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Supplemental Material

Genome-Wide Association Study of Susceptibility to Particulate Matter-Associated QT Prolongation

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Figure S3. UCSC Genome Brower displaying rs1619661 (highlighted), associated SNPs (linkage disequilibrium ≥ 0.8), and tracks representing DNAse1 hypersensitivity and DNA methylation in cardiac tissues.

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Table S1. Genotyping, Quality Control, Imputation & Analysis, by Study / Subpopulation.

Study	Race / Ethnicity	Genotyping Platform	Genotype Calling Software	Genotype Filters	Imputation Software	NCBI Build	Reference Panel
ARIC	Black	Affymetrix GeneChip SNP Array 6.0	Birdseed	Call rate ≤ 90% MAF < 1%	MaCH v1.0.16	HapMap 2 Build 36	YRI/CEU 1:1
ARIC	White	Affymetrix GeneChip SNP Array 6.0	Birdseed	Call rate ≤ 95% HWE $p < 1x10^{-6}$ MAF < 1%	MaCH v1.0.16	HapMap 2 Build 36	CEU
WHI GARNET[a]	White	Illumina Human Omni1-Quad v1-0 B	BeadStudio v3.1.3.0	Call rate ≤ 98% HWE $p < 1x10^{-4}$	BEAGLE v3.3.1	1000G v3 3/2012	EUR
WHI MOPMAP[a]	White	Affymetrix Axiom Genome-Wide Human CEU I	Birdseed	Call rate ≤ 90% HWE $p < 1x10^{-6}$ MAF < 0.5%	MaCH minimac	Hapmap 2 Build 36	CEU
WHI SHARe	Black	Affymetrix GeneChip SNP Array 6.0	Birdseed	Call rate ≤ 95% HWE $p < 1x10^{-6}$ MAF < 1%	MaCH v1.0.16	HapMap 2 Build 36	YRI/CEU 1:1
WHI SHARe	Hispanic	Affymetrix GeneChip SNP Array 6.0	Birdseed	Call rate ≤ 95% HWE $p < 1x10^{-6}$ MAF < 1%	MaCH v1.0.16	1000G v3 3/2012	All ancestries
WHI WHIMS	White	Human OmniExpress Exome-8v1_B Genome-Wide Human	Birdseed	Call rate ≤ 98% HWE $p < 1x10^{-4}$ MAF < 1%	MaCH minimac	Hapmap 2 Build 36	CEU

Abbreviations: ARIC, Atherosclerosis Risk in Communities study; CEU, Utah residents with northern and western European ancestry; EUR, European; GARNET, Genome-wide Association Research Network into Effects of Treatment; HWE, Hardy-Weinberg equilibrium; MAF, minor allele frequency; MOPMAP, Modification of PM-Mediated Arrhythmogenesis in Populations; SHARe, SNP Health Association Resource; WHI, Women's Health Initiative; WHIMS, Women's Health Initiative Memory Study; YRI, Yoruba in Ibadan, Nigeria

[a] Controls

Table S2. Analysis of Predicted Mean QT (ms) by Genotype and PM_{10} exposure

rs1619661 Genotype	PM_{10}	N Participants	Predicted QT	95% CI
CC (1.6%)[a]	≤ P90	309	402	401, 403
	> P90	34	397	396, 399
CT (21.8%)[a]	≤ P90	4348	403	402, 403
	> P90	483	401	400, 401
TT (76.7%)[a]	≤ P90	15286	403	403, 403
	> P90	1698	404	403, 404
Total (100%)		22158		

Abbreviations: CI, confidence interval; N, number; P90, 90th percentile; PM_{10}, particulate matter < 10 μm in diameter

[a] Estimated genotype frequency under Hardy-Weinberg equilibrium

Table S3. Sensitivity of the PM$_{10}$ x rs1619661 interaction

Sensitivity to	PM Size	PM Threshold (percentile)	PM Averaging Period	Additional Adjustment or Restriction	Interaction Estimate (SE)[a]	*P*
No changes	PM$_{10}$	90th	2 days		2.55 (0.46)	$2.11\text{x}10^{-8}$
PM threshold	PM$_{10}$	80th	2 days		1.70 (0.36)	$2.10\text{x}10^{-6}$
	PM$_{10}$	70th	2 days		1.48 (0.33)	$9.48\text{x}10^{-6}$
	PM$_{10}$	60th	2 days		1.05 (0.30)	$5.16\text{x}10^{-4}$
	PM$_{10}$	50th	2 days		0.71 (0.30)	$1.65\text{x}10^{-2}$
	PM$_{10}$	50 µg/m^3	2 days		2.84 (0.51)	$2.04\text{x}10^{-8}$
PM averaging period	PM$_{10}$	90th	1 week		1.18 (0.45)	$9.44\text{x}10^{-3}$
	PM$_{10}$	90th	2 weeks		1.29 (0.46)	$4.77\text{x}10^{-3}$
	PM$_{10}$	90th	3 weeks		1.18 (0.46)	$1.00\text{x}10^{-2}$
	PM$_{10}$	90th	1 month		0.80 (0.45)	$7.65\text{x}10^{-2}$
PM size	PM$_{2.5}$[b]	90th	1 month		0.80 (0.51)	$1.14\text{x}10^{-1}$
Additional adjustment	PM$_{10}$	90th	2 days	nSES[c]	2.50 (0.46)	$4.78\text{x}10^{-8}$
	PM$_{10}$	90th	2 days	Meteorological[d]	2.60 (0.45)	$9.85\text{x}10^{-9}$
	PM$_{10}$	90th	2 days	Lifestyle factors[e]	2.56 (0.45)	$1.85\text{x}10^{-8}$
	PM$_{10}$	90th	2 days	All[cde]	2.57 (0.46)	$2.96\text{x}10^{-8}$
β-antagonist restriction	PM$_{10}$	PM$_{10}$	2 days	Users	-0.61 (1.47)	$6.78\text{x}10^{-1}$
	PM$_{10}$	PM$_{10}$	2 days	Non-Users	2.91 (0.47)	$6.59\text{x}10^{-10}$

Abbreviations: PM, particulate matter; PM$_{2.5,}$ PM < 2.5 µm in diameter; PM$_{10}$, particulate matter < 10 µm in diameter; nSES, neighborhood socioeconomic status.

[a] Trans-ethnic, fixed-effects meta-analysis without genomic control implemented in METAL.

[b] Monthly average PM$_{2.5}$ exposure at geocoded participant address estimated by a spatiotemporal model with GIS-based predictors.

[c] Neighborhood socioeconomic status measured by a sum of Z scores of: median household income, % households with interest dividends or rent income, % age 25+ with high school degree, % age 16+ with professional, managerial, or executive occupations, median value of owner-occupied housing units.

[d] Temperature (°C); dew point (°C); barometric pressure (kPa)

[e] Smoker status (current, former, never), alcohol drinker status (current, former, never), total caloric intake (kcal), sedentary lifestyle

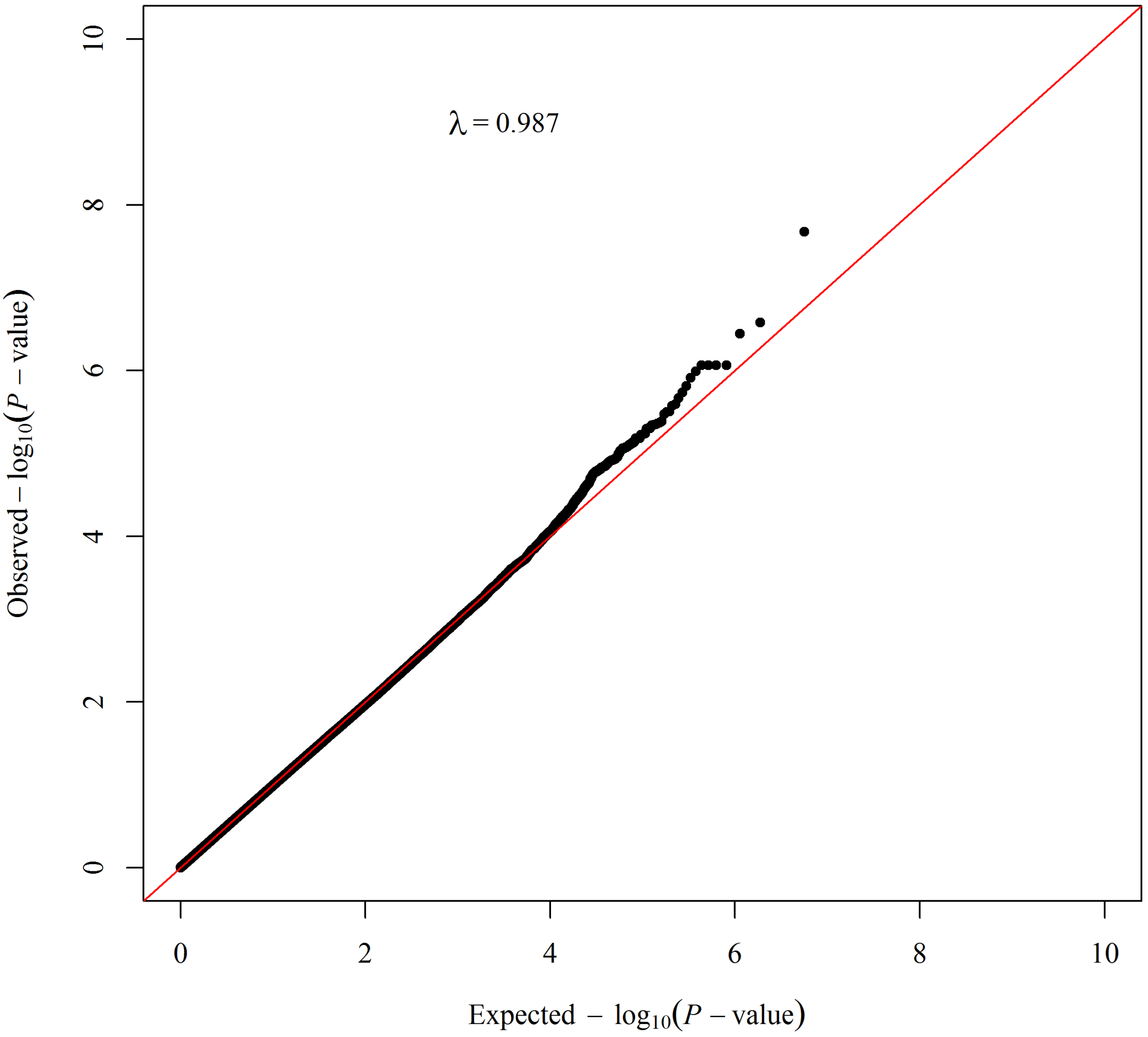

Figure S1. Quantile-Quantile (QQ) plot of observed versus expected $-\log_{10}$ *P*-values of each SNP from the trans-ethnic, fixed-effects meta-analysis of the SNP x PM_{10} interactions. Lambda (λ) is the genomic inflation factor.

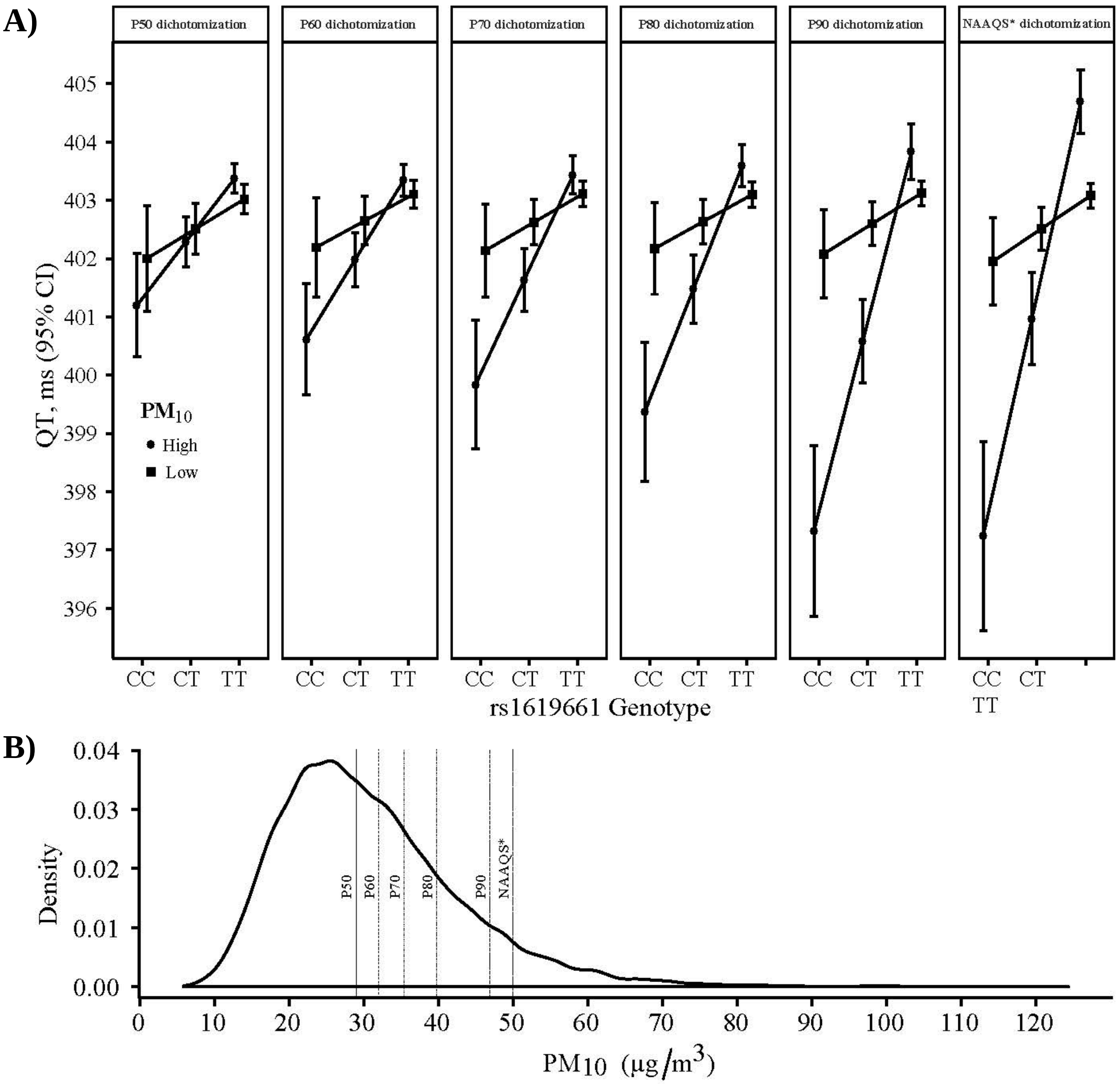

Figure S2. A) Predicted mean (95% confidence interval) QT (ms) per unit increase in the coded allele (T) dosage of rs1619661 at PM$_{10}$ concentrations dichotomized at ≤ and > the 50th – 90th percentiles (P50, P60, P70, P80, P90) and the 1987-2006 National Ambient Air Quality Standard (NAAQS*) for annual PM$_{10}$ (50 µg/m^3), while adjusting for age, geographic region or center, season, calendar year, RR interval, and ancestry. B) Distribution of observed ambient PM$_{10}$ concentrations labelled with the PM$_{10}$ dichotomizations.

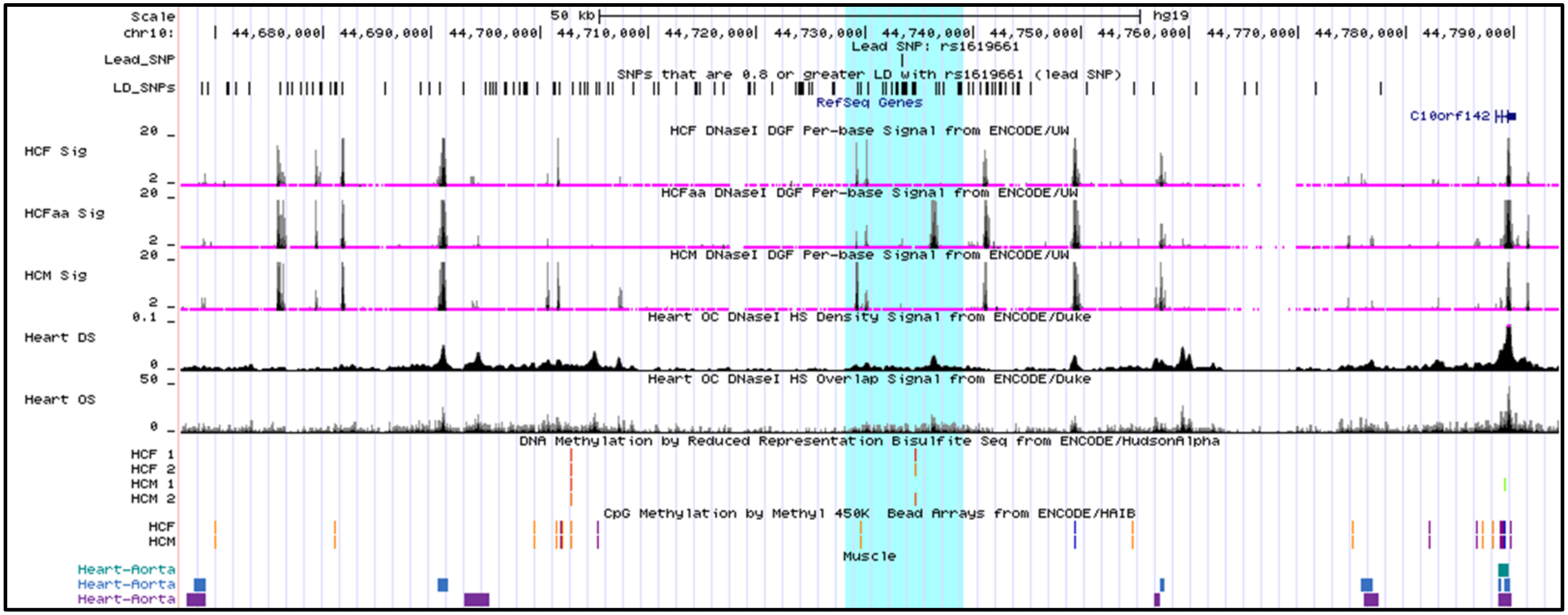

Figure S3. UCSC Genome Brower displaying rs1619661 (highlighted), associated SNPs (linkage disequilibrium ≥ 0.8), and tracks representing DNAse1 hypersensitivity and DNA methylation in cardiac tissues.

Tracks, from top to bottom:

Lead_SNP: The SNP with a genome-wide significant association in this study, rs1619661.

LD_SNP: SNPs associated with rs1619661 (linkage disequilibrium > 0.8), from HaploReg (Ward and Kellis 2012).

HCF Sig: Human cardiac fibroblast deoxyribonuclease 1 digital genomic footprinting (DNAse1 DGF) per base signal, from ENCODE/UW.

HCFaa Sig: Human cardiac (adult atrial) fibroblast DNAse1 DGF per base signal, from ENCODE/UW.

HCM Sig: Human cardiac myocyte DNAse1 DGF per-base signal, from ENCODE/UW.

Heart DS/OS: Heart tissue DNAse1 hypersensitivity density / overlap signals, from ENCODE/Duke.

HCF & HCM 1/2: Human cardiac fibroblast & myocyte DNA methylation by reduced representation bisulfite sequencing (Cokus et al. 2008), from ENCODE/HudsonAlpha. Percent of sequenced molecules that are DNA methylated: red (100%), yellow (50%), green (0%).

HCF & HCM: Human cardiac fibroblast & myocyte CpG methylation by Methyl 450K Bead Arrays from ENCODE/HAIB. Methylation status: orange (methylated), purple (partially methylated), bright blue (unmethylated), black (NA).

Heart-Aorta: Human heart aorta DNA methylation by bisulfite sequencing analysis pipeline, MethPipe (Song et al. 2013). Methylation status: green (partially methylated region), blue (hypomethylated region), purple (allele-specific methylated regions)

Supplemental Material References

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Song Q, Decato B, Hong EE, Zhou M, Fang F, Qu J, et al. 2013. A reference methylome database and analysis pipeline to facilitate integrative and comparative epigenomics.

Ward LD, Kellis M. 2012. Haploreg: A resource for exploring chromatin states, conservation, and regulatory motif alterations within sets of genetically linked variants. Nucleic acids research 40:D930-934.