SUPPLEMENTAL MATERIAL

The supporting information has the following sections in order:

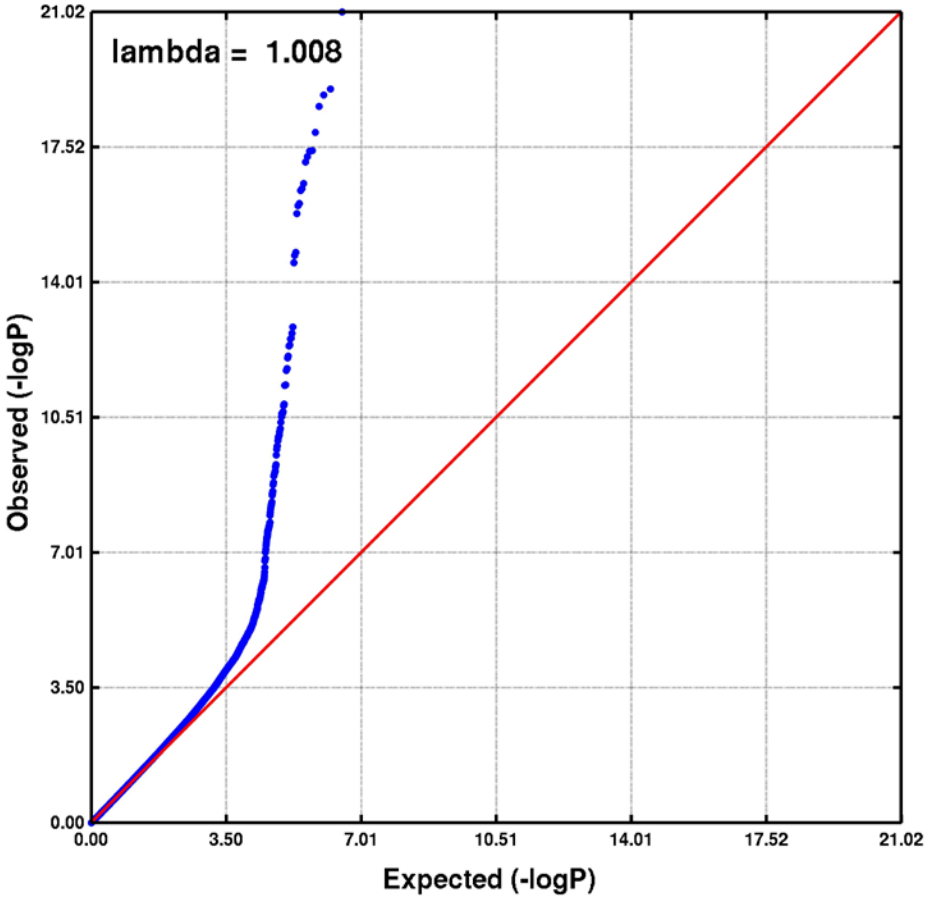
I. Supplemental Figure and Tables

II. Supplemental Materials and Methods

III. Supplemental References

I. Supplemental Figure and Tables

Supplemental Figure 1. Quantile-quantile plot showing the association of SNPs with PR interval in the meta-analysis of ten genome-wide association studies of African Americans. The red line represents the expected distribution of -log10 p-values under the null hypothesis. The blue dots represent the observed -log10 p-values.



Supplemental Table 1. Genotyping characteristics for the genome-wide association analyses of ten studies in the meta-analysis.[a]

Study	Genotyping array	Genotype calling algorithm	Study-specific filters				Imputation software	GWAS statistical analysis software	Imputation quality (Median: 25%, 75%)	N. autosomal SNPs passing QC	Method of PC estimation[e]
			Sample call rate	SNP call rate	SNP MAF[b]	HWE p-value[c]					
ARIC	Affymetrix 6.0	Birdseed	<95%	<90%	<1%	NA	MACH v1.16	PLINK	0.98 (0.91, 1.0)	796,384	EIGENSTRAT, 10 PCs
BLSA	Illumina 550K	BeadStudio	≤98.5%	<99%	<1%	$\leq 10^{-4}$	MACH 1.0	Merlin	0.95 (0.86, 1.0	501,704	EIGENSTRAT, 2 PCs
BHS	Illumina Human610 BeadChip, HumanCVD BeadChip	BeadStudio	<99%	<90%	NA	NA	MACH v1.0.16	PLINK	0.96 (0.89, 0.99)	608,756	LAMP, 10 PCs
CFS	Affymetrix 6.0	Birdseed	<95%	<90%	<1%	NA	MACH v1.16	R	0.99 (0.94, 1.0)	867,495	EIGENSTRAT, 10 PCs
CHS	Illumina HumanOmni1-Quad_v1 BeadChip system	Illumina Genome Studio	<95%	≤97%	NA	$<10^{-5}$	BEAGLE version 3.2.1	R	0.98 (0.94, 1.0)	963,248	R, 10 PCs
HABC	Illumina 1M	BeadStudio	<97%	<97%	<1%	$<10^{-6}$	MACH v1.16	R	0.97 (0.92, 1.0)	1,007,948	EIGENSTRAT, 2 PCs
HANDLS	Illumina 1M[d]	BeadStudio	≤95%	≤95%	≤1%	$\leq 10^{-7}$	MACH v1.16	R, MACH2QTL	0.98 (0.93, 1.0)	907,763	PLINKv1.06, 10 PCs
JHS	Affymetrix 6.0	Birdseed	<95%	<90%	<1%	NA	MACH v1.16	PLINK	0.98 (0.92, 1.0)	868,969	EIGENSTRAT, 10 PCs
MESA	Affymetrix 6.0	Birdseed	<95%	<90%	<1%	NA	MACH v1.16	PLINK	0.99 (0.93, 1.0)	881,666	EIGENSTRAT, 10 PCs
WHI	Affymetrix 6.0	Birdseed	<95%	<95%	<1%	$<10^{-6}$	MACH v1.0.16	PLINK, ProbABEL	0.97 (0.89, 1.0)	829,370	STRUCTURE, 4 PCs

[a]All studies used HapMap phase 2 release 22 build 36 and the HapMap Reference panel 1:1 CEU:YRI phase II.
[b]SNP MAF filter applied pre-imputation.
[c]Genotyped SNP results used to replace imputed SNP results were not filtered by HWE P-value.
[d]1024 HANDLS participants were successfully genotyped at the equivalent of Illumina 1M SNP coverage (709 samples using Illumina 1M and 1Mduo arrays, the remainder using a combination of 550K, 370K, 510S and 240S to equate the million SNP level of coverage).
[e]Software program used to estimate principal components (PC) and the number of top principal components used as covariates in the analysis.
ARIC, Atherosclerosis Risk in Communities; BLSA, Baltimore Longitudinal Study on Aging; BHS, Bogalusa Heart Study; CFS, Cleveland Family Study; CHS, Cardiovascular Health Study; HABC, The Health, Aging, and Body Composition Study; HANDLS, The Healthy Aging in Neighborhoods of Diversity across the Life Span Study; JHS, Jackson Heart Study; MESA, Multi-Ethnic Study of Atherosclerosis; WHI, Women's Health Initiative.

Supplemental Table 2. Summary of study-specific independent genome-wide significant association results for PR interval obtained at 17 independent loci.

SNP	Nearest Gene	Chr	Alleles[a]	Effect Allele Frequency	β[b] (se)									
					ARIC	BLSA	BHS[c]	CFS	CHS	HABC	HANDLS	JHS	MESA	WHI
Primary signals[d]														
rs3891585	*MEIS1*	2	A/G	0.43	2.42 (0.78)	-1.37 (2.69)	0.97 (2.47)	3.51 (2.16)	-0.91 (1.44)	0.29 (1.21)	3.86 (1.11)	3.37 (0.83)	2.69 (0.88)	1.77 (0.54)
rs267567	*ITGA9*	3	A/G	0.18	2.72 (1.07)	6.61 (3.64)	3.01 (3.54)	-1.36 (2.79)	0.92 (1.93)	2.97 (1.57)	1.84 (1.51)	3.53 (1.11)	4.64 (1.17)	2.24 (0.68)
rs3922844	*SCN5A*	3	T/C	0.58	-5.08 (0.84)	-4.56 (3.00)	-4.09 (2.43)	-0.91 (2.46)	-5.35 (1.55)	-3.38 (1.18)	-4.06 (1.13)	-6.14 (0.86)	-4.57 (0.94)	-4.12 (0.57)
rs11732231	*ARHGAP4*	4	C/G	0.23	1.59 (1.00)	4.42 (3.14)	1.89 (3.18)	0.28 (2.89)	2.21 (1.84)	5.08 (1.43)	3.04 (1.31)	0.70 (1.01)	4.08 (1.13)	1.88 (0.64)
rs11773845	*CAV1*	7	A/C	0.36	-0.33 (0.83)	-1.34 (2.83)	-3.66 (2.48)	-4.01 (2.25)	-3.43 (1.62)	-2.29 (1.25)	-1.88 (1.18)	-2.51 (0.88)	-3.07 (0.95)	-2.64 (0.55)
rs1895585	*TBX5*	12	A/G	0.30	2.45 (0.89)	4.61 (3.07)	-0.42 (2.75)	2.78 (2.48)	5.37 (1.67)	4.57 (1.35)	1.08 (1.24)	4.04 (0.92)	2.90 (1.01)	3.36 (0.59)
Secondary signals[e]														
rs6763048	*SCN5A*	3	A/G	0.73	2.25 (0.93)	7.13 (3.26)	4.61 (2.91)	3.70 (2.6)	4.20 (1.84)	2.02 (1.42)	3.89 (1.38)	3.92 (0.94)	2.95 (1.06)	3.19 (0.64)
rs6801957	*SCN10A*	3	T/C	0.17	---	---	---	---	0.97 (2.13)	3.34 (1.69)	6.31 (1.52)	---	---	2.96 (0.72)

[a]Coded allele listed first.
[b]Beta (β) estimates represent the difference in PR interval (milliseconds) per copy of the minor allele, adjusted for the covariates in the model. ARIC, Atherosclerosis Risk in Communities; BLSA, Baltimore Longitudinal Study on Aging; BHS, Bogalusa Heart Study; CFS, Cleveland Family Study; CHS, Cardiovascular Health Study; HABC, The Health, Aging, and Body Composition Study; HANDLS, The Healthy Aging in Neighborhoods of Diversity across the Life Span Study; JHS, Jackson Heart Study; MESA, Multi-Ethnic Study of Atherosclerosis; WHI, Women's Health Initiative.
[c]The Bogalusa Heart Study did not have information on two SNPs (rs10049479 and rs7627552).
[d]Defined as locus-specific SNP with the lowest P-value.
[e]Defined as significant SNPs after conditional analysis that adjusted for locus-specific primary signal. This approach was performed adjusting for successively less significant SNPs until no genome-wide significant SNPs were identified.
Chr, chromosome; se, standard error.

Supplemental Table 3. Local ancestry analyses of primary and secondary PR loci that reached genome-wide significance ($P < 5.0 \times 10^{-8}$) across up to seven studies of African American participants.*

SNP	Nearest Gene	Chr	Alleles[a]	Effect Allele Frequency	β (se)[b] ARIC	CFS	HABC	HANDLS	JHS	MESA	WHI	N	Pre-Local Ancestry Analysis *p*	Post-Local Ancestry Analysis β (se)	Post-Local Ancestry Analysis *p*
Primary signals[c, d]															
rs3891585	*MEIS1*	2	A/G	0.43	2.48 (0.78)	3.49 (2.22)	-0.12 (1.19)	3.85 (1.11)	3.44 (0.83)	2.66 (0.88)	1.81 (0.54)	12,395	7.28×10^{-13}	2.36 (0.32)	3.57×10^{-13}
rs267567	*ITGA9*	3	A/G	0.18	1.86 (1.13)	-2.57 (3.02)	2.76 (1.61)	1.84 (1.50)	3.80 (1.21)	3.36 (1.25)	1.73 (0.76)	12,395	1.31×10^{-10}	2.26 (0.46)	7.61×10^{-07}
rs3922844	*SCN5A*	3	A/G	0.58	--	--	-3.00 (1.23)	-4.05 (1.13)	--	--	--	1,999	5.03×10^{-06}	-3.57 (0.49)	1.78×10^{-05}
rs11732231	*ARHGAP4*	4	C/G	0.23	--	--	4.00 (1.65)	3.10 (1.31)	--	--	--	1,999	4.25×10^{-05}	3.45 (1.03)	7.68×10^{-04}
rs11773845	*CAV1*	7	A/C	0.36	-0.35 (0.86)	-4.56 (2.34)	-2.69 (1.30)	-1.80 (1.17)	-2.40 (0.90)	-3.12 (0.97)	-3.19 (0.58)	12,395	8.46×10^{-11}	-2.45 (0.35)	3.09×10^{-12}
rs1895585	*TBX5*	12	A/G	0.30	--	--	4.56 (1.33)	1.23 (1.23)	--	--	3.39 (0.59)	6,148	2.00×10^{-10}	3.20 (0.49)	9.15×10^{-11}

[a]Coded allele listed first.
[b]Local ancestry estimates were not available for three studies (Baltimore Longitudinal Study of Aging, Bogalusa Heart Study, and Cardiovascular Health Study).
[c]Defined as locus-specific SNP with the lowest P-value.
[d]Secondary signals were not presented because no cohort had local ancestry estimates for all relevant *SCN5A*/*SCN10A* loci.
ARIC, Atherosclerosis Risk in Communities; CFS, Cleveland Family Study; CHS, Cardiovascular Health Study; HABC, The Health, Aging, and Body Composition Study; HANDLS, The Healthy Aging in Neighborhoods of Diversity across the Life Span Study; JHS, Jackson Heart Study; MESA, Multi-Ethnic Study of Atherosclerosis; WHI, Women's Health Initiative.
Chr, chromosome; se, standard error; *p*, meta-analysis *p*-value.

Supplemental Table 4. Phenotype details for the ten studies in the meta-analysis.

Study	ECG machine	Measurement system
ARIC	Marquette MAC PC	Marquette 12SL
BLSA	GE Marquette MAC5000	Marquette 12SL
BHS	Marquette MAC PC	Marquette 12SL
CFS	Marquette MAC6	Marquette 12SL
CHS	Marquette MAC PC	Marquette 12SL
HABC	Marquette MAC PC	Marquette 12SL
HANDLS	GE Marquette MAC5500	Marquette 12SL
JHS	Marquette MAC PC	MC MEANS
MESA	Marquette MAC1200	Marquette 12SL
WHI	Marquette MAC PC	Marquette 12SL

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

II. Supplemental Materials and Methods - Description of Participating Studies

Atherosclerosis Risk in Communities Study (ARIC): The ARIC study is an ongoing, prospective population-based cohort designed to examine the etiology of cardiovascular and pulmonary disease, patterns of medical care, and disease variation over time (3). The study includes 15,792 participants selected using probability sampling from four United States communities (Forsyth County NC, Jackson MS, suburban Minneapolis MN, and Washington County MD). Between 1987 and 1989, the study enrolled participants aged 45–64 years. Standardized physical examinations and interviewer-administered questionnaires were conducted at baseline, and at three triennial follow-up examinations. Blood was drawn for DNA extraction and participants consented to genetic testing. After exclusions, 2,391 African Americans with genotype and phenotype data were included in the analysis. This study was approved by the institutional review board at each field center and all subjects provided written informed consent. This analysis was approved by the University of North Carolina at Chapel Hill School of Public Health Institutional Review Board.

Baltimore Longitudinal Study on Aging (BLSA): The BLSA study is a population-based study aimed to evaluate contributors of healthy aging in the older population residing predominantly in the Baltimore-Washington DC area (4, 5). Starting in 1958, participants were examined every one to four years, depending on their age, during visits to the NIA's Gerontology Research Center in Baltimore. Currently there are approximately 1,100 active participants enrolled in the study. Each man received an extensive interim medical and psychological history and physical examination at each visit. Blood samples were collected for DNA extraction, and genome-wide genotyping

was completed for 1,231 participants. After exclusions, 155 African Americans with genotype and phenotype data were included in the analysis. The BLSA has continuing approval from the Institutional Review Board (IRB) of the Johns Hopkins Bayview Medical Center, the Gerentology Research Center, and Medstar Research Institute. Informed consent was obtained from all participants.

Bogalusa Heart Study (BHS): The BHS is a long-term epidemiologic study of cardiovascular risk factors from birth through the age of 38 years in a biracial population with whites and African Americans. Between 1973 and 2008, nine cross-sectional surveys of children aged 4-17 years and 10 cross-sectional surveys of adults aged 18-48 years, who had been previously examined as children, were conducted for cardiovascular disease risk factor examinations in Bogalusa, Louisiana (6). In the ongoing Longitudinal Aging Study funded by NIH and NIA since 2000, there are 1,202 Caucasian and African American participants who have been examined 4-14 times from childhood to adulthood with DNA available for genotyping. After exclusions, 191 African Americans with genotype and phenotype data were included in the analysis. Study protocols were approved by the Institutional Review Board of the Tulane University Medical Center. Informed consent was obtained from all participants.

Cardiovascular Health Study (CHS): The CHS is a population-based, longitudinal cohort designed to study risk factors for cardiovascular disease in the elderly (7). Starting in 1989, 244 African American adults aged 65 years or older were sampled from four United States communities (Forsyth County, North Carolina; Pittsburgh, Pennsylvania;

Sacramento County, California; and Washington County, Maryland). Between 1992 and 1993, a second cohort of 687 African Americans was enrolled. Extensive physical and laboratory evaluations were performed at baseline to identify the presence and severity of CVD risk factors such as hypertension, hypercholesterolemia and glucose intolerance; subclinical disease such as carotid artery atherosclerosis, left ventricular enlargement, and transient ischemia; and clinically overt CVD. In 2010, genotyping was performed for 844 African-American participants who consented to genetic testing and had available DNA. After exclusions, 674 African Americans with genotype and phenotype data were included in the analysis. The institutional review board at each of the study sites approved the study protocols, and written informed consent was obtained from all participants.

Cleveland Family Study (CFS): The CFS is a family-based longitudinal study designed to study the risk factors for sleep apnea (8). Participants include first-degree or selected second-degree relatives of a proband with either laboratory diagnosed obstructive sleep apnea or neighborhood control of an affected proband. ECG recordings used for the present study were performed at the final exam cycle conducted in a Clinical Research Unit between 2001 and 2006. Families were selected for genotyping on the basis of genetic informativity, including multigenerational data or individuals from the extremes of the distribution of apnea phenotype (9, 10). The 632 African Americans with available DNA were genotyped as part of CARe. After exclusions, 267 African Americans with genotype and phenotype data were included in the analysis. The institutional review

board approved the study, and written informed consent was obtained from all participants.

The Health Aging and Body Composition (HABC): The Health ABC Study is a longitudinal study of the factors that contribute to incident disability and the decline in function of healthier older persons, with a particular emphasis on changes in body composition in old age (11, 12). Between 1997 and 1998, 3,075 adults aged 70-79 years were recruited using mass mailings with telephone follow-up. White individuals were identified through a random sample of Medicare-eligible residents and African American individuals were identified from two clinical centers in Pittsburgh, Pennsylvania, and Memphis, Tennessee. Participants had no reported difficulty in walking a quarter of a mile, climbing 10 steps without resting, or performing mobility-related activities of daily living. Exclusion criteria were any life-threatening condition, participation in any research study involving medications or modification of eating or exercise habits, plans to move from the geographical area within 3 years and difficulty in communicating with the study personnel or cognitive impairment. The key components of Health ABC included a baseline exam with blood specimen collection, annual follow-up clinical exams, and phone contacts every 6 months to identify major health events and document functional status between clinic visits. After exclusions, 1,054 African Americans with genotype and phenotype data were included in the analysis. The institutional review boards at both clinical centers approved the study, and written informed consent was obtained from all participants.

The Healthy Aging in Neighborhoods of Diversity across the Life Span Study (HANDLS): HANDLS is an interdisciplinary, community-based, prospective longitudinal epidemiologic study examining the influences of race and socioeconomic status (SES) on the development of age-related health disparities in overall longevity, cardiovascular disease, and cognitive decline among socioeconomically diverse African Americans and whites in Baltimore (13). A total of 3,722 (2200 African American and 1522 Caucasian) participants between 30 and 64 years of age were recruited as a fixed cohort of participants by household screenings from an area probability sample of Baltimore based on the 2000 Census. Data were collected in two separate phases. Phase 1 consisted of screening, recruitment, a household interview (assessing sociodemographic information and physiological and psychological chronic exposure) and a first 24 hour recall; phase 2 consisted of an in-depth examination in a mobile medical research vehicle (MRV) and included a second dietary assessment with a 24 hour recall, psychometric measures (e.g. for depressive symptoms and cognitive function), anthropometric and body composition measurements. Genotyping was performed for 1,024 participants who self-report as African Americans. After exclusions, 945 African Americans with genotype and phenotype data were included in the analysis. The study protocol was approved by the human subjects review boards at both MedStar Research Institute and the University of Delaware. All participants provided written informed consent.

Jackson Heart Study (JHS): The JHS is a prospective population-based study of the causes of the high prevalence of common complex diseases among African Americans

in the Jackson, Mississippi metropolitan area, including cardiovascular disease, type-2 diabetes, obesity, chronic kidney disease, and stroke (14). Between 2000 and 2004, 5,302 adult African American residents of a tri-county area near Jackson, Mississippi (Hinds County, Rankin County and Madison County) were recruited from four sources, including (1) randomly sampled households from a commercial listing; (2) ARIC participants; (3) a structured volunteer sample that was designed to mirror the eligible population; and (4) a nested family cohort. Unrelated participants were between 35 and 84 years old, and members of the family cohort were ≥21 years old when consent for genetic testing was obtained and blood was drawn for DNA extraction. ECG recordings and DNA extraction were performed at the baseline examination. Based on DNA availability, appropriate informed consent, and genotyping results that met quality control procedures, genotype data were available for 3,030 individuals, including 885 who were also ARIC participants. In the current study, JHS participants who were also enrolled in the ARIC study were analyzed with the ARIC dataset. After exclusions, 1,962 African Americans with genotype and phenotype data were included in the analysis. The institutional review board approved the study protocol, and written informed consent was obtained from all participants.

Multi-Ethnic Study of Atherosclerosis (MESA): MESA is a multicenter, population-based cohort initiated to investigate subclinical cardiovascular disease and the risk factors that predict progression to clinically overt cardiovascular disease (15). Between 2000 and 2002, the study enrolled 6,814 asymptomatic males and females aged 45–84 from six US field centers (Baltimore, MD; Chicago, IL; Los Angeles, CA; New York, NY; St. Paul,

MN; Winston-Salem, NC). Those with a history of CVD (defined as physician-diagnosed myocardial infarction, angina, heart failure, stroke, transient ischemic attack or history of invasive procedure for CVD) were excluded from participation. Approximately 28% of the sample was African American participants. ECG recordings and blood for DNA extraction were obtained at the baseline examination. After exclusions, 1,627 African Americans with genotype and phenotype data were included in the analysis. This study was approved by the institutional review boards of each study site, and written informed consent was obtained from all participants.

Women's Health Initiative (WHI): The WHI is a large and complex clinical investigation of strategies for the prevention and control of some of the most common causes of morbidity and mortality among postmenopausal women, including cancer, cardiovascular disease, and osteoporotic fractures. The WHI comprises both randomized clinical trials (CT) and an observational study (OS). This study is limited to WHI CT participants, as ECGs were not available for WHI OS participants. The WHI clinical trials were designed to allow randomized, controlled evaluation of estrogen with or without progestin treatment, calcium/vitamin D supplementation, and dietary modification on the risk of breast and colorectal cancer, cardiovascular disease, and bone fractures (16). Between 1993 and 1998, the trials enrolled 68,132 postmenopausal women aged 50–79 years who were followed at one of 75 US examination sites (including satellites, remote sites, and their changes in location). Women were ineligible if they had medical conditions predictive of survival time less than 3 years, if they were known to have conditions inconsistent with study participation and adherence, or if they

were active participants in another randomized, controlled trial. Those who remained eligible and interested were invited to follow-up examinations at 1, 3, 6, and 9 years. Of the CT and OS minority participants enrolled in WHI, the WHI SNP Health Association Resource (SHARe) GWA study project includes 12,157 (8,515 self-identified African American and 3,642 self-identified Hispanic) women who consented to genetic research. DNA was extracted by the Specimen Processing Laboratory at the Fred Hutchinson Cancer research Center (FHCRC) using specimens that were collected at enrollment. Specimens were stored at -80°C. After exclusions, 4,149 African Americans with genotype and phenotype data were included in the analysis. Study protocols and consent forms were approved by the Institutional Review Boards at all participating institutions.

III. Supplemental References

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