SUPPLEMENTAL MATERIAL

Genotyping and Quality Control

Genotyping of ARIC-JHS overlap and JHS specific samples were both performed at the Broad Institute of Harvard and MIT using Affymetrix Genome-Wide Human SNP array 6.0, with approximately 900K autosomal SNPs under the CARe consortium.[1] ARIC-JHS sample was genotyped separately with the parent study. Quality control of genotyped data (SNPs) was performed using the Broad genetic analysis platform via Birdseed v1.33[1] and PLINK[2] software, and included measures such as removal of samples with genotyping call rate <95%, monomorphic SNPs, and SNPs with minor allele frequency (MAF) <1%. Samples that deviated by more than 4 standard deviation units from the average heterozygosity rate were likely to have poor DNA quality or contamination, and thus were removed from downstream analysis. Genome-wide identical-by-descent measures were obtained between all pairwise combinations of samples in order to identify sample duplicates, contaminated samples, and cryptic relationships All samples that did not cluster well when subjected to multidimensional scaling or genome-wide "neighbor" analysis in PLINK . Due to the presence of individuals with known pedigrees in JHS samples, identical-by-descent (IBD) and identical-by-state (IBS) between all pairwise combinations of samples were estimated and used to confirm cryptic relationships. During imputation, individuals with pedigree relatedness or cryptic relatedness (pi_hat>0.05) were filtered out". [3] Other quality control filters included; removing SNPs for which genotype missingness can be predicted by surrounding haplotypes, SNPs with Mendelian inconsistencies, and those with significant deviation from Hardy-Weinberg equilibrium ($p<1.0\times10^{-6}$). Of the total 2.5M SNPs, 113,238 SNPs were excluded in ARIC-JHS overlap sample and 40,653 in JHS

specific samples, which ensured >99% genotyping call rate.

Genotype imputation

Genotype imputation for both JHS specific and ARIC-JHS overlap samples were performed in CARe and has been detailed elsewhere.[4] Briefly, imputation was performed using MACH software (http://www.sph.umich.edu/csg/abecasis/MaCH/) based on phased haplotypes of HapMap (release 22). Since the African-American population is admixed with the proportion of European ancestry estimated to be ~17-19% the phased haplotypes serving as a reference panel consisted of equal proportions of the YRI and CEU HapMap (using only SNPs found in both YRI and CEU panels, i.e. ~2.2M SNPs). Hao and colleagues reported that the accuracy of using the mixed panel for African-Americans is comparable to the accuracy reported when imputing population of Nigerians using YRI as a reference panel.[5]

Supplemental References:

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3. Lettre G, Palmer CD, Young T, Ejebe KG, Allayee H, Benjamin EJ, Bennett F, Bowden DW, Chakravarti A, Dreisbach A, Farlow DN, Folsom AR, Fornage M, Forrester T, Fox E, Haiman CA, Hartiala J, Harris TB, Hazen SL, Heckbert SR, Henderson BE, Hirschhorn JN, Keating BJ, Kritchevsky SB, Larkin E, Li M, Rudock ME, McKenzie CA, Meigs JB, Meng YA, Mosley TH, Newman AB, Newton-Cheh CH, Paltoo DN, Papanicolaou GJ, Patterson N, Post WS, Psaty BM, Qasim AN, Qu L, Rader DJ, Redline S, Reilly MP, Reiner AP, Rich SS, Rotter JI, Liu Y, Shrader P, Siscovick DS, Tang WH, Taylor HA, Tracy RP, Vasan RS, Waters KM, Wilks R, Wilson JG, Fabsitz RR, Gabriel SB, Kathiresan S, Boerwinkle E. Genome-wide association study of coronary heart disease and its risk factors in 8,090 african americans: The nhlbi care project. *PLoS genetics*. 2011;7:e1001300

4. Fox ER, Musani SK, Barbalic M, Lin H, Yu B, Ogunyankin KO, Smith NL, Kutlar A, Glazer NL, Post WS, Paltoo DN, Dries DL, Farlow DN, Duarte CW, Kardia SL, Meyers KJ, Sun YV, Arnett DK, Patki AA, Sha J, Cui X, Samdarshi TE, Penman AD, Bibbins-Domingo K, Buzkova P, Benjamin EJ, Bluemke DA, Morrison AC, Heiss G, Carr JJ, Tracy RP, Mosley TH, Taylor HA, Psaty BM, Heckbert SR, Cappola TP, Vasan RS. Genome-wide association study of cardiac structure and systolic function in african americans: The candidate gene association resource (care) study. *Circ.Cardiovasc.Genet.* 2012

5. Hao K, Chudin E, McElwee J, Schadt EE. Accuracy of genome-wide imputation of untyped markers and impacts on statistical power for association studies. *BMC.Genet.* 2009;10:27

Supplemental Table 1: Conditional analyses of genome-wide significant loci in JHS

Type of SNPs	SNP	CHR	NHLBI hg18 Position	Beta (SE)	P-value
Locus Specific Conditional Analyses					
	rs198389	1	11841858	…	…
	rs12406089	1	11844885	-0.24 (0.06)	3.01×10^{-05}
	rs6668659	1	11843768	-0.24 (0.06)	1.00×10^{-05}
	rs3733402	4	187395028	…	…
	rs1511801	4	187387304	0.18 (0.05)	0.00028
	rs4253238	4	187385381	-0.19 (0.05)	0.00027
	rs4253311	4	187411677	0.13 (0.04)	0.0003
	rs11132382	4	187380796	0.10 (0.04)	0.0090
	rs4253252	4	187394452	0.09 (0.04)	0.0160
	rs2048	4	187385127	-0.09 (0.04)	0.0134
	rs1912826	4	187386534	-0.09 (0.04)	0.0134
	rs4253248	4	187392482	-0.09 (0.04)	0.0135
	rs4253251	4	187393467	0.13 (0.04)	0.0035
	rs925453	4	187416204	0.11 (0.03)	0.0007

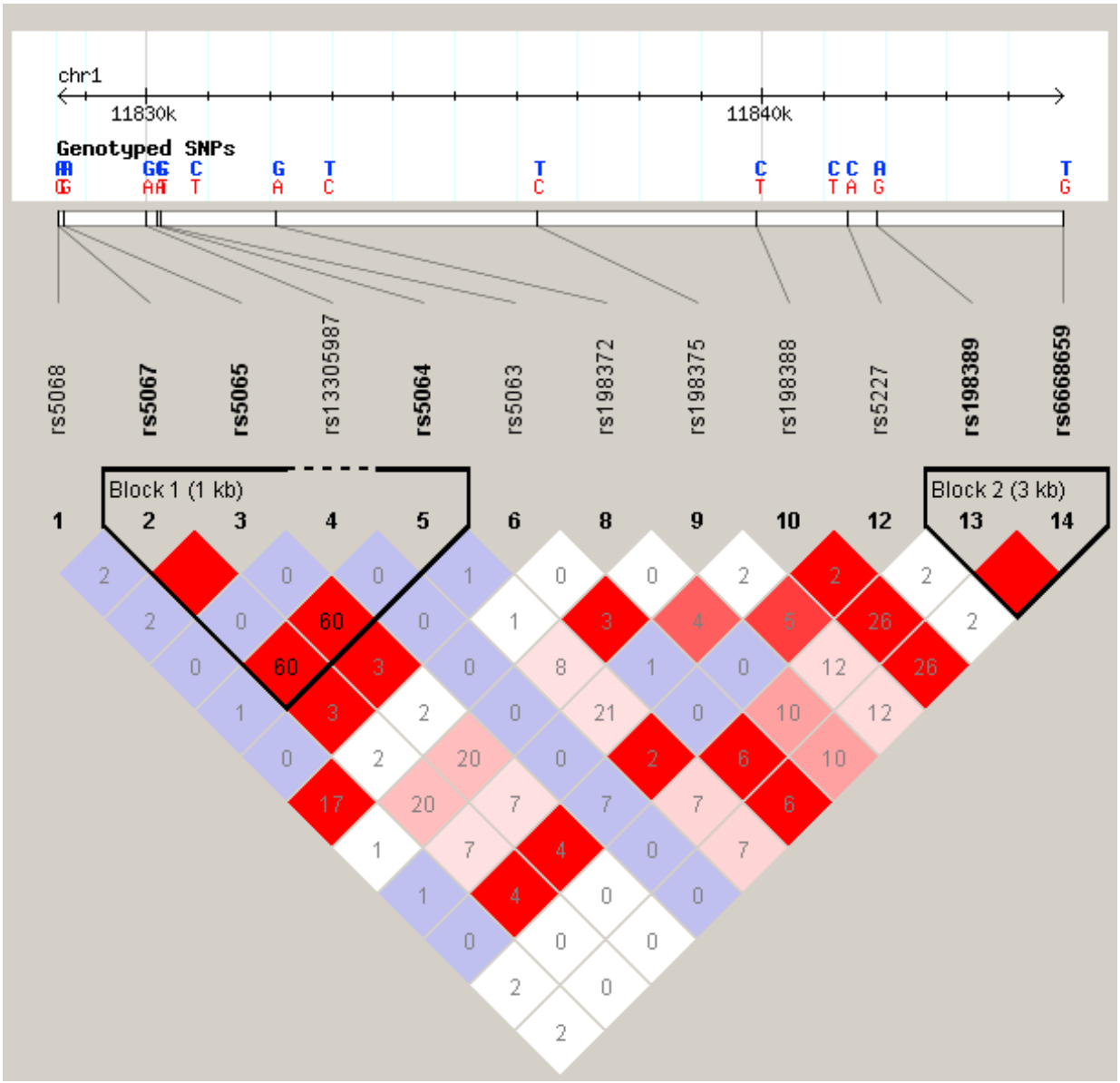
Supplemental Table 2: Unadjusted Spearman Correlation of BNP concentration with physiologically related traits

Trait	Women	Men	Pooled
Systolic Blood Pressure	0.20	0.24	0.20
Hypertension	0.13	0.25	0.17
Microalbuminuria	0.10	0.14	0.11
Glomerular Filtration Rate	-0.16	-0.20	-0.18
Chronic Kidney Disease	0.17	0.22	0.19
LV Mass	0.18	0.27	0.17

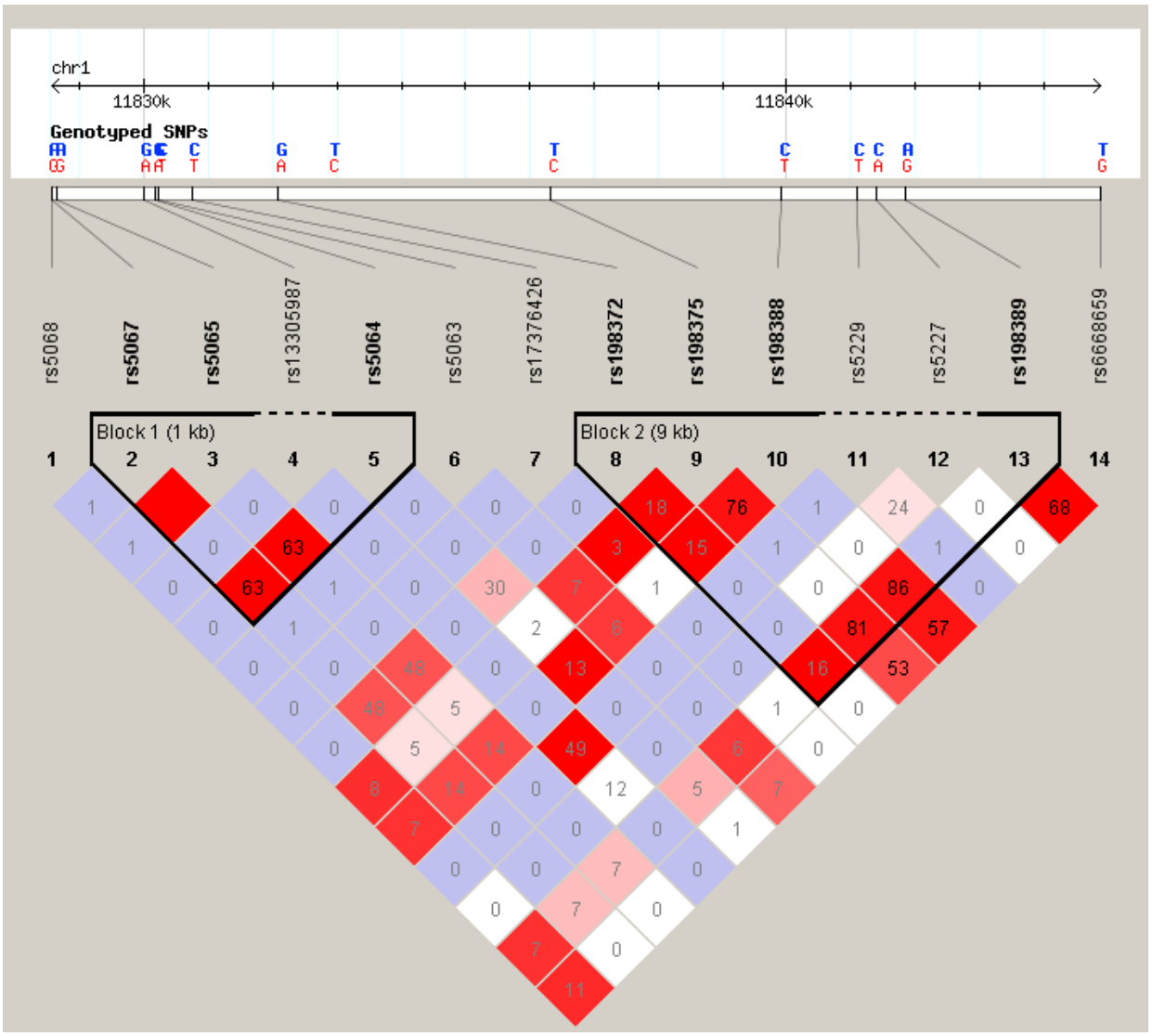
All correlations were highly significant ($p < 0.001$)

Supplemental Figure 1: LD plots within 25 kb of *NPPB* locus using genotyped HapMap Release II data in (**A**) Yoruba, YRI and (**B**) CEU populations.

A



B


chr1
11830k
11840k
Genotyped SNPs
rs5068
rs5067
rs5065
rs13305987
rs5064
rs5063
rs17376426
rs198372
rs198375
rs198388
rs5229
rs5227
rs198389
rs6668659
Block 1 (1 kb)
Block 2 (9 kb)
1
2
3
4
5
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7
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14