part of the city of Utrecht. All new inhabitants were invited by their general practitioner to participate in the UHP. Written informed consent was obtained and an individual health profile (IHP) was made by dedicated research nurses. The UHP study was approved by the Medical Ethical Committee of the University Medical Center, Utrecht, The Netherlands. A large number of measures were taken, including anthropomorphic and blood pressure measurements, andeach participant filled out a questionnaire. A 12-lead ECG was made at rest and digitally stored. PR, QRS, QT, and RR intervals were calculated automatically.

WHI

The Women's Health Iniative (WHI)[26,27] is a long-term national health study that has focused on strategies for preventing heart disease, breast and colorectal cancers, and osteoporotic fractures in postmenopausal women. The WHI was designed as a set of randomized controlled clinical trials (CTs) and an observational study (OS). The CT (n = 68,132) included 3 overlapping components: the hormone therapy trials (n = 27,347), dietary modification trial (n = 48,835), and calcium and vitamin D trial (n = 36,282). Eligible women could be part of several of the CT components. Women who were ineligible or unwilling to join the CT were invited to join the OS (n = 93,676). All participants in the CT were administered ECGs every three years. In the current paper we include the baseline ECGs of women who were genotyped on the ExomeChip.

YFS

The YFS[28] is a population-based follow up-study started in 1980. The main aim of the YFS is to determine the contribution made by childhood lifestyle, biological and psychological measures to the risk of cardiovascular diseases in adulthood. In 1980, over 3,500 children and adolescents all around Finland participated in the baseline study. The follow-up studies have been conducted mainly with 3-year intervals. The latest 30-year follow-up study was conducted in 2010-11 (ages 33-49 years) with 2,063 participants. The study was approved by the local ethics committees (University Hospitals of Helsinki, Turku, Tampere, Kuopio and Oulu) and was conducted following the guidelines of the Declaration of Helsinki. All participants gave their written informed.

Ethics Statements

AGES

The study is approved by the Icelandic National Bioethics Committee, (VSN: 00–063) and the Data Protection Authority.

ARIC

Institutional Review Board approvals were obtained by each participating ARIC study center (the Universities of NC, MS, MN, and John Hopkins University) and the coordinating center (University of NC), and the research was conducted in accordance with the principles described in the Helsinki Declaration. All subjects in the ARIC study gave informed consent. For more information see dbGaP Study Accession: phs000280.v2.p1. JHSPH IRB number H.34.99.07.02.A1. Manuscript proposal number MS2572.

BRIGHT

All subjects in the BRIGHT study participated as volunteers and were recruited via hypertension registers from the MRC General Practice Framework in the UK. Ethics Committee approval was obtained from the multi- and local research committees of the partner institutes, and all participants gave written informed consent.

CAMP

The Institutional Review Board at MGH reviews the study protocol annually. Each participant provided written, informed consent prior to enrollment.

CHS

CHS was approved by institutional review committees at each site, the subjects gave informed consent, and those included in the present analysis consented to the use of their genetic information for the study of cardiovascular disease. It is the position of the UW IRB that these studies of de-identified data, with no patient contact, do not constitute human subjects research. Therefore we have neither an approval number, nor an exemption.

ERF

The Medical Ethics Committee of the Erasmus University Medical Center approved the ERF study protocol and all participants, or their legal representatives, provided written informed consent.

FHS

The Boston University Medical Campus Institutional Review Board approved the FHS genome-wide genotyping (protocol number H-226671).

Generation Scotland

Data was collected for GS:SFHS between 2006 and 2011 with ethical approval from the NHS Tayside Committee on Medical Research Ethics A (ref 05/S1401/89). All participants gave written informed consent. GS:SFHS is now a Research Tissue Bank approved by the East of Scotland Research Ethics Service (ref 15/ES/0040).

GOCHA

The Institutional Review Board at MGH reviewed and approved the study. Participants or their next of kin provided informed consent at the time of enrollment.

GRAPHIC

GRAPHIC was approved by the Leicestershire Research Ethics Committee (LREC Ref N. 6463).

Inter99
Written informed consent was obtained from all participants and the study was approved by the Scientific Ethics Committee of the Capital Region of Denmark (KA98155, H-3-2012-155) and was in accordance with the principles of the Declaration of Helsinki II.

JHS
Written informed consent was obtained from all participants. The Jackson Heart Study is conducted with approval of the Institutional Review Board of the University of Mississippi Medical Center, DHHS FWA #00003630.

KORA
Written informed consent was obtained from all participants and the study was approved by the local ethics committee (Bayerische Landesärztekammer).

KORCULA
Ethical approval was given for recruitment of all Korcula study participants by ethics committees in both Scotland and Croatia. All volunteers gave informed consent prior to participation.

Lifelines
The Lifelines study followed the recommendations of the Declaration of Helsinki and was in accordance with research code of the University Medical Center Groningen (UMCG). The LifeLines study is approved by the medical ethical committee of the UMCG, the Netherlands. All participants signed an informed consent form before they received an invitation for the physical examination. For a comprehensive overview of the data collection, please visit the LifeLines catalogue at www.LifeLines.net.

MESA
All MESA participants provided written and informed consent to participate in genetic studies. All study sites received approval to conduct this research from local Institutional Review Boards at: Columbia University (for the MESA New York Field Center), Johns Hopkins University (for the MESA Baltimore Field Center), Northwestern University (for the MESA Chicago Field Center), University of California, Los Angeles (for the MESA Los Angeles Field Center), University of Minnesota (for the MESA Twin Cities Field Center), Wake Forest University Health Sciences Center (for the MESA Winston-Salem Field Center).

NEO
The Netherlands Epidemiology of obesity (NEO) study is supported by the participating Departments, the Division and the Board of Directors of the Leiden University Medical Center, and by the Leiden University, Research Profile Area Vascular and Regenerative Medicine. All participants gave written informed consent and the Medical Ethical Committee of the Leiden University Medical Center (LUMC) approved the study design.

RS
The Rotterdam Study has been approved by the medical ethics committee according to the Population Study Act Rotterdam Study, executed by the Ministry of Health, Welfare and Sports of the Netherlands. A written informed consent was obtained from all participants.

SHIP
The SHIP study followed the recommendations of the Declaration of Helsinki. The study protocol of SHIP was approved by the medical ethics committee of the University of Greifswald. Written informed consent was obtained from each of the study participants. The SHIP study is described in PMID: 20167617.

TwinsUK
The study has ethical approval from the NRES Committee London–Westminster, London, UK (EC04/015). Written consent was obtained from all participants. Research was carried out in accordance with the Helsinki declaration.

UHP
The Utrecht Health Project has been approved by the Medical Ethics Committee of the University Medical Centre Utrecht. All participants give written informed consent. The masking of all personal data for researchers and for other possible users of UHP has been regulated in a legal document.

WHI
All WHI participants provided written and informed consent. All study sites received approval to conduct this research from local Institutional Review Boards at the Fred Hutchinson Cancer research Center.

YFS
The Young Finns Study was approved by the local ethics committees (University Hospitals of Helsinki, Turku, Tampere, Kuopio and Oulu) and was conducted following the guidelines of the Declaration of Helsinki. All participants gave their written informed consent.

Cohort Specific Acknowledgments

AGES

The Age, Gene/Environment Susceptibility Reykjavik Study is funded by NIH contract N01-AG-12100, the NIA Intramural Research Program, Hjartavernd (the Icelandic Heart Association), and the Althingi (the Icelandic Parliament), in addition an Intramural Research Program Award (ZIAEY000401) from the National Eye Institute, an award from the National Institute on Deafness and Other Communication Disorders (NIDCD) Division of Scientific Programs (IAA Y2-DC_1004-02). The study is approved by the Icelandic National Bioethics Committee, VSN: 00-063. The researchers are indebted to the participants for their willingness to participate in the study.

ARIC

The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C), R01HL087641, R01HL59367 and R01HL086694; National Human Genome Research Institute contract U01HG004402; and National Institutes of Health contract HHSN268200625226C. The authors thank the staff and participants of the ARIC study for their important contributions. Infrastructure was partly supported by Grant Number UL1RR025005, a component of the National Institutes of Health and NIH Roadmap for Medical Research. Funding support for "Building on GWAS for NHLBI-diseases: the U.S. CHARGE consortium" was provided by the NIH through the American Recovery and Reinvestment Act of 2009 (ARRA) (5RC2HL102419).

BRIGHT

The BRIGHT study was funded by the Wellcome Trust (Strategic Award 083948) for genotyping of the Exome chip, the Medical Research Council of Great Britain (grant number: G9521010D) and British Heart Foundation. The BRIGHT study is extremely grateful to all the patients who participated in the study and the BRIGHT nursing team. This work forms part of the research themes contributing to the translational research portfolio for the NIHR Barts Cardiovascular Biomedical Research Unit. N.J.S. holds a British Heart Foundation Chair of Cardiology and is a Senior National Institute for Health Research Investigator. A.F.D. was supported by the British Heart Foundation (grant numbers RG/07/005/23633, SP/08/005/25115); and by the European Union Ingenious HyperCare Consortium: Integrated Genomics, Clinical Research, and Care in Hypertension (grant number LSHM-C7-2006-037093).

CAMP

The recruitment, collection of samples, and genotyping was supported by Pfizer. Analysis of data was a three way collaboration between MGH, the Broad Institute, and Pfizer. Dr. Huang is supported by grants from the NIH (NS33335, NS055104). Dr. Lubitz was supported by NIH/NHLBI K23HL114724 and a Doris Duke Charitable Foundation Clinical Scientist Development Award 2014105. This work was supported by grants from the National Institutes of Health to Dr. Ellinor (1RO1HL092577, R01HL128914, K24HL105780). Dr. Ellinor is also supported by an Established Investigator Award from the American Heart Association (13EIA14220013) and by the Fondation Leducq (14CVD01).

CHS

Cardiovascular Health Study: This CHS research was supported by NHLBI contracts HHSN268201200036C, HHSN268200800007C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086; and NHLBI grants U01HL080295, R01HL068986, R01HL087652, R01HL105756, R01HL103612, R01HL120393, and R01HL130114 with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was provided through R01AG023629 from the National Institute on Aging (NIA). A full list of principal CHS investigators and institutions can be found at CHS-NHLBI.org.

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ERF
The ERF study as a part of EUROSPAN (European Special Populations Research Network) was supported by European Commission FP6 STRP grant number 018947 (LSHG-CT-2006-01947) and also received funding from the European Community's Seventh Framework Programme (FP7/2007-2013)/grant agreement HEALTH-F4-2007-201413 by the European Commission under the programme “Quality of Life and Management of the Living Resources” of 5th Framework Programme (no. QLG2-CT-2002-01254). The ERF study was further supported by ENGAGE consortium and CMSB. High-throughput analysis of the ERF data was supported by joint grant from Netherlands Organisation for Scientific Research and the Russian Foundation for Basic Research (NWO-RFBR 047.017.043). We are grateful to all study participants and their relatives, general practitioners and neurologists for their contributions to the ERF study and to P Veraart for her help in genealogy, J Vergeer for the supervision of the laboratory work and P Snijders for his help in data collection.

FHS
HL120393

Generation Scotland
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GOCHA
The Genetics of Cerebral Hemorrhage with Anticoagulation was carried out as a collaborative study supported by grants R01NS073344, R01NS059727, and 5K23NS059774 from the NIH–National Institute of Neurological Disorders and Stroke (NIH-NINDS)

GRAPHIC
The GRAPHIC study was funded by the BHF.

Inter99
The Inter99 was initiated by Torben Jørgensen (PI), Knut Borch-Johnsen (co-PI), Hans Ibsen and Troels F. Thomsen. The steering committee comprises the former two and Charlotta Pisinger. The study was financially supported by research grants from the Danish Research Council, the Danish Centre for Health Technology Assessment, Novo Nordisk Inc., Research Foundation of Copenhagen County, Ministry of Internal Affairs and Health, the Danish Heart Foundation, the Danish Pharmaceutical Association, the Augustinus Foundation, the Ib Henriksen Foundation, the Becket Foundation, and the Danish Diabetes Association. The Novo Nordisk Foundation Center for Basic Metabolic Research is an independent Research Center at the University of Copenhagen partially funded by an unrestricted donation from the Novo Nordisk Foundation (www.metabol.ku.dk).

JHS
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KORA
The KORA research platform (KORA, Cooperative Research in the Region of Augsburg) was initiated and financed by the Helmholtz Zentrum München - German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education and Research and by the State of Bavaria. Furthermore, KORA research was supported within the Munich Center of Health Sciences (MC Health), Ludwig-Maximilians-Universität, as part of LMUinnovativ. The work was further supported by the European Commission's 7th Framework Programme FP7-HEALTH-2013 No. 602299: EU-CERT-ICD to Dr. Kääb and by the DZHK (German Centre for Cardiovascular Research), partner site: Munich Heart Alliance, Munich, Germany.

CROATIA-Korcula
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Lifelines
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http://www.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Long%20List.pdf

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Supplemental Table 1: Clinical Characteristics Summary Statistics and Genotyping Information for Each Cohort

Short Name	AGES	ARIC – EA	ARIC – AA	BRIGHT	CAMP	CHS – EA	CHS – AA
Long Name	Age, Gene/Environment Susceptibility Study	The Atherosclerosis Risk in Communities Study	The Atherosclerosis Risk in Communities Study	British Genetics of Hypertension	MGH Cardiology and Metabolic Patient Cohort	The Cardiovascular Health Study	The Cardiovascular Health Study
N, after exclusion	2381	10,246	3567	821	2873	3363	648
Sex, women, %	61.74	53.85	62.88	60.9	41.7	59.41	64.51
Age, years, mean±SD	76.12±5.405	54.2±5.683	53.37±5.788	57.54±10.65	61.6±11.4	72.42 (5.43)	72.57 (5.64)
Age, min-max	66-95	44-66	44-66	22-85	31-81	65-100	65-93
Height, cm, mean±SD	166.4±9.152	168.5±9.394	167.9±8.876	165.9±9.05	171.5±10.1	164.6 (9.36)	164.27 (9.08)
BMI, kg/m2, mean±SD	27.09±4.464	26.99±4.862	29.59±6.17	27.42±3.84	28.75±5.85	26.32 (4.48)	28.48 (5.5)
Heart rate, bpm, mean±SD	66.45±11.38	66.15±9.815	66.58±11.01	63.97±11.5	66.82±12.10	64.36 (10.23)	67.51 (11.49)
QT interval, ms, mean±SD	405.3±34.47	398.8±28.97	400±33.01	421.9±24.4	417.15±23.00	414.99 (32.22)	407.28 (34.96)
QT interval, ms, min-max	292-584	288-646	308-696	363-531	336-574	308-544	312-540
JT interval, ms, mean±SD	314±33.49	307.6±28.67	310±32.48	328.4±23.97	327.97±24.71	326.16 (31.47)	319.56 (34.87)
JT interval, ms, min-max	214-492	208-556	212-612	266-448	253-482	212-452	216-456
Study design	Population-based	Population-based	Population-based	Hypertensive Cases	Population-based	Population-based	Population-based
Ethnicity and origin	White Europeans	Americans with European Ancestry	Americans with African Ancestry	White Europeans from UK	European Ancestry	Americans with European Ancestry	Americans with African Ancestry
Exome Chip version	“1.0”	“1.0”	“1.0”	“1.0”	Infinium HumanCoreExome-24 BeadChips	“1.0”	“1.0”
Genotype calling software	centrally at CHARGE	centrally at CHARGE	centrally at CHARGE	GenCall + zCall	GeneCall + zCall	centrally at CHARGE	centrally at CHARGE
Quality Control	centrally at CHARGE	centrally at CHARGE	centrally at CHARGE	followed Oxford's "ExomeChip_QC_SOP_v5" protocol	SNP call rate ≥95%, HWE *P*≥1E-6	centrally at CHARGE	centrally at CHARGE
Related individuals (yes/no)	No	No	No	No	No	No	No
Familial adjustment	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Principals Components (PCs)	2	10	10	10	10	10	10
Analysis software	seqMeta v1.6.0	seqMeta v1.6.0	seqMeta v1.6.0	seqMeta (1.3)	seqMeta v1.6.0	seqMeta v1.6.0	seqMeta v1.6.0

Short Name	ERF	FHS	GS:SFHS	GOCHA	GRAPHIC	Inter99
Long Name	Erasmus Rucphen Family Study	Framingham Heart Study	Generation Scotland: Scottish Family Health Study	Genetics of Cerebral Hemorrhage with Anticoagulation	The Genetic Regulation of Arterial Pressure of Humans in the Community	Inter99
N, after exclusion	965	7062	9027	360	1736	5695
Sex, women, %	55.23	54.87	59.3	195 (54.2)	49.06	52.1
Age, years, mean±SD	48.14 (14.30)	39.33±9.87	51.83, 13.57	73.2±8.3	39.07±14.52	46.2±7.9
Age, min-max	16.65 - 85.27	19-72	18-80	48-100	18-61	29.7-61.3
Height, cm, mean±SD	167.60 (9.48)	168.93±9.54	167.6, 9.54	168.5±10.5	171.08±9.47	172.2±9.1
BMI, kg/m2, mean±SD	26.82 (4.59)	26.10±4.98	26.95, 5.17	26.1±4.6	26.03±4.62	26.3±4.7
Heart rate, bpm, mean±SD	62.89 (10.41)	68.97±13.64	69.65, 11.36	68.3±13.7	66.0±10.34	67.0±10.9
QT interval, ms, mean±SD	398.82 (28.20)	393.19±36.77	405.92, 30.99	428.6±30.6	404.05±19.91	403.5±26.8
QT interval, ms, min-max	304 - 520	260-610	304-552	373-667	343-469	310-538
JT interval, ms, mean±SD	301.37 (27.34)	328±30	316.49, 30.56	N/A	301.80±27.88	312.5±26.7
JT interval, ms, min-max	200 - 408	217-511	216-464	N/A	228-406	228-436
Study design	Population-based family	Population-based	Population-based with families	Population-based	Population-based	Population-based
Ethnicity and origin	European	Americans with European Ancestry	European-ancestry from Scotland	Americans with European Ancestry	European Caucasian	European
Exome Chip version	“1.1”	“1.0”	Exome8v1-2_A/8v1_A	“1.0”	“1.0”	“1.0”
Genotype calling software	zCall	centrally at CHARGE	Beadstudio-Gencall v3.0	zCall at Broad	GenCall + zCall	GenCall + zCall
Quality Control	using CHARGE recommendation	centrally at CHARGE	ID call rate >97%, SNP call rate >98%, HWE cutoff <1E-6	sample call rate ≤98%; IBD allele sharing pi-hat>0.185; SNV call rate <95%; mean heterozygosity >±3 SD; HWE p<1×10-6 in controls; differential missingness in cases and controls	using CHARGE recommendations	SNP call rate >98%; HWE P>10-4; cryptic relatedness (>20 individuals)
Related individuals (yes/no)	Yes	Yes	Yes	No	Yes	No
Familial adjustment	kinship matrix	famSKAT	Kinship matrix	N/A	Kinship matrix	N/A
Principals Components (PCs)	N/A	10	N/A	2	N/A	10
Analysis software	seqMeta v1.6.0	seqMeta v1.6.0	seqMeta v1.6.5	seqMeta v1.5.0	seqMeta	seqMeta v1.5

Short Name	JHS	KORA	CROATIA-Korcula	Lifelines	MESA – EA	MESA – AA	MESA – HA
Long Name	The Jackson Heart Study	Kooperative Gesundheitsforschung in der Region Augsburg	CROATIA-Korcula	The Lifelines Cohort Study	Multi-Ethnic Study of Atherosclerosis (MESA) Cohort	Multi-Ethnic Study of Atherosclerosis (MESA) Cohort	Multi-Ethnic Study of Atherosclerosis (MESA) Cohort
N, after exclusion	2216	2672	295	1943	2324	1501	1382
Sex, women, %	62.54	52.3	62.4	59.59	53.7	54.9	52.6
Age, years, mean±SD	53.06±12.69	48.8±13.1	54.23, 13.38	45.27±13.09	62.36±10.17	62.06±10.03	61.16±10.24
Age, min-max	21-91	25-74	18-88	18-87	44-84	45-84	44-84
Height, cm, mean±SD	169.35±9.34	168.3±9.3	168.3, 8.91	174.66±9.32	168.4±9.266	168.36±9.52	161.68±9.34
BMI, kg/m2, mean±SD	31.34±6.42	27.0±4.4	27.99, 4.24	25.89±4.55	27.66±5.354	30.1±5.88	29.5±5.15
Heart rate, bpm, mean±SD	68.39±10.14	65.1±10.2	65.85, 9.44	68.65±11.06	66.26±10.14	63.01±10.28	63.5±9.39
QT interval, ms, mean±SD	414.14±31.62	407.5±26.7	401.64, 29.44	393.53±26.89	399.1±30.07	410.33±31.73	408.8±29.75
QT interval, ms, min-max	290-580	316-542	270.0-510.0	289-525	334-538	320-512	328-530
JT interval, ms, mean±SD	320.37±30.46	315.7±26.6	305.79, 29.36	299.92±26.79	319.32±28.65	319.4±30.99	317.79±29.42
JT interval, ms, min-max	212-466	234-442	176.0-408.0	202-415	240-438	240-420	238-428
Study design	Mixed family and population-based	Population-based	Isolate population	Population-based	Population-based	Population-based	Population-based
Ethnicity and origin	African American	European / Germany	European Ancestry	European, Netherlands	European Ancestry	African American	Hispanic
Exome Chip version	“1.0”	“1.0”	12v1_A	“1.1”	“1.0”	“1.0”	“1.0”
Genotype calling software	centrally at CHARGE	GeneCall + zCall	GenCall v3.0	GeneCall + zCall	centrally at CHARGE	centrally at CHARGE	centrally at CHARGE
Quality Control	centrally at CHARGE	pairwise exclusion of samples with PI_HAT>0.1875	ID call rate >97%, SNP call rate filter 98%, HWE cutoff <1E-6	SNP Callrate ≥95%; HWE >10-6; sample exclusion callrate <95%; PCA outliers	centrally at CHARGE	centrally at CHARGE	centrally at CHARGE
Related individuals (yes/no)	Yes	No	Yes	No	No	No	No
Familial adjustment	Kinship matrix	N/A	Kinship matrix	N/A	N/A	N/A	N/A
Principals Components (PCs)	10		N/A	5	2	2	2
Analysis software	seqMeta v1.6.0	seqMeta v1.6.0	seqMeta v1.6.5	seqMeta v1.6.0	seqMeta v1.6.0	seqMeta v1.6.0	seqMeta v1.6.0

Short Name	MESA – CH	NEO	RS	SHIP	TwinsUK
Long Name	Multi-Ethnic Study of Atherosclerosis (MESA) Cohort	The Netherlands Epidemiology of Obesity (NEO) Study	The Rotterdam Elderly Study	Study of Health In Pomerania	TwinsUK
N, after exclusion	750	6047	2419	6224	466
Sex, women, %	51.6	52.03	55.25	52.52	93.56
Age, years, mean±SD	62.21±10.37	56.0±5.94	68.6±8.363	49.56±15.32	52.08±11.65
Age, min-max	44-84	44-66	55-101	20-82	18-83
Height, cm, mean±SD	161.49±8.58	173.62±9.59	167.5±9.384	169.54±9.31	163.2±6.930
BMI, kg/m2, mean±SD	23.99±3.29	30.05±4.82	26.21±3.591	27.57±4.98	26.72±5.328
Heart rate, bpm, mean±SD	63.06±8.63	65.7±11.39	70.73±12.28	NA	66.63±10.45
QT interval, ms, mean±SD	410.97±29.38	406.6±30.5	396.7±29.197	406.82±28.43	403.2±27.81
QT interval, ms, min-max	334-554	244-666	282-524	308-540	308-500
JT interval, ms, mean±SD	321.67±29.55	312.9±28.7	299.82±28.158	312.15±29.36	315.2±27.37
JT interval, ms, min-max	256-450	188-484	196-416	212-436	228-402
Study design	Population-based	Population-based	Population-based	Population-based	Twin study
Ethnicity and origin	Chinese American	European Ancenstry from the Netherlands	Europeans with European Ancestry	EA from Germany	European ancestry, individuals from the United Kingdom
Exome Chip version	“1.0”	24v1-0	“1.0”	“1.0”	“1.0”
Genotype calling software	centrally at CHARGE	GenCall	centrally at CHARGE	GenCall + zCall	Gencall
Quality Control	centrally at CHARGE	Outlying individuals were excluded on the basis of relatedness, non-European ancestry, sex discrepancy and heterzygosity	centrally at CHARGE	Samples: Genotype call rate <98%; high heterozygosity; high cryptic relatedness; IBS clustering; sex mismatches Variants: call rate <95%; HWE p-value <10E-4	Excluded samples with callrate <97%; autosomal heterozygosity outliers (+/- 4SD); ethnic outliers from 1000 Genomes Project data (PCA); GWAS concordance (when available). Removed variants with call rate <95% and pHWE< 1x10-6.
Related individuals (yes/no)	No	No	No	No	No
Familial adjustment	N/A	N/A	N/A	N/A	N/A
Principals Components (PCs)	2	10	5	10	10
Analysis software	seqMeta v1.6.0	seqMeta v1.5	seqMeta v1.6.0	seqMeta v1.4.0 (seqMeta v1.3.0 for QT analysis)	seqMeta v1.3

Short Name	UHP	WHI – EA	WHI – AA	YFS
Long Name	Utrecht Health Project	The Women's Health Initiative	The Women's Health Initiative	The Cardiovascular Risk in Young Finns Study
N, after exclusion	1731	13450	1678	1784
Sex, women, %	55	100	100	55.72
Age, years, mean±SD	39.10±12.956	66.1±6.547	64.55±6.46	41.92±4.98
Age, min-max	18-91	50-81	50-79	34-49
Height, cm, mean±SD	174.78±9.779	161.5±6.6.307	161.9±6.708	172.04±9.22
BMI, kg/m2, mean±SD	24.90±3.875	28.70±5.637	31.13±5.85	26.45±4.94
Heart rate, bpm, mean±SD	64.60±10.612	66.56±10.125	66.77±10.84	60.04±9.47
QT interval, ms, mean±SD	403.48±27.422	401.399±29.9322	402.23±31.77	415.11±33.54
QT interval, ms, min-max	308-512	290-624	310-520	284-636
JT interval, ms, mean±SD	306.65±27.054	315.2±29.49	317.13±30.85	324.66±33.47
JT interval, ms, min-max	216-402	204-534	218-426	206-564
Study design	Population-based	Population-based	Population-based	Population-based
Ethnicity and origin	Dutch citizens of European Ancestry	Americans with European Ancestry	Americans with African Ancestry	Finnish with European Ancestry
Exome Chip version	1.1	“1.0”	“1.0”	CoreExome v1.0
Genotype calling software	GenomeStudio and zCall			GenomeStudio
Quality Control	Plink v1.07 was used for QC. Samples with missing SNP rate >5% or discordant sex were excluded. Using SNPs with missingness<1%, MAF>5%, Hardy-Weinberg P<0.001, LD-pruned r2>0.2, we removed samples with heterozygosity >4 SD, related samples randomly, and samples from non-European descent based on manual inspection of PCA results. SNPs with missing >5% or HWE P<0.001 were removed.			SNP and sample call-rate 95%, excess heterozygosity, cryptic relatedness, MDS outliers
Related individuals (yes/no)	No	No	No	No
Familial adjustment	N/A	N/A	N/A	N/A
Principals Components (PCs)	1 PC	2 PCs	2 PCs	4 PCs
Analysis software	seqMeta v1.6.0	seqMeta v1.6.0	seqMeta v1.6.0	seqMeta v1.3.0

Supplemental Table 2: ExomeChip-wide Significant Variants in QT Meta-analysis

								Combined			
Locus Name	**SNV**	**Chr**	**Position**	**Gene**	**Functional Category**	**Damaging**	**CAF**	**N**	**P**	**BETA**	**SE**
RNF207	rs709209	1	6,278,414	*RNF207*	exonic;nonsynonymous	0	0.379	95,626	1.33E-48	1.23	0.09
RNF207	rs846111	1	6,279,370	*RNF207*	exonic;nonsynonymous	0	0.241	76,129	1.51E-46	1.51	0.11
TCEA3	rs1077514	1	23,766,233	*ASAP3*	intronic	0	0.179	92,753	4.08E-08	-0.58	0.11
NOS1AP	rs6676438	1	161,983,089	*OLFML2B*	intronic	0	0.347	92,753	1.38E-37	1.15	0.09
NOS1AP	rs2880058	1	162,014,632		intergenic	0	0.380	95,626	9.54E-177	2.41	0.09
NOS1AP	rs12143842	1	162,033,890		intergenic	0	0.240	95,626	2.90E-255	3.18	0.10
NOS1AP	rs1415259	1	162,085,309	*NOS1AP*	intronic	0	0.391	92,753	1.14E-145	2.15	0.08
NOS1AP	rs10494366	1	162,085,685	*NOS1AP*	intronic	0	0.391	95,626	2.81E-149	2.15	0.08
NOS1AP	rs16857031	1	162,112,910	*NOS1AP*	intronic	0	0.155	89,579	2.11E-66	1.94	0.12
NOS1AP	rs12029454	1	162,133,117	*NOS1AP*	intronic	0	0.163	95,626	1.15E-123	2.53	0.11
NOS1AP	rs12725553	1	162,168,116	*NOS1AP*	intronic	0	0.412	95,626	5.30E-59	1.34	0.08
NOS1AP	rs4657178	1	162,210,610	*NOS1AP*	intronic	0	0.270	95,626	2.24E-92	1.84	0.09
ATP1B1	rs10919071	1	169,099,483	*ATP1B1*	intronic	0	0.115	95,626	2.55E-30	-1.37	0.13
ATP1B1	rs6027	1	169,483,561	*F5*	exonic;nonsynonymous	1	0.053	74,803	1.34E-10	-1.27	0.21
ATP1B1	rs6018	1	169,511,878	*F5*	exonic;nonsynonymous	0	0.055	73,622	1.20E-09	-1.25	0.21
ATP1B1	rs6033	1	169,521,853	*F5*	exonic;nonsynonymous	0	0.066	95,626	1.40E-08	-0.87	0.16
PM20D1	rs1361754	1	205,801,872	*PM20D1*	exonic;nonsynonymous	0	0.511	95,626	1.20E-09	0.47	0.08
TTN-CCDC141	rs72648998	2	179,575,511	*TTN*	exonic;nonsynonymous	0	0.054	95,626	3.20E-09	1.00	0.18
TTN-CCDC141	rs10497520	2	179,644,855	*TTN*	exonic;nonsynonymous	1	0.184	92,753	8.61E-09	0.63	0.11
SLC4A3	rs55910611	2	220,500,412	*SLC4A3*	exonic;nonsynonymous	0	0.006	74,508	1.53E-07	-3.06	0.61
SCN5A-SCN10A	rs116202356	3	38,103,776	*DLEC1*	exonic;nonsynonymous	0	0.015	95,626	3.08E-11	2.22	0.33
SCN5A-SCN10A	rs11129795	3	38,589,163	*SCN5A*	downstream	0	0.233	95,626	1.07E-23	-0.93	0.10
SCN5A-SCN10A	rs12053903	3	38,593,393	*SCN5A*	intronic	0	0.379	95,626	1.20E-26	-0.88	0.09
SCN5A-SCN10A	rs3922844	3	38,624,253	*SCN5A*	intronic	0	0.336	92,753	1.75E-19	0.82	0.09
SCN5A-SCN10A	rs11708996	3	38,633,923	*SCN5A*	intronic	0	0.135	89,579	7.31E-20	-1.08	0.12
SCN5A-SCN10A	rs1805124	3	38,645,420	*SCN5A*	exonic;nonsynonymous	0	0.238	95,626	7.48E-12	0.66	0.10
SCN5A-SCN10A	rs11710077	3	38,657,899	*SCN5A*	intronic	0	0.191	89,579	4.11E-14	0.78	0.11
SCN5A-SCN10A	rs9851724	3	38,719,935		intergenic	0	0.306	80,498	1.58E-10	0.62	0.10
SCN5A-SCN10A	rs6795970	3	38,766,675	*SCN10A*	exonic;nonsynonymous	0	0.365	95,626	2.55E-17	-0.67	0.09
SCN5A-SCN10A	rs6800541	3	38,774,832	*SCN10A*	intronic	0	0.371	95,626	2.23E-16	-0.66	0.08
CASR	rs1801725	3	122,003,757	*CASR*	exonic;nonsynonymous	0	0.126	95,626	4.30E-08	-0.58	0.12
SLC4A4	rs7689609	4	72,083,374	*SLC4A4*	intronic	0	0.212	85,380	3.88E-08	0.64	0.12
SLC35F1-PLN	rs281868	6	118,574,061	*SLC35F1*	intronic	0	0.487	92,753	1.92E-18	0.66	0.08
SLC35F1-PLN	rs89107	6	118,578,043	*SLC35F1*	intronic	0	0.490	95,626	4.92E-53	1.19	0.08
SLC35F1-PLN	rs12210810	6	118,653,204		intergenic	0	0.046	89,579	2.11E-35	-2.28	0.20
SLC35F1-PLN	rs11153730	6	118,667,522		intergenic	0	0.467	95,626	4.88E-74	1.41	0.08
SLC35F1-PLN	rs11970286	6	118,680,374		intergenic	0	0.429	95,626	7.86E-61	1.29	0.08
SLC35F1-PLN	rs3734382	6	118,886,961	*CEP85L*	exonic;nonsynonymous	0	0.257	95,626	3.97E-13	-0.63	0.09
SLC35F1-PLN	rs3734381	6	118,887,303	*CEP85L*	exonic;nonsynonymous	0	0.461	91,615	3.75E-36	-1.00	0.08
CAV1	rs3807989	7	116,186,241	*CAV1*	intronic	0	0.429	95,626	4.37E-12	0.54	0.08
KCNH2	rs2968864	7	150,622,162		intergenic	0	0.216	92,753	5.13E-51	-1.48	0.10
KCNH2	rs2968863	7	150,623,137		intergenic	0	0.216	92,753	3.86E-51	-1.48	0.10
KCNH2	rs4725982	7	150,637,863		intergenic	0	0.224	95,626	1.16E-46	1.36	0.10
KCNH2	rs1805123	7	150,645,534	*KCNH2*	exonic;nonsynonymous	0	0.214	95,626	6.67E-51	-1.47	0.10
KCNH2	rs3807375	7	150,667,210	*KCNH2*	intronic	0	0.399	92,753	6.66E-37	1.08	0.08

ZNF37A	rs2474570	10	38,383,757	*ZNF37A*	intronic	0	0.488	95,626	8.85E-10	-0.48	0.08
ZNF37A	rs4934956	10	38,814,815		intergenic	0	0.497	70,792	2.29E-10	0.58	0.10
NRAP	rs3189030	10	115,393,929	*NRAP*	exonic;nonsynonymous	0	0.299	95,626	3.77E-08	-0.48	0.09
NRAP	rs2185913	10	115,410,234	*NRAP*	exonic;nonsynonymous	1	0.271	95,626	1.92E-07	-0.48	0.09
KCNQ1	rs800336	11	2,473,131	*KCNQ1*	intronic	0	0.312	92,753	5.94E-17	-0.77	0.10
KCNQ1	rs2074238	11	2,484,803	*KCNQ1*	intronic	0	0.074	89,284	8.22E-130	-3.58	0.16
KCNQ1	rs12296050	11	2,489,342	*KCNQ1*	intronic	0	0.228	95,626	8.87E-58	1.57	0.10
KCNQ1	rs12576239	11	2,502,319	*KCNQ1*	intronic	0	0.139	95,626	2.10E-40	1.51	0.12
KCNQ1	rs1080015	11	2,511,527	*KCNQ1*	intronic	0	0.397	95,626	1.68E-09	0.48	0.08
KCNQ1	rs179429	11	2,550,730	*KCNQ1*	intronic	0	0.171	95,626	3.51E-08	-0.59	0.11
KCNQ1	rs17215500	11	2,790,111	*KCNQ1*	exonic;stopgain	1	0.000	95,626	1.11E-11	46.38	5.71
FEN1-FADS2	rs102275	11	61,557,803	*C11orf10*	intronic	0	0.382	92,753	2.26E-08	-0.43	0.09
FEN1-FADS2	rs174546	11	61,569,830	*FADS1*	UTR3	0	0.315	95,626	1.65E-09	-0.48	0.09
FEN1-FADS2	rs174547	11	61,570,783	*FADS1*	intronic	0	0.315	95,626	1.65E-09	-0.48	0.09
FEN1-FADS2	rs174550	11	61,571,478	*FADS1*	intronic	0	0.315	95,626	1.86E-09	-0.48	0.09
FEN1-FADS2	rs174570	11	61,597,212	*FADS2*	intronic	0	0.134	95,626	2.39E-07	-0.58	0.12
FEN1-FADS2	rs1535	11	61,597,972	*FADS2*	intronic	0	0.325	95,626	8.28E-10	-0.48	0.09
FEN1-FADS2	rs174583	11	61,609,750	*FADS2*	intronic	0	0.344	95,626	4.89E-09	-0.45	0.09
KLF12	rs1886512	13	74,520,186	*KLF12*	intronic	0	0.381	80,552	1.53E-10	0.57	0.09
LITAF	rs8049607	16	11,691,753		intergenic	0	0.503	95,626	8.42E-44	1.05	0.08
MKL2	rs1659127	16	14,388,305		intergenic	0	0.338	30,645	4.49E-08	0.90	0.16
MKL2	rs30208	16	14,428,853		intergenic	0	0.501	95,626	2.28E-09	0.45	0.08
CNOT1	rs4356470	16	58,529,615	*NDRG4*	intronic	0	0.326	95,626	1.37E-20	-0.80	0.09
CNOT1	rs7188697	16	58,622,178	*CNOT1*	intronic	0	0.247	91,615	3.78E-63	-1.57	0.10
LIG3	rs2230553	17	33,269,648	*CCT6B*	exonic;nonsynonymous	1	0.343	89,579	1.65E-10	-0.56	0.09
LIG3	rs9635769	17	33,288,363	*CCT6B*	exonic;nonsynonymous	0	0.451	95,626	2.77E-08	0.47	0.08
LIG3	rs2074518	17	33,324,382	*LIG3*	intronic	0	0.428	92,753	2.16E-21	-0.79	0.08
GOSR2	rs17608766	17	45,013,271	*GOSR2*	UTR3	0	0.123	95,626	2.83E-09	0.72	0.12
PRKCA	rs56152251	17	64,280,153		intergenic	0	0.434	95,626	4.89E-11	-0.57	0.08
PRKCA	rs9912468	17	64,318,357	*PRKCA*	intronic	0	0.417	89,579	1.54E-15	-0.68	0.08
KCNJ2	rs17779747	17	68,494,992		Intergenic	0	0.304	93,948	3.34E-37	-1.08	0.09

Damaging: loss of function or predicted damaging by at least 2 of the following methods: Polyphen, LRT, SIFT, Mutation Taster (1=True, 0=False)[1]. CAF=coded allele frequency; N=sample size; BETA= effect size in milliseconds; SE=standard error of effect size estimate. Combined=all ethnicities meta-analysis; EA=European ancestry-only meta-analysis; AA=African American-only meta-analysis.

Supplemental Table 2: ExomeChip-wide Significant Variants in QT Meta-analysis -Continued-

	EA					AA					JT Combined		
SNV	**CAF**	**N**	**P**	**BETA**	**SE**	**CAF**	**N**	**P**	**BETA**	**SE**	**P**	**BETA**	**SE**
rs709209	0.343	83,884	1.14E-50	1.32	0.09	0.708	9,610	6.38E-02	0.53	0.29	2.03E-52	1.29	0.09
rs846111	0.271	64,387	1.55E-49	1.59	0.11	0.057	9,610	7.88E-01	0.22	0.58	6.10E-50	1.60	0.11
rs1077514	0.140	81,011	3.11E-09	-0.71	0.13	0.487	9,610	6.30E-01	-0.11	0.27	3.79E-11	-0.71	0.11
rs6676438	0.284	81,011	4.37E-37	1.18	0.10	0.858	9,610	3.09E-02	0.93	0.41	4.13E-41	1.21	0.09
rs2880058	0.338	83,884	1.68E-181	2.55	0.09	0.718	9,610	2.03E-04	1.23	0.30	1.13E-184	2.48	0.09
rs12143842	0.253	83,884	2.10E-258	3.33	0.10	0.123	9,610	3.24E-06	1.78	0.40	2.61E-272	3.32	0.10
rs1415259	0.362	81,011	3.62E-155	2.34	0.09	0.614	9,610	5.46E-03	0.84	0.27	1.20E-153	2.23	0.09
rs10494366	0.363	83,884	8.80E-159	2.34	0.09	0.614	9,610	6.17E-03	0.84	0.27	2.87E-157	2.23	0.08
rs16857031	0.138	77,837	2.45E-70	2.19	0.13	0.292	9,610	5.32E-04	1.05	0.29	1.87E-68	1.99	0.12
rs12029454	0.146	83,884	5.37E-134	2.89	0.12	0.285	9,610	8.15E-04	0.92	0.29	1.01E-127	2.60	0.11
rs12725553	0.390	83,884	5.75E-60	1.43	0.09	0.586	9,610	2.88E-03	0.81	0.27	1.68E-59	1.36	0.08
rs4657178	0.256	83,884	1.52E-104	2.09	0.10	0.358	9,610	5.57E-01	0.24	0.28	1.16E-93	1.88	0.09
rs10919071	0.125	83,884	5.21E-32	-1.44	0.13	0.026	9,610	6.40E-01	-0.55	0.84	7.19E-29	-1.36	0.13
rs6027	0.058	64,739	3.45E-11	-1.34	0.21	0.012	7,932	3.19E-01	-1.68	1.40	3.54E-11	-1.36	0.21
rs6018	0.060	63,558	2.74E-10	-1.33	0.21	0.012	7,932	4.23E-01	-1.43	1.40	1.44E-10	-1.35	0.21
rs6033	0.073	83,884	3.28E-09	-0.92	0.17	0.014	9,610	8.79E-01	-0.56	1.15	1.59E-09	-0.94	0.16
rs1361754	0.530	83,884	4.41E-10	0.52	0.09	0.407	9,610	9.43E-01	-0.06	0.27	9.75E-06	0.35	0.08
rs72648998	0.059	83,884	2.59E-09	1.03	0.18	0.013	9,610	7.57E-01	0.32	1.16	1.91E-09	1.02	0.18
rs10497520	0.132	81,011	7.20E-08	0.65	0.13	0.527	9,610	1.78E-01	0.41	0.27	1.28E-08	0.63	0.11
rs55910611	0.007	64,444	2.37E-07	-3.03	0.62	0.001	7,932	1.46E-01	-8.71	5.75	6.02E-08	-3.24	0.62
rs116202356	0.017	83,884	4.64E-11	2.27	0.34	0.004	9,610	2.18E-01	1.55	2.10	2.49E-18	2.93	0.33
rs11129795	0.241	83,884	2.11E-24	-1.00	0.10	0.181	9,610	3.32E-01	-0.14	0.34	3.66E-45	-1.30	0.10
rs12053903	0.329	83,884	9.05E-28	-0.95	0.09	0.788	9,610	5.70E-01	-0.11	0.33	4.59E-47	-1.19	0.09
rs3922844	0.308	81,011	3.42E-18	0.83	0.09	0.581	9,610	2.96E-03	0.95	0.27	4.19E-38	1.15	0.09
rs11708996	0.148	77,837	1.02E-19	-1.10	0.12	0.041	9,610	2.30E-01	-0.78	0.67	6.14E-39	-1.55	0.12
rs1805124	0.234	83,884	4.24E-10	0.64	0.10	0.286	9,610	7.07E-03	0.83	0.29	5.26E-25	0.97	0.10
rs11710077	0.203	77,837	2.19E-12	0.75	0.11	0.104	9,610	2.76E-03	1.44	0.44	7.19E-31	1.19	0.11
rs9851724	0.324	70,434	8.94E-12	0.67	0.10	0.154	7,932	3.86E-01	0.58	0.42	2.96E-23	0.97	0.10
rs6795970	0.399	83,884	1.70E-16	-0.67	0.09	0.099	9,610	2.03E-02	-1.23	0.46	1.06E-34	-0.99	0.09
rs6800541	0.405	83,884	1.46E-15	-0.65	0.09	0.100	9,610	2.50E-02	-1.20	0.45	4.34E-33	-0.97	0.09
rs1801725	0.138	83,884	4.82E-08	-0.59	0.13	0.036	9,610	6.83E-01	-0.28	0.72	2.38E-09	-0.65	0.12
rs7689609	0.140	75,316	6.05E-08	0.67	0.13	0.837	7,932	1.83E-02	1.03	0.46	6.81E-08	0.64	0.12
rs281868	0.497	81,011	1.55E-18	0.71	0.09	0.444	9,610	1.50E-01	0.29	0.27	8.42E-15	0.59	0.08
rs89107	0.500	83,884	5.32E-56	1.30	0.09	0.446	9,610	1.46E-01	0.29	0.27	3.37E-39	1.03	0.08
rs12210810	0.052	77,837	1.94E-36	-2.36	0.20	0.010	9,610	1.64E-01	-1.14	1.35	2.81E-31	-2.16	0.20
rs11153730	0.494	83,884	1.32E-76	1.51	0.09	0.281	9,610	2.27E-02	0.68	0.29	4.33E-55	1.23	0.08
rs11970286	0.457	83,884	3.39E-62	1.36	0.09	0.222	9,610	1.19E-02	0.88	0.32	1.29E-44	1.12	0.08
rs3734382	0.251	83,884	1.00E-11	-0.63	0.10	0.248	9,610	7.99E-03	-0.78	0.30	1.72E-08	-0.50	0.09
rs3734381	0.457	80,521	6.47E-38	-1.08	0.09	0.442	8,962	7.91E-02	-0.46	0.27	3.22E-25	-0.84	0.08
rs3807989	0.406	83,884	3.63E-10	0.51	0.09	0.647	9,610	2.92E-03	0.83	0.28	6.27E-06	0.35	0.08
rs2968864	0.239	81,011	1.05E-51	-1.51	0.10	0.046	9,610	7.74E-01	-0.31	0.64	3.67E-52	-1.51	0.10
rs2968863	0.239	81,011	1.42E-51	-1.51	0.10	0.051	9,610	5.40E-01	-0.51	0.61	1.97E-52	-1.52	0.10
rs4725982	0.214	83,884	2.48E-48	1.50	0.10	0.261	9,610	9.80E-02	0.34	0.31	8.11E-49	1.41	0.10
rs1805123	0.236	83,884	7.43E-52	-1.50	0.10	0.046	9,610	9.64E-01	-0.17	0.64	1.06E-51	-1.49	0.10
rs3807375	0.357	81,011	6.22E-41	1.21	0.09	0.696	9,610	8.58E-01	-0.11	0.29	5.00E-37	1.10	0.09

rs2474570	0.485	83,884	5.29E-10	-0.52	0.09	0.505	9,610	5.71E-01	-0.17	0.26	7.70E-09	-0.46	0.08
rs4934956	0.496	61,376	3.47E-11	0.66	0.10	0.512	7,284	8.14E-01	0.05	0.31	2.92E-08	0.53	0.10
rs3189030	0.316	83,884	7.27E-08	-0.49	0.09	0.143	9,610	1.46E-01	-0.56	0.37	2.78E-08	-0.49	0.09
rs2185913	0.295	83,884	8.58E-08	-0.50	0.09	0.059	9,610	9.86E-01	-0.09	0.57	6.14E-08	-0.51	0.09
rs800336	0.248	81,011	4.42E-18	-0.82	0.10	0.827	9,610	4.85E-01	-0.44	0.36	1.19E-19	-0.84	0.10
rs2074238	0.082	77,542	3.01E-127	-3.63	0.16	0.018	9,610	7.51E-04	-2.40	1.02	5.40E-135	-3.72	0.16
rs12296050	0.191	83,884	7.54E-64	1.79	0.11	0.523	9,610	7.02E-02	0.51	0.27	1.62E-64	1.66	0.10
rs12576239	0.134	83,884	1.41E-48	1.79	0.13	0.177	9,610	7.64E-01	-0.19	0.35	1.96E-46	1.62	0.12
rs1080015	0.363	83,884	2.77E-11	0.57	0.09	0.675	9,610	4.93E-01	-0.34	0.28	3.66E-11	0.52	0.09
rs179429	0.171	83,884	1.47E-07	-0.58	0.11	0.196	9,610	2.67E-01	-0.54	0.34	1.97E-08	-0.60	0.11
rs17215500	0.000	83,884	5.20E-09	43.00	6.31	0.000	9,610	3.55E-04	61.59	13.40	6.24E-12	46.25	5.60
rs102275	0.344	81,011	3.98E-09	-0.48	0.09	0.658	9,610	2.77E-01	-0.29	0.28	1.26E-05	-0.33	0.09
rs174546	0.336	83,884	5.11E-10	-0.51	0.09	0.082	9,610	2.24E-01	-0.54	0.50	2.24E-06	-0.38	0.09
rs174547	0.336	83,884	5.22E-10	-0.51	0.09	0.082	9,610	2.17E-01	-0.54	0.50	2.13E-06	-0.38	0.09
rs174550	0.336	83,884	5.70E-10	-0.51	0.09	0.082	9,610	2.24E-01	-0.54	0.50	2.51E-06	-0.38	0.09
rs174570	0.135	83,884	5.70E-08	-0.64	0.13	0.041	9,610	1.53E-01	-0.82	0.67	1.18E-05	-0.51	0.12
rs1535	0.338	83,884	4.77E-10	-0.51	0.09	0.157	9,610	1.31E-01	-0.45	0.37	7.84E-07	-0.39	0.09
rs174583	0.346	83,884	1.99E-09	-0.49	0.09	0.279	9,610	1.21E-01	-0.47	0.30	1.43E-06	-0.37	0.09
rs1886512	0.370	68,810	7.74E-11	0.61	0.09	0.471	9,610	3.86E-01	0.33	0.27	1.09E-15	0.71	0.09
rs8049607	0.509	83,884	1.13E-41	1.11	0.09	0.454	9,610	9.16E-04	0.68	0.27	5.10E-45	1.08	0.08
rs1659127	0.338	30,645	4.49E-08	0.90	0.16	0.000	0	NA	NA	Inf	7.91E-06	0.72	0.16
rs30208	0.510	83,884	1.89E-11	0.53	0.09	0.432	9,610	5.71E-01	-0.12	0.27	4.59E-09	0.44	0.08
rs4356470	0.307	83,884	1.37E-22	-0.90	0.09	0.448	9,610	4.08E-01	-0.16	0.27	1.28E-19	-0.79	0.09
rs7188697	0.255	80,521	8.49E-65	-1.66	0.10	0.153	8,962	1.53E-02	-0.95	0.37	4.65E-64	-1.60	0.10
rs2230553	0.368	77,837	2.90E-10	-0.57	0.09	0.171	9,610	1.91E-01	-0.51	0.35	4.57E-09	-0.53	0.09
rs9635769	0.425	83,884	1.72E-08	0.50	0.09	0.686	9,610	8.31E-01	0.04	0.29	2.02E-08	0.48	0.08
rs2074518	0.460	81,011	3.60E-20	-0.79	0.09	0.178	9,610	1.49E-02	-0.92	0.35	6.60E-20	-0.78	0.08
rs17608766	0.136	83,884	4.63E-09	0.72	0.13	0.026	9,610	1.59E-01	1.08	0.84	7.21E-04	0.43	0.13
rs56152251	0.421	83,884	1.58E-09	-0.55	0.09	0.526	9,610	1.56E-02	-0.72	0.27	2.07E-17	-0.72	0.08
rs9912468	0.421	77,837	2.56E-12	-0.64	0.09	0.379	9,610	6.40E-05	-1.03	0.28	7.15E-25	-0.87	0.09
rs17779747	0.327	83,884	2.32E-37	-1.10	0.09	0.091	7,932	7.36E-03	-1.42	0.54	2.81E-35	-1.08	0.09

Damaging: loss of function or predicted damaging by at least 2 of the following methods: Polyphen, LRT, SIFT, Mutation Taster (1=True, 0=False)[1]. CAF=coded allele frequency; N=sample size; BETA= effect size in milliseconds; SE=standard error of effect size estimate. Combined=all ethnicities meta-analysis; EA=European ancestry-only meta-analysis; AA=African American-only meta-analysis.

Supplemental Table 3: ExomeChip-wide Significant Variants in JT Meta-analysis

							Combined			
Locus Name	**SNV**	**Chr**	**Pos**	**Gene**	**Functiional Category**	**Damaging**	**CAF**	**N**	**P**	**BETA**	**SE**
RNF207	rs709209	1	6,278,414	*RNF207*	exonic;nonsynonymous	0	0.380	92,046	2.03E-52	1.29	0.09
RNF207	rs200882245	1	6,279,316	*RNF207*	exonic;nonsynonymous	0	0.002	92,046	2.06E-08	-4.56	0.85
RNF207	rs846111	1	6,279,370	*RNF207*	exonic;nonsynonymous	0	0.240	72,859	6.10E-50	1.60	0.11
TCEA3	rs627304	1	23,537,555		intergenic	0	0.434	92,046	1.90E-07	-0.40	0.08
TCEA3	rs3889814	1	23,731,819	*TCEA3*	intronic	0	0.202	89,173	8.82E-08	-0.59	0.12
TCEA3	rs1077514	1	23,766,233	*ASAP3*	intronic	0	0.180	89,173	3.79E-11	-0.71	0.11
NOS1AP	rs6676438	1	161,983,089	*OLFML2B*	intronic	0	0.349	89,173	4.13E-41	1.21	0.09
NOS1AP	rs2880058	1	162,014,632		intergenic	0	0.381	92,046	1.13E-184	2.48	0.09
NOS1AP	rs12143842	1	162,033,890		intergenic	0	0.239	92,046	2.61E-272	3.32	0.10
NOS1AP	rs1415259	1	162,085,309	*NOS1AP*	intronic	0	0.392	89,173	1.20E-153	2.23	0.09
NOS1AP	rs10494366	1	162,085,685	*NOS1AP*	intronic	0	0.392	92,046	2.87E-157	2.23	0.08
NOS1AP	rs16857031	1	162,112,910	*NOS1AP*	intronic	0	0.155	86,309	1.87E-68	1.99	0.12
NOS1AP	rs12029454	1	162,133,117	*NOS1AP*	intronic	0	0.164	92,046	1.01E-127	2.60	0.11
NOS1AP	rs12725553	1	162,168,116	*NOS1AP*	intronic	0	0.412	92,046	1.68E-59	1.36	0.08
NOS1AP	rs4657178	1	162,210,610	*NOS1AP*	intronic	0	0.270	92,046	1.16E-93	1.88	0.09
ATP1B1	rs10919071	1	169,099,483	*ATP1B1*	intronic	0	0.115	92,046	7.19E-29	-1.36	0.13
ATP1B1	rs6027	1	169,483,561	*F5*	exonic;nonsynonymous	1	0.053	71,223	3.54E-11	-1.36	0.21
ATP1B1	rs6018	1	169,511,878	*F5*	exonic;nonsynonymous	0	0.054	70,404	1.44E-10	-1.35	0.21
ATP1B1	rs6037	1	169,513,583	*F5*	exonic;synonymous	0	0.068	72,538	8.16E-08	-0.93	0.19
ATP1B1	rs6033	1	169,521,853	*F5*	exonic;nonsynonymous	0	0.066	92,046	1.59E-09	-0.94	0.16
TTN-CCDC141	rs72648998	2	179,575,511	*TTN*	exonic;nonsynonymous	0	0.053	92,046	1.91E-09	1.02	0.18
TTN-CCDC141	rs34819099	2	179,628,918	*TTN*	exonic;nonsynonymous	0	0.014	92,046	6.29E-08	1.81	0.34
TTN-CCDC141	rs10497520	2	179,644,855	*TTN*	exonic;nonsynonymous	1	0.185	89,173	1.28E-08	0.63	0.11
SLC4A3	rs55910611	2	220,500,412	*SLC4A3*	exonic;nonsynonymous	0	0.006	70,928	6.02E-08	-3.24	0.62
SCN5A-SCN10A	rs116202356	3	38,103,776	*DLEC1*	exonic;nonsynonymous	0	0.015	92,046	2.49E-18	2.93	0.33
SCN5A-SCN10A	rs2070492	3	38,357,817	*SLC22A14*	exonic;nonsynonymous	0	0.096	92,046	4.26E-08	-0.67	0.14
SCN5A-SCN10A	rs2070488	3	38,442,490	*XYLB*	intronic	0	0.518	92,046	4.38E-09	0.42	0.08
SCN5A-SCN10A	rs11129795	3	38,589,163	*SCN5A*	downstream	0	0.233	92,046	3.66E-45	-1.30	0.10
SCN5A-SCN10A	rs12053903	3	38,593,393	*SCN5A*	intronic	0	0.381	92,046	4.59E-47	-1.19	0.09
SCN5A-SCN10A	rs3922844	3	38,624,253	*SCN5A*	intronic	0	0.336	89,173	4.19E-38	1.15	0.09
SCN5A-SCN10A	rs11708996	3	38,633,923	*SCN5A*	intronic	0	0.135	86,309	6.14E-39	-1.55	0.12
SCN5A-SCN10A	rs1805124	3	38,645,420	*SCN5A*	exonic;nonsynonymous	0	0.238	92,046	5.26E-25	0.97	0.10
SCN5A-SCN10A	rs11710077	3	38,657,899	*SCN5A*	intronic	0	0.191	86,309	7.19E-31	1.19	0.11
SCN5A-SCN10A	rs9841329	3	38,687,803	*SCN5A*	intronic	0	0.433	92,046	1.58E-09	-0.48	0.08
SCN5A-SCN10A	rs9851724	3	38,719,935		intergenic	0	0.306	76,918	2.96E-23	0.97	0.10
SCN5A-SCN10A	rs12632942	3	38,764,998	*SCN10A*	exonic;nonsynonymous	0	0.245	92,046	1.37E-07	0.47	0.10
SCN5A-SCN10A	rs6795970	3	38,766,675	*SCN10A*	exonic;nonsynonymous	0	0.364	92,046	1.06E-34	-0.99	0.09
SCN5A-SCN10A	rs57326399	3	38,768,300	*SCN10A*	exonic;nonsynonymous	0	0.244	92,046	2.10E-10	0.59	0.10
SCN5A-SCN10A	rs6800541	3	38,774,832	*SCN10A*	intronic	0	0.370	92,046	4.34E-33	-0.97	0.09
CASR	rs1801725	3	122,003,757	*CASR*	exonic;nonsynonymous	0	0.125	92,046	2.38E-09	-0.65	0.12
SENP2	rs6762208	3	185,331,165	*SENP2*	exonic;nonsynonymous	0	0.358	92,046	1.50E-07	0.44	0.08
SLC4A4	rs7689609	4	72,083,374	*SLC4A4*	intronic	0	0.215	81,800	6.81E-08	0.64	0.12
SLC12A7	rs737154	5	1,065,399	*SLC12A7*	exonic;splicing;synonymous	1	0.500	92,046	1.81E-07	-0.40	0.08
CDKN1A	rs1321311	6	36,622,900		intergenic	0	0.254	89,173	6.14E-14	-0.73	0.10
CDKN1A	rs9470361	6	36,623,379		intergenic	0	0.249	92,046	1.69E-15	-0.76	0.09

SLC35F1-PLN	rs281868	6	118,574,061	*SLC35F1*	intronic	0	0.487	89,173	8.42E-15	0.59	0.08
SLC35F1-PLN	rs89107	6	118,578,043	*SLC35F1*	intronic	0	0.490	92,046	3.37E-39	1.03	0.08
SLC35F1-PLN	rs12210810	6	118,653,204		intergenic	0	0.046	86,309	2.81E-31	-2.16	0.20
SLC35F1-PLN	rs11153730	6	118,667,522		intergenic	0	0.467	92,046	4.33E-55	1.23	0.08
SLC35F1-PLN	rs11970286	6	118,680,374		intergenic	0	0.429	92,046	1.29E-44	1.12	0.08
SLC35F1-PLN	rs3734382	6	118,886,961	*CEP85L*	exonic;nonsynonymous	0	0.257	92,046	1.72E-08	-0.50	0.09
SLC35F1-PLN	rs3734381	6	118,887,303	*CEP85L*	exonic;nonsynonymous	0	0.461	88,035	3.22E-25	-0.84	0.08
KCNH2	rs2968864	7	150,622,162		intergenic	0	0.215	89,173	3.67E-52	-1.51	0.10
KCNH2	rs2968863	7	150,623,137		intergenic	0	0.215	89,173	1.97E-52	-1.52	0.10
KCNH2	rs4725982	7	150,637,863		intergenic	0	0.223	92,046	8.11E-49	1.41	0.10
KCNH2	rs1805123	7	150,645,534	*KCNH2*	exonic;nonsynonymous	0	0.214	92,046	1.06E-51	-1.49	0.10
KCNH2	rs3807375	7	150,667,210	*KCNH2*	intronic	0	0.400	89,173	5.00E-37	1.10	0.09
ZNF37A	rs2474570	10	38,383,757	*ZNF37A*	intronic	0	0.488	92,046	7.70E-09	-0.46	0.08
ZNF37A	rs4934956	10	38,814,815		intergenic	0	0.497	67,212	2.92E-08	0.53	0.10
NRAP	rs3189030	10	115,393,929	*NRAP*	exonic;nonsynonymous	0	0.299	92,046	2.78E-08	-0.49	0.09
NRAP	rs2185913	10	115,410,234	*NRAP*	exonic;nonsynonymous	1	0.270	92,046	6.14E-08	-0.51	0.09
KCNQ1	rs800336	11	2,473,131	*KCNQ1*	intronic	0	0.314	89,173	1.19E-19	-0.84	0.10
KCNQ1	rs2074238	11	2,484,803	*KCNQ1*	intronic	0	0.073	86,014	5.40E-135	-3.72	0.16
KCNQ1	rs12296050	11	2,489,342	*KCNQ1*	intronic	0	0.230	92,046	1.62E-64	1.66	0.10
KCNQ1	rs12576239	11	2,502,319	*KCNQ1*	intronic	0	0.139	92,046	1.96E-46	1.62	0.12
KCNQ1	rs1080015	11	2,511,527	*KCNQ1*	intronic	0	0.397	92,046	3.66E-11	0.52	0.09
KCNQ1	rs179429	11	2,550,730	*KCNQ1*	intronic	0	0.171	92,046	1.97E-08	-0.60	0.11
KCNQ1	rs17215500	11	2,790,111	*KCNQ1*	exonic;stopgain	1	0.000	92,046	6.24E-12	46.25	5.60
NACA	rs2958149	12	57,109,792	*NACA*	exonic;nonsynonymous	0	0.252	88,035	7.81E-08	0.53	0.10
NACA	rs2926743	12	57,114,100	*NACA*	exonic;nonsynonymous	0	0.252	92,046	5.82E-08	0.53	0.09
KLF12	rs1886512	13	74,520,186	*KLF12*	intronic	0	0.381	77,282	1.09E-15	0.71	0.09
LITAF	rs8049607	16	11,691,753		intergenic	0	0.502	92,046	5.10E-45	1.08	0.08
MKL2	rs30208	16	14,428,853		intergenic	0	0.501	92,046	4.59E-09	0.44	0.08
CNOT1	rs4356470	16	58,529,615	*NDRG4*	intronic	0	0.328	92,046	1.28E-19	-0.79	0.09
CNOT1	rs7188697	16	58,622,178	*CNOT1*	intronic	0	0.247	88,035	4.65E-64	-1.60	0.10
LIG3	rs2230553	17	33,269,648	*CCT6B*	exonic;nonsynonymous	1	0.343	86,309	4.57E-09	-0.53	0.09
LIG3	rs9635769	17	33,288,363	*CCT6B*	exonic;nonsynonymous	0	0.452	92,046	2.02E-08	0.48	0.08
LIG3	rs2074518	17	33,324,382	*LIG3*	intronic	0	0.428	89,173	6.60E-20	-0.78	0.08
PRKCA	rs56152251	17	64,280,153		intergenic	0	0.433	92,046	2.07E-17	-0.72	0.08
PRKCA	rs9912468	17	64,318,357	*PRKCA*	intronic	0	0.416	86,309	7.15E-25	-0.87	0.09
KCNJ2	rs17779747	17	68,494,992		intergenic	0	0.303	90,368	2.81E-35	-1.08	0.09

Damaging: loss of function or predicted damaging by at least 2 of the following methods: Polyphen, LRT, SIFT, Mutation Taster (1=True, 0=False)[1]. CAF=coded allele frequency; N=sample size; BETA= effect size in milliseconds; SE=standard error of effect size estimate. Combined=all ethnicities meta-analysis; EA=European ancestry-only meta-analysis; AA=African American-only meta-analysis.

Supplemental Table 3: ExomeChip-wide Significant Variants in JT Meta-analysis -Continued-

	EA					AA					QT Combined		
SNV	**CAF**	**N**	**P**	**BETA**	**SE**	**CAF**	**N**	**P**	**BETA**	**SE**	**P**	**BETA**	**SE**
rs709209	0.343	80,330	3.49E-55	1.40	0.09	0.708	9,584	7.43E-02	0.50	0.29	1.33E-48	1.23	0.09
rs200882245	0.003	80,330	7.61E-09	-4.70	0.85	0.000	9,584	1.52E-01	12.17	9.57	2.70E-07	-4.16	0.85
rs846111	0.272	61,143	9.74E-53	1.69	0.11	0.056	9,584	8.65E-01	0.43	0.57	1.51E-46	1.51	0.11
rs627304	0.407	80,330	3.39E-07	-0.44	0.09	0.645	9,584	3.22E-01	-0.07	0.27	5.36E-06	-0.34	0.08
rs3889814	0.130	77,457	2.21E-10	-0.78	0.13	0.760	9,584	8.50E-01	0.11	0.32	9.92E-06	-0.48	0.12
rs1077514	0.139	77,457	1.39E-12	-0.86	0.13	0.487	9,584	4.31E-01	-0.17	0.26	4.08E-08	-0.58	0.11
rs6676438	0.284	77,457	1.43E-40	1.25	0.10	0.858	9,584	1.94E-02	0.96	0.41	1.38E-37	1.15	0.09
rs2880058	0.337	80,330	2.67E-191	2.65	0.09	0.718	9,584	3.57E-04	1.18	0.30	9.54E-177	2.41	0.09
rs12143842	0.252	80,330	1.47E-275	3.49	0.10	0.123	9,584	5.08E-07	1.87	0.40	2.90E-255	3.18	0.10
rs1415259	0.361	77,457	7.37E-164	2.43	0.09	0.614	9,584	2.64E-03	0.90	0.27	1.14E-145	2.15	0.08
rs10494366	0.362	80,330	2.02E-167	2.42	0.09	0.614	9,584	2.98E-03	0.89	0.27	2.81E-149	2.15	0.08
rs16857031	0.138	74,593	9.24E-73	2.25	0.13	0.291	9,584	3.44E-04	1.07	0.29	2.11E-66	1.94	0.12
rs12029454	0.146	80,330	5.29E-139	2.99	0.12	0.285	9,584	4.79E-04	0.94	0.29	1.15E-123	2.53	0.11
rs12725553	0.389	80,330	1.02E-60	1.45	0.09	0.586	9,584	2.85E-03	0.80	0.27	5.30E-59	1.34	0.08
rs4657178	0.256	80,330	4.05E-106	2.14	0.10	0.359	9,584	4.44E-01	0.30	0.28	2.24E-92	1.84	0.09
rs10919071	0.125	80,330	2.48E-30	-1.42	0.13	0.026	9,584	4.56E-01	-0.76	0.83	2.55E-30	-1.37	0.13
rs6027	0.058	61,185	1.09E-11	-1.43	0.22	0.012	7,906	1.93E-01	-2.12	1.40	1.34E-10	-1.27	0.21
rs6018	0.060	60,366	3.60E-11	-1.44	0.22	0.012	7,906	2.77E-01	-1.84	1.39	1.20E-09	-1.25	0.21
rs6037	0.073	64,389	1.93E-08	-0.99	0.19	0.013	6,017	5.53E-01	-1.10	1.51	1.18E-06	-0.80	0.19
rs6033	0.073	80,330	3.84E-10	-0.99	0.17	0.014	9,584	6.94E-01	-0.82	1.14	1.40E-08	-0.87	0.16
rs72648998	0.058	80,330	1.25E-09	1.06	0.19	0.013	9,584	8.84E-01	0.19	1.16	3.20E-09	1.00	0.18
rs34819099	0.016	80,330	2.20E-08	1.88	0.35	0.003	9,584	5.11E-01	-1.06	2.36	2.48E-07	1.72	0.34
rs10497520	0.132	77,457	6.01E-08	0.66	0.13	0.528	9,584	2.51E-01	0.36	0.27	8.61E-09	0.63	0.11
rs55910611	0.007	60,890	1.05E-07	-3.22	0.63	0.001	7,906	1.03E-01	-9.26	5.81	1.53E-07	-3.06	0.61
rs116202356	0.017	80,330	6.23E-18	2.99	0.34	0.004	9,584	8.30E-02	2.42	2.09	3.08E-11	2.22	0.33
rs2070492	0.098	80,330	1.87E-07	-0.67	0.15	0.075	9,584	1.47E-01	-0.58	0.51	9.31E-06	-0.51	0.14
rs2070488	0.559	80,330	1.90E-10	0.49	0.09	0.216	9,584	2.73E-01	-0.56	0.32	2.76E-06	0.32	0.08
rs11129795	0.242	80,330	2.33E-46	-1.39	0.10	0.181	9,584	9.74E-02	-0.37	0.34	1.07E-23	-0.93	0.10
rs12053903	0.329	80,330	1.13E-49	-1.29	0.09	0.788	9,584	4.30E-01	-0.16	0.33	1.20E-26	-0.88	0.09
rs3922844	0.308	77,457	1.03E-34	1.17	0.10	0.580	9,584	4.82E-06	1.33	0.27	1.75E-19	0.82	0.09
rs11708996	0.149	74,593	1.89E-38	-1.58	0.13	0.041	9,584	4.31E-02	-1.23	0.67	7.31E-20	-1.08	0.12
rs1805124	0.233	80,330	1.01E-22	0.98	0.10	0.286	9,584	1.49E-03	0.94	0.29	7.48E-12	0.66	0.10
rs11710077	0.203	74,593	9.20E-28	1.16	0.11	0.105	9,584	6.08E-05	1.83	0.43	4.11E-14	0.78	0.11
rs9841329	0.433	80,330	7.45E-09	-0.48	0.09	0.410	9,584	7.16E-02	-0.48	0.27	1.94E-04	-0.30	0.08
rs9851724	0.326	66,880	3.69E-26	1.06	0.10	0.154	7,906	4.63E-01	0.50	0.42	1.58E-10	0.62	0.10
rs12632942	0.258	80,330	8.58E-09	0.55	0.10	0.139	9,584	7.52E-01	-0.33	0.38	3.23E-04	0.33	0.09
rs6795970	0.399	80,330	4.21E-33	-0.99	0.09	0.099	9,584	1.02E-03	-1.60	0.45	2.55E-17	-0.67	0.09
rs57326399	0.260	80,330	1.18E-11	0.66	0.10	0.111	9,584	9.63E-01	-0.14	0.42	2.48E-05	0.41	0.09
rs6800541	0.405	80,330	1.90E-31	-0.97	0.09	0.100	9,584	1.16E-03	-1.59	0.45	2.23E-16	-0.66	0.08
rs1801725	0.136	80,330	2.16E-09	-0.66	0.13	0.036	9,584	7.64E-01	-0.29	0.71	4.30E-08	-0.58	0.12
rs6762208	0.345	80,330	1.77E-10	0.55	0.09	0.477	9,584	2.03E-01	-0.26	0.26	1.76E-04	0.31	0.08
rs7689609	0.140	71,762	2.09E-07	0.66	0.13	0.837	7,906	5.86E-03	1.17	0.45	3.88E-08	0.64	0.12
rs737154	0.502	80,330	1.40E-06	-0.40	0.09	0.499	9,584	5.92E-02	-0.43	0.26	4.77E-06	-0.36	0.08
rs1321311	0.239	77,457	2.13E-14	-0.79	0.10	0.383	9,584	1.06E-01	-0.55	0.27	1.12E-04	-0.39	0.09
rs9470361	0.242	80,330	4.64E-15	-0.79	0.10	0.315	9,584	2.16E-02	-0.77	0.28	5.55E-05	-0.40	0.09

rs281868	0.497	77,457	5.35E-15	0.63	0.09	0.444	9,584	2.37E-01	0.21	0.26	1.92E-18	0.66	0.08
rs89107	0.500	80,330	1.53E-41	1.13	0.09	0.446	9,584	2.28E-01	0.22	0.27	4.92E-53	1.19	0.08
rs12210810	0.052	74,593	1.30E-32	-2.25	0.20	0.010	9,584	3.50E-01	-0.60	1.34	2.11E-35	-2.28	0.20
rs11153730	0.494	80,330	4.72E-57	1.32	0.09	0.281	9,584	4.40E-02	0.59	0.29	4.88E-74	1.41	0.08
rs11970286	0.458	80,330	1.12E-45	1.18	0.09	0.222	9,584	2.61E-02	0.77	0.32	7.86E-61	1.29	0.08
rs3734382	0.251	80,330	3.46E-07	-0.48	0.10	0.249	9,584	1.03E-02	-0.73	0.30	3.97E-13	-0.63	0.09
rs3734381	0.457	76,967	3.24E-26	-0.91	0.09	0.442	8,936	9.17E-02	-0.43	0.27	3.75E-36	-1.00	0.08
rs2968864	0.239	77,457	4.32E-53	-1.55	0.10	0.046	9,584	8.66E-01	-0.26	0.64	5.13E-51	-1.48	0.10
rs2968863	0.239	77,457	4.76E-53	-1.55	0.10	0.051	9,584	5.84E-01	-0.50	0.61	3.86E-51	-1.48	0.10
rs4725982	0.213	80,330	9.09E-52	1.57	0.11	0.261	9,584	1.88E-01	0.27	0.30	1.16E-46	1.36	0.10
rs1805123	0.236	80,330	7.69E-53	-1.53	0.10	0.046	9,584	9.73E-01	-0.14	0.64	6.67E-51	-1.47	0.10
rs3807375	0.357	77,457	5.23E-42	1.24	0.09	0.697	9,584	5.87E-01	-0.18	0.29	6.66E-37	1.08	0.08
rs2474570	0.484	80,330	3.81E-09	-0.50	0.09	0.506	9,584	6.70E-01	-0.15	0.26	8.85E-10	-0.48	0.08
rs4934956	0.497	57,822	4.10E-09	0.61	0.11	0.512	7,258	9.96E-01	-0.02	0.31	2.29E-10	0.58	0.10
rs3189030	0.316	80,330	5.40E-08	-0.51	0.09	0.143	9,584	1.40E-01	-0.54	0.37	3.77E-08	-0.48	0.09
rs2185913	0.296	80,330	2.71E-08	-0.53	0.09	0.059	9,584	9.41E-01	-0.10	0.57	1.92E-07	-0.48	0.09
rs800336	0.247	77,457	3.68E-21	-0.91	0.10	0.827	9,584	4.91E-01	-0.41	0.35	5.94E-17	-0.77	0.10
rs2074238	0.082	74,298	2.93E-133	-3.78	0.16	0.018	9,584	2.78E-03	-2.11	1.01	8.22E-130	-3.58	0.16
rs12296050	0.191	80,330	3.99E-72	1.91	0.11	0.522	9,584	6.71E-02	0.53	0.26	8.87E-58	1.57	0.10
rs12576239	0.135	80,330	7.71E-57	1.94	0.13	0.177	9,584	5.90E-01	-0.27	0.34	2.10E-40	1.51	0.12
rs1080015	0.362	80,330	1.82E-13	0.63	0.09	0.675	9,584	4.12E-01	-0.34	0.28	1.68E-09	0.48	0.08
rs179429	0.170	80,330	9.96E-08	-0.59	0.12	0.196	9,584	2.24E-01	-0.54	0.33	3.51E-08	-0.59	0.11
rs17215500	0.000	80,330	3.66E-09	42.79	6.19	0.000	9,584	2.71E-04	61.97	13.18	1.11E-11	46.38	5.71
rs2958149	0.270	76,967	3.39E-08	0.56	0.10	0.102	8,936	2.75E-01	0.41	0.45	2.57E-04	0.37	0.10
rs2926743	0.271	80,330	2.14E-08	0.56	0.10	0.103	9,584	3.05E-01	0.40	0.44	2.68E-04	0.36	0.09
rs1886512	0.370	65,566	1.85E-16	0.77	0.10	0.471	9,584	3.20E-01	0.34	0.26	1.53E-10	0.57	0.09
rs8049607	0.508	80,330	1.90E-42	1.13	0.09	0.454	9,584	3.25E-04	0.75	0.26	8.42E-44	1.05	0.08
rs30208	0.510	80,330	1.23E-10	0.51	0.09	0.432	9,584	9.77E-01	0.00	0.27	2.28E-09	0.45	0.08
rs4356470	0.307	80,330	1.22E-21	-0.90	0.09	0.448	9,584	4.19E-01	-0.16	0.27	1.37E-20	-0.80	0.09
rs7188697	0.254	76,967	3.38E-66	-1.70	0.10	0.153	8,936	1.97E-02	-0.92	0.37	3.78E-63	-1.57	0.10
rs2230553	0.369	74,593	8.86E-09	-0.54	0.09	0.170	9,584	1.86E-01	-0.50	0.35	1.65E-10	-0.56	0.09
rs9635769	0.425	80,330	1.26E-08	0.51	0.09	0.687	9,584	7.96E-01	0.05	0.29	2.77E-08	0.47	0.08
rs2074518	0.461	77,457	9.48E-19	-0.77	0.09	0.177	9,584	1.81E-02	-0.88	0.35	2.16E-21	-0.79	0.08
rs56152251	0.421	80,330	3.43E-15	-0.71	0.09	0.526	9,584	2.47E-03	-0.84	0.26	4.89E-11	-0.57	0.08
rs9912468	0.420	74,593	4.07E-20	-0.84	0.09	0.379	9,584	1.23E-06	-1.24	0.27	1.54E-15	-0.68	0.08
rs17779747	0.327	80,330	3.50E-36	-1.11	0.09	0.091	7,906	5.01E-02	-1.06	0.54	3.34E-37	-1.08	0.09

Damaging: loss of function or predicted damaging by at least 2 of the following methods: Polyphen, LRT, SIFT, Mutation Taster (1=True, 0=False)[1]. CAF=coded allele frequency; N=sample size; BETA= effect size in milliseconds; SE=standard error of effect size estimate. Combined=all ethnicities meta-analysis; EA=European ancestry-only meta-analysis; AA=African American-only meta-analysis.

Supplemental Table 4: GWiS Results

Locus Name	Gene	SNV	Chr	Position	SNPs Tested	# Tests	N	r^2	SNV *P*	Function	LD w/ QTIGC
RNF207	*RNF207*	rs709209	1	6,278,414	191	175.551	83,884	0.000	1E-50	Nonsynonymous	**0.696**
	RNF207	rs200882245	1	6,279,316	191	175.551	83,884	0.001	1E-07	Nonsynonymous	0.001
TCEA3	*ASAP3*	rs1077514	1	23,766,233	241	208.235	81,011	0.000	3E-09	Intronic	0.060
NOS1AP		rs12143842	1	162,033,890	214	195.062	83,884	0.000	2E-258	Intergenic	**0.989**
	NOS1AP	rs4657178	1	162,210,610	214	195.062	83,884	0.055	2E-104	Intronic	0.053
	NOS1AP	rs16857031	1	162,112,910	214	195.062	77,837	0.067	2E-70	Intronic	0.047
ATP1B1	*ATP1B1*	rs10919071	1	169,099,483	182	160.218	83,884	0.000	5E-32	Intronic	**0.964**
PM20D1	*PM20D1*	rs1361754	1	205,801,872	228	206.79	83,884	0.000	4E-10	Nonsynonymous	QT Novel
SLC8A1		None	2	39,959,060	26	25.3846					
SP3	*SP3*	rs1047640	2	174,820,750	79	77.9712	83,884	0.000	2E-06	Nonsynonymous	0.218
TTN-CCDC141	*TTN*	rs72648998	2	179,575,511	651	482.158	83,884	0.000	3E-09	Nonsynonymous	0.044
	TTN	rs72646869	2	179,446,381	651	482.158	83,884	0.002	7E-07	Nonsynonymous	0.017
	TTN	rs16866378	2	179,393,111	651	482.158	83,884	0.001	8E-07	Nonsynonymous	0.009
SPATS2L		None	2	201,303,848	140	129.204					
SLC4A3	*SLC4A3*	rs55910611	2	220,500,412	500	436.507	64,444	0.000	2E-07	Nonsynonymous	QT Novel
	STK11IP	rs620698	2	220,466,199	500	436.507	81,011	0.000	9E-07	Intronic	QT Novel
SCN5A-SCN10A	*SCN5A*	rs12053903	3	38,593,393	413	365.284	83,884	0.000	9E-28	Intronic	**0.970**
	SCN5A	rs3922844	3	38,624,253	413	365.284	81,011	0.002	3E-18	Intronic	0.002
	SCN10A	rs6795970	3	38,766,675	413	365.284	83,884	0.001	2E-16	Nonsynonymous	0.001
		rs9851724	3	38,719,935	413	365.284	70,434	0.010	9E-12	Intergenic	0.000
C3ORF75		None	3	47,282,303	327	279.961					
CASR	*CASR*	rs1801725	3	122,003,757	322	275.414	83,884	0.000	5E-08	Nonsynonymous	QT Novel
SENP2	*SENP2*	rs6762208	3	185,331,165	156	142.145	80,330	0.000	2E-10	Nonsynonymous	JT Novel
SLC4A4	*SLC4A4*	rs7689609	4	72,083,374	160	148.664	75,316	0.000	6E-08	Intronic	**0.673**
SMARCAD1	*SMARCAD1*	rs7439869	4	95,173,779	52	45.2488	83,884	0.000	1E-06	Nonsynonymous	**0.539**
SLC12A7	*SLC12A7*	rs737154	5	1,065,399	272	245.212	80,330	0.000	1E-06	Splicing/Synonymous	JT Novel
GFRA3		None	5	137,441,767	136	124.32					
GMPR	*GMPR*	rs1042391	6	16,290,761	61	57.9877	77,837	0.000	1E-06	Nonsynonymous	**0.989**
CDKN1A		rs9470361	6	36,623,379	223	207.828	80,330	0.000	5E-15	Intergenic	JT Novel
SLC35F1-PLN		rs11153730	6	118,667,522	104	95.8603	83,884	0.000	1E-76	Intergenic	**0.988**
		rs12210810	6	118,653,204	104	95.8603	77,837	0.055	2E-36	Intergenic	0.050
CAV1	*CAV1*	rs3807989	7	116,186,241	93	87.7895	83,884	0.000	4E-10	Intronic	0.168
KCNH2	*KCNH2*	rs1805123	7	150,645,534	316	285.068	83,884	0.000	7E-52	Nonsynonymous	**0.823**
		rs4725982	7	150,637,863	316	285.068	83,884	0.087	2E-48	Intergenic	0.088
NCOA2		None	8	71,164,680	91	87.976					
LAPTM4B		None	8	99,045,866	117	112.946					
AZIN1		None	8	104,432,659	81	75.9971					
ZNF37A		rs4934956	10	38,814,815	30	26.7679	61,376	0.000	3E-11	Intergenic	QT Novel
GBF1		None	10	104,174,986	187	167.445					
NRAP	*NRAP*	rs3189030	10	115,393,929	232	204.795	83,884	0.000	7E-08	Nonsynonymous	QT Novel
KCNQ1	*KCNQ1*	rs2074238	11	2,484,803	210	197.041	77,542	0.000	3E-127	Intronic	0.021
	KCNQ1	rs12296050	11	2,489,342	210	197.041	83,884	0.018	8E-64	Intronic	0.992
	KCNQ1	rs17215500	11	2,790,111	210	197.041	83,884	0.000	5E-09	Stop	0.000
	KCNQ1	rs800336	11	2,473,131	210	197.041	81,011	0.018	4E-18	Intronic	0.000

FEN1-FADS2	*FADS2*	rs1535	11	61,597,972	439	394.132	83,884	0.000	5E-10	Intronic	0.952
NACA	*NACA*	rs2926743	12	57,114,100	554	482.888	80,330	0.000	2E-08	Nonsynonymous	JT Novel
ATP2A2	*GIT2*	rs11068997	12	110,383,141	182	166.358	83,884	0.000	6E-07	Nonsynonymous	0.018
	TCTN1	rs75714509	12	111,080,097	182	166.358	83,884	0.000	2E-06	Nonsynonymous	0.018
KLF12	*KLF12*	rs1886512	13	74,520,186	25	23.8208	68,810	0.000	8E-11	Intronic	0.955
ANKRD9		None	14	102,808,655	154	136.308					
USP50-TRPM7		None	15	50,878,630	177	165.088					
CREBBP		None	16	3,336,067	507	450.414					
LITAF		rs8049607	16	11,691,753	173	159.823	83,884	0.000	1E-41	Intergenic	0.736
MKL2		rs30208	16	14,428,853	63	60.4452	83,884	0.000	2E-11	Intergenic	0.342
CNOT1	*CNOT1*	rs7188697	16	58,622,178	196	184.334	80,521	0.000	8E-65	Intronic	0.984
LIG3	*LIG3*	rs2074518	17	33,324,382	281	254.997	81,011	0.000	4E-20	Intronic	0.994
GOSR2	*GOSR2*	rs17608766	17	45,013,271	117	108.077	83,884	0.000	5E-09	UTR3	QT Novel
PRKCA	*PRKCA*	rs9912468	17	64,318,357	95	88.6125	77,837	0.000	3E-12	Intronic	0.993
KCNJ2		rs17779747	17	68,494,992	27	26.8937	83,884	0.000	2E-37	Intergenic	0.388
KCNE1		None	21	35,880,072	129	118.746					

GWiS was run on all variants in each locus (most significant SNP ±1 MB) from the European ancestry-only QT or JT interval association. SNVs are added into the GWiS model in the order they are listed. $r^2 = r^2$ between the SNV being added to the model and the previous SNV held in the model (or zero for the first SNV); # Tests= number of independent tests after accounting for LD between SNVs. For the 35 previously identified loci, LD calculations are shown in Supplemental Table 3 between the QTIGC representative SNV and each of the independent representative SNVs picked by GWiS. LD calculations are performed in the merged ExomeChip and HapMap-imputed ARIC Europeans dataset with 9,537 samples. LD is made bold if >0.5. Loci with no SNPs are those in which no SNPs were significant after multi-test correction.

Supplemental Table 5: Multi-SNV Analysis of the *SCN5A-SCN10A* Locus

Supplemental Table 5A: Significant Coding Variants

Gene	SNV	Chr	Coded/ Noncoded Allele	CAF	Effect in ms	*P*	Function
DLEC1	rs116202356	3	G/A	0.02	2.22	**3E-11**	Nonsynonymous
SCN5A	rs1805124	3	T/C	0.24	0.66	**7E-12**	Nonsynonymous
SCN10A	rs6795970	3	A/G	0.37	-0.67	**3E-17**	Nonsynonymous

Supplemental Table tB: GWiS Results

Nearby Gene	SNV	Chr	SNVs Tested	# Tests	r^2	*P*	Function
SCN5A	rs12053903	3	413	365.3	0.000	**9E-28**	Intronic
SCN5A	rs3922844	3	413	365.3	0.002	**3E-18**	Intronic
SCN10A	rs6795970	3	413	365.3	0.001	**2E-16**	Nonsynonymous
	rs9851724	3	413	365.3	0.010	**9E-12**	Intergenic

Supplemental Table 5A lists the 3 ExomeChip-wide significant coding variants in the *SCN5A-SCN10A* locus from the all ancestries QT association. Supplemental Table 5B contains the result of running GWiS on all 413 variants in the locus from the European ancestry-only QT association. 4 variants representing 4 independent effects in the locus are shown with one of them being represented by a coding variant in *SCN10A*. "r^2" is the correlation between the SNV being added to the model and the previous SNV held in the model (or zero for the first SNV). "# Tests" is the effective number of independent tests in the locus, which is fewer than "SNPs Tested" due to LD between SNVs. Supplemental Table 5A uses data from 95,626 multi-ethnic individuals. Supplemental Table 5B uses data from 83,884 European ancestry individuals.

Supplemental Table 6: Conditional Analyses in ARIC European Ancestry Individuals for ExomeChip SNVs and QTIGC SNPs

	EA Meta-analysis						ARIC					ARIC Conditional Analyses					
Locus Name	EC SNV	EC CAF	EC Beta	QTIGC SNV	QTIGC CAF	QTIGC Beta	EC Beta	EC *P*	QTIGC Beta	QTIGC *P*	LD	EC Beta	EC *P*	QTIGC Beta	QTIGC *P*	Con Survive	Notes
RNF207	rs709209	0.38	1.23	rs846111	0.28	1.73	1.11	**1.65E-06**	1.38	**3.49E-08**	**0.70**	0.16	6.92E-01	1.23	**5.91E-03**	QTIGC	QTIGC signal (also a coding SNV) explains ExomeChip signal
SP3	rs1047640	0.12	0.60	rs938291	0.39	0.53	1.11	**7.61E-04**	0.77	**6.41E-04**	0.22	0.75	**4.37E-02**	0.52	**3.95E-02**	Both	The two signals are independent
TTN-CCDC141	rs72648998	0.05	1.00	rs7561149	0.42	-0.52	1.29	**4.72E-03**	-0.12	5.76E-01	0.04	1.30	**5.50E-03**	0.01	9.65E-01	Inconclusive	QTIGC signal not present in ARIC before the conditional analysis
SMARCAD1	rs7439869	0.38	0.41	rs3857067	0.46	-0.51	0.63	**4.30E-03**	-0.65	**3.13E-03**	**0.54**	0.33	3.12E-01	-0.41	2.06E-01	Inconclusive	Variants may tag the same haplotype, possibly a third variant is causal
GMPR	rs1042391	0.55	-0.42	rs7765828	0.40	0.55	-0.50	**2.33E-02**	0.52	**1.84E-02**	**0.99**					Inconclusive	Variants are equivalent due to high LD
KCNH2	rs1805123	0.21	-1.47	rs2072413	0.27	-1.68	-1.32	**2.51E-07**	-1.43	**6.39E-09**	**0.82**	0.17	7.82E-01	-1.58	**7.27E-03**	QTIGC	QTIGC intronic signal explains ExomeChip signal
ATP2A2	rs11068997	0.04	-0.94	rs3026445	0.36	0.62	-0.07	9.05E-01	0.46	**4.57E-02**	0.02	0.11	8.67E-01	0.46	**4.54E-02**	Inconclusive	ExomeChip signal not present in ARIC before the conditional analysis

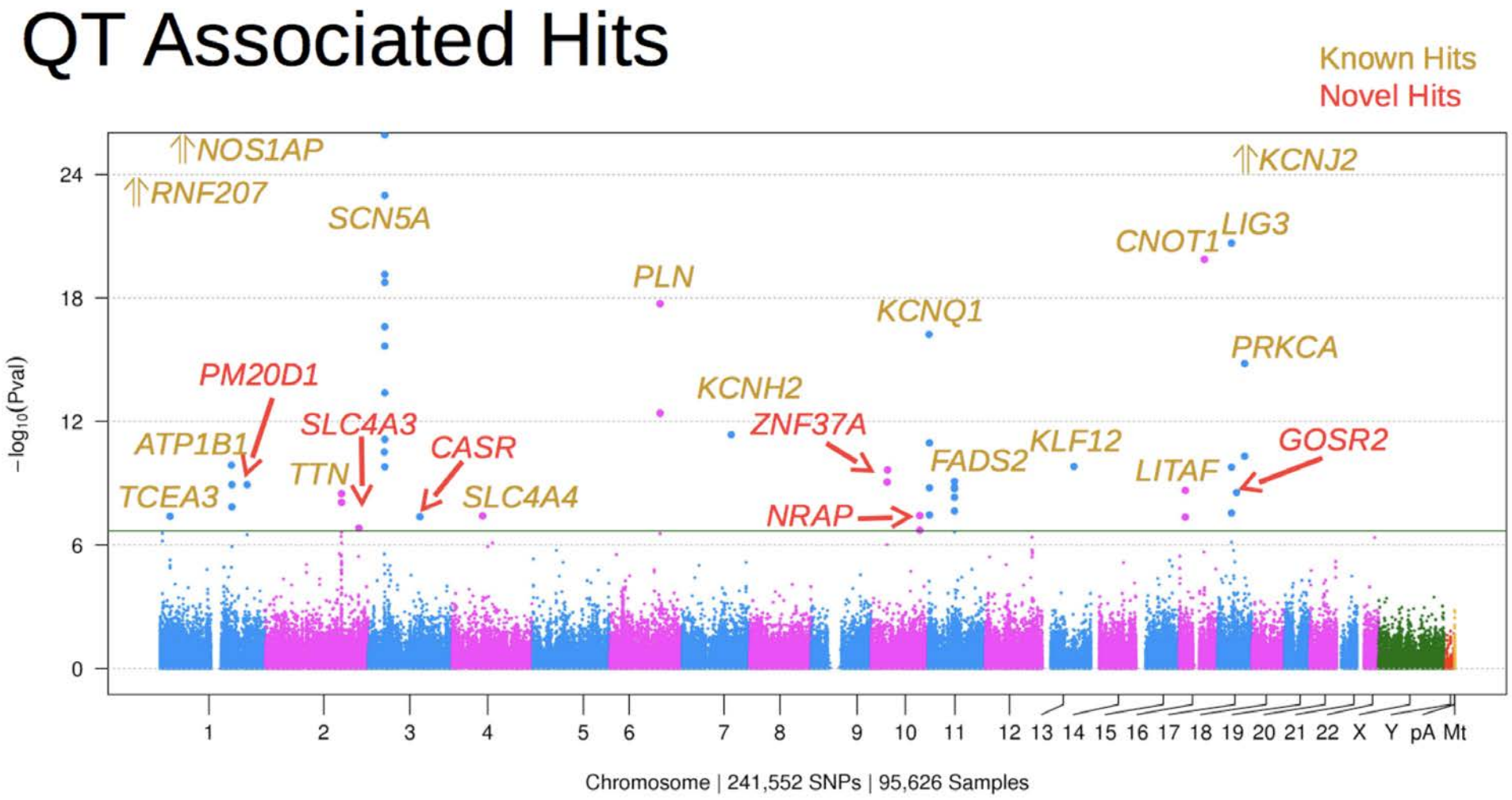
Conditional analyses demonstrate that the coding variant in *SP3* is independent of the top noncoding SNV at this locus discovered from QT-IGC, implicating this gene in QT interval modulation. For *GMPR*, the coding variant is in almost perfect linkage disequilibrium with the noncoding QT-IGC variant (r^2=0.99 in ARIC), suggesting that the coding variant may be the causal variant explaining the QT-IGC signal. For a third locus, *RNF207*, while conditional analysis suggested that the QT-IGC SNV accounts for the association at this locus, both the top QT-IGC SNV as well as the top SNV from this study are coding variants in high LD, thus implicating the *RNF207* gene in myocardial repolarization. For the remaining 4 loci, one coding variant is associated due to the stronger noncoding QT-IGC signal (*KCNH2*); two were not properly tested due to no effect in ARIC of the ExomeChip variant (*ATP2A2*) or the QT-IGC variant (*TTN*), though there was low LD (r^2<0.04) between the coding and non-coding variants, suggesting independence; and 1 was unclear (*SMARCAD1*), as putting both SNPs in the model significantly altered the beta estimates for both SNPs.

EC=ExomeChip (this study); The “Con Survive” column indicates if the ExomeChip SNV or QTIGC SNP or both have effect size estimates that remain unchanged in the conditional model. LD calculations are performed in the merged ExomeChip and HapMap-imputed most likely genotype ARIC Europeans dataset with 9,537 samples. Conditional analyses were run in the same ARIC Europeans dataset, however limited to 9,005 individuals due to phenotype exclusions. Effect sizes (Beta) are in milliseconds.

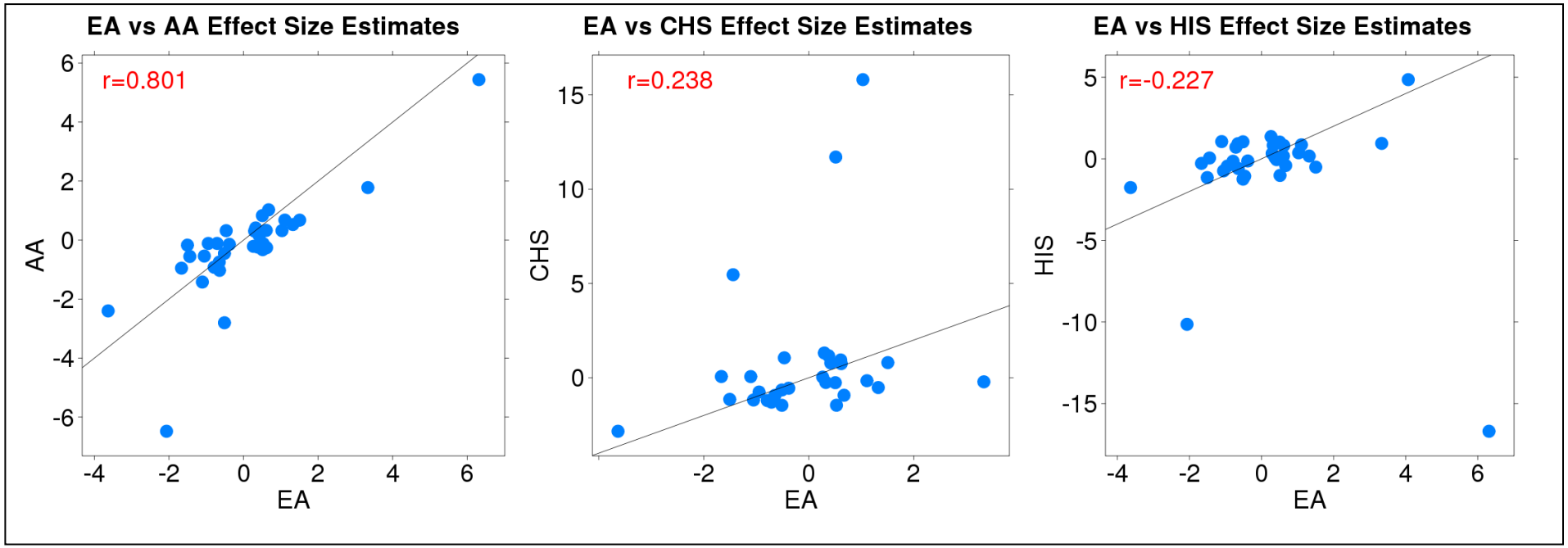
Supplemental Table 7: DEPICT Loci Description

SNV	Chr	Locus Start	Locus Stop	Nearest Genes	Genes in Locus
rs1042391	6	16,205,060	16,295,589	ENSG00000137198	ENSG00000137198
rs1047640	2	174,739,352	174,820,900	ENSG00000172845	ENSG00000172845
rs1077514	1	23,735,241	23,823,798	ENSG00000088280	ENSG00000088280;ENSG00000204219
rs10919071	1	169,088,679	169,429,035	ENSG00000143153	ENSG00000143153;ENSG00000143156
rs11068997	12	110,298,498	111,171,342	ENSG00000139437;ENSG00000139436	ENSG00000122970;ENSG00000122986
rs11153730	6	118,561,348	119,027,325	ENSG00000196376	ENSG00000198523;ENSG00000196376
rs11704	14	102,808,330	102,974,999	ENSG00000022976	ENSG00000156381;ENSG00000022976
rs12053903	3	38,575,865	38,601,556	ENSG00000183873	ENSG00000157036;ENSG00000183873
rs12143842	1	162,014,632	162,053,060	ENSG00000198929	ENSG00000198929
rs1361754	1	205,676,088	205,809,642	ENSG00000162877	ENSG00000117280;ENSG00000069275
rs1535	11	61,543,499	61,623,140	ENSG00000149485;ENSG00000134824	ENSG00000168496;ENSG00000149485
rs17608766	17	45,013,238	45,054,564	ENSG00000108433	ENSG00000108433
rs17779747	17	68,411,445	68,515,552	ENSG00000123700	
rs17831160	8	98,994,459	99,046,298	ENSG00000156482;ENSG00000132561	ENSG00000156482;ENSG00000132561
rs1801725	3	121,993,247	122,130,141	ENSG00000036828	ENSG00000036828;ENSG00000114023
rs1805123	7	150,600,845	150,657,209	ENSG00000055118	ENSG00000055118
rs1886512	13	74,511,991	74,558,505	ENSG00000118922	ENSG00000118922
rs2074238	11	2,482,918	2,485,092	ENSG00000053918	ENSG00000053918
rs2074518	17	33,313,729	33,440,166	ENSG00000005156	ENSG00000092871;ENSG00000005156
rs2276853	3	46,982,737	47,583,156	ENSG00000227398;ENSG00000088727	ENSG00000227398;ENSG00000181555
rs2540226	2	39,884,712	40,062,975	ENSG00000138050	ENSG00000152154;ENSG00000138050
rs2926707	8	71,042,430	71,340,989	ENSG00000140396	ENSG00000213003;ENSG00000140396
rs2926743	12	56,983,252	57,212,827	ENSG00000196531	ENSG00000198056;ENSG00000076067
rs30208	16	14,405,892	14,440,874	ENSG00000186260	
rs3189030	10	115,350,100	115,484,660	ENSG00000197893	ENSG00000165806;ENSG00000197893
rs3807989	7	116,073,567	116,225,704	ENSG00000105974	ENSG00000105971;ENSG00000105974
rs4835768	5	137,179,924	137,544,397	ENSG00000112981	ENSG00000120729;ENSG00000031003
rs6762208	3	185,289,989	185,353,235	ENSG00000163904	ENSG00000163904
rs709209	1	6,272,137	6,305,053	ENSG00000158286	ENSG00000225077;ENSG00000116237
rs7188697	16	58,543,746	58,668,652	ENSG00000125107	ENSG00000103037;ENSG00000103034
rs727957	21	35,853,176	35,883,030	ENSG00000180509	ENSG00000180509
rs737154	5	1,028,876	1,094,389	ENSG00000113504	ENSG00000113504;ENSG00000145506
rs7439869	4	95,012,684	95,334,650	ENSG00000163104	ENSG00000163106;ENSG00000163104
rs7689609	4	72,083,058	72,299,192	ENSG00000080493	ENSG00000080493
rs8042919	15	50,847,978	51,103,393	ENSG00000092439	ENSG00000092439;ENSG00000138600
rs8049607	16	11,689,015	11,693,536	ENSG00000189067	
rs9470361	6	36,613,812	36,647,289	ENSG00000164530	ENSG00000164530;ENSG00000124762
rs9912468	17	64,197,259	64,331,037	ENSG00000154229	ENSG00000154229;ENSG00000091583

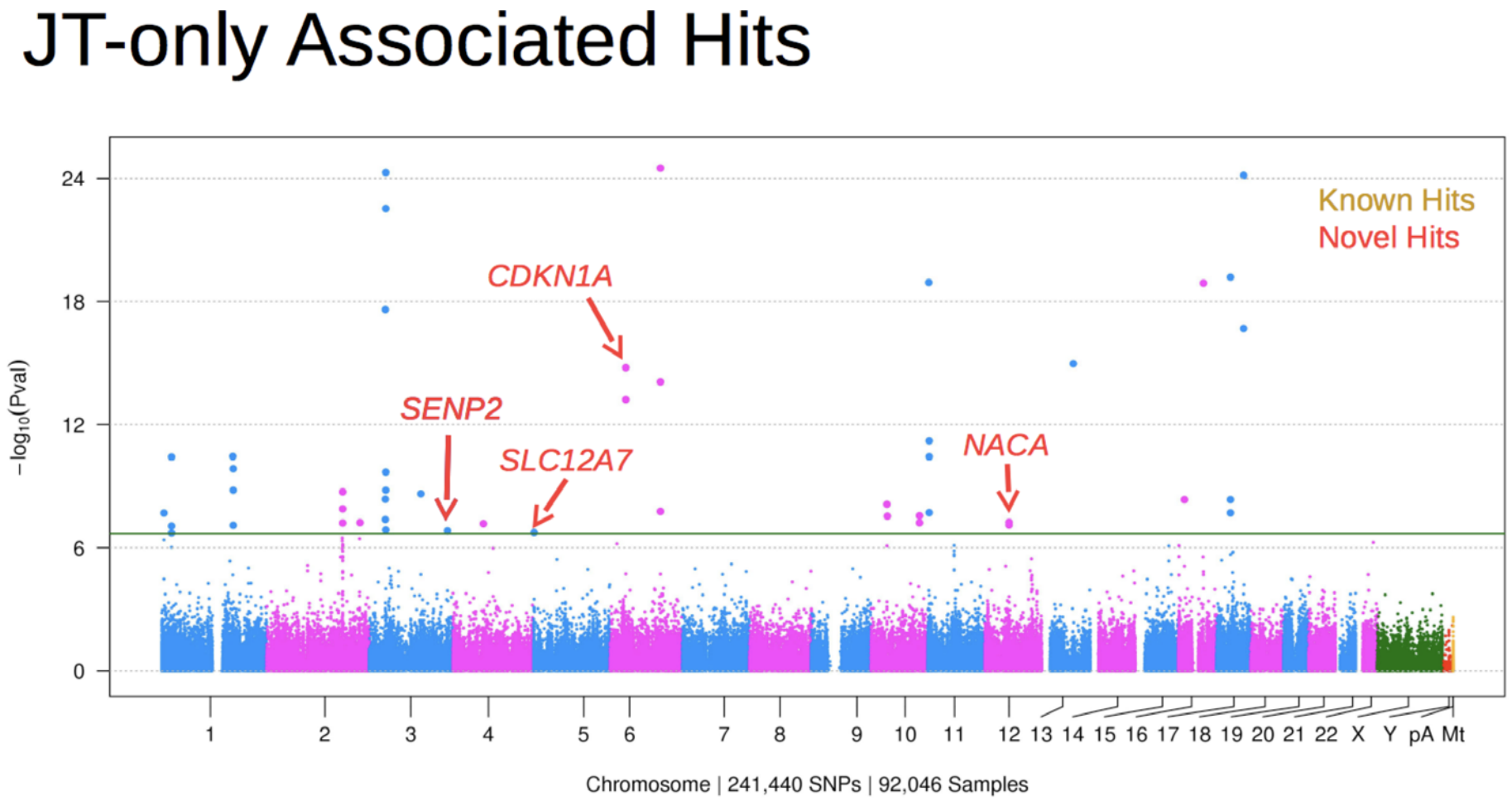
Supplemental Figure 1: Manhattan Plot of QT Associated Hits. Significance level ($-\log_{10}(P)$) for each tested variant from single variant statistical models is plotted by genomic location. Loci of interest are labeled by nearby gene. Figure truncated at $-\log_{10}(P)=24$.



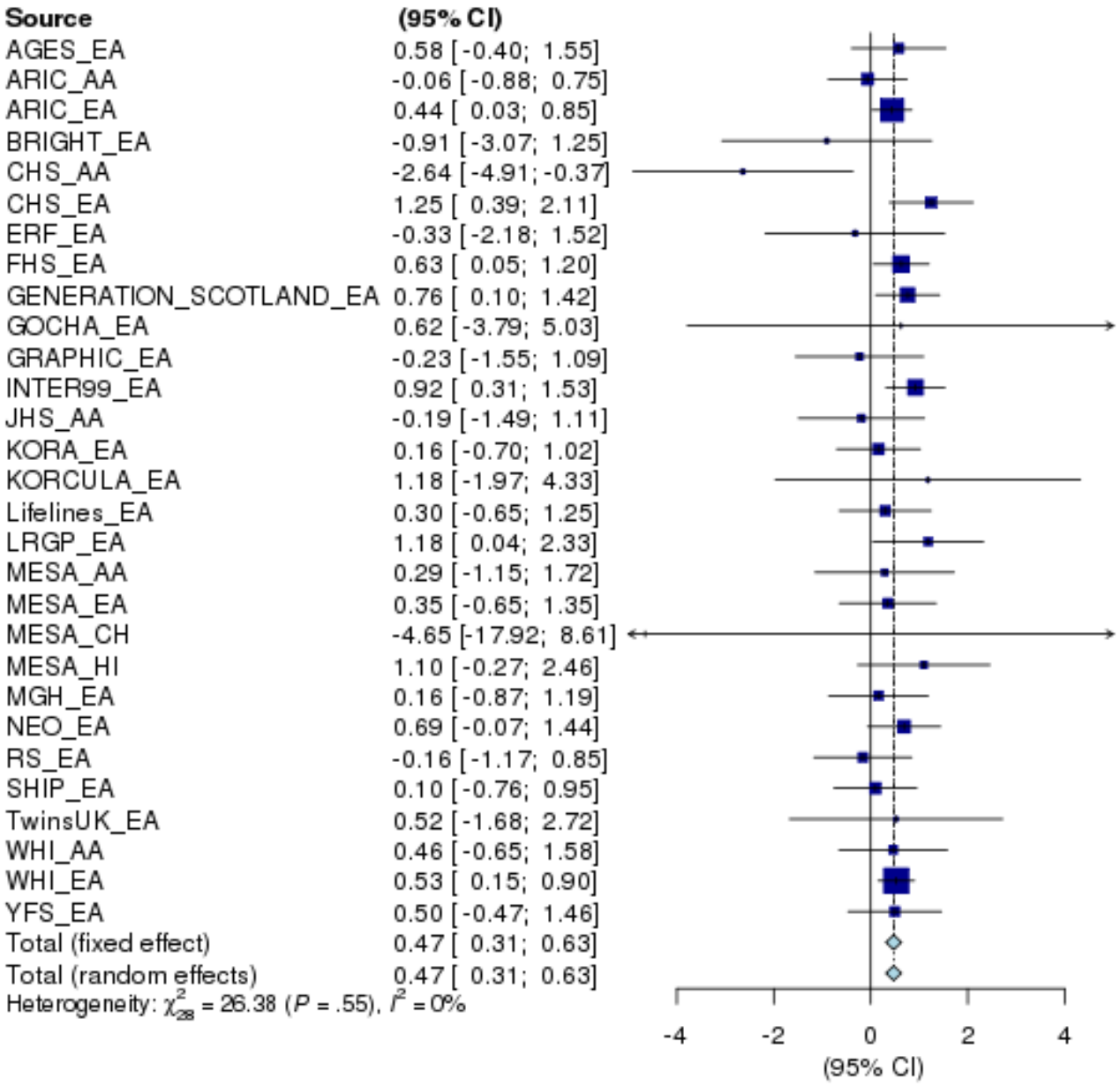
Supplemental Figure 2: Correlation of Effect Estimates between Ethnic Groups. Correlation of effect estimates (Beta) between European Ancestry (EA) individuals and African American (AA) individuals (left panel) Hispanic (HIS) individuals (center panel) and Chinese (CHS) individuals (right panel). Effect estimates are in milliseconds. The line is the 45 degree identity line.



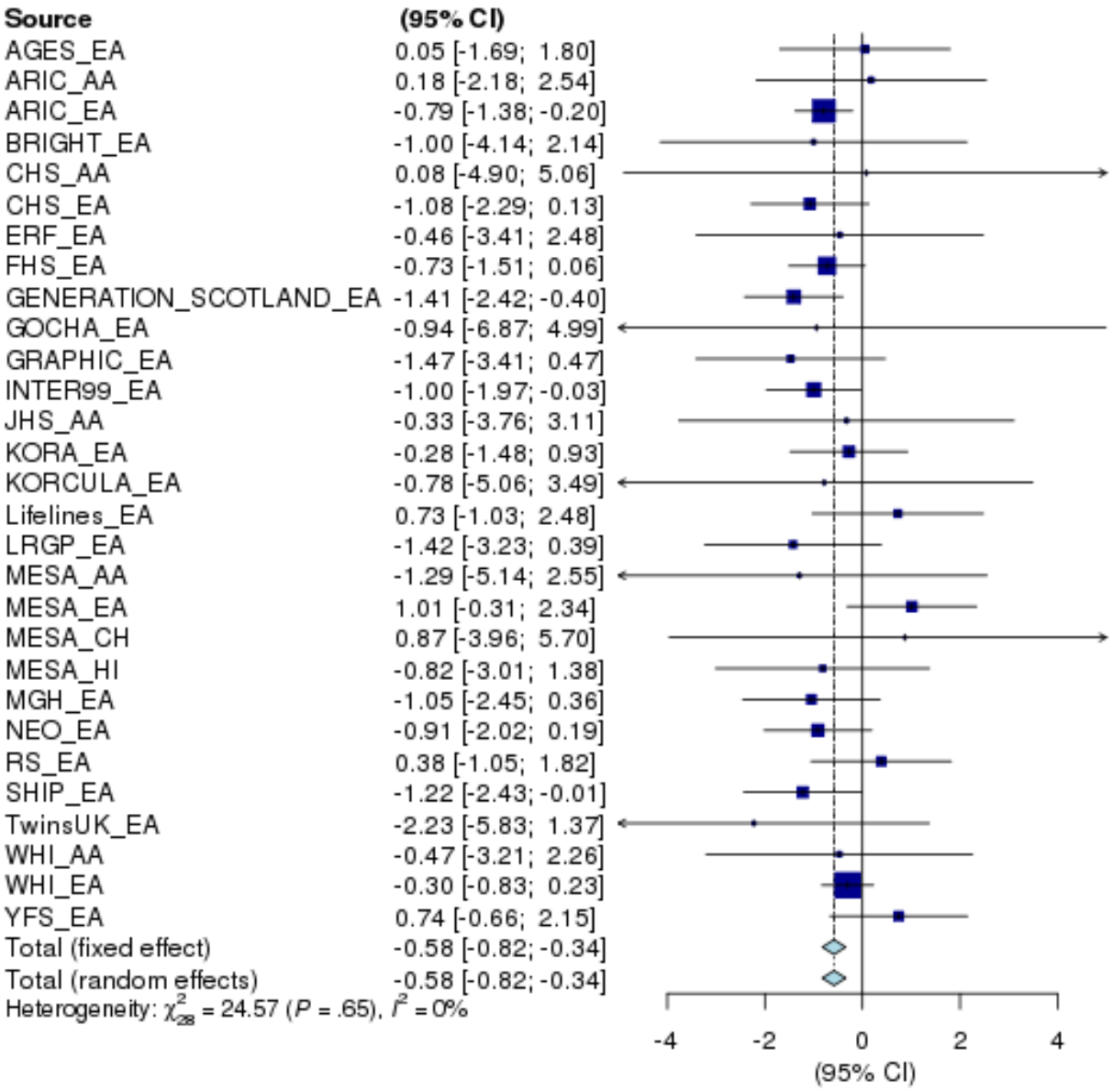
Supplemental Figure 3: **Manhattan plot of JT-only Associated Hits.** Significance level ($-\log_{10}(P)$) for each tested variant from single variant statistical models is plotted by genomic location. Loci of interest are labeled by nearby gene. Figure truncated at $-\log_{10}(P)=24$. Only non-QT associated loci labeled.



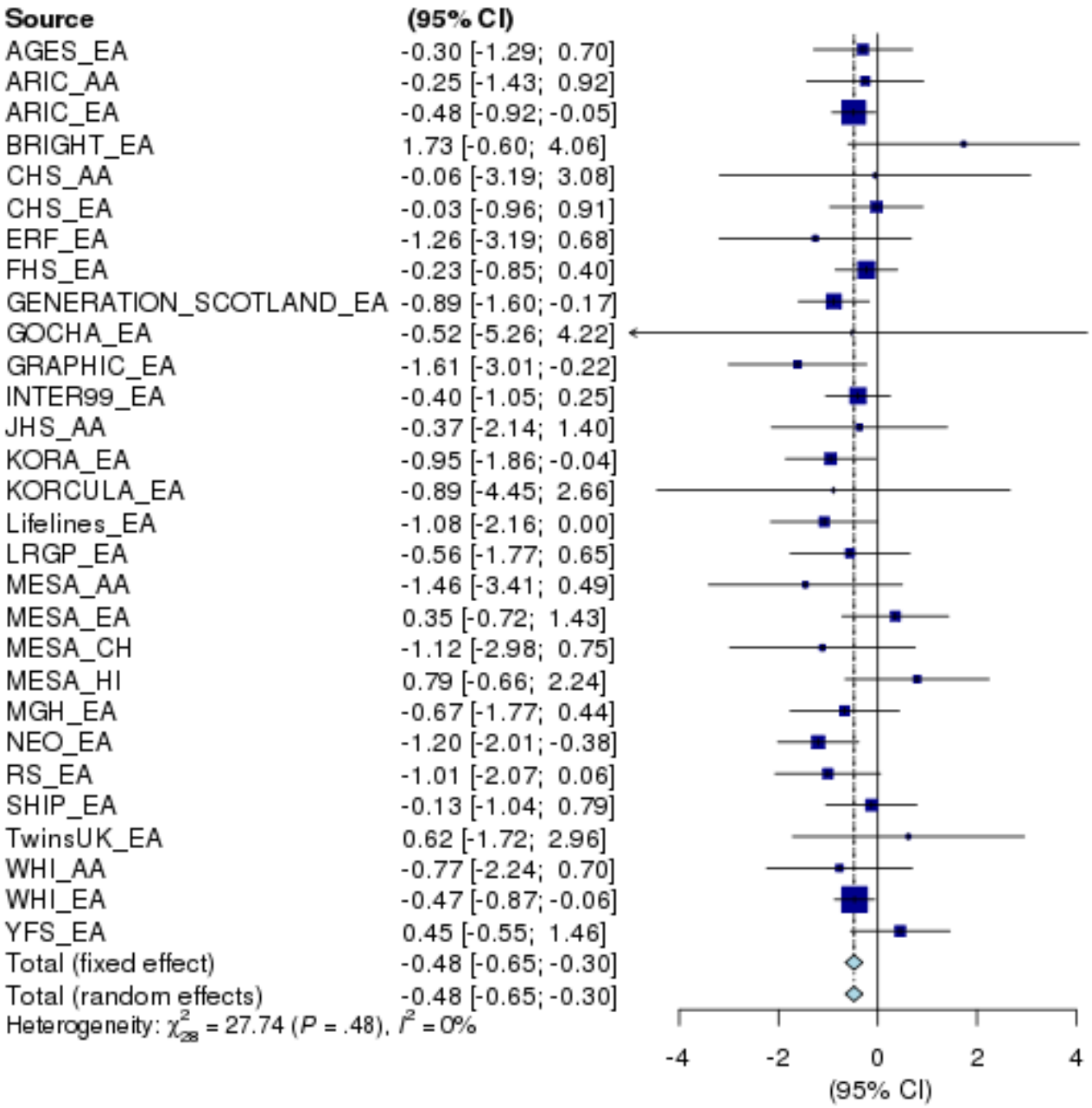
Supplemental Figure 4: Forest Plot of rs1361754 Association with QT interval.



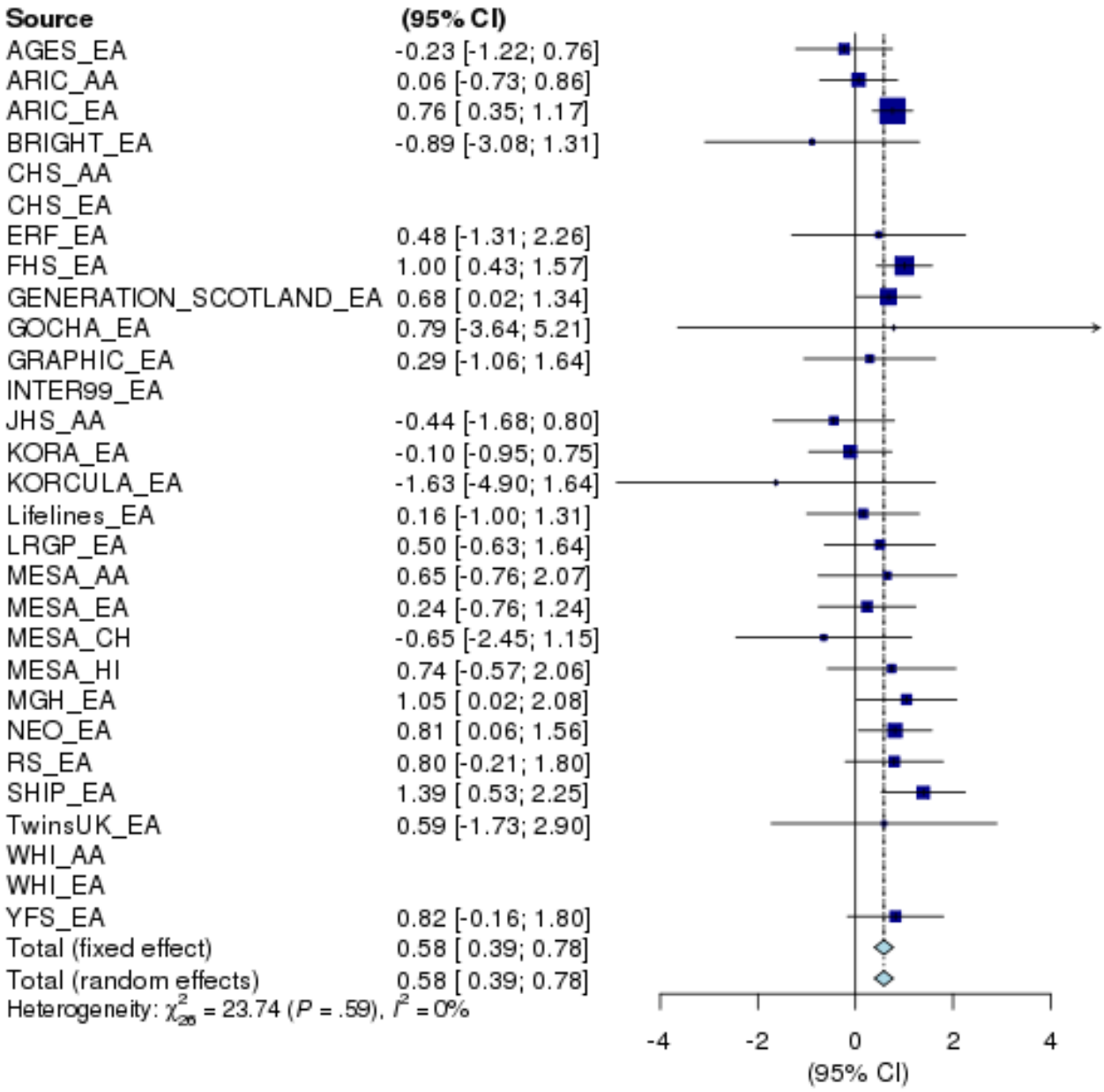
Supplemental Figure 5: Forest Plot of rs1801725 Association with QT interval.



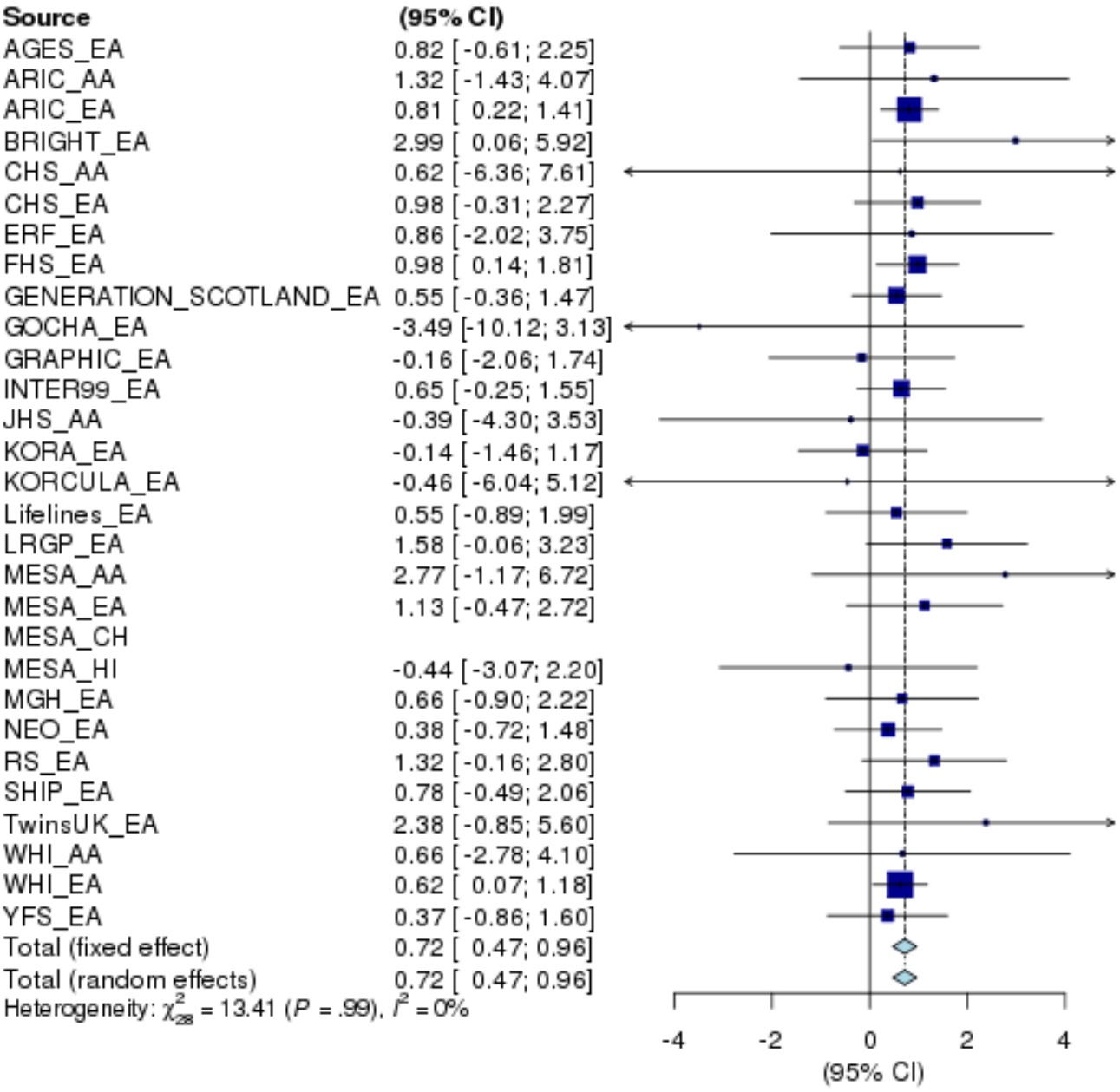
Supplemental Figure 6: Forest Plot of rs3189030 Association with QT interval.



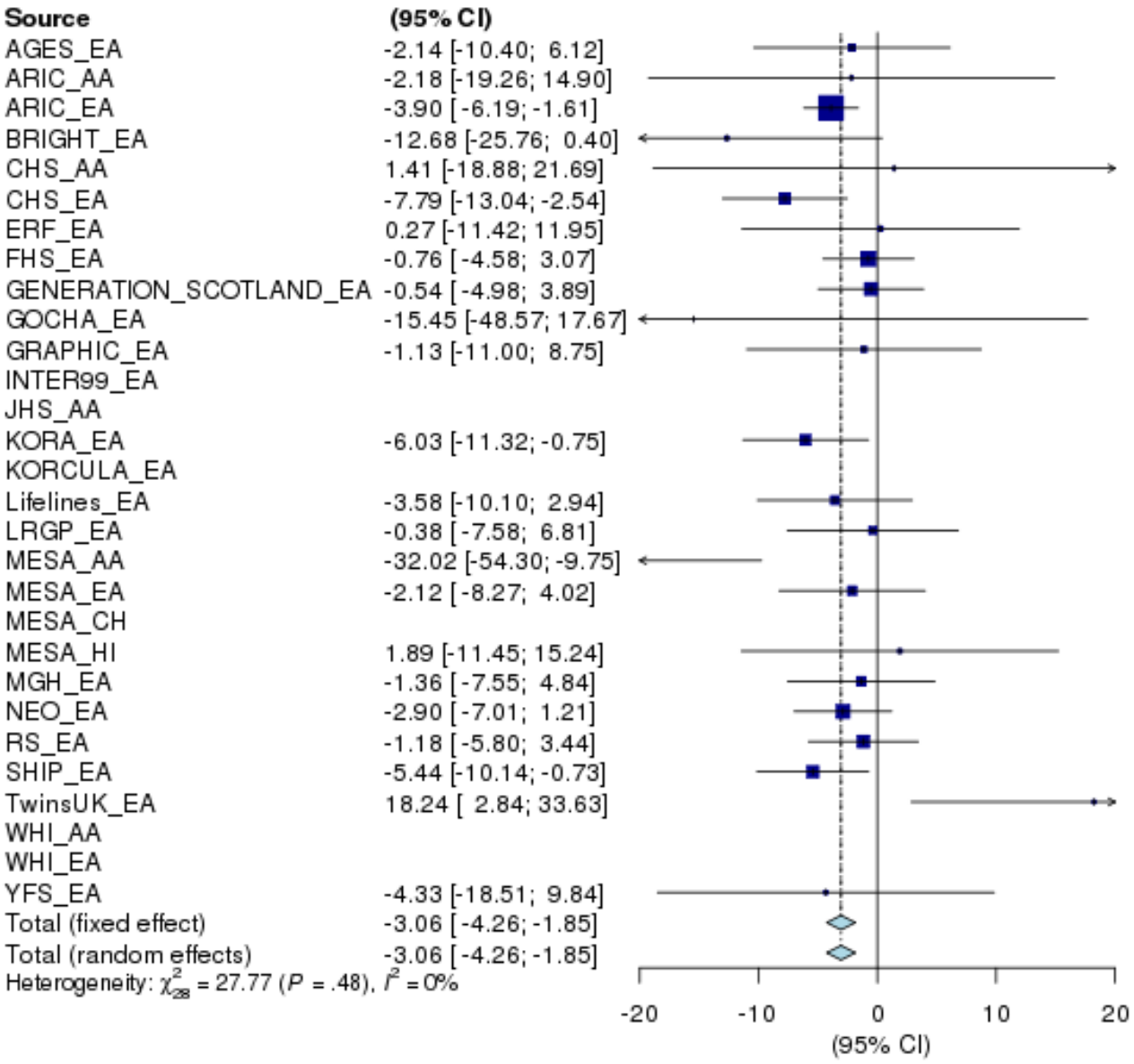
Supplemental Figure 7: Forest Plot of rs4934956 Association with QT interval.



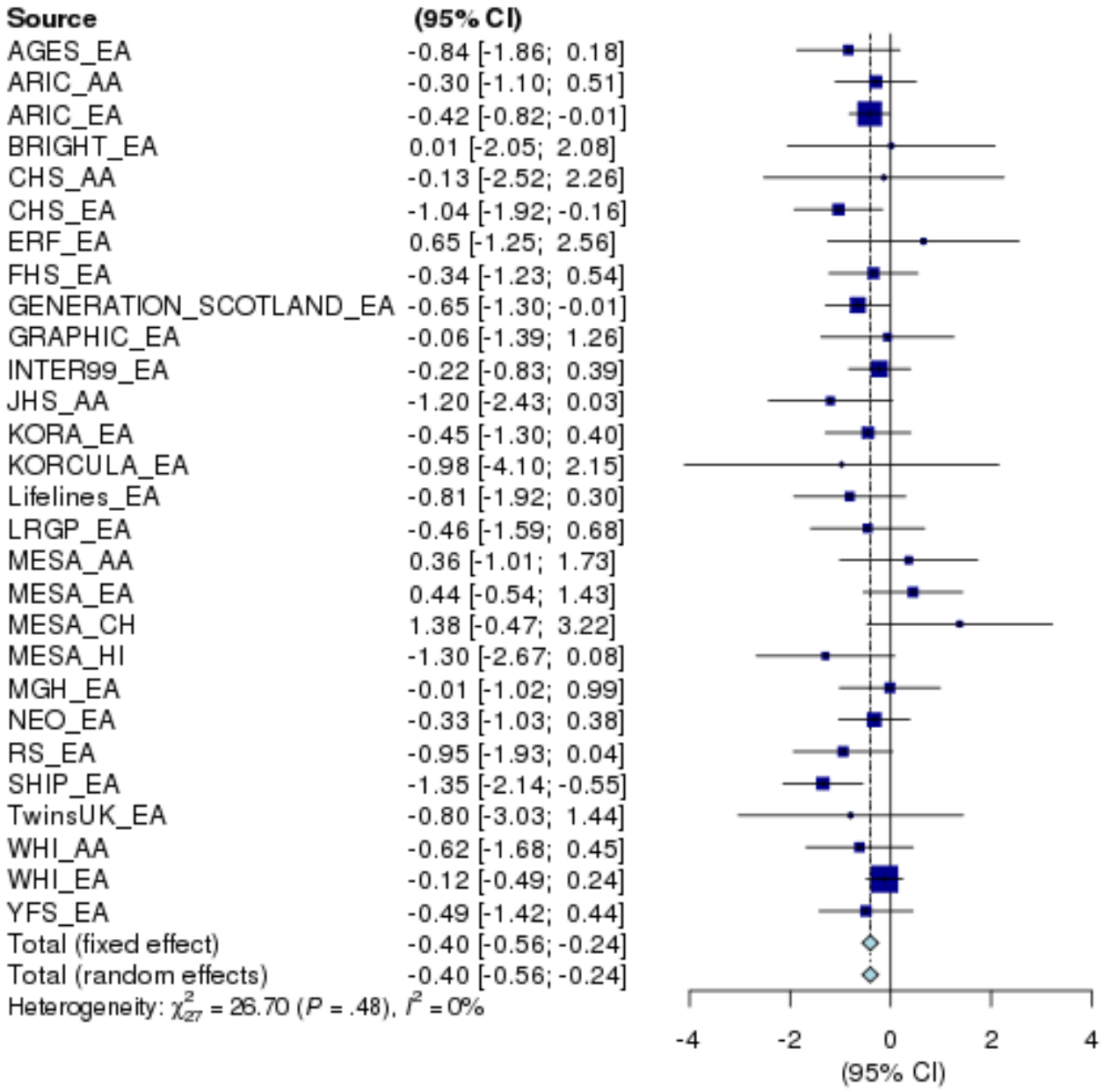
Supplemental Figure 8: Forest Plot of rs17608766 Association with QT interval.



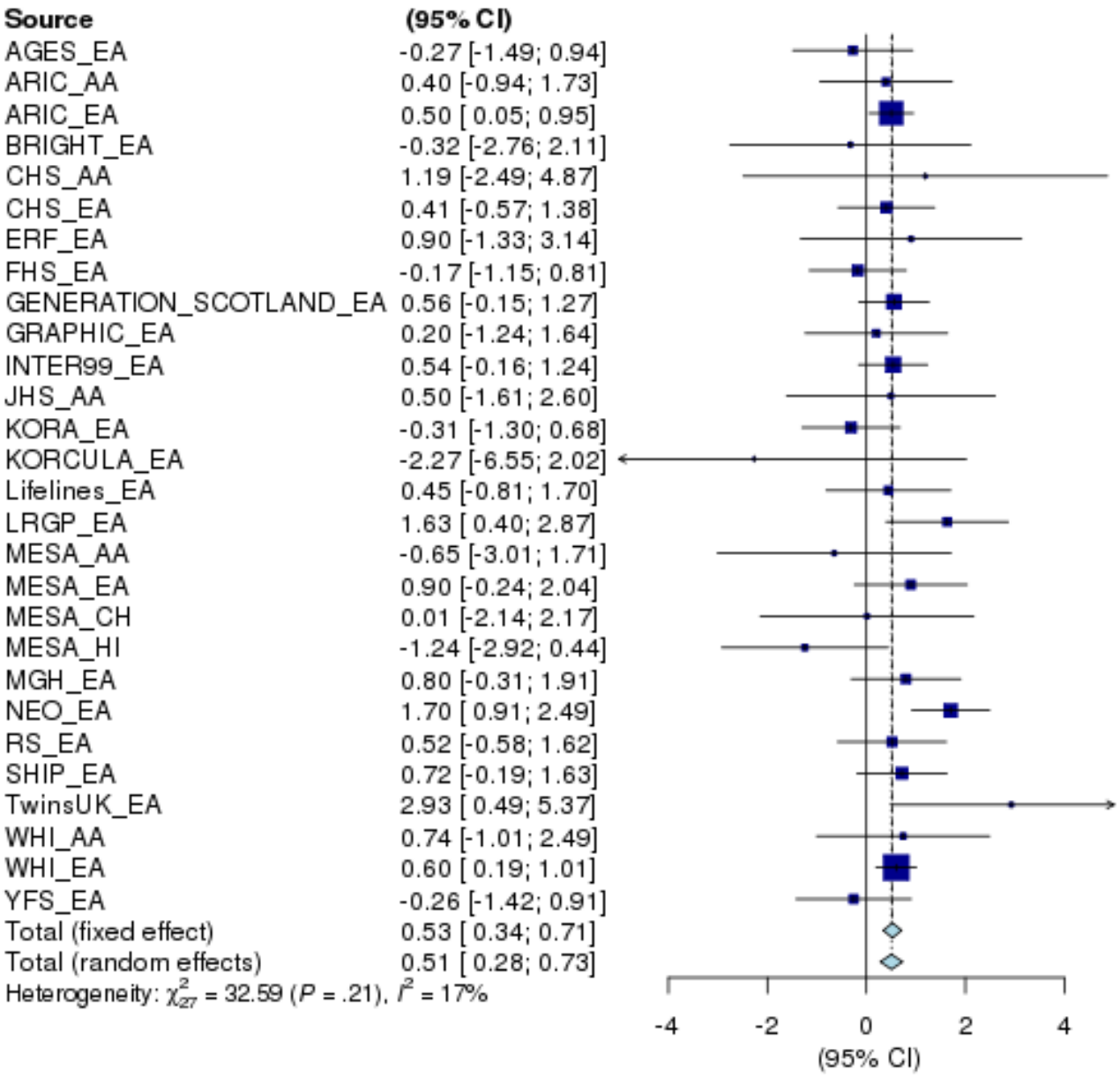
Supplemental Figure 9: Forest Plot of rs55910611 Association with QT interval.



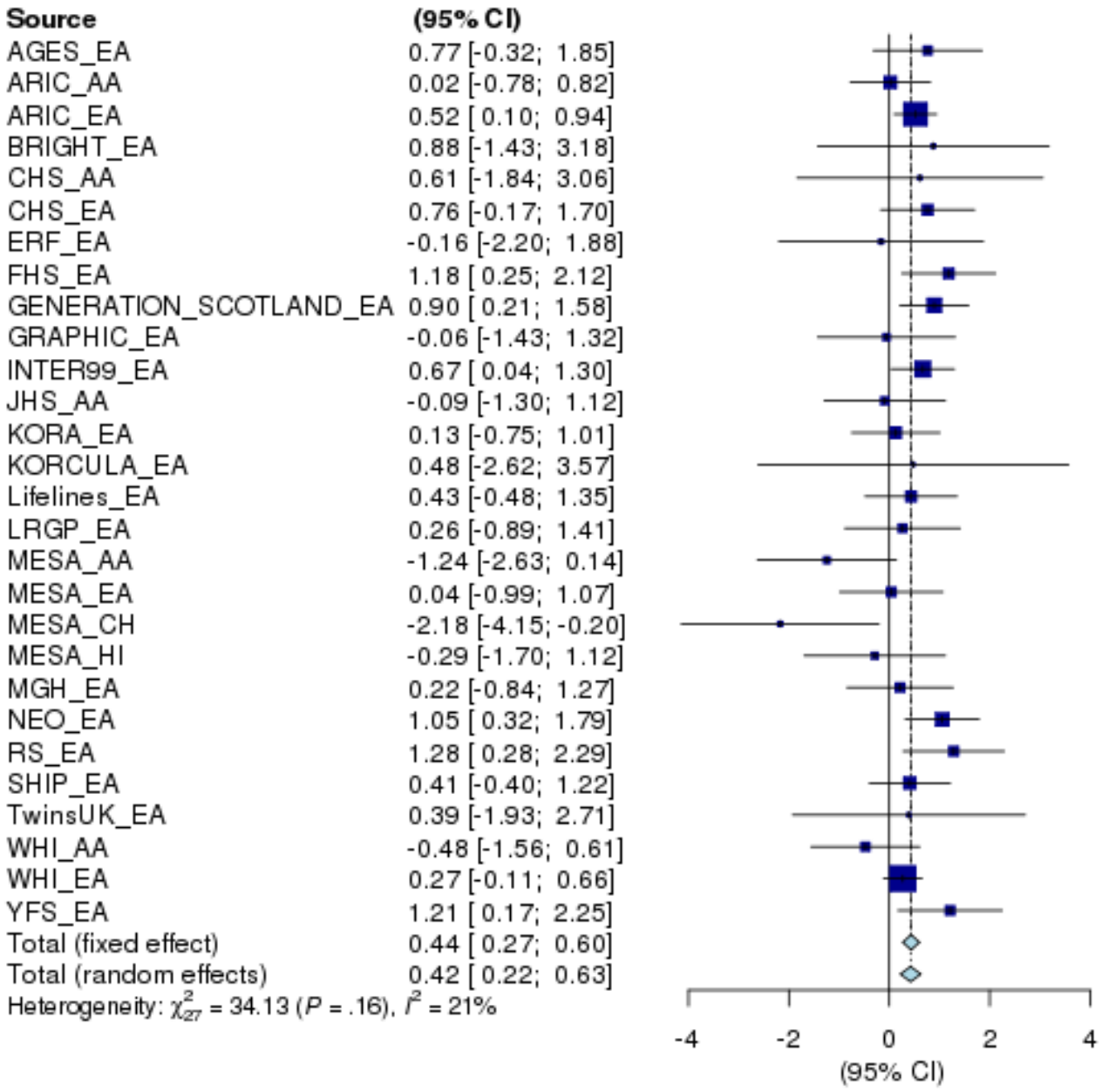
Supplemental Figure 10: Forest Plot of rs737154 Association with JT interval.



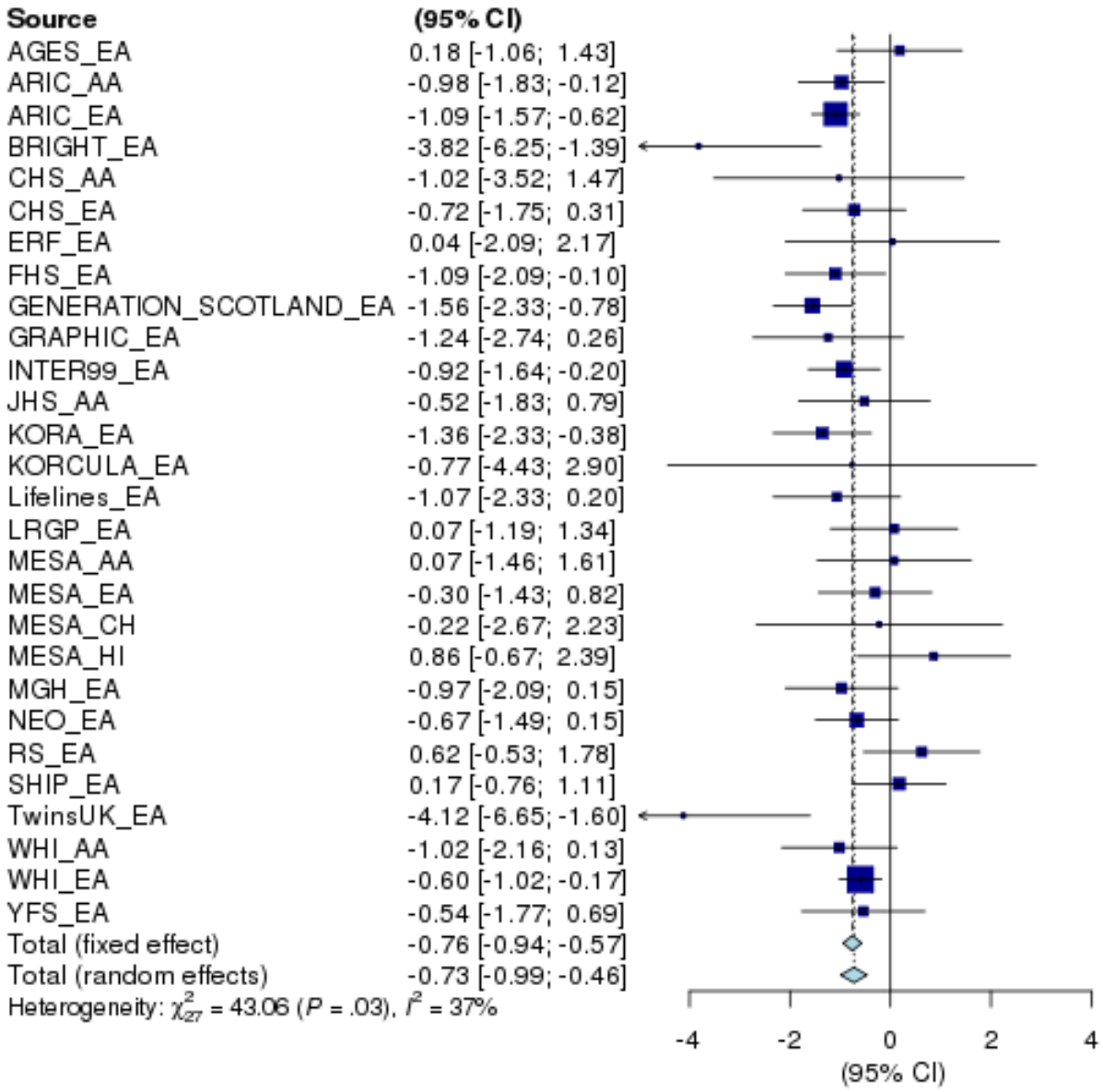
Supplemental Figure 11: Forest Plot of rs2926743 Association with JT interval.



Supplemental Figure 12: Forest Plot of rs6762208 Association with JT interval.



Supplemental Figure 13: Forest Plot of rs9470361 Association with JT interval.



This is an overview of an article entitled "ExomeChip-Wide Analysis of 95,626 Individuals Identifies 10 Novel Loci Associated with QT and JT Intervals", published in the January 2018 issue of *Circulation: Genomic and Precision Medicine*.

The electrocardiographic QT interval spans from the beginning of the QRS complex to the end of the T wave, as shown in the schematic here. The QT interval is measured in order to assess the length of duration of ventricular repolarization. Abnormality of the QT interval in either direction, too long or too short, predisposes to arrhythmias and sudden cardiac death. The JT interval, as shown here, is a more precise measure of ventricular repolarization since it subtracts the QRS interval, which is when ventricular depolarization occurs, from the QT interval.

To assess for genetic factors that contribute to clinical traits, genetic association studies are performed. The most commonly done association study has been the genome-wide association study, or GWAS, which assesses common DNA variants throughout the genome for strength of association with the phenotype of interest. These common variants are for the most part noncoding variants. More recently, exome chips that can directly interrogate coding variants in genes have become available. While the exome chips do cover some noncoding variants, they are very comprehensive with respect to coding variants, covering all coding variants that were found in at least 3 individuals out of 12,000 individuals who had undergone exome sequencing. This comprises almost 200,000 coding variants in more than 17,000 genes.

The authors of the paper under discussion performed an exome chip genotyping association study in more than 95,000 individuals, most of whom were of European descent, although several other ethnicities were represented in smaller numbers. The rationale for using the exome chip is that GWASs tend to identify noncoding variants that often do not pinpoint specific genes, since noncoding variants can affect genes at a large distance, meaning that each GWAS hit might implicate numerous candidate genes in the vicinity of the locus. In contrast, exome chip studies tend to identify coding variants within genes, which implicate those specific genes as the causal genes.

Here are the results of the exome chip analysis with the QT interval. In this graph, the x-axis is the position in the genome, split into different chromosomes, and the y-axis is the strength of association. The green line indicates a stringent threshold for statistical significance, taking into account the hundreds of thousands of variants tested in the study. Many known loci implicated by previous association studies were validated in this study, indicated in yellow. In red are genes or loci being linked to the QT interval for the first time in this study.

Here are the genes or loci associated with the JT interval but not the QT interval. There were no prior loci linked only to the JT interval. This study found 4 novel genes or loci, indicated in red.

There were several key findings in this study. First, the exome chip analysis identified coding variants in two notable genes as being linked to the QT interval, *SCN10A* and *KCNQ1*. Both have previously been linked to cardiac repolarization—*SCN10A* to Brugada syndrome by GWAS, and *KCNQ1* is the well-established causal gene for long QT syndrome type 1. [pause] Second, the study found 4 hits associated only with the JT interval. Third, functional annotation of the various exome chip hits identified several known pathways—potassium, sodium, or calcium ion regulation, and autonomic control—and new pathways—the physical force of contraction of cardiomyocytes, as well as conduction of the electrical signal between cardiomyocytes.

In conclusion, this study identified a total of 10 new loci associated with the QT and/or JT interval. The exome chip analysis pinpointed variants in 17 genes, 7 of which are in new loci. These findings validated previously identified molecular pathways involved in cardiac repolarization and nominated new pathways. Finally, by identifying hits linked to the JT interval but not the QT interval, this study suggests that different genetic factors might influence the depolarization and repolarization phases of the ventricles. Together, these findings shed new light on normal cardiac electrophysiology, diseases with repolarization abnormalities, and potential treatments for the diseases.