Supplemental Material for:

Large-scale pharmacogenomic study of sulfonylureas and the QT, JT, and QRS intervals: CHARGE Pharmacogenomics Working Group

I) DESCRIPTION OF COHORTS

Age, Gene/Environment Susceptibility – Reykjavik Study (AGES): The Reykjavik Study cohort originally was composed of a random sample of 30,795 men and women born in 1907-1935 and living in Reykjavik in 1967.[1] A total of 19,381 attended, resulting in 71% recruitment rate. The study sample was divided into six groups by birth year and birth date within month. One group was designated for longitudinal follow-up and was examined in all stages. Another group was designated a control group and was not included in examinations until 1991. Other groups were invited to participate in specific stages of the study. Between 2002 and 2006, the AGES-Reykjavik study re-examined 5,764 survivors of the original cohort who had participated before in the Reykjavik Study.

Atherosclerosis Risk in Communities (ARIC) Study: The ARIC study is an ongoing population-based cohort of 15,792 predominantly Caucasian and African-American males and females aged 45-64 years at baseline and selected using probability sampling from four United States communities (Forsyth County NC, Jackson MS, suburban Minneapolis MN, and Washington County MD).[2] Participants were recruited in 1987-1989 to examine cardiovascular and pulmonary disease, patterns of medical care, and disease variation over time. Standardized physical examinations and interviewer-administered questionnaires were conducted at baseline (1987-1989), and at three triennial follow-up examinations (1990-1998).

Cardiovascular Health Study (CHS): The CHS is a population-based cohort study of risk factors for CHD and stroke in adults ≥65 years conducted across four field centers.[3] The original predominantly Caucasian 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 was enrolled for a total sample of 5,888. DNA was extracted

from blood samples drawn on all participants at their baseline examination in 1989-90. In 2007-2008, genotyping was performed at the General Clinical Research Center's Phenotyping/Genotyping Laboratory at Cedars-Sinai using the Illumina 370CNV BeadChip system on 3,980 CHS participants who were free of CVD at baseline, consented to genetic testing, and had DNA available for genotyping.

Health, Aging, and Body Composition Study (Health ABC): The Health ABC Study is a NIA-sponsored cohort study of the factors that contribute to incident disability and the decline in function of healthy older persons, with a particular emphasis on changes in body composition in old age. Between 4/15/97 and 6/5/98 the Health ABC study has recruited 3,075 70-79 year old community-dwelling adults (41% African-American), who were initially free of mobility and activities of daily living disability. The key components of Health ABC include a baseline exam, annual follow-up clinical exams, and phone contacts every 6 months to identify major health events and document functional status between clinic visits. Provision has been made for banking of blood specimens and extracted DNA (Health ABC repository).

Hispanic Community Health Study / Study of Latinos (HCHS/SOL): The Hispanic Community Health Study/Study of Latinos (HCHS/SOL) is a community based cohort study of 16,415 self-identified Hispanic/Latino persons aged 18-74 years from randomly selected households in four U.S. field centers (Chicago, IL; Miami, FL; Bronx, NY; San Diego, CA) with baseline examination (2008 to 2011) and yearly telephone follow-up assessment for at least three years.[4] The two-stage sampling design selected households within census block groups. Households with Hispanic/Latino surnames and individuals over 45 years of age were oversampled to achieve increased representation of Hispanic/Latino individuals with a uniform age distribution. Due to this study design, sampling weights that reflect the probability of sampling individuals to the study were calculated for all individuals. These sampling weights were used in downstream

analyses to protect against potential selection bias arising from the sampling scheme. The HCHS/SOL cohort includes participants who self-identified as having Hispanic/Latino background, the largest groups being Central American, Cuban, Dominican, Mexican, Puerto-Rican, and South American. The HCHS/SOL study was approved by institutional review boards at participating institutions, and written informed consent was obtained from all participants. 12,803 individuals were successfully genotyped on an Illumina Omni 2.5M array, and the genotype and phenotype data are posted on dbGaP (accession numbers phs000880.v1.p1 and phs000810.v1.p1).

Jackson Heart Study (JHS): The JHS is a single-site, prospective, population-based study designed to explore the environmental, behavioral, and genetic factors that influence the development of cardiovascular disease (CVD) among African Americans. A total of 5,301 women and men between the ages of 21 and 94 were recruited between September 2000 and May 2004 from a tri-county area of Mississippi: Hinds, Madison, and Rankin Counties. Participants were recruited from four sources, including (1) randomly sampled households from a commercial listing; (2) ARIC study participants; (3) a structured volunteer sample that was designed to mirror the eligible population; and (4) a nested family cohort. Of the enrolled participants, 3,630 were recruited uniquely to JHS and did not participate in ARIC. Overviews of the JHS including the sampling and recruitment, sociocultural, and laboratory methods have been described previously.[5] All of the participants provided written informed consent. Participants were between 35 and 84 years old at first visit, and members of the family cohort were ≥ 21 years old when consent for genetic testing was obtained and blood was drawn for DNA extraction. The details of first clinic visit procedures, including supine 12-lead digital electrocardiography (ECG), venipuncture, and other testing, have been previously described. The definitions of co-morbidities as well as the details of ECG measurements and medication collection and coding have also been reported.[6, 7]

Multi-Ethnic Study of Atherosclerosis (MESA): MESA 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. MESA researchers study a diverse, population-based sample of 6,814 asymptomatic men and women aged 45-84. 38 percent of the recruited participants are white, 28 percent African-American, 22 percent Hispanic, and 12 percent Asian, predominantly of Chinese descent.[8] Participants were recruited from six field centers across the United States. Two physical examinations (at baseline-1st and at 5th time points) were conducted since the electrocardiography was taken only at baseline and at 5th time points. The tenets of the Declaration of Helsinki were followed and institutional review board approval was granted at all MESA sites. Written informed consent was obtained from each participant.

The Netherlands Epidemiology of Obesity (NEO) study: The NEO study 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.

Prospective Study of Pravastatin in the Elderly at Risk (PROSPER): A detailed description of the PROSPER study has been published elsewhere.[9, 10] PROSPER was a prospective multicenter randomized placebo-controlled trial to assess whether treatment with pravastatin diminishes the risk of major vascular events in elderly. Between December 1997 and May 1999, we screened and enrolled subjects in Scotland (Glasgow), Ireland (Cork), and the Netherlands (Leiden). Men and women aged 70-82 years were recruited if they had pre-existing vascular disease or increased risk of such disease because of smoking, hypertension, or diabetes. A total number of 5,804 subjects were randomly assigned to pravastatin or placebo. A large number of prospective tests were performed including Biobank tests and cognitive function measurements.

Rotterdam Study (RS): The RS is a prospective population based cohort study comprising 7,983 participants aged 55 years or older (RS1), which started in 1990. In 2000-2001, an additional 3,011 individuals aged 55 years or older were recruited (RS2).[11] At baseline, participants were interviewed at home and were examined at the research center, which included a 10 second, 12-lead electrocardiogram (ECG). Since then, participants are followed continuously and re-examined during several follow-up examination rounds. Medical information is available of all participants by collaboration with the general practitioners and with the pharmacies in the area of Ommoord. The Rotterdam Study has been approved by the medical ethics committee according to the “Wet Bevolkingsonderzoek: ERGO” (Population Study Act Rotterdam Study),

executed by the Ministry of Health, Welfare and Sports of the Netherlands and written informed consent was obtained from all study participants.

Women's Health Initiative Clinical Trials (WHI CT): The WHI is a long-term national health study focused on strategies for preventing heart disease, breast and colorectal cancer, and osteoporotic fractures in postmenopausal women. Between 1993 and 1998, it randomized 68,132 women aged 50-79 years into one or more clinical trials of hormone therapy, dietary modification, or calcium/vitamin D supplementation.[12] In this context, white WHI CT women were controls drawn from the Genome-wide Association Research Network into Effects of Treatment (GARNET),[13] controls drawn from the Modification of PM-Mediated Arrhythmogenesis in Populations (MOPMAP),[14] or participants in the Women's Health Initiative Memory Study (WHIMS).[15] Black and Hispanic WHI CT women were participants in the single nucleotide polymorphism (SNP) Health Association Resource project (SHARe).[16]

II) TABLES AND FIGURES

Supplemental Table 1. List of sulfonylurea drugs

First-generation sulfonylureas
Acetohexamide
Chlorpropamide
Tolazamide
Tolbutamide
Second-generation sulfonylureas
Glimepiride
Gliclazide
Glipizide
Glyburide

Supplemental Table 2. Medication assessment and electrocardiogram (ECG) measurement methods for each cohort

Cohort	Maximum Number of Visits	Medication Assessment	Time Period for Medication Assessment	ECG Machine	ECG Measurement System
AGES	≤ 2	Medication Inventory	At time of visit	Marquette MAC 5000	Marquette 12SL
ARIC	4	Medication Inventory	2 weeks before visit	Marquette MAC PC	Marquette 12SL
CHS	10	Medication Inventory	2 weeks before visit	Marquette MAC PC	Marquette 12SL
Health ABC	1	Medication Inventory	2 weeks before visit	Marquette MAC PC	Marquette 12SL
HCHS/SOL	1	Medication Inventory	4 weeks before visit	Marquette MAC 1200	Marquette 12SL
JHS	1	Medication Inventory	At time of visit	Marquette MAC PC	MEANS[17, 18]
MESA	2	Medication Inventory	2 weeks before visit	Marquette MAC 1200	Marquette 12SL
NEO	1	Medication Inventory	At time of visit	Burdick Eclips 850i	University of Glasgow
PROSPER	1	Medication Inventory	At time of visit	Burdick Eclips 850i	University of Glasgow
Rotterdam 1	5	Pharmacy database	30 days before visit	ACTA	MEANS[17, 18]
Rotterdam 2	3	Pharmacy database	30 days before visit	ACTA	MEANS[17, 18]
WHI GARNET	4	Medication Inventory	2 weeks before visit	Marquette MAC PC	Marquette 12SL
WHI MOPMAP	4	Medication Inventory	2 weeks before visit	Marquette MAC PC	Marquette 12SL
WHI SHARe	4	Medication Inventory	2 weeks before visit	Marquette MAC PC	Marquette 12SL
WHIMS	4	Medication Inventory	2 weeks before visit	Marquette MAC PC	Marquette 12SL

Study abbreviations: AGES = Age, Gene/Environment Susceptibility – Reykjavik Study, ARIC = Atherosclerosis Risk in Communities Study, CHS = Cardiovascular Health Study, Health ABC = Health, Aging, and Body Composition Study, HCHS/SOL = Hispanic Community Health Study/Study of Latinos, JHS = Jackson Heart Study, MESA = Multi-Ethnic Study of Atherosclerosis, NEO = Netherlands Epidemiology of Obesity, PROSPER = Prospective Study of Pravastatin in the Elderly at Risk, Rotterdam 1 = first cohort of the Rotterdam Study, Rotterdam 2 = second cohort of the Rotterdam study, WHI GARNET = Women's Health Initiative Genome-wide Association Research Network into Effects of Treatment, WHI MOPMAP = Women's Health Initiative Modification of Particulate Matter-Mediated Arrhythmogenesis in Populations, WHI SHARe = Women's Health Initiative SNP Health Association Resource, WHIMS = Women's Health Initiative Memory Study.

Supplemental Table 3. Genotyping characteristics for each cohort

Cohort	Genotyping array	Genotype calling	Sample call rate filter	SNP call rate filter	SNP MAF filter	HWE p-value filter	Imputation software	Imputation platform	SNPs passing QC, N
AGES	Ilumina 370CNV	BeadStudio	>95%	>97%	<1%	$<10^{-6}$	MACH v1.0.16	HapMap2	308,340
ARIC (EA)	Affymetrix 6.0	Birdseed	>95%	>90%	<1%	$<10^{-6}$	MACH v1.0.16	HapMap2	669,450
ARIC (AA)	Affymetrix 6.0	Birdseed	>95%	>90%	<1%	$<10^{-5}$	MACH v1.0.16	HapMap2	669,450
CHS (EA)	Illumina 370CNV	GenomeStudio	>95%	>97%	NA	$<10^{-5}$	BIMBAM 0.99	HapMap2	306,655
CHS (AA)	Illumina 370CNV	GenomeStudio	>95%	>97%	NA	$<10^{-5}$	BEAGLE 3.2.1	HapMap3 (YRI,ASW,CEU)	940,567
Health ABC (EA)	Illumina 1M	BeadStudio	>97%	>97%	<1%	$<10^{-6}$	MACH v1.0.16	HapMap2	914,263
Health ABC (AA)	Illumina 1M	BeadStudio	>97%	>97%	<1%	$<10^{-6}$	MACH v1.0.16	HapMap2 (YRI,CEU)	1,007,948
HCHS/SOL	Illumina Omni 2.5M + Custom	GenomeStudio	>98%	>98%	NA	$<10^{-5}$	IMPUTE2	1000G Phase 3	2,294,032
JHS	Affymetrix 6.0	Birdseed	>95%	>95%	NA	NA	IMPUTE v2.1.0	HapMap2 (CEU,YRI)	868,969
MESA (EA)	Affymetrix 6.0	Birdseed	>95%	>95%	<1%	$<10^{-4}$	IMPUTE v2.1.0	HapMap2	730,000
MESA (AA)	Affymetrix 6.0	Birdseed	>95%	>95%	<1%	$<10^{-4}$	IMPUTE v2.1.0	HapMap2	790,581
MESA (HA)	Affymetrix 6.0	Birdseed	>95%	>95%	<1%	$<10^{-4}$	IMPUTE v2.1.0	HapMap2	743,004
NEO	Illumina CoreExome-24v1	GenCall	>98%	>98%	NA	$<10^{-5}$	IMPUTE v2	1000G Phase 1v3	361,046
PROSPER	Illumina 660K	BeadStudio	>90%	>97.5%	NA	$<10^{-6}$	MACH v1.0.15	HapMap2	557,192
Rotterdam 1	Illumina 550K-Duo	BeadStudio	>98%	>98%	<1%	$<10^{-6}$	MACH v1.0.15	HapMap2	512,349
Rotterdam 2	Illumina 550K-Duo, 610K-Quad	GenomeStudio	>98%	>95%	<1%	$<10^{-6}$	MACH v1.0.16	HapMap2	537,405
WHI GARNET	Illumina HumanOmni1-Quad	BeadStudio	NA	>98%	NA	$<10^{-4}$	BEAGLE v3.3.1	1000G Phase 1v3	NA
WHI MOPMAP	Affymetrix Genome-Wide Human CEU 1	Birdseed	NA	>90%	<0.5%	$<10^{-6}$	MaCH minimac	Hapmap 2	NA
WHI SHARe (AA)	Affymetrix 6.0	Birdseed	NA	>95%	<1%	$<10^{-6}$	MaCH v1.0.16	Hapmap 2 (CEU,YRI)	NA
WHI SHARe (HA)	Affymetrix 6.0	Birdseed	NA	>95%	<1%	$<10^{-6}$	MaCH v1.0.16	1000G Phase 1v3	NA
WHIMS	Illumina OmniExpress 8.1	Birdseed	NA	>98%	<1%	$<10^{-4}$	MaCH minimac	Hapmap 2	NA

EA = European ancestry, AA = African American, HA = Hispanic/Latino ancestry, MAF = minor allele frequency. Study abbreviations: AGES = Age, Gene/Environment Susceptibility – Reykjavik Study, ARIC = Atherosclerosis Risk in Communities Study, CHS = Cardiovascular Health Study, Health ABC = Health, Aging, and Body Composition Study, HCHS/SOL = Hispanic Community Health Study/Study of Latinos, JHS = Jackson Heart Study, MESA = Multi-Ethnic Study of Atherosclerosis, NEO = Netherlands Epidemiology of Obesity, PROSPER = Prospective Study of Pravastatin in the Elderly at Risk, Rotterdam 1 = first cohort of the Rotterdam Study, Rotterdam 2 = second cohort of the Rotterdam

study, WHI GARNET = Women's Health Initiative Genome-wide Association Research Network into Effects of Treatment, WHI MOPMAP = Women's Health Initiative Modification of Particulate Matter-Mediated Arrhythmogenesis in Populations, WHI SHARe = Women's Health Initiative SNP Health Association Resource, WHIMS = Women's Health Initiative Memory Study.

Supplemental Table 4. Analysis methods for each cohort

Cohort	Statistical Analysis Method	Analysis Software
AGES	GEE	R bosswithdf
ARIC	GEE	R bosswithdf
CHS	GEE	R bosswithdf
Health ABC	GEE	R bosswithdf
HCHS/SOL	Mixed model	R
JHS	GEE	R bosswithdf
MESA	GEE	R bosswithdf
NEO	Linear regression	Probabel v0.4.3
PROSPER	Linear regression	Probabel v0.4.3
Rotterdam 1	GEE	R bosswithdf
Rotterdam 2	GEE	R bosswithdf
WHI GARNET	GEE	R bosswithdf
WHI MOPMAP	GEE	R bosswithdf
WHI SHARe	GEE	R bosswithdf
WHIMS	GEE	R bosswithdf

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Supplemental Table 5. Genomic inflation factors

Cohort	Genomic inflation factors (λ) QT interval	JT interval	QRS interval
European Ancestry			
AGES	1.04	1.01	1.05
ARIC	1.05	1.04	1.03
CHS	1.04	1.03	1.03
Health ABC	1.11	1.10	1.07
MESA	1.05	1.08	1.08
NEO	1.06	1.08	1.06
PROSPER	1.02	1.02	1.02
Rotterdam 1	1.04	1.02	1.04
Rotterdam 2	1.06	1.07	1.06
WHI GARNET	1.01	1.03	1.02
WHI MOPMAP	1.13	1.13	1.13
WHI WHIMS	1.04	1.05	1.05
All European	1.01	1.00	1.02
African American			
ARIC	1.05	1.01	1.03
CHS	1.05	1.06	1.06
Health ABC	1.07	1.08	1.04
JHS	1.04	1.04	1.01
MESA	1.04	1.05	1.06
WHI SHARe	1.03	1.02	1.01
All African American	1.00	1.01	1.04
Hispanic/Latino			
HCHS/SOL	1.13	1.12	0.99
MESA	1.05	1.05	1.03
WHI SHARe	1.09	1.06	1.02
All Hispanic	0.97	0.99	0.98

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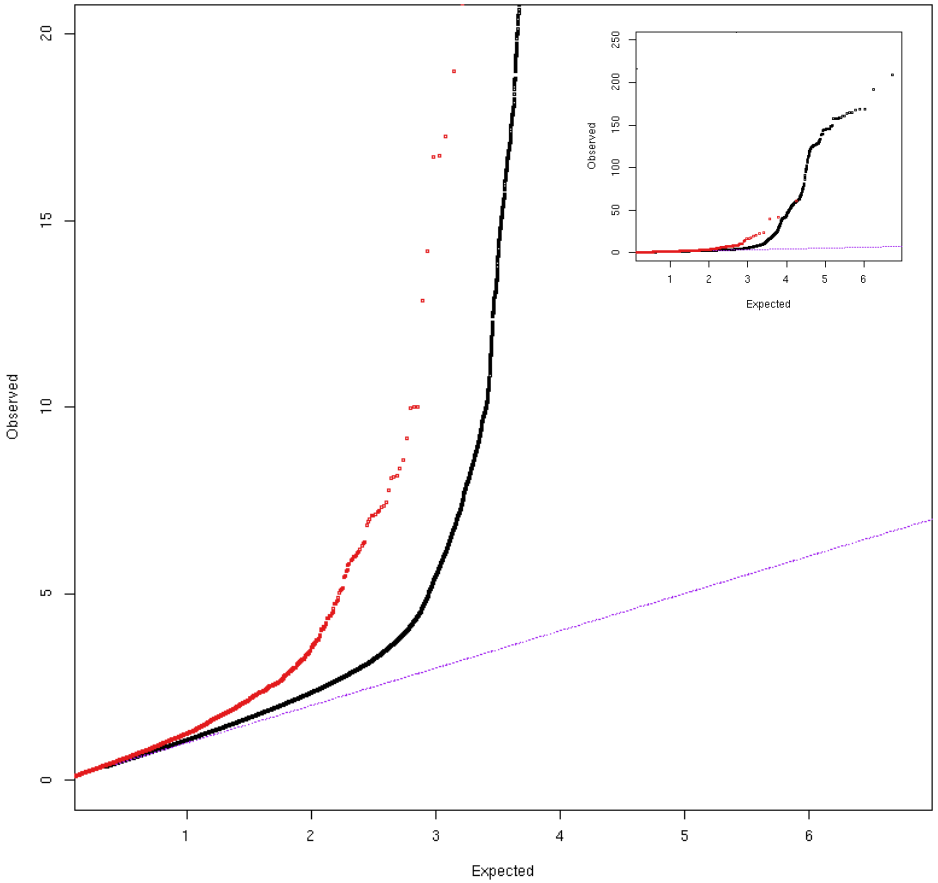
Supplemental Table 6. Summary of suggestive sulfonylurea-SNP interaction associations with QT, JT, and QRS intervals from ancestry-specific GWAS meta-analyses, $P < 10^{-6}$

Lead SNP	Chr:position (hg19)	Nearest gene	Studies	Min/alt alleles	MAF	Effect	SE	P	Function	Coding	eQTL (P < 5x10-8)
QT - ALL											
rs1439840	2:123408943		11	C/T	0.07	-4.7	1.0	6.90E-07	Intergenic		
rs17081313	4:32376727		2	T/C	0.03	11.2	2.1	1.69E-07	Intergenic		
QT - EA											
rs1890262	1:62114402	*TM2D1, NFIA*	2	A/G	0.03	13.8	2.8	7.97E-07	Intergenic		
rs6718130	2:18632585	*NT5C1B, KCNS3*	4	C/A	0.02	9.1	1.7	8.25E-08	Intergenic		
rs6035275	20:19272210	*SLC24A3*	2	C/T	0.02	-12.0	2.2	1.03E-07	Intronic		
QT - AA											
rs12132562	1:172353471	*DNM3*	6	T/C	0.05	8.5	1.7	3.60E-07	Intronic		
rs1606812	2:147715326	*PABPC1P2*	3	C/T	0.05	-11.5	2.2	2.60E-07	Intergenic		
rs1106399	2:201003837	*SPATS2L, TYW5*	3	C/A	0.04	10.5	2.0	2.72E-07	Intergenic		*SPATS2L*[19],
rs7726558	5:118912598	*HSD17B4, FAM170A*	5	C/G	0.09	-6.2	1.2	4.39E-07	Intergenic		*FAM170A*[20, 21], *HSD17B4*[22]
QT - HA											
rs17639063	3:62534435	*CADPS*	2	G/T	0.04	9.7	1.9	2.84E-07	Intronic		
JT - ALL											
rs9853921	3:117959502	*LOC105374060*	21	C/T	0.33	-2.3	0.5	8.41E-07	Intergenic		
rs624896	5:113856054	*KCNN2*	7	A/G	0.07	-6.0	1.2	9.05E-07	Intergenic		
rs200214	6:5478793	*FARS2*	15	G/A	0.02	-3.6	0.7	3.63E-07	Intronic		
rs17156495	7:108763669	*THAP5, PNPLA8*	5	G/A	0.08	-8.5	1.7	5.30E-07	Intergenic		
JT - EA											
rs16895033	8:122297441	*HAS2, SNTB1*	3	A/G	0.03	-7.9	1.6	9.97E-07	Intergenic		
JT - AA											
rs1388107	5:118909006	*HSD17B4, FAM170A*	6	T/G	0.08	-6.2	1.2	5.34E-07	Intergenic		
rs2182486	13:36367082	*MIR548F5*	4	C/T	0.07	-13.3	2.5	1.03E-07	Intronic		

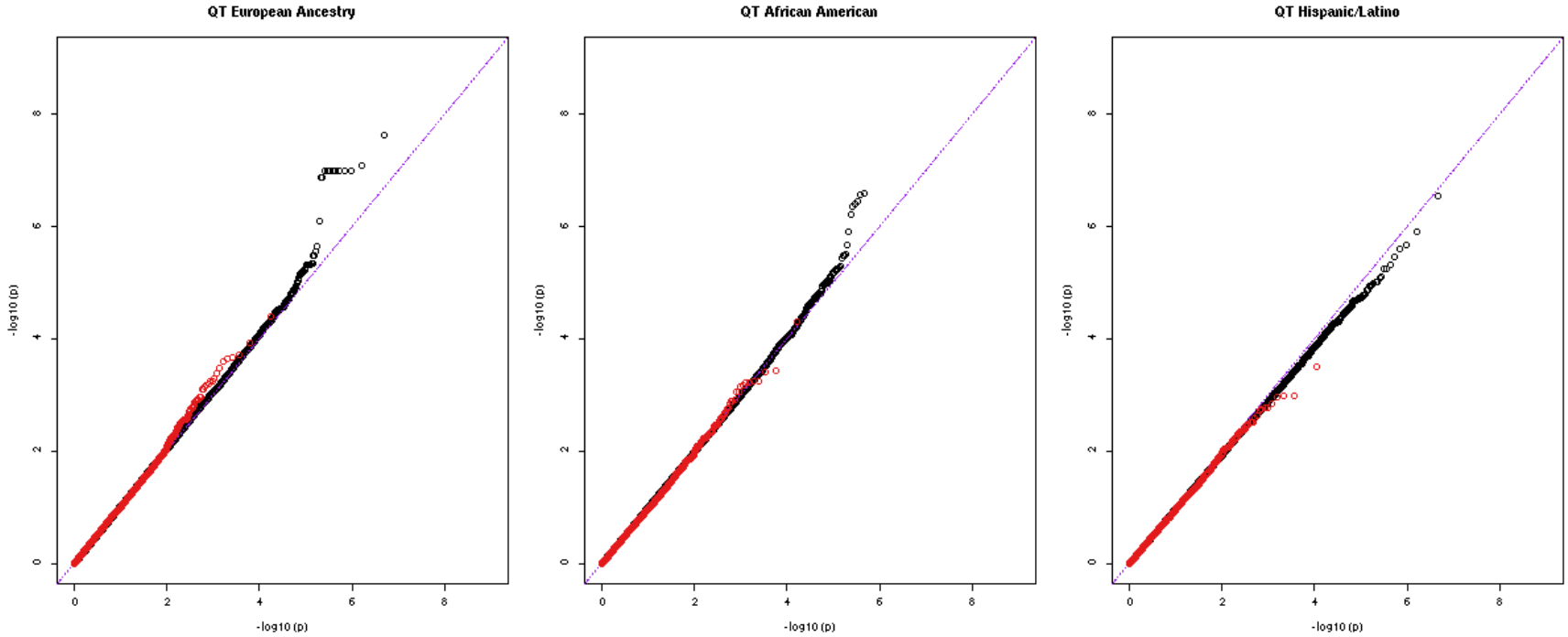
JT - HA											
rs17211409	11:86325887	*ME3*	2	G/A	0.04	-11.6	2.1	6.02E-08	Intronic		*ME3*[22, 23]
rs17107548	14:78892142	*NRXN3*	3	T/C	0.15	6.6	1.3	9.87E-07	Intronic		
QRS - TRANS											
rs2134953	8:4185553	*CSMD1*	2	G/A	0.04	-7.8	1.4	7.84E-08	Intronic		
rs7861565	9:17346855	*CNTLN*	5	T/A	0.07	-3.7	0.7	2.14E-07	Intronic		
rs3736352	9:54254589	*TINAG*	13	C/A	0.06	2.7	0.5	3.44E-07	Missense		
rs10507540	13:46841552	*LRRC63*	13	G/C	0.14	-2.2	0.4	5.86E-08	Intronic	Missense	
rs1397988	18:42022802	*SETBP1*	18	T/G	0.12	-1.6	0.3	7.15E-07	Intergenic		
rs6088791	20:33907909	*UQCC*	17	C/T	0.47	-1.1	0.2	7.71E-07	Intronic	Missense	*CEP250*[22, 23], *CPNE1*[19, 23], *EDEM2*[22], *EIF6*[22], *ITGB4BP*[19], *PROCR*[19], *UQCC*[21, 23-27]
QRS - EA											
rs4591595	4:84124440	*PLAC8, COQ2*	9	T/C	0.09	-2.8	0.6	3.49E-07	Intergenic		
rs4362469	18:70936558	*LOC400655*	5	A/C	0.04	-4.8	1.0	6.52E-07	Intergenic		
rs4911179	20:33972899	*UQCC*	12	A/C	0.39	-1.7	0.3	7.50E-08	Intronic	Missense	*CEP250*[22, 23], *CPNE1*[19, 23], *EDEM2*[22], *EIF6*[22], *ITGB4BP*[19], *PROCR*[19], *UQCC*[21, 23-27]
QRS - AA											
rs7861565	9:17346855	*CNTLN*	4	T/A	0.07	-4.0	0.7	6.25E-08	Intronic		
rs1997103	7:55395390	*LANCL2, ELDR*	2	C/G	0.05	-9.0	1.7	6.40E-08	Intergenic		
rs12430683	13:99427730	*DOCK9, SLC15A1*	6	A/G	0.15	-3.2	0.6	1.63E-07	Intergenic		
rs10767455	11:25800278		6	T/A	0.37	2.1	0.4	4.26E-07	Intergenic		
rs10484885	6:90395016	*MDN1*	2	C/T	0.05	3.5	0.7	9.12E-07	Intronic		*ANKRD6*[23], *RRAGD*[23]
rs985292	11:127677874		6	G/A	0.33	2.4	0.5	9.90E-07	Intergenic		
rs4855537	3:68955484	*FAM19A4*	4	C/A	0.10	-4.6	0.9	9.94E-07	Intronic		
QRS - HA											
rs1777084	14:43178407		2	A/G	0.34	-3.3	0.7	9.70E-07	Intergenic		

EA = European ancestry, AA = African American, HA = Hispanic/Latino ancestry. Studies = number of cohorts contributing to ancestry-specific analysis. Coding = lead SNP in linkage disequilibrium ($r^2 > 0.8$) with a protein coding variant. eQTL = transcripts associated with SNPs in linkage disequilibrium ($r^2 > 0.8$) with lead SNP.

Supplemental Figure 1. Bioinformatic candidate SNP analysis – QT main effects. Quantile-quantile plot of QT main-effect genome-wide association results from the QT Interval-International GWAS Consortium.[28] The unfiltered GWAS results are shown in black and the candidate SNPs, selected to be likely functional based on bioinformatic analysis of ENCODE and eQTL studies, are plotted in red. The candidate SNPs are shifted to the left compared with the unfiltered results, indicating enrichment for signal among the candidate SNPs. The lower left sub region of the quantile-quantile plot is displayed as the main panel and the full distribution is plotted as the inset.



Supplemental Figure 2. Bioinformatic candidate SNP analysis – sulfonylurea-QT interaction effects. Quantile-quantile plot of sulfonylurea-QT interaction genome-wide association results. The unfiltered GWAS results are shown in black and the candidate SNPs, selected to be likely functional based on bioinformatic analysis of ENCODE and eQTL studies, are plotted in red. The candidate SNPs overlap with the unfiltered results, indicating a lack of enrichment for signal among the candidate SNPs.



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