

RESEARCH ARTICLE

# Single-trait and multi-trait genome-wide association analyses identify novel loci for blood pressure in African-ancestry populations

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**Data Availability Statement:** Study-specific phenotypes and genotypes are available from dbGaP (ARIC: phs000280.v1.p1, CHS: phs000287.v1.p1, WHI: phs000200.v1.p1, MESA: phs000283.v1.p1, Cleveland Family Study: phs000284.v1.p1, CARDIA: phs000285.v3.p). Discovery meta-analyses results for this study and readme file related to meta-analyses are available in GRASP and can be accessed from <http://apps.nhlbi.nih.gov/GRASP/>.

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## Abstract

Hypertension is a leading cause of global disease, mortality, and disability. While individuals of African descent suffer a disproportionate burden of hypertension and its complications, they have been underrepresented in genetic studies. To identify novel susceptibility loci for blood pressure and hypertension in people of African ancestry, we performed both single and multiple-trait genome-wide association analyses. We analyzed 21 genome-wide association studies comprised of 31,968 individuals of African ancestry, and validated our results with additional 54,395 individuals from multi-ethnic studies. These analyses identified nine loci with eleven independent variants which reached genome-wide significance ( $P < 1.25 \times 10^{-8}$ ) for either systolic and diastolic blood pressure, hypertension, or for combined traits. Single-trait analyses identified two loci (*TARID/TCF21* and *LLPH/TMBIM4*) and

multiple-trait analyses identified one novel locus (*FRMD3*) for blood pressure. At these three loci, as well as at *GRP20/CDH17*, associated variants had alleles common only in African-ancestry populations. Functional annotation showed enrichment for genes expressed in immune and kidney cells, as well as in heart and vascular cells/tissues. Experiments driven by these findings and using angiotensin-II induced hypertension in mice showed altered kidney mRNA expression of six genes, suggesting their potential role in hypertension. Our study provides new evidence for genes related to hypertension susceptibility, and the need to study African-ancestry populations in order to identify biologic factors contributing to hypertension.

### Author summary

Hypertension is a global health problem which affects disproportionately people of African descent. We conducted a genome-wide association study of blood pressure in 31,968 Africans and African Americans to identify genes conferring susceptibility to increased blood pressure. This research identified three novel genomic regions associated with blood pressure which have not been previously reported in studies of other race/ethnicity. Using experimental models, we also showed an altered expression of these genes in kidney tissue in hypertension. These findings provide new evidence for genes influencing hypertension risk and supports the need to study diverse ancestry populations in order to identify biologic factors contributing to hypertension.

### Introduction

Genetic studies hold the promise of providing tools to better understand and treat clinical conditions. To achieve the clinical and public health goals of reducing hypertension and its sequelae, and to understand ethnic disparities in the risk for hypertension, there is a need to study susceptible populations for genetic determinants of blood pressure (BP). BP traits are highly heritable across world populations (30 to 55%).<sup>[1–4]</sup> Over 200 genetic loci have been identified in genome-wide association studies <sup>[5–13]</sup> and admixture mapping studies.<sup>[14–17]</sup> These variants explain approximately 3.5% of inter-individual variation in BP.<sup>[5, 7]</sup> However, there is still a paucity of studies focused on individuals of African descent. Most of the loci identified in the literature have not been replicated in individuals of African ancestry.<sup>[18, 19]</sup>

African Americans have higher mean BP, an earlier onset of hypertension, and a greater likelihood to have treatment-resistant hypertension than other ethnic groups.<sup>[20–23]</sup> Emerging research on Africans shows increasing prevalence of hypertension in urban African communities <sup>[24, 25]</sup> which are more Westernized than rural African communities and, so, more closely resemble communities in which African Americans live in the U.S. Hypertension contributes to a greater risk of coronary heart disease, stroke, and chronic kidney disease.<sup>[26–30]</sup> African Americans experience increased risk of these hypertension-related outcomes <sup>[31–34]</sup> but the underlying mechanisms, whether environmental exposures or increased genetic susceptibility, are unknown.

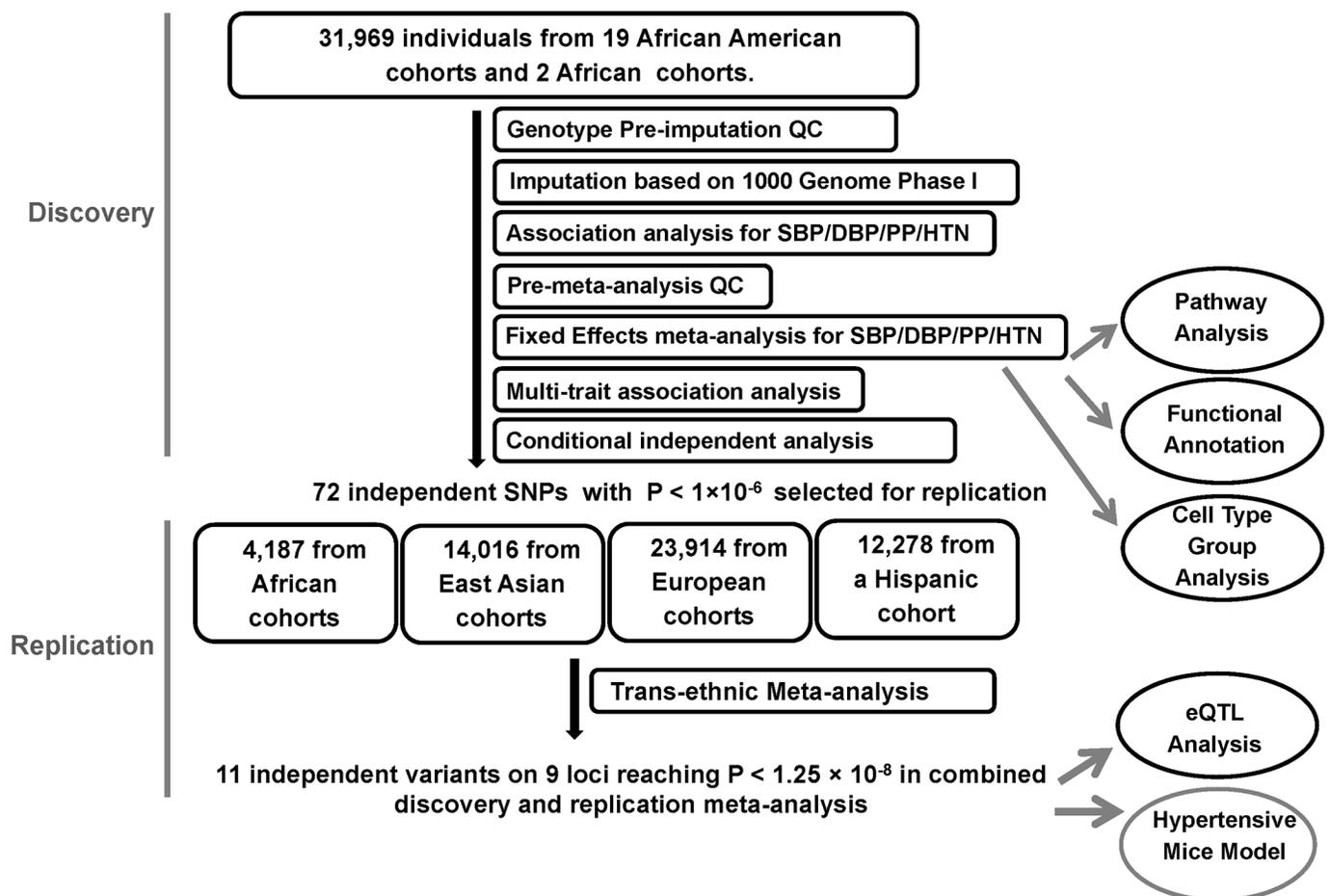
We hypothesized that additional variants associated with BP can be identified in people of African ancestry; some variants may be African-specific, as has been observed for multiple traits, including kidney disease <sup>[35]</sup> and metabolic syndrome.<sup>[36, 37]</sup> Other variants may be identified in novel loci based on a higher frequency of risk alleles in this population. We used

high density imputed genotypes from the 1000 Genomes Project (1000G) to expand the genome coverage of genetic variants so that we could examine the evidence for association with BP traits.

Here, we report three novel loci associated with BP which are driven by variants that are common in or unique to African-ancestry populations. Through bioinformatics and experimental evidence of kidney gene expression in mice submitted to angiotensin-II (Ang II) induced hypertension, we provide evidence for a key role of these genes in the pathogenesis of hypertension. In addition, our study extends the discovery of BP loci to genes related to kidney and the immune systems, and provides biological relevance for these loci to BP regulation.

### Results

The study design and analysis process are shown in Fig 1. Study characteristics, genotyping, and quality control (QC) for discovery and replication samples are shown in S1 and S2 Tables. The discovery samples included 31,968 individuals of African ancestry from 19 studies. The replication samples included 4,184 individuals of African ancestry from three studies, 23,914 individuals of European ancestry from five studies, 14,016 individuals of Korean ancestry from three studies, and 12,278 individuals of Hispanic/Latino ancestry from one study.



**Fig 1. Study design schematic for discovery and replication of loci.** QC, quality control; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; HTN, hypertension; eQTL, expression quantitative loci.

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## Single-trait and multi-trait meta-analysis genome-wide association study (GWAS) results

Study-specific genomic-control inflation ranged from 0.98–1.06 (S3 Table, S1 Fig) and the linkage disequilibrium (LD) score regression intercepts of the single-trait BP meta-analyses calculated by the LD score regression approach ranged from 1.02–1.04. [38] These results suggest well-controlled population stratification.

The single-trait BP meta-analyses identified several genome-wide significant single nucleotide polymorphisms (SNP) at eight loci ( $P < 5.0 \times 10^{-8}$ , systolic BP (SBP): three loci, four SNPs; diastolic BP (DBP): three loci, three SNPs; pulse pressure (PP): three loci, four SNPs; and hypertension (HTN): one locus, one SNP), with the *EVX1/HOXA* locus identified for SBP, DBP and HTN (S2A–S2D Fig). When combining summary statistics for SBP, DBP, and HTN using the multi-trait approach CPASSOC,[39] we identified one locus by the multi-trait statistic  $S_{\text{Hom}}$  (*EVX1/HOXA*) and six loci by  $S_{\text{Het}}$  (*ULK4*, *TCF21*, *EVX1/HOXA*, *IGFBP3*, *CDH17*, *ZNF746*) at  $P < 5 \times 10^{-8}$  (S2E and S2F Fig). Note some loci overlap between single-trait and multi-trait findings.

We observed 264 variants with  $P < 1 \times 10^{-6}$  for either single- or multi- trait GWAS and these variants were further analyzed by conditional association on the most associated SNPs at each locus (S4 Table). These analyses resulted in 72 independent associations, which included 58 SNPs with minor allele frequency (MAF)  $\geq 0.05$  and 14 with low frequency variants ( $0.01 < \text{MAF} < 0.05$ ) (S5 Table).

## Trans-ethnic replication

Among these 72 variants carried forward for trans-ethnic replication, nine variants, all low frequency variants (MAF < 0.02), were not available in replication cohorts because they were either monomorphic in the replication population or had a low imputation quality, reducing our replication effort to 63 variants (S6 Table). Eleven independent variants at nine loci were significantly associated with BP traits at  $P < 1.25 \times 10^{-8}$  in the combined discovery and replication analyses and are reported in Table 1. This significance level was determined by adjusting for two independent traits for SBP, DBP, PP and HTN, and two tests of multiple trait analysis. This includes six variants that reached significance level at discovery stage ( $P < 5 \times 10^{-8}$ ). Two loci were identified only through multi-trait analyses (*FRMD3*, *IGFBP3*). Three of these nine loci are novel: *TARID/TCF21*, *FRMD3*, and *LLPH/TMBIM4* (Fig 2A–2C). Four loci (*ULK4*, *PLEKHG1*, *EVX1/HOXA* cluster, and *GPR20*) have been reported in our previous BP GWAS of African ancestry (S3 Fig), [7, 18] and two loci (*IGFBP3*, *CDH17*) have been reported in multiple-trait analyses of African-ancestry studies (Fig 2D–2F). [39] A composite genetic-risk score using the eleven variants identified accounted for 1.89%, 2.92%, 1.03% and 1.08% of the variance for SBP, DBP, PP and HTN respectively.

## Newly identified loci harbor variants common only in African-ancestry populations

Five of the eleven replicated variants are common in individuals of African ancestry but rare or monomorphic in individuals of non-African ancestry (rs76987554, rs115795127, rs113866309, rs7006531, and rs78192203) (Table 1). These five variants were 1) either low frequency or common variants in COGENT-BP African-ancestry samples; 2) low frequency in 1000G Phase I Integrated Release Ad Mixed-American ancestry (AMR); and 3) monomorphic in 1000G Asian ancestry (ASN) or European ancestry (EUR). One common variant was present in only 1000G samples of African ancestry (rs115795127 at *FRMD3*, Table 1). These variants were located at the

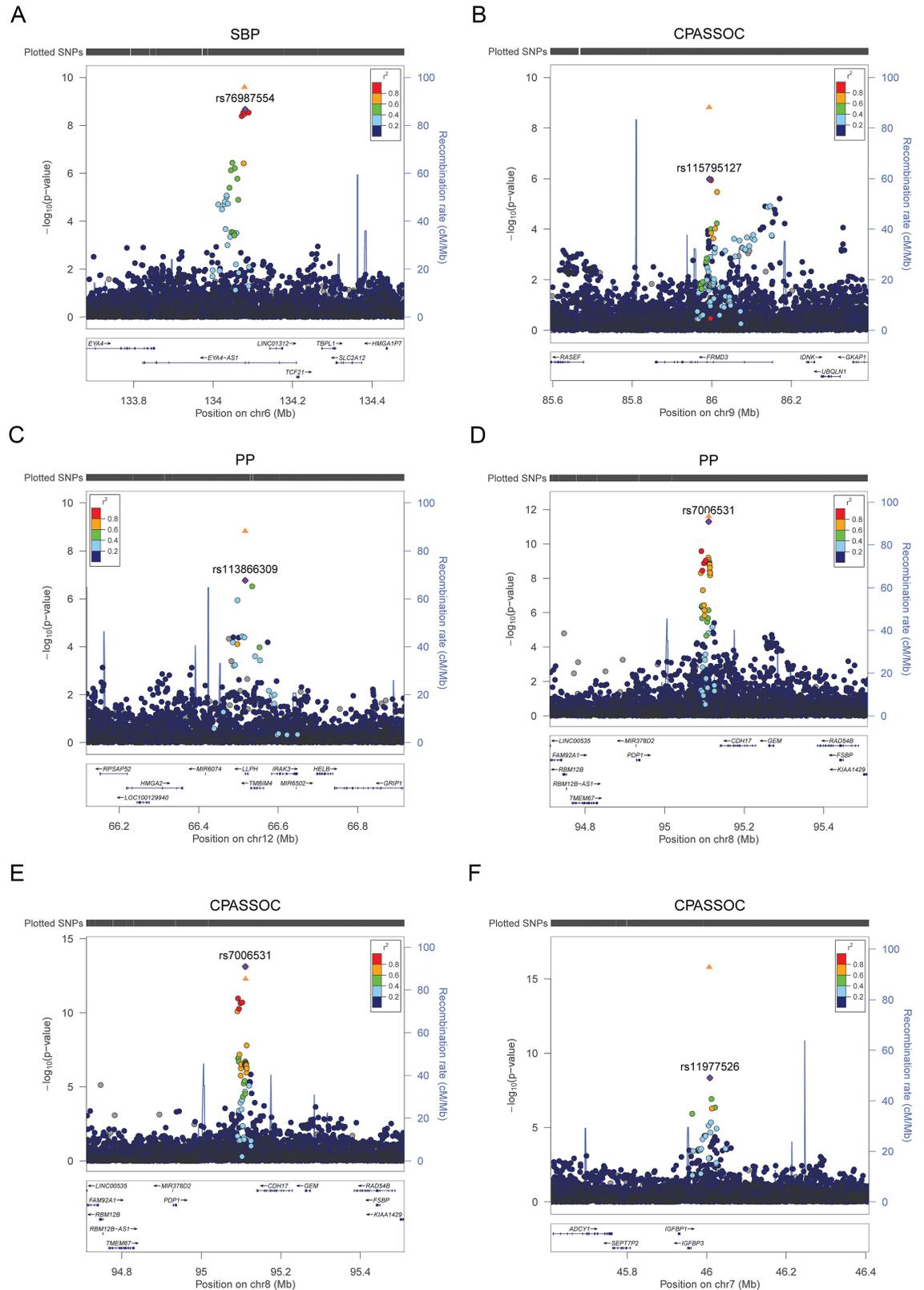
**Table 1. Loci identified in combined COGENT-BP African ancestry discovery samples and multi-ethnic replication samples.**

SNP	Effect Allele/ Other Allele	Chr	Nearby Gene	COGENT-BP Allele Frequency	1000G Phase 1 Allele Frequency				Single or Multi-Trait (CPASSOC) Statistic	COGENT-BP Discovery (Up to N = 31,155)		Trans-Ethnic Replication (Up to N = 54,245)	Combined Meta-analyses (Up to N = 85,397)
					AFR	AMR	ASN	EUR		Beta (SE)	P		
<b>SNPs in novel loci</b>													
rs76987554	C/T	6	TARID/ TCF21	0.91	0.91	0.99	1	1	SBP	1.85 (0.31)	<b>2.2x10<sup>-9</sup></b>	2.0x10 <sup>-2</sup>	<b>2.3x10<sup>-10</sup></b>
rs115795127	T/C	9	FRMD3	0.89	0.86	1	1	1	CPASSOC S <sub>Het</sub>	NA	1.1x10 <sup>-6</sup>	8.4x10 <sup>-6</sup>	<b>7.3x10<sup>-9</sup></b>
rs113866309	C/T	12	LLPH/ TMBIM4	0.02	0.02	0.01	0.00	0.00	PP	3.28 (0.63)	1.7x10 <sup>-7</sup>	1.5x10 <sup>-3</sup>	<b>8.2x10<sup>-9</sup></b>
<b>SNPs in published BP loci</b>													
rs7651190	G/A	3	ULK4	0.65	0.72	0.17	0.15	0.19	DBP	0.45 (0.11)	4.2x10 <sup>-5</sup>	1.0x10 <sup>-5</sup>	<b>2.0x10<sup>-9</sup></b>
									CPASSOC S <sub>Het</sub>	NA	<b>6.9x10<sup>-9</sup></b>	2.0x10 <sup>-4</sup>	<b>9.8x10<sup>-11</sup></b>
rs7372217	G/A	3	ULK4	0.66	0.71	0.20	0.16	0.20	DBP	0.55 (0.11)	9.5x10 <sup>-7</sup>	8.1x10 <sup>-7</sup>	<b>5.3x10<sup>-12</sup></b>
									CPASSOC S <sub>Het</sub>	NA	8.2x10 <sup>-6</sup>	6.5x10 <sup>-8</sup>	<b>1.4x10<sup>-11</sup></b>
rs62434120	T/A	6	PLEKHG1	0.85	0.83	0.82	0.95	0.92	SBP	1.19 (0.24)	1.1x10 <sup>-6</sup>	2.7x10 <sup>-3</sup>	<b>5.7x10<sup>-9</sup></b>
									CPASSOC S <sub>Het</sub>	NA	1.1x10 <sup>-6</sup>	2.7x10 <sup>-3</sup>	<b>5.7x10<sup>-9</sup></b>
rs11563582	A/G	7	EVX1/ HOXA cluster	0.13	0.16	0.09	0.05	0.08	SBP	1.61 (0.28)	<b>7.1x10<sup>-9</sup></b>	4.2x10 <sup>-4</sup>	<b>4.5x10<sup>-10</sup></b>
									DBP	1.02 (0.17)	<b>8.4x10<sup>-10</sup></b>	1.4x10 <sup>-4</sup>	<b>1.7x10<sup>-11</sup></b>
									CPASSOC S <sub>Hom</sub>	NA	<b>1.5x10<sup>-10</sup></b>	8.0x10 <sup>-4</sup>	<b>1.9x10<sup>-11</sup></b>
									CPASSOC S <sub>Het</sub>	NA	<b>1.1x10<sup>-9</sup></b>	9.4x10 <sup>-3</sup>	<b>1.8x10<sup>-9</sup></b>
rs6969780	C/G	7	HOXA	0.30	0.35	0.21	0.13	0.10	SBP	0.82 (0.19)	1.7x10 <sup>-5</sup>	6.5x10 <sup>-5</sup>	<b>6.2x10<sup>-9</sup></b>
									DBP	0.62 (0.12)	7.0x10 <sup>-8</sup>	2.1x10 <sup>-4</sup>	<b>3.3x10<sup>-10</sup></b>
									CPASSOC S <sub>Hom</sub>	NA	4.1x10 <sup>-7</sup>	4.0x10 <sup>-4</sup>	<b>9.9x10<sup>-9</sup></b>
rs11977526	A/G	7	IGFBP3	0.34	0.34	0.31	0.78	0.41	CPASSOC S <sub>Het</sub>	NA	<b>4.5x10<sup>-9</sup></b>	2.9x10 <sup>-9</sup>	<b>7.3x10<sup>-16</sup></b>
rs7006531	G/A	8	CDH17	0.15	0.19	0.02	0.00	0.00	PP	1.16 (0.17)	<b>5.0x10<sup>-12</sup></b>	9.7x10 <sup>-2</sup>	<b>5.9x10<sup>-12</sup></b>
									CPASSOC S <sub>Het</sub>	NA	<b>7.6x10<sup>-14</sup></b>	6.1x10 <sup>-3</sup>	<b>2.2x10<sup>-13</sup></b>
rs78192203	T/A	8	GPR20	0.80	0.79	0.98	1	1	DBP	0.77 (0.14)	<b>1.3x10<sup>-8</sup></b>	2.7x10 <sup>-4</sup>	<b>4.1x10<sup>-11</sup></b>

Bold P-values represent either significance level at 5.0x10<sup>-8</sup> in discovery sample or at 1.25x10<sup>-8</sup> at combined discovery and replication samples. 1000G samples: AFR, African ancestry; AMR, American ancestry; ASN, Asian ancestry; EUR, European ancestry

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three novel loci (*TARID/TCF21*, *FRMD3*, and *LLPH/TMBIM4*). Given the differences in allele frequency across continental-ancestry populations, we examined the evidence for selection at each of these loci using iHS, which measures the amount of extended haplotype homozygosity at a given SNP along the ancestral allele relative to the derived allele.[40] The iHS score for



**Fig 2.** Regional plots of the significant loci **A.** *TARID/TCF21* for SBP **B.** *FRMD3* for  $S_{Het}$  of CPASSOC **C.** *LLPH* locus for PP **D.** *CDH17* for PP **E.** *CDH17* for  $S_{Het}$  of CPASSOC **F.** *IGFBP3* for  $S_{Het}$  of CPASSOC. The y axis shows the  $-\log_{10}$  P values of SNP associations, and the x axis shows their chromosomal positions. The lowest P value SNP is plotted as a purple

diamond and its correlation with other SNPs in the region is shown in color. The orange triangle is P value in the combined discovery and replication trans-ethnic meta-analysis of the lowest P value SNP.

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rs115795127 was 2.7 in African American samples from the Candidate-gene Association Resource (CARE) consortium (see [Methods](#)), suggesting selection at the *FRMD3* locus ([S7 Table](#)).

### Distinct associations at *EVX1/HOXA*, *ULK4*, and *GPR20* in African-ancestry populations

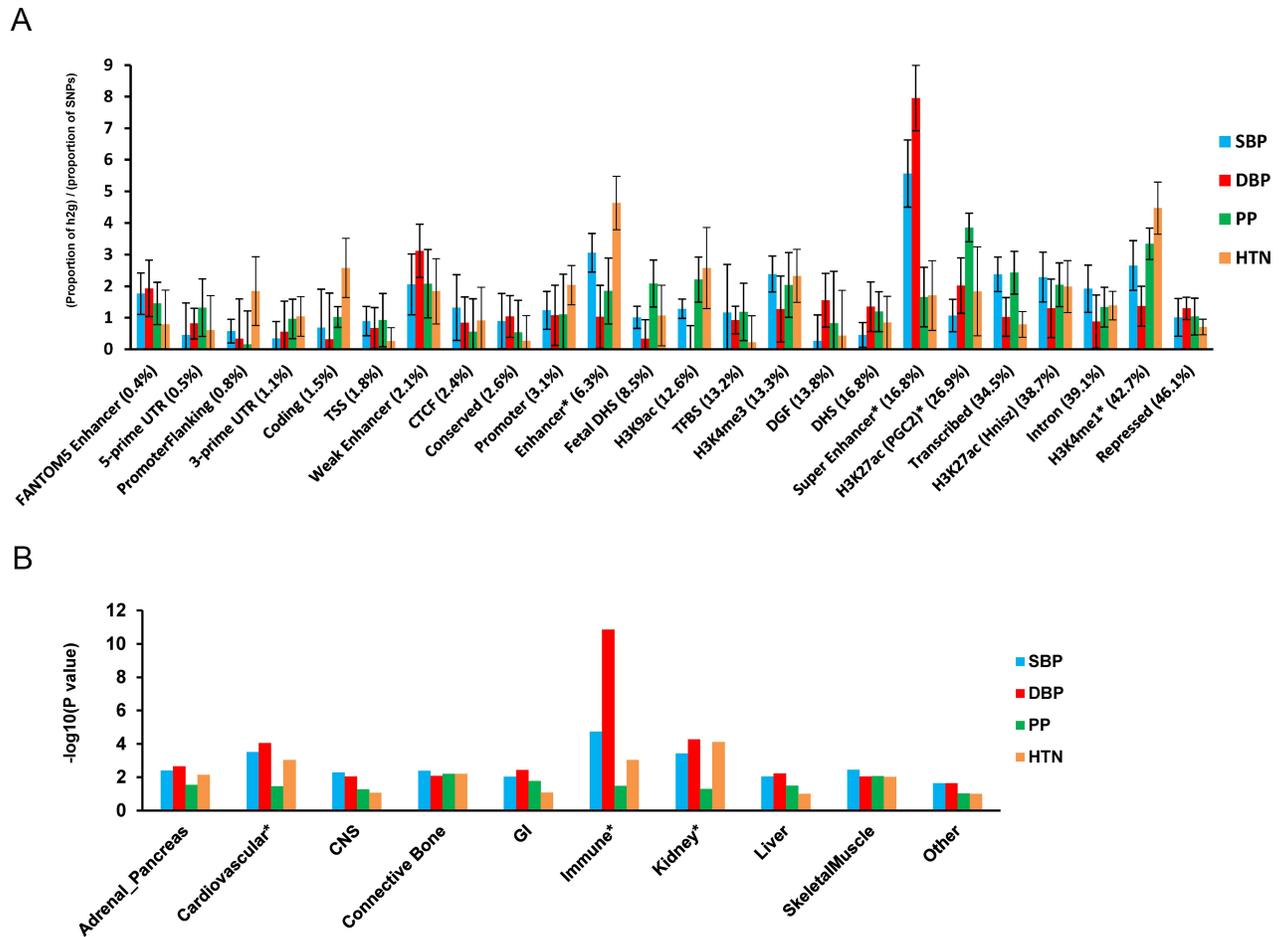
We observed two independent genome-wide significant variants at the *EVX1/HOXA* locus ( $P < 1.25 \times 10^{-8}$ ). The two variants, rs11563582 and rs6969780, are in weak LD ( $r^2 = 0.21$ ) ([S3A–S3C Fig](#)), and the LD pattern suggests that these SNPs are located in two blocks ([S4 Fig](#)). SNP rs11563582 is in strong LD with the previously reported SNP in the region (rs17428741). [18] SNP rs6969780 remained significant when conditioning on rs11563582 ([S4 Table](#)), thus demonstrating the presence of allelic heterogeneity at this locus. Two independent variants at *ULK4* reached the significance threshold: rs7651190 and rs7372217 (LD  $r^2 = 0.15$ ) ([S4E Fig](#)). SNP rs7372217 is in strong LD with the previous reported SNP rs1717027. [18] The association evidence of rs1717027 can be explained by rs7372217 but not by rs7651190 in conditional analysis ([S4 Table](#)). Thus, rs7651190 is an independent association at this locus. At the *GPR20* locus, our most significant SNP, rs78192203, is 8kb away and it is not in LD with the published SNP, rs34591516 ( $r^2 = 0.008$ ,  $D' = 0.68$  in African American CARE participants).

### Pathway analyses suggest enrichment of immune pathways for BP traits

To gain insight into biologic mechanisms underlying genes associated with BP traits, we performed pathway analysis using publicly available databases. [41] The most relevant pathways identified were GSK3, Th1/Th2 differentiation, and Sonic Hedgehog (SHH) pathways (BioCarta); pyrimidine metabolism, apoptosis signaling pathway, and B cell activation (Panther); JAK Stat signaling, T cell receptor signaling, and B cell receptor signaling (Ingenuity); cytokine-cytokine receptor interaction and vascular smooth muscle contraction (KEGG); and neuronal activity, T cell mediated immunity, and tumor suppressor (Panther Biological Process) (Gene Set Enrichment Analysis [GSEA] P-value  $< 0.01$ , [S8 Table](#)). These analyses suggest enrichment of immune pathways for BP traits.

### Tissue and cell type group enrichment analyses identify immune, kidney, and cardiovascular enriched systems

We performed functional annotation and cell type group enrichment analysis using the stratified LD score regression approach which uses data from ENCODE and the Roadmap Epigenetic Project, as well as GWAS results while accounting for the correlation among markers. [42] We estimated functional categories of enrichment using an enrichment score, which is the proportion of SNP-heritability in the category divided by the proportion of SNPs. We identified super enhancer ( $P_{\text{Enrich}} = 5.4 \times 10^{-5}$ , Enrichment = 5.6 for DBP), enhancer ( $P_{\text{Enrich}} = 4.8 \times 10^{-4}$ , Enrichment = 4.3 for HTN), and H3K27ac ( $P_{\text{Enrich}} = 3.2 \times 10^{-4}$ , Enrichment = 3.6 for HTN) significant enrichment ([Fig 3](#)). These results support a role of identified noncoding regulatory regions in BP regulation. In addition, the following cell types showed significant enrichment ( $P \leq 2.5 \times 10^{-3}$ ): the immune ( $P_{\text{Enrich}} = 1.4 \times 10^{-9}$ , Enrichment = 8.4 for DBP), kidney ( $P_{\text{Enrich}} = 5.4 \times 10^{-5}$ , Enrichment = 4.8 for DBP), and cardiovascular ( $P_{\text{Enrich}} = 8.9 \times 10^{-5}$ , Enrichment = 4.2 for SBP) systems ([Fig 3](#)).



**Fig 3. Enrichment for functional annotations and cell-type groups using stratified LD score regression.** **A.** Enrichment estimates of 24 main annotations for each of four BP traits. Annotations are ordered by size. Error bars represent jackknife standard errors around the estimates of enrichment, and stars indicate significance at  $P < 0.05$  after Bonferroni correction for 24 hypotheses tested and four BP traits. **B.** Significance of enrichment of 10 cell-type groups for four BP traits. Dotted line and stars indicate significance at  $P < 0.05$  after Bonferroni correction for 10 hypotheses tested and four BP traits.

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We next determined the enrichment of variants at the eleven genome-wide significant loci for DNase I hypersensitive (DHS) sites in 34 tissue categories from ENCODE. At each locus, we identified variants in  $r^2 > 0.1$  with the index variant and calculated causal evidence (Bayes Factors) for each variant. We then tested for enrichment in the causal evidence of variants in DHS sites using fGWAS.[43] We found enrichment of blood/immune DHS (Enrichment = 3.1) and cardiovascular DHS (blood vessel Enrichment = 28.7, heart Enrichment = 2.0), in addition to DHS in several fetal tissues (S5 Fig). Candidate causal variants at several loci overlapped enriched DHS sites. For example, at the *LLPH/TMBIM4* locus, the most likely causal variant, rs12426813, overlaps a DHS site active in immune (CD14+, CD4+, CD34+), blood vessel (HMVEC), and heart (HCF) cells (S5 Fig).

### Overlap with eQTL at specific tissues

To examine whether the eleven significant SNPs are eQTL, we searched the genotype-tissue expression (GTEx) pilot database, which includes non-disease human tissue.[42] Among the eleven SNPs, three SNPs have been identified as eQTL: rs6969780 (*HOXA2*), rs7651190

(*ULK4*), and rs62434120 (*PLEKHG1*) (S9 Table). SNP rs6969780 is an eQTL for expression of *HOXA2*, *HOXA7*, *HOTAIRM1*, and *HOXA5* in multiple tissues, including esophagus, artery, lung, skin, nerve, adipose, skeletal muscle, and stomach tissues. SNP rs7651190 is an eQTL for *ULK4* and *RPL36P20* in artery, whole blood, thyroid, nerve, esophagus, skeletal muscle, skin, brain, and stomach cells/tissues. SNP rs62434120 is an eQTL for *PLEKHG1* in testis tissue.

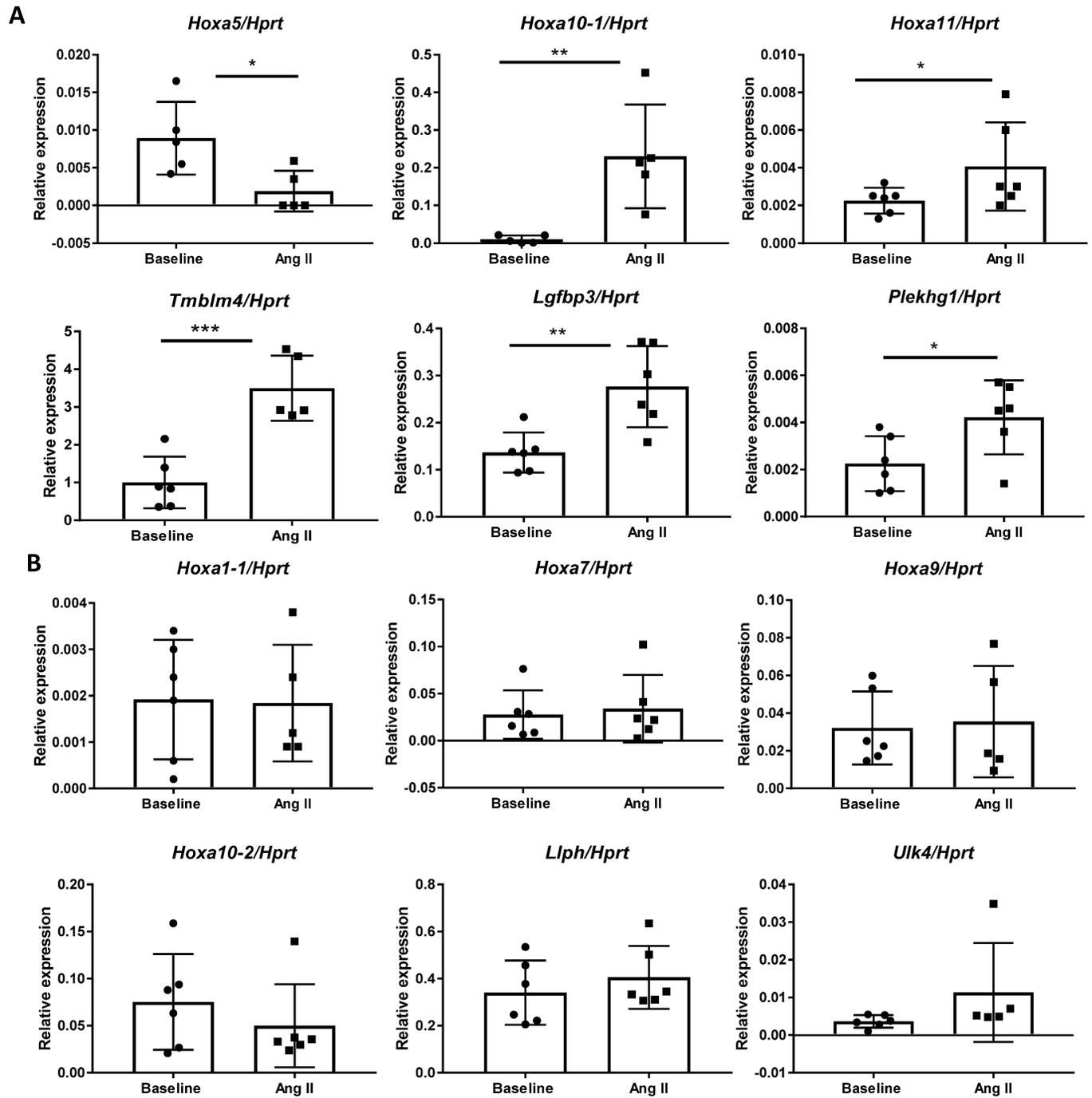
## Kidney gene expression in experimental angiotensin II-induced hypertension

To determine if identified genes are functionally involved in BP regulation in the kidney during hypertension,[44] we quantified gene expression in mice kidneys at baseline and during the hypertensive state induced by Ang II. This hypertensive model was chosen for two reasons: 1) to mimic the low plasma renin state, albeit more exaggerated than the level observed, in African-ancestry individuals that has been suggested to reflect the elevated renin-angiotensin system activity at the tissue level in the kidney [45], and 2) maintenance of hypertension in the Ang II model requires activation of the immune system that is implicated in several identified loci.[46, 47] Kidney gene expressions of the identified genes were compared to age-matched untreated mice after two weeks of Ang II infusion, which increases SBP. For the *HOXA* locus, we examined the expression of genes that are known to be expressed in the mouse kidney: *Hoxa1* (2 isoforms), 5, 7, 9, 10 (2 isoforms), and 11. Among all the genes examined, *Tmbim4* was the most abundantly expressed gene in the kidney at baseline. Six genes—*Hoxa5*, *Hoxa10-1* isoform, *Hoxa11*, *Tmbim4*, *Igfbp3*, and *Plekhg1*—were significantly differentially expressed in the kidney after Ang II treatment compared to baseline (Fig 4). Except for *Hoxa5*, which showed a significant decrease (Fig 4A), the expression of all these genes increased after the intervention. The expression of six genes—*Hoxa1-1* isoform, *Hoxa7*, *Hoxa9*, *Hoxa10-2* isoform, *Llph*, and *Ulk4*—were unchanged after Ang II infusion (Fig 4B). The following genes were not expressed in the adult mouse kidney at baseline or after Ang II intervention: *Frmd3-1* isoform, *Frmd3-2* isoform, *Grp20*, *Tcf21*, *Cdh17*, and *Hoxa1-2* isoform.

## Discussion

To date, this is the largest genome-wide analysis of African-ancestry populations to study genetic variants underlying BP traits using dense-coverage imputed genotypes. Our main findings are eleven independent variants at nine loci, significantly associated with BP traits, including three newly identified loci (*TARID/TCF21*, *FRMD3*, *LLPH/TMBIM4*). We also found evidence for additional independent SNP associations in fine-mapping of three previously described loci, *ULK4*, *EVX1/HOXA*, and *GRP20*. [18, 39]

The most significant variants at *TARID/TCF21*, *FRMD3*, *GPR20*, and *CDH17* are common variants in COGENT-BP African-ancestry participants, but monomorphic or low frequency in non-African-ancestry populations. For example, rs115795127 at *FRMD3* is rare in European populations (MAF = 0.0007) and absent in East Asian and Hispanic/Latino populations. Therefore, they could not be identified in GWAS of non-African-ancestry populations even when increasing sample sizes. We also show evidence for selection for the variant at *FRMD3*, although additional studies should confirm these findings. The African-specific variants were not well tagged by HAPMAP2 data and therefore were not detected in our previous African-ancestry GWAS.[18] Overall, our results suggest additional gain in discovery when using dense imputed genotypes and support a role of population-specific alleles in African and African-admixed populations contributing to BP regulation and hypertension. Furthermore, they support the rationale and the need to study diverse populations in order to more effectively characterize the genetic architecture of BP in populations and the ethnic disparities in hypertension.



**Fig 4. Relative renal mRNA levels of genes identified at baseline and after 2 weeks of Ang II-induced hypertension.** *HPRT* gene was used for normalization.  $N \geq 5$  in each group. **A.** Genes that were differentially expressed between baseline and Ang II conditions. **B.** Genes that were not altered between the two conditions. \*  $P < 0.05$ . \*\*  $P < 0.01$ . \*\*\*  $P < 0.001$ .

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Functional annotation of our lead variants showed co-localization with annotated elements, including super enhancer, enhancer, and H3K27ac chromatic mapping in immune cells and kidney tissues, which has not been previously reported, in addition to cardiovascular tissues. There was also evidence for regulatory function in these relevant tissues through gene

expression regulation (eQTL) and through overlaps with DHS in relevant tissues/cells. This evidence was additionally supported by experimental findings of differential expression of six genes (*Hoxa5*, *Hoxa10-1* isoform, *Hoxa11*, *Tmbim4*, *Igfbp3*, and *Plekhg1*) in the mouse kidney after HTN induced by Ang II treatment. Overall, our results suggest the functional importance of identified genes in regulating BP in both normal and hypertension states.

At the newly identified loci, SNP rs76987554 is an intronic variant in *TARID* (*TCF21* anti-sense RNA inducing promoter demethylation) which has not been previously reported to be associated with BP traits. A nearby gene, *TCF21* (transcription factor 21), is a transcription factor of the basic helix-loop-helix family, which is mainly expressed in the liver, kidney, and heart. *TCF21* is involved in epithelial differentiation and branching morphogenesis in kidney development,[48] and was associated with hypertension in a study of individuals of Japanese ancestry.[49] At the chromosome 7, rs115795127 is an intronic variant to *FRMD3* (FERM domain containing 3) which encodes a protein involved in maintaining cell shape and integrity. *FRMD3* has been associated with type 1 and type 2 diabetic kidney diseases in different ethnic populations, including those of European, African, and Asian ancestries.[50] The diabetes variant, rs10868025, is not in LD with rs115795127 in our African American samples or in 1000G EUR samples ( $r^2 = 0.00028$  and  $0.0018$ , respectively), thus representing an independent association at this locus.

At chromosome 9, the functions of *LLPH* and *TMBIM4* genes in BP regulation are currently unknown. *LLPH* belongs to the learning-associated protein family and is highly expressed in the immune system and the adrenal gland. *TMBIM4* encodes the transmembrane BAX inhibitor motif-containing protein 4 and is highly expressed in whole blood, the immune system, and the adrenal gland.[51] The most significant variant at this locus, rs113866309, overlaps a DHS in immune, blood vessel, and heart cells. In our experimental model in mice, *Tmbim4* gene expression was significantly increased after Ang II-induced HTN. This gene has been shown to inhibit apoptosis[52] and to decrease the efficacy of inositol 1,4,5-triphosphate ( $IP_3$ )-dependent release of intracellular  $Ca^{2+}$ . [53] This raises the possibility that the *TMBIM4* protein may serve to dampen the effect of Ang II, which activates  $IP_3$  in vascular smooth muscle cells through the stimulation of the angiotensin type 1 receptor.[51, 53, 54] Therefore, it is possible that in conditions of activated renin-angiotensin system, genetic variants that lower the expression of *TMBIM4* may augment BP, whereas genetic variants that increase its expression may attenuate BP.

Other genes, such as *Hoxa5*, *Hoxa10-1*, *Hoxa11*, *Igfbp3*, and *Plekhg1*, were significantly differentially expressed after Ang II-induced HTN in our mice experimental models. The *HOXA*-cluster has been identified in our previous GWAS of BP in African ancestry and in a recent GWAS of BP in European ancestry[5] though the underlying mechanisms related to BP control are unknown. We identified two independent variants at this locus; further studies are needed to delineate which of the *HOXA* genes are most likely involved in the association. In our experimental mice model, the *Hoxa10-1* isoform had a greater than 20-fold increase in kidney expression during Ang II-induced HTN compared to baseline levels. However, it remains to be determined whether it is an effect of Ang II in hypertension, or a compensatory response to hypertension. Future studies using genetic manipulation in rodents are required to determine whether these changes are specific response related to BP and Ang II or simply a generic response to stress.

We identified several additional pathways involved in BP traits, including the GSK3 pathway, which has been reported to influence Wnt-mediated central BP regulation.[55] The Th1/Th2 pathway is involved in the regulation of immune responses[56] and has been linked to hypertension and atherosclerosis.[57, 58] The role of the immune system in the development of hypertension has been suggested in clinical studies and experimental animal models.[59–

[64] This includes reports of overlap of genetic variant associations between BP traits and immune-disorders [65] and evidence of enrichment of immune pathways from GWAS of BP. [66] Mutations of *SH2B3*, a gene identified in a GWAS of hypertension, have been recently shown to attenuate Dahl salt-sensitivity hypertension through inflammatory modulation. [67] In addition, the actions of Ang II in the pathophysiology and maintenance of hypertension are in part mediated through the activation of the immune system. [46]

Our assessment of the clinical implications of identified variants is limited by available data on African-ancestry populations. For example, there are currently no large publicly available GWAS of coronary heart disease or stroke outcomes in African-ancestry populations. It should also be noted that most of our replication cohorts were from populations other than those of African ancestry. Therefore, the power of replication analysis could still be low, which explains why only 11 of 63 variants were successfully replicated.

In summary, we report 11 independent variants at nine loci that are potential regulators of BP in our African-ancestry population study. Three loci are new. Identified BP variants are enriched in immune, kidney, heart, and vascular system pathways. Our experimental findings suggest that several of these genes may be involved in the renin-angiotensin pathways in the kidney during hypertension. Further population studies and experimental models are required for a comprehensive assessment of the identified genes across the immune, kidney, and cardiovascular systems. Our study demonstrates the need to further study individuals of African ancestry in order to identify loci and new biological pathways for BP.

## Methods

### Samples and BP phenotypes

Each study followed protocols for phenotype harmonization. For individuals taking anti-hypertensive medications, we added 15 and 10 mm Hg to measured SBP and DBP, respectively, a standard method used in other BP GWAS. [6, 68] PP was calculated as the difference between SBP and DBP after addition of the constant values. HTN was defined by a SBP  $\geq$  140 mm Hg, a DBP  $\geq$  90 mm Hg, or use of antihypertensive drugs. [69]

### Genotyping and imputation

Each cohort was genotyped on either Affymetrix or Illumina genotyping platforms. Pre-imputation quality criteria were applied as described in S2 Table, and included exclusion of individuals with discordant self-reported gender and genetic gender. Imputation was performed using the software MACH-ADMIX, MACH-minimac or IMPUTE2 [70–72] using the Phase 1 integrated (March 2012 release) multi-ethnic reference panel from the 1000G Consortium (<http://www.internationalgenome.org/>). [73]

### Association analysis

Autosomal chromosome SNP associations for SBP, DBP, and PP were assessed by linear regression for unrelated data or by the generalized linear mixed-effects model for family data, under the assumption of an additive genetic model. All models were adjusted for age, age<sup>2</sup>, sex, and body mass index. Up to ten principal components were included, as needed as covariates in the regression models, to control population stratification. [74, 75] We used standardized pre-meta-analysis QC criteria for all 21 discovery studies. [76] At the SNP level, we excluded variants with 1) imputation quality  $r^2 < 0.3$  in MACH or  $< 0.4$  in IMPUTE2; 2) the number of informative individuals ( $2 \times \text{MAF} \times N \times r^2$ )  $\leq 30$ ; 3) an effect allele frequency (EAF) difference larger than 0.3 in comparison with the mixture of 80% YRI and 20% CEU of 1000G; and 4) the

absolute regression coefficient  $\geq 10$ . SNPs that passed the QC were carried forward for inverse variance weighted meta-analyses, implemented in METAL.[77]

## Multi-trait statistical analyses using CPASSOC

We applied the CPASSOC software to combine association evidence of SBP, DBP, and HTN. CPASSOC provides two statistics,  $S_{Hom}$  and  $S_{Het}$ , as previously described.[39]  $S_{Hom}$  is similar to the fixed effect meta-analysis method[77] but accounts for the correlation of summary statistics of the multi-traits and for overlapping or related samples among the cohorts.  $S_{Hom}$  uses the trait sample size as the weight, so that it is possible to combine traits with different measurement scales.  $S_{Het}$  is an extension of  $S_{Hom}$ , and it can increase the statistical power over  $S_{Hom}$  when a variant affects only a subset of traits. The distribution of  $S_{Het}$  under the null hypothesis was obtained through an estimated beta distribution. To calculate the statistics,  $S_{Hom}$  and  $S_{Het}$  and to account for the correlation among the traits, a correlation matrix is required. In this study, we used the correlation matrix calculated from the residuals of the three BP traits after adjustments for covariates and principal components.

## Replication and meta-analyses

All independent SNPs identified with  $P < 10^{-6}$  (threshold chosen for suggestive association) in the discovery stage were carried forward for replication in African-ancestry individuals and in multi-ethnic samples of European Americans, East Asians, or Hispanics/Latinos (Fig 1). For single-trait analyses, we conducted fixed effect meta-analyses in the replication sets for each of four BP traits (SBP, DBP, PP and HTN), followed by a combined trans-ethnic meta-analysis of each trait. This was followed by a mega-meta-analyses, combining the results of discovery and replication for single traits using fixed-effects meta-analysis. We also performed a multi-trait CPASSOC analysis of SBP, DBP, and HTN in each replication study. Because CPASSOC only generated test statistics  $S_{Hom}/S_{Het}$  and corresponding P values without effect sizes, we combined the association P values from all four replication populations using Fisher's method (<http://hal.case.edu/zhu-web/>). Finally, we combined the CPASSOC meta-analysis results from the discovery and replication stages using Fisher's method.

## Multiple-testing thresholds

For a single trait GWAS discovery analysis, we used genome-wide significant level  $P = 5.0 \times 10^{-8}$ . We performed six different analyses, four single trait (SBP, DBP, PP and HTN) analyses and two CPASSOC ( $S_{Hom}$  and  $S_{Het}$ ) analyses for each SNP. For the four single correlated traits (SBP, DBP, PP and HTN), we calculated the number of independent traits using the eigenvalues of the correlation matrix, [78] which resulted two independent traits. Therefore, we counted four independent analyses, which were two independent single traits and two statistics of CPASSOC analyses, and applied an experimental significance level  $P = 1.25 \times 10^{-8}$  for claiming a genome-wide significance when combining discovery and replication samples. We should point out that the two CPASSOC test statistics and a single trait statistic are not independent. Thus, the significance level  $P = 1.25 \times 10^{-8}$  is conservative.

## Conditional analysis

Since a locus may consist of multiple independent signals, we applied approximate conditional analysis implemented in GCTA-COJO[79, 80] using the summary statistics of SNPs with  $P < 1.0 \times 10^{-6}$  from both of the individual trait meta-analyses (<http://cnsgenomics.com/>

[software/gcta/cojo.html](http://software/gcta/cojo.html)). The LD among variants was estimated from the five African American cohorts from the CARE consortium.[79]

## Pathway analysis

Pathway analysis was performed using the Meta-Analysis Gene-set Enrichment of variant Associations (MAGENTA) program (<http://www.broadinstitute.org/mpg/magenta/>).[41] Using the summary statistics from the four BP traits and two statistics from CPASSOC, from the discovery stage, we tested whether sets of functionally-related genes are enriched for associations. This method first converts the P values of SNPs into gene scores with correcting for confounders, such as gene site, number of variants in a gene, and their LD patterns, and then calculated a gene set enrichment P value for each biological pathway or gene set of interest using a non-parametric statistical test. The nominal GSEA P value refers to the nominal gene set enrichment P value for a gene set. The database of pathway/gene-sets to be tested include Ingenuity (June 2008), KEGG (2010), GO, and the Panther, signaling pathways downloaded from MSigDB and PANTHER (<http://www.broad.mit.edu/gsea/msigdb/collections.jsp>; <http://www.pantherdb.org/>).[81] We applied the parameters suggested by the authors, which includes the 75<sup>th</sup> percentile cut off of gene scores, the nominal GSEA P-value < 0.01 and the false discovery rate (FDR) < 0.3.

## Functional annotation enrichment analysis

The enrichment of heritability of genomic regions to different functional categories, including cell type-specific elements, was evaluated using the method of LD score regression (<https://github.com/bulik/ldsc>).[42, 82] This method partitioned the heritability from the discovery GWAS summary statistics of four BP traits (SBP, DBP, PP, and HTN) while accounting for LD among markers.[42] We calculated enrichment, in functional regions and in expanded regions (+500bp) around each functional class, based on functional annotation, using a “full baseline model” previously created from 24 publicly available main annotations that are not specific to any cell type.[42] Enrichment was calculated based on the ratio of explained heritability and the proportion of SNPs in each annotation category. The standard error of enrichment was estimated with a block jackknife to calculate z scores and P values.[42] The multiple testing threshold was determined using the Bonferroni correction while accounting for two independent-trait analyses based on Ji and Li’s method[78] (P of 0.05/[25 classes × 2 traits]). We also performed cell-type-specific group enrichment analysis using cell-type-specific annotations from four histone marks (H3K4me1, H3K4me3, H3K9ac, and H3K27ac), which corresponded to 220 cell types. We divided the 220 cell-type-specific annotations into 10 groups: adrenal/pancreas, central nervous system (CNS), cardiovascular, connective/bone, gastrointestinal, immune/hematopoietic, kidney, liver, skeletal muscle and other. The analysis characterized cell-type-specific annotations within each group and calculated the enrichment of heritability for each group.[42]

## Genomic annotation enrichment

We selected sets of variants in LD  $r^2 > 0.1$  from the eleven replicated variants, and calculated Bayes Factors and posterior causal probabilities for each variant from the effect sizes and standard errors, as previously described.[83] Each distinct variant associated with multiple traits was included in the analysis only once. The genomic annotations of DHS sites for 348 cell types from the ENCODE project were obtained and grouped into cell types associated with 34 tissues (<http://genome.ucsc.edu/ENCODE/cellTypes.html>). Four gene-based annotations—coding exon, 5-UTR, 3-UTR, and 1kb upstream of transcription start site (TSS)—from

GENCODE transcripts were also obtained. Variants overlapping each of these annotations were then identified. Using the variant annotations and fGWAS (<https://github.com/joepickrell/fgwas>), we tested for enrichment of variants across all signals in 38 DHS categories, including in the four gene-based annotations in each model.[43]

## Expression quantitative trait loci (eQTL) analysis

We used the GTEx pilot database [82] (<http://www.gtexportal.org/home/>) to identify eQTLs in the successfully replicated SNPs.

## Integrated haplotype score (iHS) analysis

To evaluate population differentiation and natural selection, using Haplotter,[40] we calculated the integrated haplotype score (iHS) in five cohorts of CARE so that we could measure the amount of extended haplotype homozygosity (<http://coruscant.itmat.upenn.edu/whamm/ihs.html>). Hence, we tested the evidence of recent positive selection at five significant SNPs with differences in allele frequency across continental-ancestry populations. The measures were standardized (mean 0, variance 1) empirically to the distribution of observed iHS scores over a range of SNPs with similar derived allele frequencies. This method assesses the evidence for selection by comparing the extended homozygosity for haplotypes on a high frequency derived allele relative to the ancestry background.[40]

## Experimental mouse models

Experiments were carried out in accordance with local and the National Institutes of Health guidelines. The animal protocol was approved by the University of Virginia Institutional Animal Care and Use Committee. Wild-type male mice on the 129S6 background at ~ 3 months of age were used for gene expression analyses. All mice were maintained on a 12-hour light-dark cycle with free access to standard chow and water in the animal facility of the University of Virginia.

The hypertension experimental model was induced using Ang II (Sigma-Aldrich, St. Luis, MO) delivered at 600 ng/kg/min for 2 weeks via Alzet mini-osmotic pumps (Durect Corporation, Cupertino, CA, model 2004), as previously described.[84] For gene expression analyses, RNA from kidney tissue was isolated by RNeasy Mini kit (Qiagen) and transcribed to cDNA by iScript™ cDNA synthesis kit (Bio-Rad). Real time PCR analyses were performed on iQ™5 Multicolor real time PCR Bio-Rad instruments using iQ™ SYBER® Green Supermix. *Hprt* was used as a reference gene for normalization. Sequences of forward and reversed primers (FP and RP) for the gene expression studies are shown in [S10 Table](#).

**Ethic statement.** All research involving human participants have been approved by the Institutional Review Board (IRB) # 04-95-72 and study-related Publication and Presentation committees. All participants have provided informed consent for DNA research and data are publicly available in dbGap.

Animal experiments were carried out following the guidelines established locally at the University of Virginia (UVA) and by the National Institutes of Health. The animal protocol was approved by the UVA Institutional Animal Care and Use Committee (Protocol # 3791, Protocol Title: Genes regulating Hypertension and Kidney Disease). Wild-type male mice on the 129S6 background at ~ 3 months of age were used for gene expression analyses. All mice were maintained on a 12-hour light-dark cycle with free access to standard chow and water in the animal facility UVA.

## Supporting information

- S1 Fig. Quantile-quantile plots for both individual traits and CPASSOC analysis in discovery stage.**  
(PDF)
- S2 Fig. Manhattan plots of single trait and CPASSOC analyses at the discovery stage.**  
(PDF)
- S3 Fig. Regional interrogation of the *HOXA/EVX1*, *ULK4* and *PLEKHG1*.**  
(PDF)
- S4 Fig. Discovery stage results and linkage disequilibrium maps of the candidate regions.**  
(PDF)
- S5 Fig. Enrichment for functional annotations of variants in 11 replicated loci reaching genome-wide significance.**  
(PDF)
- S1 Table. Descriptive characteristics of the discovery studies.**  
(PDF)
- S2 Table. Genotyping, pre-imputation quality control, imputation and analysis methods in the participating studies.**  
(PDF)
- S3 Table. Genomic inflation factors by study and analysis.**  
(PDF)
- S4 Table. Conditional analysis of SNPs with  $P < 1.0 \times 10^{-6}$  in discovery stage for SBP, DBP, PP, HTN or CPASSOC analysis.**  
(PDF)
- S5 Table. 72 Independent SNPs with  $P < 1.0 \times 10^{-6}$  in discovery stage for SBP, DBP, PP, HTN or CPASSOC analysis.**  
(PDF)
- S6 Table. Trans-ethnic replication of 72 independent SNPs with  $P < 1.0 \times 10^{-6}$  in discovery stage for SBP, DBP, PP, HTN or CPASSOC.**  
(PDF)
- S7 Table. Summary of iHS signals in significant loci with frequency differences across ancestry populations.**  
(PDF)
- S8 Table. MAGENTA analysis.**  
(PDF)
- S9 Table. eQTL analysis of significant SNPs in tissues.**  
(PDF)
- S10 Table. Primes for mouse expression experiments.**  
(PDF)
- S1 Note. Single-trait and multi-trait genome wide association analyses identify novel loci for blood pressure in African-ancestry populations.**  
(DOCX)

## Acknowledgments

This is included in the Supplemental Note.

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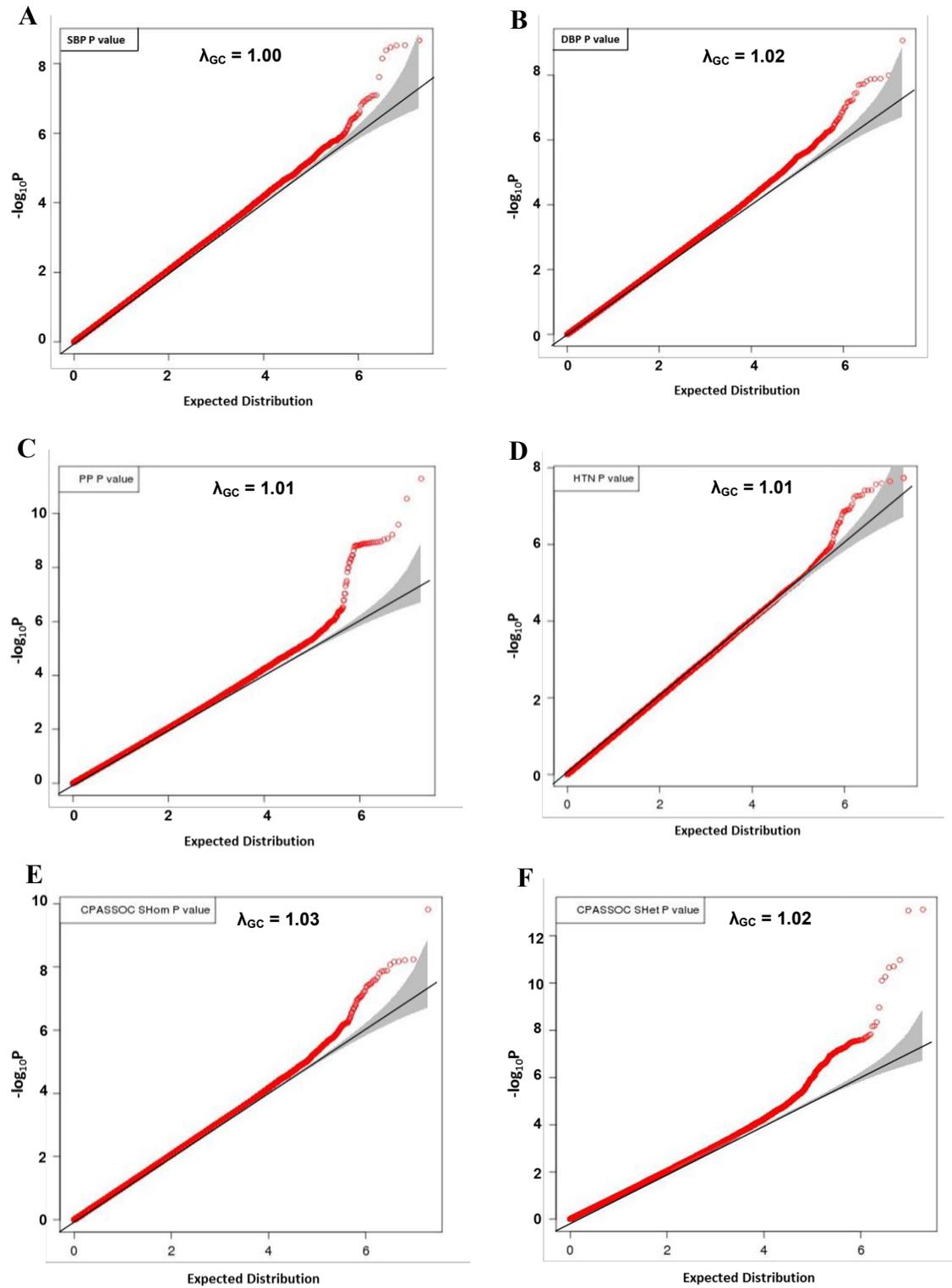
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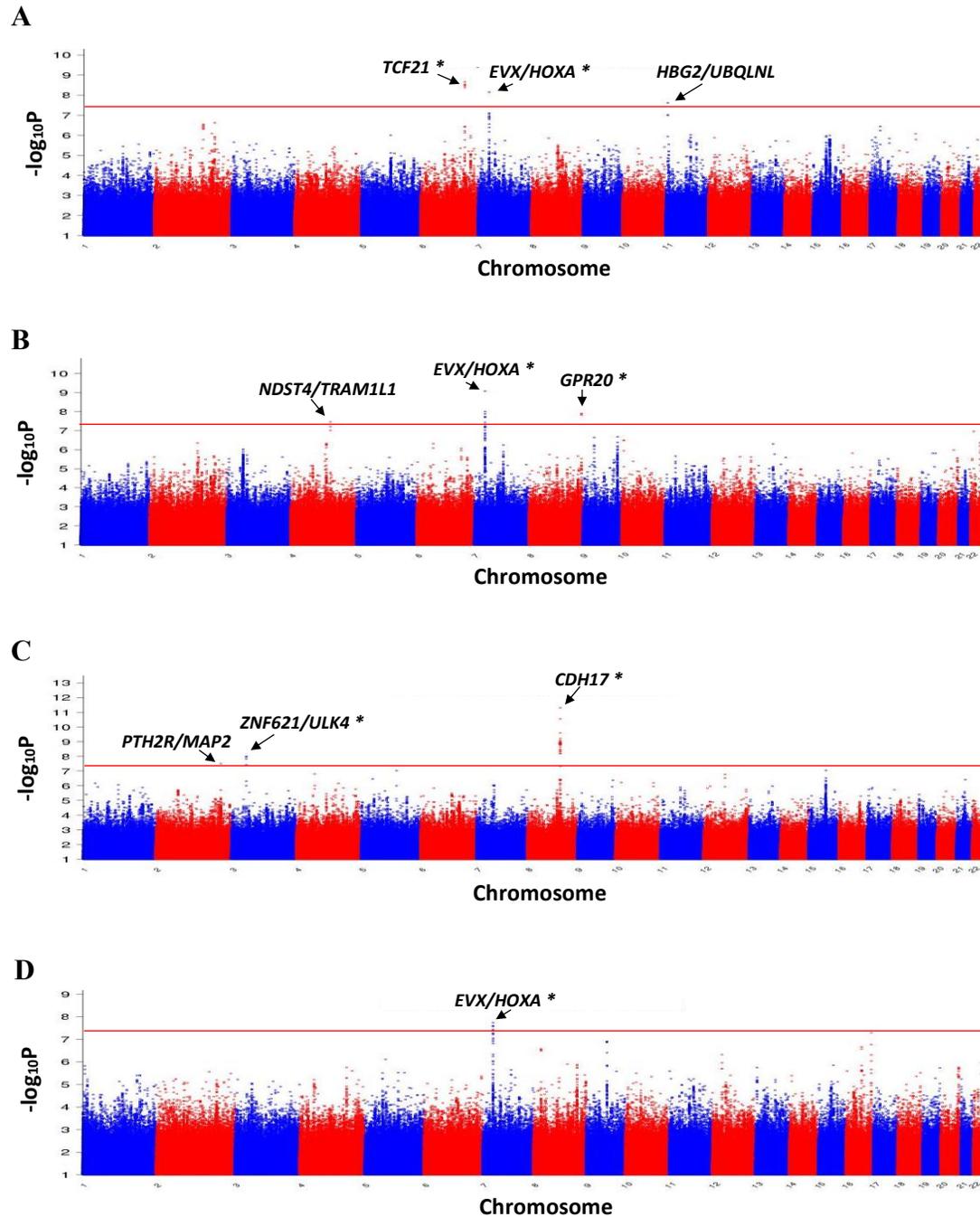
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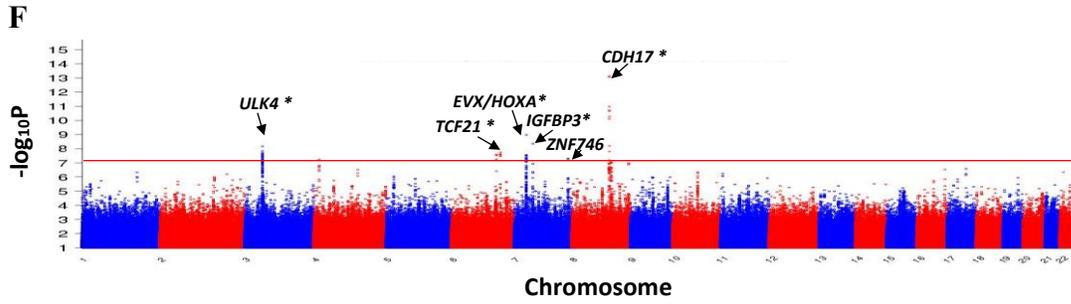
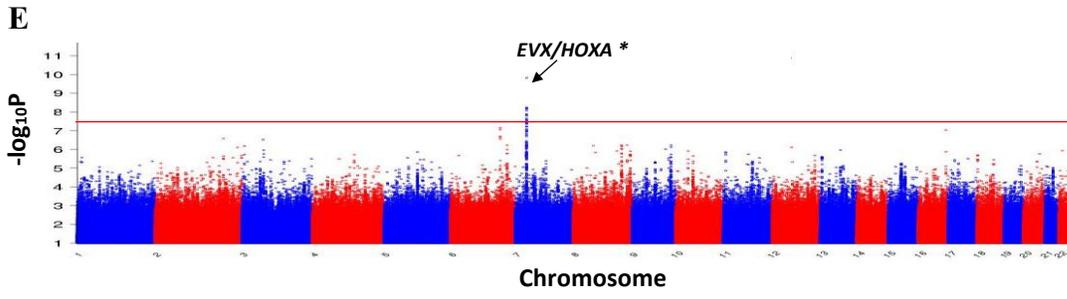
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**S1 Fig.** Quantile-quantile plots for both individual traits and CASSOC analysis in discovery stage. **A.** SBP. **B.** DBP. **C.** PP. **D.** HTN. **F.**  $S_{Hom}$  in CPASSOC. **G.**  $S_{Het}$  in CPASSOC



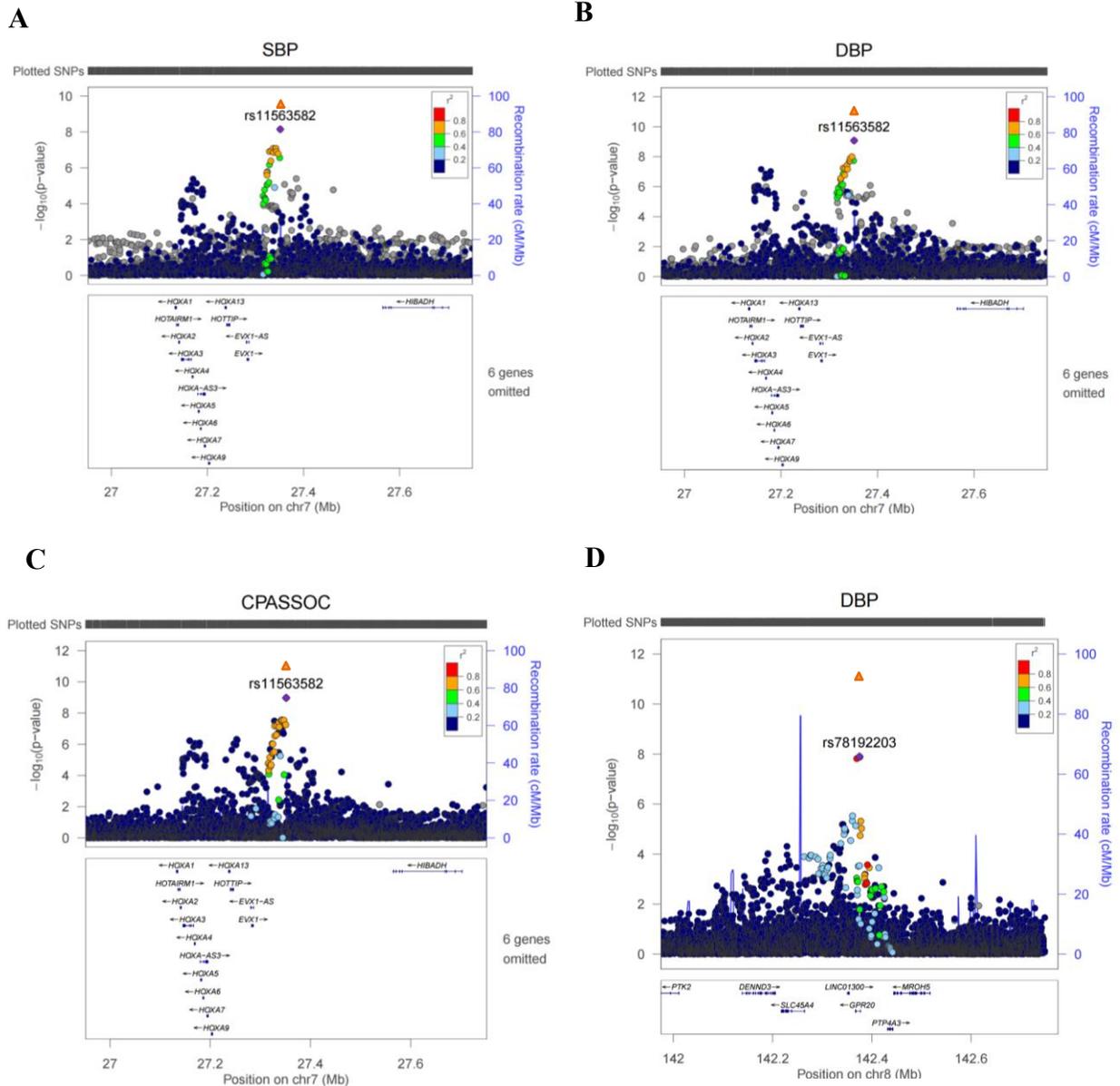
**S2 Fig.** Manhattan plots of single trait and CPASSOC analyses at the discovery stage. **A.** SBP. **B.** DBP. **C.** PP. **D.** HTN. **E.**  $S_{Hom}$  in CPASSOC. **F.**  $S_{Het}$  in CPASSOC. The red line is genome-wide significance cutoff of  $P = 5.0 \times 10^{-8}$ . Loci that replicated in the combined discovery and replication trans-ethnic meta-analyses at the experimental-wide significance threshold ( $P < 1.25 \times 10^{-8}$ ) are highlighted using asterix.

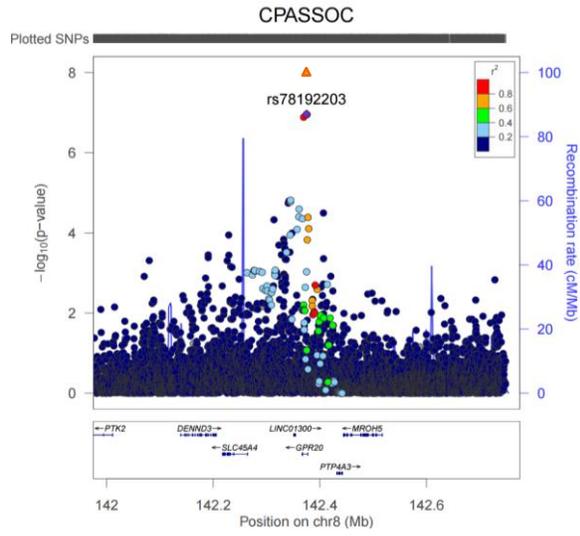
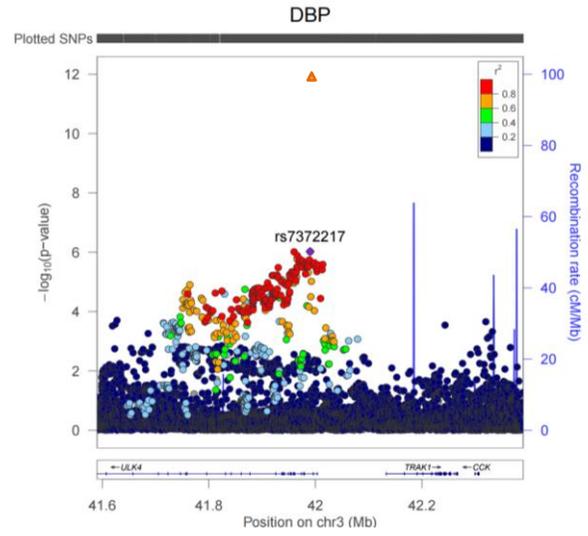
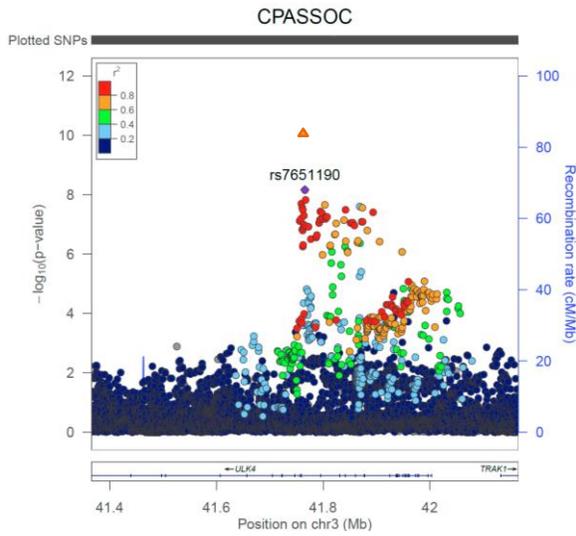
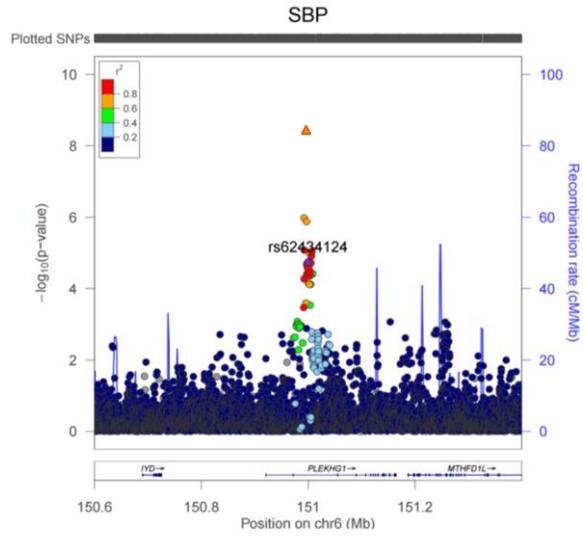




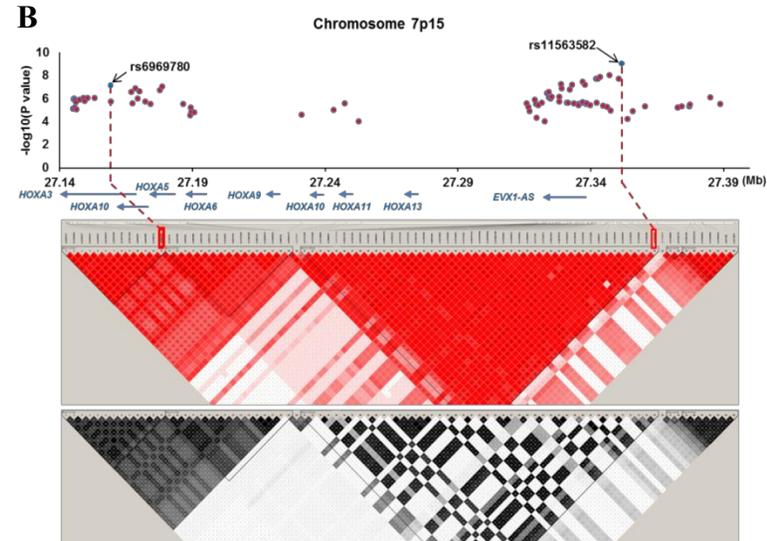
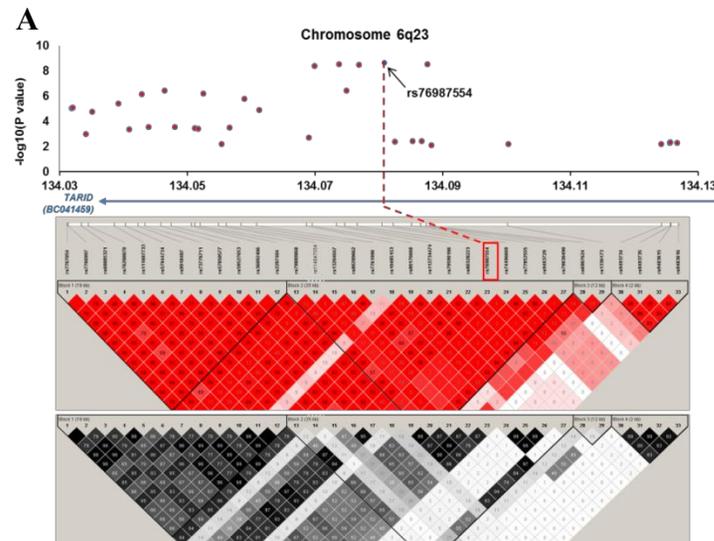
**S3 Fig.** Regional Interrogation of the **A.** *HOXA/EVXI* locus for SBP **B.** *HOXA/EVXI* locus for DBP **C.** *HOXA/EVXI* locus for  $S_{\text{Het}}$  of CPASSOC **D.** *GPR20* for DBP **E.** *GPR20* for  $S_{\text{Het}}$  of CPASSOC **F.** *ULK4* for DBP **G.** *ULK4* for  $S_{\text{Het}}$  of CPASSOC **H.** *PLEKHG1* for SBP.

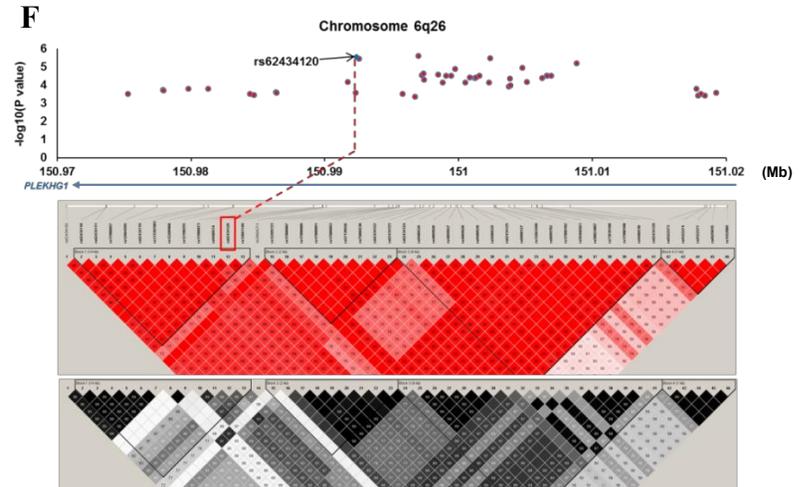
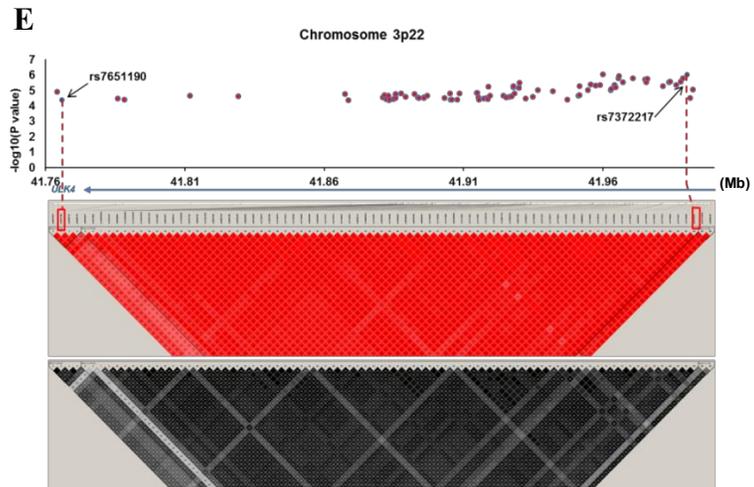
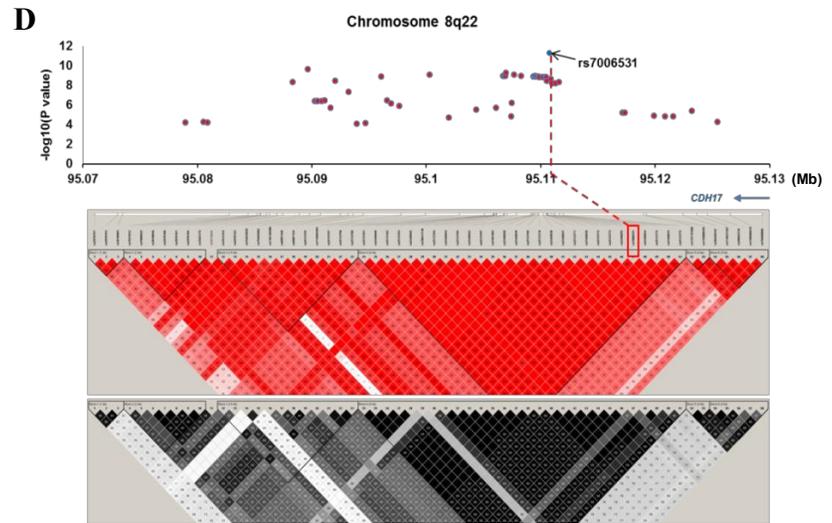
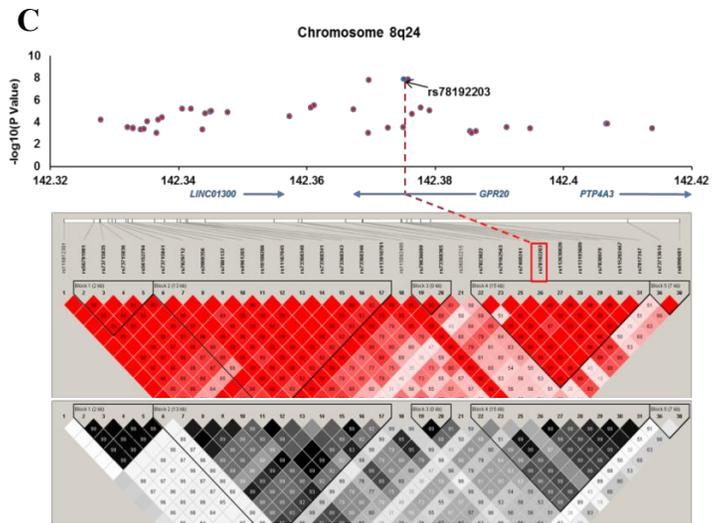
The y axis shows the  $-\log_{10}$  P values of SNPs, and the x axis shows their chromosomal positions. The lowest P value SNP is plotted as a purple diamond and its correlation with other SNPs in the region is shown in color. The orange triangle is P value in the combined discovery and replication trans-ethnic meta-analysis of the lowest P value SNP.

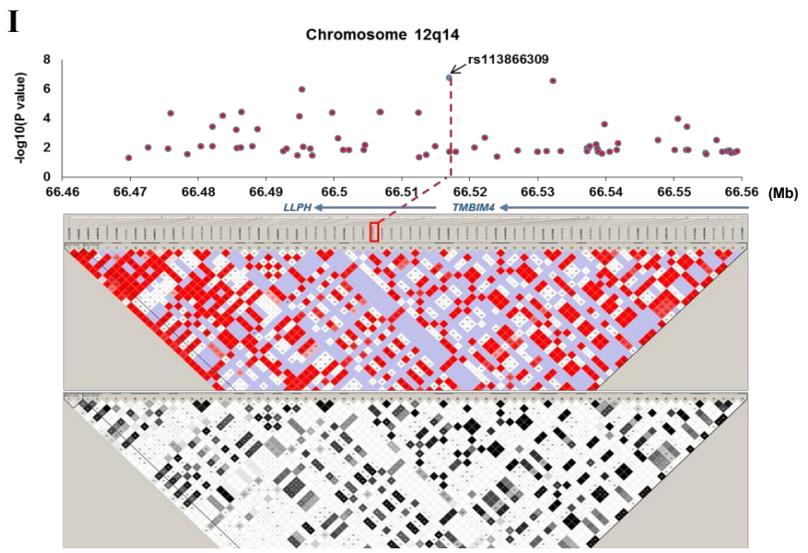
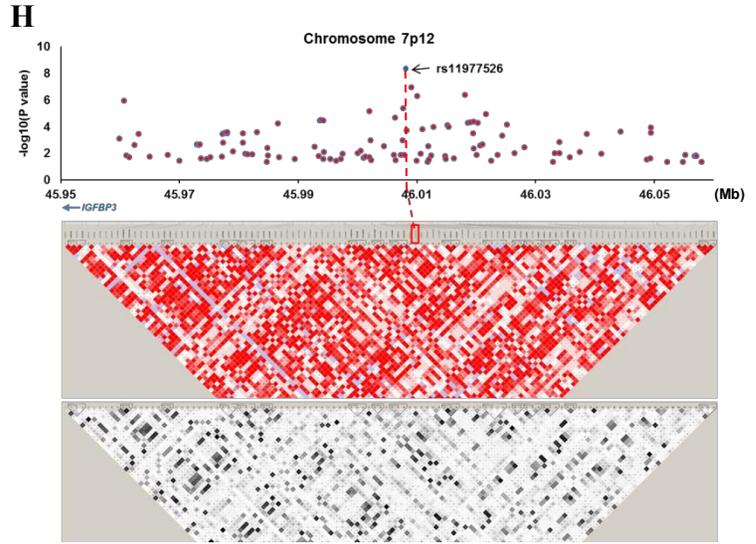
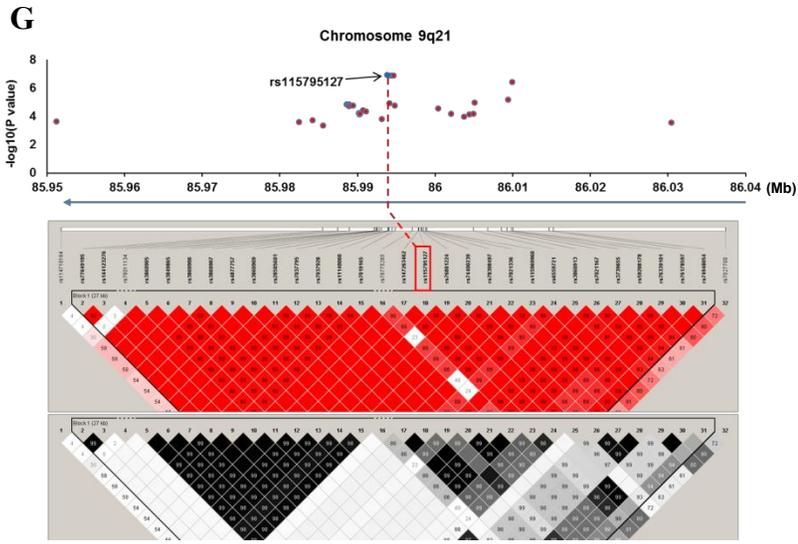


**E****F****G****H**

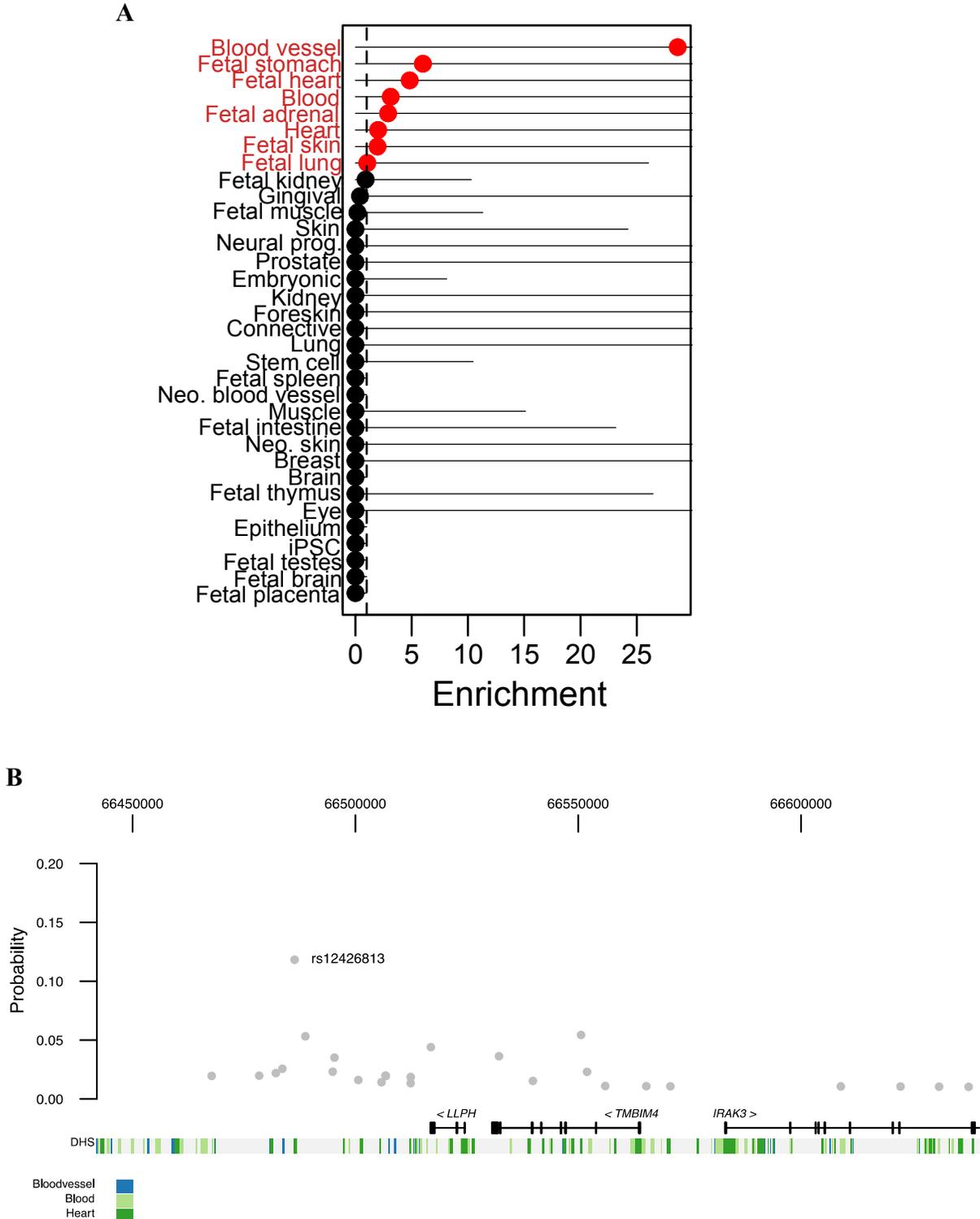
**S4 Fig.** Discovery stage results and linkage disequilibrium maps of the candidate regions. P value plots, genomic structures and LD maps of chromosomes 6q23 (A), p15 (B), 8q24 (C), 8q22 (D), 3p22 (E), 6q26 (F), 9q21 (G), 7p21 (H), 12q14 (I). The red plots represent the  $-\log_{10}$  of the P values for association results. The LD maps based on  $D'$  (above) and  $r^2$  (below) were drawn using the genotype data of 7717 CARE cohorts. Black triangles indicate the LD blocks identified by Haploview using Gabriel's method. Red dot lines indicate positions of marker SNPs.







**S5 Fig. A.** Enrichment of DNase hypersensitive (DHS) sites in 34 tissue categories for variants in  $r^2 > 0.1$  with 11 replicated SNPs reaching genome-wide significance using FGWAS **B.** Causal probabilities of variants at the *LLPH/TMBIM4* locus. The most probably causal variant rs12426813 overlaps a DHS site active in blood and cardiovascular cells



S1 Table. Descriptive Characteristics of the Discovery Studies

Study	N	Age (SD)	No. of Males (%)	BMI (SD)	No. with HTN (%)	No. with Hypertensive Medication (%)	SBP, mmHg (SD)	DBP, mmHg (SD)	PP in mmHg
<b>Discovery Cohorts</b>									
ARIC_AA	2502	53 (6)	926 (37)	30 (6)	1451 (58)	1076 (43)	135 (23)	84 (13)	51 (16)
CARDIA	826	39 (4)	339 (41)	31 (7)	206 (25)	107 (13)	118 (18)	78 (13)	41 (11)
CFS	608	39 (20)	258 (42)	32 (10)	182 (13)	109 (18)	126 (20)	76 (13)	50 (13)
JHS	2135	55 (13)	807 (38)	32 (7)	1328 (62)	1153 (54)	134 (21)	84 (12)	51 (17)
MESA	1646	62 (10)	746 (45)	30 (6)	1022 (62)	839 (51)	139 (25)	80 (12)	60 (18)
CHS	2064	76 (5)	834 (40)	26 (4)	1132 (55)	979 (47)	133 (20)	69 (11)	63 (18)
GeneSTAR	1129	48 (12)	428 (38)	32 (8)	616 (55)	462 (41)	129 (19)	81 (11)	48 (14)
GENOA	996	56 (11)	295 (30)	31 (7)	688 (69)	550 (56.9)	136 (22)	78 (12)	57 (12)
HANDLS	950	49 (9)	424 (45)	30 (8)	519 (53)	348 (36)	128 (21)	77 (13)	51 (14)
HyperGEN	1256	45 (13)	408 (33)	33 (8)	769 (61)	--	136 (25)	79 (13)	57 (17)
Maywood-Loyola	743	42 (8)	465 (63)	27 (8)	158 (21)	6 (1)	121 (20)	77 (13)	44 (13)
Nigeria-Loyola	1614	49 (15)	674 (42)	24 (5)	797 (49)	399 (25)	135 (30)	84 (19)	52 (16)
Loyola	967	53 (14)	737 (76)	28 (7)	660 (68)	155 (16)	149 (30)	92 (18)	57 (17)
WHI-SHARe	7989	61 (7)	0	32 (7)	4435 (56)	3692 (46)	132 (18)	78 (9)	54 (15)
HUFS	1192	46 (14)	477 (40)	31 (9)	688 (58)	442 (37)	132 (22)	82 (14)	50 (15)
BioMe Biobank	2464	49 (14)	870 (35)	30 (8)	1126 (46)	854 (35)	132 (22)	80 (14)	52 (16)
HRS	1337	67 (10)	483 (36)	31 (7)	1073 (80)	849 (64)	144 (24)	86 (13)	58 (16)
FBPP-AXIOM	917	50 (14)	367 (40)	31 (7)	642 (70)	596 (65)	129 (22)	74 (12)	55 (16)
BioVU eMERGE I AA	1048	49 (16)	330 (31)	32 (9)	510 (49)	246 (23)	135 (22)	81 (13)	54 (17)
BioVU eMERGE II AA 1M	427	48 (15)	204 (48)	30 (8)	264 (62)	169 (40)	138 (24)	83 (14)	56 (17)
BioVU Fibroids AA	407	44 (15)	0 (0)	33 (9)	174 (43)	81 (20)	134 (24)	82 (14)	53 (17)
<b>Replication Cohorts</b>									
Jamaica_GXE	613	40 (8)	141 (23)	13 (8)	142 (23)	0	118 (14)	71 (10)	47 (11)
Jamaica_SPT	905	47 (14)	351 (39)	27 (6)	285 (31)	123 (14)	122 (23)	71 (15)	52 (16)
Uganda	2668	35 (14)	774 (29)	24 (5)	1948 (73)	0	126 (21)	80 (12)	46 (15)
WHI_GARNET	4279	65 (7)	0	30 (6)	1721 (40)	1311 (31)	131 (18)	76 (9)	55 (15)
WHI_WHIMS	5478	68 (6)	0	28 (6)	1859 (34)	1403 (26)	130 (18)	75 (9)	56 (15)
ARIC_EA	9687	54 (6)	4650 (48)	27 (5)	2626 (27)	--	118 (16)	72 (10)	47 (13)
BioVU eMERGE II EA 1M	3428	54 (17)	1598 (47)	29 (7)	2500 (73)	1041 (30)	129 (20)	75 (19)	53 (16)
BioVU eMERGE II EA 5M	1045	51 (18)	499 (48)	30 (10)	642 (61)	239 (23)	128 (20)	75 (12)	54 (17)
Korea_hexa	3702	53 (8)	1651 (45)	24 (3)	665 (18)	0	122 (14)	78 (10)	45 (9)
Korea_kare	8773	52 (9)	4117 (47)	25 (3)	2284 (26)	0	122 (19)	80 (11)	41 (12)
Korea_nc2	1814	61 (7)	858 (47)	25 (3)	796 (44)	0	134 (18)	84 (11)	50 (13)
HCHS/SOL	12278	46 (14)	5019 (41)	30 (6)	3445 (28)	2070 (17)	125 (20)	75 (12)	50 (13)

**S3 Table: Genomic inflation factors by study and analysis.**

<b>Study</b>	<b>N</b>	<b>SBP - <math>\lambda_{GC}</math></b>	<b>DBP - <math>\lambda_{GC}</math></b>	<b>HTN - <math>\lambda_{GC}</math></b>	<b>PP - <math>\lambda_{GC}</math></b>
ARIC	2502	1	1.02	1.01	1.01
CARDIA	826	0.99	0.99	1	1.01
CFS	608	1.05	1.03	1.02	1.04
CHS	815	1.01	1	1	1.02
FBPP	917	0.96	0.98	0.97	0.99
GENOA	996	0.99	0.99	1	0.99
JHS	2135	0.98	0.99	0.99	1.01
MESA	1646	0.98	1.01	1	0.99
HyperGen	1256	1.08	1.07	1.05	1.06
Loyola	967	0.99	1	0.98	0.99
HRS	1337	0.99	1.01	0.99	1
HUFS	1192	1.06	1.03	1.03	1.02
IPM	2464	0.98	0.99	1	1
Maywood	743	1.01	1.02	1.01	1
WHI	7989	1.01	1.03	1.03	1.02
HANDLS	950	0.99	1	1	1.02
Nigeria	1614	1.09	1.05	1.02	1.02
GeneSTAR	1129	1.02	1.06	1.04	1
eMERGE	1048	1.03	1.05	1.01	1.02
OMNI	427	1.01	1	0.99	1.01
FIBROID	407	0.99	1.02	1.04	1
<b>Total</b>	<b>31968</b>	<b>1</b>	<b>1.02</b>	<b>1.01</b>	<b>1.01</b>

$\lambda$  indicates the genomic inflation factor. N indicates sample size.

S4 Table. Conditional analysis of SNPs with P < 1.0E-06 in discover stage for single trait analysis

Conditional SNP (Independent SNP for replication)	SNP	Chr	Pos	A1	A2	Gene	Effect	SE	P.value	Effect (conditional)	SE (conditional)	P.value (conditional)		
<b>SBP</b>														
rs76987554	rs9918487	6	134042960	A	G	<i>TARID/ TCF21*</i>	-1.2639	0.2555	7.55E-07	-0.2810	0.1957	0.1511		
	rs57850577	6	134046495	A	G		1.2660	0.2489	3.64E-07	0.3393	0.1949	0.0817		
	rs79889868	6	134052576	C	G		-1.2168	0.2440	6.13E-07	-0.3251	0.1932	0.0925		
	rs80176668	6	134069965	A	G		1.7082	0.2906	4.15E-09	0.1825	0.1395	0.1908		
	rs112734474	6	134073797	T	G		1.7256	0.2910	3.02E-09	0.1921	0.1379	0.1638		
	rs79590186	6	134075021	T	C		-1.3953	0.2749	3.87E-07	-0.1150	0.1726	0.5054		
	rs80328223	6	134076947	T	C		-1.7232	0.2915	3.39E-09	-0.1808	0.1362	0.1844		
	rs76987554	6	134080855	T	C		-1.8492	0.3090	2.17E-09	NA	NA	NA		
rs79030490	6	134087689	A	C	-1.8344	0.3091	2.96E-09	NA	NA	NA				
rs11563582	rs17428380	7	27328929	T	C	<i>EVXI/HOXA</i>	1.3794	0.2609	1.24E-07	0.0863	0.1347	0.5220		
	rs12535894	7	27329173	C	G		-1.2687	0.2553	6.72E-07	-0.0601	0.1469	0.6825		
	rs113318709	7	27332148	T	C		1.3424	0.2651	4.12E-07	0.0128	0.1323	0.9231		
	rs148340546	7	27333162	A	G		-1.3761	0.2590	1.08E-07	-0.1058	0.1375	0.4418		
	rs7777128	7	27337113	C	G		1.3821	0.2577	8.13E-08	0.1173	0.1366	0.3905		
	rs17428471	7	27337867	T	G		1.3276	0.2522	1.41E-07	0.1690	0.1534	0.2706		
	rs17438166	7	27341976	T	C		1.3827	0.2581	8.43E-08	0.1100	0.1351	0.4158		
	rs1009547	7	27342727	A	G		1.3847	0.2582	8.15E-08	0.1111	0.1351	0.4110		
	rs55831032	7	27343535	T	C		1.3716	0.2593	1.23E-07	0.0878	0.1343	0.5134		
	rs17438292	7	27347127	A	G		-1.3848	0.2644	1.62E-07	-0.0577	0.1317	0.6612		
	rs17502580	7	27350607	A	G		-1.3376	0.2603	2.77E-07	-0.0581	0.1374	0.6724		
rs11563582	7	27351650	A	G	1.6125	0.2786	7.09E-09	NA	NA	NA				
rs7941648	rs7941648	11	5532222	T	G	<i>HGB2</i>	-1.2323	2.21E-01	2.43E-08	NA	NA	NA		
	rs3763880	11	5533606	T	G		1.4268	0.2679	1.01E-07	0.4701	0.2059	0.0224		
	rs72887764	11	5545271	T	C		1.2862	0.2413	9.77E-08	0.4505	0.1893	0.0173		
<b>DBP</b>														
rs7372217	rs7651190	3	41765955	A	G	<i>ULK4</i>	-0.45	0.1099	4.20E-05	-0.3366	0.1824	0.0010		
	rs1716975	3	41960006	T	C		0.5759	0.1176	9.67E-07	NA	NA	NA		
	rs7372217	3	41990122	A	G		-0.5514	0.1125	9.50E-07	NA	NA	NA		
rs62312401	rs7676999	4	116987529	A	G	<i>NDST4/TRAMILI</i>	1.3123	2.38E-01	3.50E-08	NA	NA	NA		
	4:116968554:GTTT/4	4	116934079	T	C		-1.2314	0.2311	9.86E-08	-0.1433	0.1203	0.2337		
	rs62312401	4	116968554	G	GTTTAT		-1.2686	0.2344	6.19E-08	-0.2317	0.1400	0.0979		
rs11563582	rs2428433	7	27145517	T	C	<i>EVXI/HOXA</i>	-0.5765	0.1178	9.94E-07	-0.5602	0.1178	1.98E-06		
	rs73071550	7	27149099	T	C		-0.5692	0.116	9.17E-07	-0.5541	0.1160	1.78E-06		
	rs6461985	7	27150634	T	C		-0.5699	0.1158	8.60E-07	-0.5551	0.1158	1.64E-06		
	rs7798733	7	27153281	C	G		-0.5691	0.1159	9.05E-07	-0.5541	0.1159	1.75E-06		
	rs6969780	7	27159136	C	G		0.6214	0.1152	6.95E-08	0.5591	0.1148	1.11E-06		
	rs6461987	7	27166956	C	G		0.6364	0.1238	2.73E-07	0.5453	0.1229	9.17E-06		
	rs1801085	7	27168590	A	G		-0.5972	0.1134	1.40E-07	-0.5351	0.1130	2.17E-06		
	rs6962314	7	27170159	T	C		0.6283	0.1218	2.46E-07	0.5416	0.1210	7.63E-06		
	rs6976129	7	27177746	T	C		0.6462	0.1243	2.03E-07	0.5558	0.1235	6.73E-06		
	rs17471520	7	27178790	T	C		-0.6073	0.1138	9.58E-08	-0.5381	0.1133	2.02E-06		
	rs17502232	7	27323604	T	G		-0.8317	0.163	3.35E-07	0.0601	0.0738	0.4154		
	rs17473410	7	27324196	T	G		-0.8396	0.1632	2.68E-07	0.0547	0.0735	0.4566		
	rs17473424	7	27324369	A	G		0.7873	0.1592	7.65E-07	-0.0475	0.0827	0.5662		
	rs73073487	7	27324984	A	G		0.8186	0.1672	9.83E-07	-0.0810	0.0804	0.3141		
	rs17502260	7	27325313	T	C		-0.7875	0.1592	7.49E-07	0.0474	0.0827	0.5664		
	rs6961048	7	27328187	C	G		-0.7732	0.1563	7.49E-07	0.0381	0.0834	0.6473		
	rs17428380	7	27328929	T	C		0.8543	0.1575	5.78E-08	0.0088	0.0763	0.9079		
	rs12535894	7	27329173	C	G		-0.8122	0.1541	1.36E-07	-0.0222	0.0847	0.7933		
	rs113318709	7	27332148	T	C		0.8363	0.1599	1.70E-07	-0.0321	0.0745	0.6667		
	rs148340546	7	27333162	A	G		-0.846	0.1563	6.21E-08	-0.0159	0.0783	0.8392		
	rs7777128	7	27337113	C	G		0.8556	0.1555	3.74E-08	0.0294	0.0778	0.7057		
	rs17428471	7	27337867	T	G		0.8208	0.1521	6.85E-08	0.0648	0.0892	0.4675		
	rs17438166	7	27341976	T	C		0.8739	0.1557	2.01E-08	0.0429	0.0769	0.5769		
	rs1009547	7	27342727	A	G		0.8756	0.1558	1.90E-08	0.0435	0.0768	0.5705		
	rs55831032	7	27343535	T	C		0.8894	0.1565	1.32E-08	0.0502	0.0761	0.5095		
	rs17438292	7	27347127	A	G		-0.9136	0.1594	1.00E-08	-0.0481	0.0743	0.5173		
	rs17502580	7	27350607	A	G		-0.8833	0.157	1.86E-08	-0.0478	0.0782	0.5412		
	rs11563582	7	27351650	A	G		1.0151	0.1654	8.45E-10	NA	NA	NA		
	rs917206	7	27385004	A	G		-1.2058	0.2447	8.32E-07	-0.7071	0.2310	0.0022		
	rs11563582 rs6969780	rs2428433	7	27145517	T		C	<i>EVXI/HOXA</i>	-0.5765	0.1178	9.94E-07	-0.0402	0.0498	0.4194
		rs73071550	7	27149099	T		C		-0.5692	0.116	9.17E-07	-0.0353	0.0459	0.4421
		rs6461985	7	27150634	T		C		-0.5699	0.1158	8.60E-07	-0.0359	0.0453	0.4273
		rs7798733	7	27153281	C		G		-0.5691	0.1159	9.05E-07	-0.0336	0.0449	0.4538
rs6969780		7	27159136	C	G	0.6214	0.1152		6.95E-08	NA	NA	NA		
rs6461987		7	27166956	C	G	0.6364	0.1238		2.73E-07	0.0514	0.0695	0.4594		
rs1801085		7	27168590	A	G	-0.5972	0.1134		1.40E-07	NA	NA	NA		
rs6962314		7	27170159	T	C	0.6283	0.1218		2.46E-07	0.0476	0.0660	0.4708		
rs6976129		7	27177746	T	C	0.6462	0.1243		2.03E-07	0.0635	0.0709	0.3701		
rs17471520		7	27178790	T	C	-0.6073	0.1138		9.58E-08	-0.0241	0.0411	0.5575		
rs17502232		7	27323604	T	G	-0.8317	0.163		3.35E-07	0.0679	0.0738	0.3575		
rs17473410		7	27324196	T	G	-0.8396	0.1632		2.68E-07	0.0623	0.0734	0.3964		
rs17473424		7	27324369	A	G	0.7873	0.1592		7.65E-07	-0.0552	0.0827	0.5045		
rs73073487		7	27324984	A	G	0.8186	0.1672		9.83E-07	-0.0858	0.0804	0.2862		
rs17502260		7	27325313	T	C	-0.7875	0.1592		7.49E-07	0.0551	0.0827	0.5048		
rs6961048		7	27328187	C	G	-0.7732	0.1563		7.49E-07	0.0470	0.0833	0.5730		
rs17428380		7	27328929	T	C	0.8543	0.1575		5.78E-08	-0.0014	0.0763	0.9852		
rs12535894		7	27329173	C	G	-0.8122	0.1541		1.36E-07	-0.0119	0.0847	0.8884		
rs113318709		7	27332148	T	C	0.8363	0.1599		1.70E-07	-0.0405	0.0744	0.5863		
rs148340546		7	27333162	A	G	-0.846	0.1563		6.21E-08	-0.0061	0.0783	0.9375		
rs7777128		7	27337113	C	G	0.8556	0.1555		3.74E-08	0.0189	0.0778	0.8078		
rs17428471		7	27337867	T	G	0.8208	0.1521		6.85E-08	0.0469	0.0892	0.5990		
rs17438166		7	27341976	T	C	0.8739	0.1557		2.01E-08	0.0340	0.0768	0.6585		
rs1009547		7	27342727	A	G	0.8756	0.1558		1.90E-08	0.0347	0.0767	0.6511		
rs55831032		7	27343535	T	C	0.8894	0.1565		1.32E-08	0.0418	0.0761	0.5825		
rs17438292		7	27347127	A	G	-0.9136	0.1594		1.00E-08	-0.0410	0.0743	0.5808		
rs17502580		7	27350607	A	G	-0.8833	0.157		1.86E-08	-0.0447	0.0782	0.5673		
rs11563582		7	27351650	A	G	1.0151	0.1654		8.45E-10	NA	NA	NA		
rs917206		7	27385004	A	G	-1.2058	0.2447		8.32E-07	-0.6353	0.2306	0.0059		
rs2123202		9	28153553	A	C	0.6117	0.1229		6.46E-07	0.1099	0.0755	0.1454		
rs13294724		9	28157548	A	G	0.6036	0.1231		9.38E-07	0.1035	0.0762	0.1745		

rs71512425	rs114334738	9	28165671	T	C		1.2762	0.2552	5.73E-07	0.9782	0.2490	0.0001
	rs71512425	9	28165694	A	G		0.6974	0.1348	2.32E-07	NA	NA	NA
	rs115412864	9	28165783	T	C	<i>LINGO2</i>	1.2684	0.2551	6.65E-07	0.9704	0.2488	9.63E-05
rs71512425 rs114334738	rs2123202	9	28153553	A	C		0.6117	0.1229	6.46E-07	0.1080	0.0755	0.1524
	rs13294724	9	28157548	A	G		0.6036	0.1231	9.38E-07	0.1006	0.0762	0.1868
	rs114334738	9	28165671	T	C		1.2762	0.2552	5.73E-07	NA	NA	NA
	rs71512425	9	28165694	A	G		0.6974	0.1348	2.32E-07	NA	NA	NA
	rs115412864	9	28165783	T	C		1.2684	0.2551	6.65E-07	NA	NA	NA
<b>HTN</b>												
rs10279895	rs17501431	7	27251549	T	C		-0.1876	0.0355	1.24E-07	-0.0690	0.0286	0.0157
	rs17472588	7	27252767	A	C		0.2005	0.0369	5.33E-08	0.0670	0.0283	0.0177
	rs17501438	7	27253688	C	G		-0.197	0.0364	6.18E-08	-0.0673	0.0282	0.0169
	rs57330666	7	27274187	A	T		-0.1757	0.0351	5.73E-07	-0.0448	0.0263	0.0880
	rs17473046	7	27287676	A	C		0.1691	0.0344	9.17E-07	0.0381	0.0253	0.1320
	rs17501898	7	27289410	A	G		-0.1682	0.0344	9.93E-07	-0.0376	0.0254	0.1381
	rs28570591	7	27319622	A	G		-0.1768	0.0351	4.66E-07	-0.0015	0.0161	0.9249
	rs10279895	7	27328210	A	G		0.1894	0.0337	1.84E-08	NA	NA	NA
	rs17473487	7	27331139	T	C		-0.1879	0.0337	2.54E-08	NA	NA	NA
	rs185372147	7	27331552	T	G	<i>EVX1/HOXA</i>	0.1879	0.0337	2.54E-08	NA	NA	NA
	rs142887200	7	27333712	T	C		-0.1868	0.0336	2.68E-08	NA	NA	NA
	rs11564025	7	27335536	T	G		0.1843	0.0335	3.80E-08	NA	NA	NA
	rs11564024	7	27335561	T	G		0.179	0.0341	1.55E-07	NA	NA	NA
	rs10227075	7	27338363	T	C		0.1823	0.0335	5.45E-08	NA	NA	NA
	rs10270510	7	27338373	C	G		-0.1844	0.0335	3.87E-08	NA	NA	NA
	rs11564019	7	27338558	A	G		-0.1844	0.0335	3.87E-08	NA	NA	NA
	rs17473690	7	27342386	T	G		-0.183	0.0337	5.45E-08	NA	NA	NA
rs11564010	7	27344629	C	G		-0.1802	0.0337	8.93E-08	NA	NA	NA	
rs17502552	7	27346216	T	G		-0.1801	0.0339	1.04E-07	NA	NA	NA	
rs12149202	rs12149202	16	85700360	A	G		-0.1877	0.0345	5.14E-08	NA	NA	NA
	rs12149210	16	85700481	A	G		-0.1608	0.032	4.90E-07	NA	NA	NA
	16:85708762:T_TTA	16	85708762	T	TTAAG	<i>GSE1</i>	0.1576	0.0321	9.22E-07	0.0352	0.0229	0.1244
	rs3815795	16	85712105	T	C		-0.1659	0.0317	1.72E-07	-0.0213	0.0173	0.2173
<b>PP</b>												
rs192457787	rs138594252	4	58730210	T	C	<i>IGFBP7/ROLR2B</i>	-7.3815	1.5072	9.70E-07	-1.5290	1.0133	0.1313
	rs192457787	4	58795698	A	C		-8.4329	1.6081	1.57E-07	NA	NA	NA
rs150785606	rs1723953	7	45993668	A	C		1.9482	0.3976	9.61E-07	1.9547	0.3977	8.86E-07
	rs11977526	7	46008110	A	G		-0.6674	0.1362	9.53E-07	-0.6658	0.1362	1.02E-06
	rs138317269	7	46989518	T	G		-8.0214	1.6386	9.82E-07	NA	NA	NA
	rs150785606	7	46990467	T	C	<i>IGFBP3</i>	8.0378	1.6358	8.94E-07	NA	NA	NA
rs150785606, rs1723953	rs1723953	7	45993668	A	C		1.9482	0.3976	9.61E-07	NA	NA	NA
	rs11977526	7	46008110	A	G		-0.6674	0.1362	9.53E-07	-0.6280	0.1360	3.88E-06
	rs138317269	7	46989518	T	G		-8.0214	1.6386	9.82E-07	NA	NA	NA
	rs150785606	7	46990467	T	C		8.0378	1.6358	8.94E-07	NA	NA	NA
rs7006531	rs7831012	8	95088353	C	G		-0.9495	0.1622	4.78E-09	-0.0309	0.0928	0.7391
	rs7006922	8	95089653	A	C		1.0757	0.1701	2.56E-10	0.0046	0.0698	0.9472
	rs3018846	8	95090293	A	G		0.7509	0.1487	4.41E-07	0.0406	0.1074	0.7053
	rs2978160	8	95090481	A	C		-0.7518	0.1487	4.25E-07	-0.0415	0.1074	0.6991
	rs2978161	8	95090517	C	G		0.7516	0.1486	4.28E-07	0.0431	0.1075	0.6881
	rs2978165	8	95090906	C	G		-0.7519	0.1483	3.98E-07	-0.0439	0.1071	0.6819
	rs7845175	8	95091144	A	C		0.7526	0.1483	3.87E-07	0.0446	0.1071	0.6772
	8:95091340:T_TG	8	95091340	T	TG		-0.9808	0.1998	9.14E-07	-0.0412	0.1464	0.7782
	rs7013153	8	95092061	A	C		-1.0402	0.1761	3.46E-09	0.0215	0.0859	0.8025
	rs2978143	8	95093235	A	C		0.8404	0.154	4.82E-08	0.0176	0.0975	0.8567
	rs116136580	8	95096074	T	C		-1.0546	0.1738	1.30E-09	0.0406	0.0711	0.5673
	rs6997440	8	95096603	A	G		0.7975	0.1567	3.60E-07	-0.0257	0.1017	0.8007
	rs9987124	8	95096956	A	G		0.7387	0.1489	6.99E-07	-0.0051	0.1028	0.9604
	rs114684581	8	95100302	T	C		-1.0687	0.1745	9.11E-10	0.0343	0.0703	0.6251
	8:95106468:GACAA	8	95106468	G	GACAA		1.2208	0.1834	2.80E-11	NA	NA	NA
	rs2513761	8	95106732	A	T		0.8945	0.1472	1.24E-09	0.1848	0.1054	0.0795
	rs2446846	8	95106768	T	C		0.8956	0.1472	1.16E-09	0.1861	0.1054	0.0775
	rs2513762	8	95106775	A	C		0.8963	0.1472	1.13E-09	0.1868	0.1054	0.0764
	rs2513763	8	95106936	A	C		-0.8954	0.1472	1.18E-09	-0.1860	0.1054	0.0778
	rs2446845	8	95106957	T	G		0.9025	0.1458	6.06E-10	0.2137	0.1064	0.0445
	rs2513764	8	95107477	A	C		-0.6961	0.1402	6.92E-07	-0.1051	0.1110	0.3439
	rs2446844	8	95107693	A	G	<i>CDH17</i>	-0.904	0.1473	8.38E-10	-0.1935	0.1054	0.0664
	rs2513765	8	95108327	T	C		-0.8948	0.1472	1.21E-09	-0.1842	0.1053	0.0802
	rs2446842	8	95109361	A	G		-0.8936	0.1473	1.31E-09	-0.1807	0.1051	0.0855
	rs2513767	8	95109404	A	G		0.8936	0.1473	1.31E-09	0.1807	0.1051	0.0855
	rs3101283	8	95109499	T	G		0.8936	0.1473	1.31E-09	0.1806	0.1051	0.0856
	rs2446840	8	95109531	T	G		0.8970	0.1472	1.11E-09	0.1850	0.1051	0.0783
	rs2446839	8	95109671	A	G		-0.8934	0.1473	1.33E-09	-0.1804	0.1051	0.0859
	rs2513769	8	95109812	T	C		-0.8928	0.1473	1.37E-09	-0.1799	0.1051	0.0869
	rs2513770	8	95109882	A	C		0.8934	0.1477	1.47E-09	0.1877	0.1067	0.0785
	rs2446838	8	95110200	T	G		0.8908	0.1474	1.53E-09	0.1712	0.1043	0.1006
	rs2446837	8	95110206	T	G		0.8909	0.1474	1.52E-09	0.1713	0.1043	0.1004
	rs2513771	8	95110421	A	T		0.8908	0.1475	1.53E-09	0.1702	0.1043	0.1026
	rs2446836	8	95110444	C	G		-0.8874	0.1474	1.75E-09	-0.1678	0.1043	0.1076
	rs2513772	8	95110454	A	C		-0.8905	0.1474	1.54E-09	-0.1705	0.1042	0.1018
	rs2513773	8	95110512	T	G		0.8904	0.1474	1.55E-09	0.1704	0.1042	0.1020
	rs2446835	8	95110552	T	G		-0.8733	0.1481	3.69E-09	-0.1588	0.1060	0.1339
rs2446834	8	95110924	T	C		0.8799	0.1473	2.34E-09	0.1607	0.1042	0.1229	
rs2513774	8	95111025	T	C		-0.8516	0.1466	6.29E-09	-0.1490	0.1055	0.1582	
rs2446833	8	95111326	T	C		0.9017	0.1554	6.56E-09	0.0293	0.0905	0.7457	
rs2513775	8	95111617	C	G		0.8650	0.1477	4.68E-09	0.1511	0.1055	0.1521	
rs7006531	8	95110744	A	G		-1.1600	0.1680	5.03E-12	NA	NA	NA	
rs113866309	rs113866309	12	66516948	T	C	<i>LLPH/TMBIM4</i>	-3.2809	0.6275	1.71E-07	NA	NA	NA
	rs145704323	12	66532537	A	C		3.3753	0.6589	3.01E-07	0.6762	0.4097	0.0989
rs2414856	rs7403071	15	65048309	A	G		-0.6186	0.126	9.11E-07	-0.0299	0.0611	0.6242
	rs7180635	15	65048912	T	C		-0.6258	0.1246	5.07E-07	-0.0502	0.0625	0.4223
	rs1976112	15	65059220	A	T		-0.6287	0.1245	4.39E-07	-0.0540	0.0626	0.3886
	rs1008917	15	65059651	T	C		0.6188	0.1257	8.61E-07	0.0329	0.0614	0.5915
	rs12899738	15	65060028	C	G	<i>RBPM2</i>	0.6188	0.1251	7.48E-07	0.0386	0.0621	0.5335
	rs2414856	15	65072461	A	G		0.6783	0.127	9.18E-08	NA	NA	NA
	rs4777594	15	65076993	A	G		0.6543	0.1277	3.00E-07	NA	NA	NA
	rs2087027	15	65089675	A	G		0.6376	0.13	9.39E-07	0.0503	0.0693</	

SS Table. 72 independent SNPs with  $P < 1.0 \times 10^{-6}$  in discover stage for SBP, DBP, PP, HTN or CPASSOC analysis.

ID	chr	pos	A1	A2	SBP				DBP				HTN				PP				CPASSOC-SHom		CPASSOC-SHet		1KG_African_freq	1KG_European_freq
					Effect	StdErr	P.value	N	Effect	StdErr	P.value	N	Effect	StdErr	P.value	N	Effect	StdErr	P.value	N	P.value	P.value				
rs11302595	1	38880204	t	c	0.99	-7.38	4.21	7.90E-02	5212	-2.19	2.04	2.80E-01	10249	-0.96	0.62	1.20E-01	9282	-11.25	2.27	6.80E-07	10249	9.19E-02	2.52E-01	0.99	1	
rs36064592	1	114462662	a	g	0.43	0.78	0.18	1.80E-05	31970	0.2	0.11	7.40E-02	31967	0.05	0.02	1.90E-02	28230	0.64	0.13	8.60E-07	31967	1.61E-03	1.51E-04	0.5	0.34	
rs12063100	1	188834544	t	g	0.02	2.95	0.88	8.30E-04	19870	1.13	0.53	3.20E-02	19867	-0.19	0.11	7.70E-02	16108	1.88	0.63	3.00E-03	19867	2.37E-01	4.76E-07	0.02	0	
rs59922837	2	154175435	a	g	0.01	4.55	1.21	1.70E-04	20703	3.54	0.7	4.50E-07	20700	0.36	0.14	1.10E-02	18451	0.67	0.83	4.20E-01	22314	1.39E-05	3.88E-06	0	0	
rs1918172	2	156888500	c	g	0.36	-0.92	0.18	2.90E-07	30714	-0.51	0.11	2.60E-06	30711	-0.03	0.02	9.30E-02	27244	-0.44	0.13	6.00E-04	30711	1.82E-05	1.04E-06	0.41	0.11	
rs7602674	2	184538648	t	c	0.39	-0.95	0.19	8.10E-07	30714	-0.36	0.12	2.00E-03	30711	-0.06	0.02	9.70E-03	27230	-0.61	0.14	1.20E-05	30711	6.63E-05	7.00E-06	0.34	0.47	
rs62180365	2	192934117	t	g	0.77	1.05	0.2	2.40E-07	31970	0.47	0.12	1.00E-04	31967	0.1	0.02	1.30E-05	27923	0.62	0.14	1.90E-05	31967	2.63E-07	6.41E-07	0.79	0.47	
<b>2:210033781:AT_A<sup>a</sup></b>	2	210033781	a	at	0.06	-1.39	0.39	4.00E-04	28554	0.07	0.23	7.50E-01	28551	-0.1	0.05	3.20E-02	20616	<b>-1.62</b>	<b>0.29</b>	<b>3.10E-08</b>	<b>24802</b>	4.67E-02	1.68E-06	0.06	0.13	
rs737126	2	231896779	a	g	0.24	0.77	0.23	7.20E-04	30841	0.61	0.13	6.00E-06	30838	0.12	0.03	3.30E-06	26789	0.16	0.16	3.30E-01	28703	7.79E-07	1.51E-06	0.28	0.25	
rs17042306	3	5381728	a	g	0.88	-1.25	0.28	1.10E-05	31970	-0.79	0.17	3.00E-06	31967	-0.13	0.03	1.30E-04	27728	-0.54	0.21	8.80E-03	30918	6.58E-07	5.69E-06	0.89	0.9	
<b>rs114821199<sup>a</sup></b>	3	40965875	a	g	0.01	4.42	1.04	2.30E-05	22648	0.2	0.6	7.40E-01	22645	0.18	0.12	1.40E-01	20396	<b>4.21</b>	<b>0.73</b>	<b>1.00E-08</b>	<b>22645</b>	2.92E-02	1.87E-04	0.02	0	
<b>rs7651190<sup>b</sup></b>	3	41765955	a	g	0.35	0.04	0.18	8.10E-01	30356	-0.45	0.11	4.20E-05	30353	-0.06	0.02	8.80E-03	26906	0.43	0.13	1.30E-03	30918	7.47E-03	<b>6.87E-09</b>	0.28	0.81	
<b>rs147428270<sup>b</sup></b>	3	41868721	t	c	0.63	0.09	0.21	6.80E-01	31970	-0.51	0.13	4.60E-05	31967	-0.05	0.02	5.80E-02	28443	0.47	0.15	2.00E-03	30918	2.16E-02	<b>2.49E-08</b>	0.57	0.97	
rs7372217	3	41990122	a	g	0.34	-0.14	0.19	4.60E-01	29585	-0.55	0.11	9.50E-07	29582	-0.07	0.02	1.40E-03	25731	0.33	0.14	1.60E-02	28533	3.55E-04	8.21E-06	0.29	0.8	
rs9864989	3	52684365	t	g	0.03	2.95	0.63	3.20E-06	19178	1.78	0.37	1.90E-06	19175	0.31	0.08	9.70E-05	15416	1.3	0.47	6.00E-03	19740	2.99E-07	2.59E-06	0.05	0	
rs7654819	4	11618714	a	c	0.27	-0.6	0.19	2.00E-03	31970	-0.4	0.12	5.20E-04	31967	0.04	0.02	1.10E-01	27987	-0.23	0.14	9.20E-02	31540	9.15E-02	5.77E-08	0.29	0.3	
rs192457787	4	58795698	a	c	0.99	-9.35	2.33	6.10E-05	14601	-0.95	1.28	4.60E-01	15515	-0.4	0.29	1.70E-01	14605	-8.43	1.61	1.60E-07	15515	2.60E-02	4.83E-04	1	1	
rs150834401	4	103164224	t	c	0.11	1.16	0.28	4.80E-05	31970	0.86	0.17	4.80E-07	31967	0.04	0.03	1.90E-01	27648	0.31	0.2	1.20E-01	31540	9.27E-05	4.11E-06	0.14	0	
<b>rs62312401<sup>a</sup></b>	4	116987529	a	g	0.94	1.64	0.4	3.80E-05	30356	<b>1.31</b>	<b>0.24</b>	<b>3.50E-08</b>	<b>30353</b>	0.13	0.05	5.00E-03	24655	0.61	0.29	3.50E-02	31540	1.91E-06	3.04E-07	0.96	0.77	
rs182783477	4	123592734	c	g	0.98	-2.82	0.7	6.10E-05	29578	-0.45	0.43	2.90E-01	29575	-0.1	0.08	2.20E-01	24849	-2.51	0.51	7.00E-07	29575	2.24E-02	4.86E-04	0.99	1	
rs115236533	5	19745715	c	g	0.01	-2.96	1.07	5.50E-03	22648	0.29	0.62	6.30E-01	22645	0.19	0.12	1.30E-01	20396	-2.92	0.74	7.70E-05	24259	9.37E-01	9.16E-07	0.01	0	
rs35353431	5	31910483	a	t	0.43	-0.87	0.23	1.20E-04	30356	-0.07	0.14	6.20E-01	30353	-0.03	0.03	2.60E-01	26120	-0.82	0.16	3.50E-07	31967	4.97E-02	9.08E-04	0.44	0.5	
rs143572614	5	62024475	c	g	0.99	7.93	2.8	4.60E-03	10582	6.21	1.54	5.80E-05	10579	1.44	0.29	7.80E-07	10636	2.06	1.98	3.00E-01	10579	2.81E-06	3.38E-06	0.99	1	
rs189315540	5	108796312	t	c	0.01	6.05	1.8	7.80E-04	16865	0.84	0.99	3.90E-01	17688	0.32	0.18	7.10E-02	18871	6.48	1.21	9.40E-08	17688	2.50E-02	5.49E-03	0.02	0	
rs2584077	6	46267046	a	c	0.01	-5.05	1.46	5.30E-04	17352	-4.16	0.83	4.90E-07	17349	-0.24	0.16	1.40E-01	17406	-0.86	1.04	4.10E-01	17349	1.64E-04	4.22E-06	0	0.06	
rs9385284	6	123400105	a	g	0.8	-0.47	0.25	6.10E-02	29227	-0.43	0.15	3.20E-03	29224	0.08	0.03	6.40E-03	25126	0.04	0.18	8.40E-01	30838	5.58E-01	5.56E-08	0.82	0.76	
rs4487596	6	123407496	t	c	0.8	-0.59	0.23	1.10E-02	30356	-0.4	0.14	4.10E-03	30353	0.05	0.03	5.20E-02	26266	-0.11	0.16	4.90E-01	31967	2.61E-01	3.92E-07	0.81	0.76	
<b>rs76987554<sup>ab</sup></b>	6	134080855	t	c	0.09	<b>-1.85</b>	<b>0.31</b>	<b>2.20E-09</b>	<b>31970</b>	-0.91	0.19	1.10E-06	31967	-0.12	0.04	9.20E-04	27480	-0.99	0.22	5.70E-06	31967	8.69E-08	<b>1.84E-08</b>	0.09	0	
<b>rs79030490<sup>ab</sup></b>	6	134087689	a	c	0.09	<b>-1.83</b>	<b>0.31</b>	<b>3.00E-09</b>	<b>31970</b>	-0.92	0.19	8.70E-07	31967	-0.12	0.04	7.00E-04	27480	-0.96	0.22	1.00E-05	31967	7.01E-08	<b>2.50E-08</b>	0.91	1	
rs62434120	6	150992370	a	t	0.15	-1.19	0.24	1.10E-06	31970	-0.69	0.15	2.80E-06	31967	-0.1	0.03	4.70E-04	27742	-0.55	0.17	1.50E-03	31967	5.89E-07	2.23E-06	0.17	0.08	
rs6969780	7	27159136	c	g	0.3	0.82	0.19	1.70E-05	31155	0.62	0.12	6.90E-08	31152	0.08	0.02	5.30E-04	26701	0.23	0.13	8.90E-02	31152	4.06E-07	5.97E-07	0.35	0.1	
<b>rs10279895<sup>ab</sup></b>	7	27328210	a	g	0.9	1.09	0.29	1.40E-04	31970	0.83	0.17	1.80E-06	31967	<b>0.19</b>	<b>0.03</b>	<b>1.80E-08</b>	<b>26977</b>	0.36	0.2	8.10E-02	31967	<b>2.16E-08</b>	<b>3.24E-08</b>	0.89	1	
<b>rs11563582<sup>ab</sup></b>	7	27351650	a	g	0.13	<b>1.61</b>	<b>0.28</b>	<b>7.10E-09</b>	<b>30841</b>	<b>1.02</b>	<b>0.17</b>	<b>8.40E-10</b>	<b>30838</b>	0.16	0.03	2.20E-06	26059	0.64	0.19	1.10E-03	30838	<b>1.51E-10</b>	<b>1.08E-09</b>	0.16	0.08	
rs1723953	7	45993668	a	c	0.03	1.87	0.56	9.00E-04	30393	-0.03	0.34	9.20E-01	30390	0.13	0.07	4.60E-02	26631	1.95	0.4	9.60E-07	30390	5.25E-02	3.58E-05	0.03	0	
<b>rs11977526<sup>b</sup></b>	7	46008110	a	g	0.34	-0.24	0.19	2.10E-01	29227	0.39	0.12	7.50E-04	29224	0.01	0.02	8.40E-01	25372	-0.67	0.14	9.50E-07	30838	4.10E-01	<b>4.53E-09</b>	0.35	0.41	
rs150785606	7	46990467	t	c	0.01	9.71	2.34	3.30E-05	10212	1.72	1.27	1.70E-01	11126	0.71	0.29	1.50E-02	10216	8.04	1.64	8.90E-07	11126	2.95E-03	2.69E-04	0	0	
7:80293263:A_AAT	7	80293263	a	aatactc	0.85	-0.78	0.29	8.00E-03	25479	-0.86	1.17	5.70E-07	25476	-0.13	0.04	4.10E-04	20999	0.15	0.21	4.80E-01	23862	1.11E-05	4.96E-06	0.82	1	
<b>rs115476423<sup>b</sup></b>	7	149199964	c	g	0.94	0.32	0.38	4.10E-01	31970	0.58	0.23	1.20E-02	31967	-0.14	0.05	2.20E-03	27226	-0.22	0.27	4.20E-01	31967	9.42E-01	<b>4.99E-08</b>	0.92	1	
rs115706913	8	14081817	t	c	0.95	0.77	0.43	7.10E-02	29227	0.36	0.25	1.50E-01	29224	0.26	0.05	2.70E-07	23954	0.33	0.3	2.80E-01	30838	6.40E-04	2.31E-06	0.93	0.07	
rs10096908	8	41641557	t	c	0.2	1.03	0.21	1.40E-06	31970	0.47	0.13	2.30E-04	31967	0.11	0.02	1.00E-05	27871	0.55	0.15	2.30E-04	31967	6.21E-07	1.63E-06	0.19	0.97	
<b>rs7006531<sup>ab</sup></b>																										

S6 Table. Trans-ethnic replication of 72 independent SNPs with  $P < 1.0 \times 10^{-6}$  in discover stage for SBP, DBP, PP, HTN or CPASSOC analysis.

ID	Chromosome	Physical Position	Allele1	Allele2	EAF	Trait	Discovery				Trans-ethnic Replication				META Analysis (All)						
							Effect	SE	P Value	N	Effect	SE	P Value	N	Effect	SE	P Value	N			
rs113025995	1	38880204	t	c	0.99	SBP	-7.3798	4.2054	7.93E-02	5212	NA	NA	NA	NA	NA	NA	NA	NA	NA		
							DBP	-2.192	2.0445	2.84E-01	10249	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
							PP	-11.2545	2.2652	6.75E-07	10249	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
							HTN	-0.9586	0.6153	1.19E-01	9282	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
							CPASSOC (SHom)	NA	NA	9.19E-02	5212/10249/9282	NA	NA	NA	NA	NA	NA	NA	9.19E-02	NA	
							CPASSOC (SHet)	NA	NA	2.52E-01	5212/10249/9282	NA	NA	NA	NA	NA	NA	NA	2.52E-01	NA	
rs36064592	1	114462662	a	g	0.43	SBP	0.7792	0.1819	1.85E-05	31970	-0.0888	0.1512	5.57E-01	35270	0.2658	0.1163	2.22E-02	67240	NA		
							DBP	0.1954	0.1094	7.41E-02	31967	-0.0482	0.0926	6.03E-01	35270	0.0535	0.0707	4.49E-01	67237	NA	
							PP	0.6374	0.1295	8.64E-07	31967	-0.018	0.1093	8.69E-01	35270	0.2546	0.0835	2.30E-03	67237	NA	
							HTN	0.0494	0.021	1.88E-02	28229.5	-0.0336	0.0197	8.85E-02	35532	0.0053	0.0144	7.12E-01	63761.5	NA	
							CPASSOC (SHom)	NA	NA	1.61E-03	31970/31976/28229	NA	NA	2.49E-01	35270/35270/35532	NA	NA	5.62E-03	67240/67237/63762	NA	
							CPASSOC (SHet)	NA	NA	1.51E-04	31970/31976/28229	NA	NA	2.27E-01	35270/35270/35532	NA	NA	7.21E-04	67240/67237/63762	NA	
rs12063100	1	188834544	t	g	0.02	SBP	2.9461	0.8816	8.33E-04	19869.9	NA	NA	NA	NA	NA	NA	NA	NA	NA		
							DBP	1.1281	0.5251	3.17E-02	19866.9	NA	NA	NA	NA	NA	NA	NA	NA	NA	
							PP	1.8752	0.6315	2.99E-03	19866.9	NA	NA	NA	NA	NA	NA	NA	NA	NA	
							HTN	-0.19	0.1074	7.67E-02	16108	NA	NA	NA	NA	NA	NA	NA	NA	NA	
							CPASSOC (SHom)	NA	NA	2.37E-01	19869/19869/16108	NA	NA	NA	NA	NA	NA	NA	2.37E-01	NA	
							CPASSOC (SHet)	NA	NA	4.76E-07	19869/19869/16108	NA	NA	NA	NA	NA	NA	NA	4.76E-07	NA	
rs59922837	2	154175435	a	g	0.01	SBP	4.5541	1.2119	1.71E-04	20703	NA	NA	NA	NA	NA	NA	NA	NA	NA		
							DBP	3.5366	0.7007	4.48E-07	20700	NA	NA	NA	NA	NA	NA	NA	NA	NA	
							PP	0.6653	0.827	4.21E-01	22314	NA	NA	NA	NA	NA	NA	NA	NA	NA	
							HTN	0.3643	0.1433	1.10E-02	18451	NA	NA	NA	NA	NA	NA	NA	NA	NA	
							CPASSOC (SHom)	NA	NA	1.39E-05	20703/20700/18451	NA	NA	NA	NA	NA	NA	NA	1.39E-05	NA	
							CPASSOC (SHet)	NA	NA	3.88E-06	20703/20700/18451	NA	NA	NA	NA	NA	NA	NA	3.88E-06	NA	
rs1918172	2	156888500	c	g	0.36	SBP	-0.9154	0.1785	2.90E-07	30714	-0.1877	0.1908	3.25E-01	37930	-0.5758	0.1303	1.00E-05	68644			
							DBP	-0.5079	0.1081	2.61E-06	30711	-0.0854	0.118	4.69E-01	37930	-0.3151	0.0797	7.70E-05	68641		
							PP	-0.4356	0.127	6.04E-04	30711	-0.1969	0.1319	1.35E-01	37930	-0.3207	0.0915	4.54E-04	68641		
							HTN	-0.0346	0.0206	9.26E-02	27243.7	0.0023	0.0233	9.21E-01	38203	-0.0184	0.0154	2.33E-01	65446.7		
							CPASSOC (SHom)	NA	NA	1.82E-05	30714/30711/27243	NA	NA	8.43E-01	37930/37930/37930	NA	NA	7.22E-04	68644/68641/65447		
							CPASSOC (SHet)	NA	NA	1.04E-06	30714/30711/27243	NA	NA	8.82E-01	37930/37930/37930	NA	NA	6.84E-05	68644/68641/65447		
rs7602674	2	184538648	t	c	0.39	SBP	-0.954	0.1934	8.13E-07	30714	-0.118	0.1458	4.18E-01	36162	-0.4211	0.1164	2.99E-04	66876			
							DBP	-0.3614	0.1167	1.96E-03	30711	-0.1669	0.0893	6.18E-02	36162	-0.2387	0.0709	7.64E-04	66873		
							PP	-0.6061	0.1387	1.23E-05	30711	0.038	0.1043	7.15E-01	36162	-0.1945	0.0833	1.96E-02	66873		
							HTN	-0.0578	0.0223	9.66E-03	27230.4	-0.0077	0.0187	6.81E-01	36416	-0.0284	0.0143	4.76E-02	63646.4		
							CPASSOC (SHom)	NA	NA	6.63E-05	30714/30711/27230	NA	NA	9.78E-02	36162/36162/36416	NA	NA	1.40E-04	66876/66873/63646		
							CPASSOC (SHet)	NA	NA	7.00E-06	30714/30711/27230	NA	NA	1.73E-01	36162/36162/36416	NA	NA	3.75E-05	66876/66873/63646		
rs62180365	2	192934117	t	g	0.77	SBP	1.0454	0.2024	2.41E-07	31970	-0.0247	0.1277	8.47E-01	38978	0.2799	0.108	9.54E-03	70948			
							DBP	0.4723	0.1217	1.05E-04	31967	0.0638	0.0785	4.16E-01	38978	0.1838	0.066	5.32E-03	70945		
							PP	0.6162	0.1439	1.86E-05	31967	-0.1154	0.0912	2.06E-01	38978	0.0942	0.077	2.22E-01	70945		
							HTN	0.1016	0.0233	1.31E-05	27922.8	-0.0192	0.0168	2.51E-01	39247	0.022	0.0136	1.06E-01	67169.8		
							CPASSOC (SHom)	NA	NA	2.63E-07	31970/31967/27922	NA	NA	5.44E-01	38978/38978/39247	NA	NA	2.36E-05	70948/70945/67170		
							CPASSOC (SHet)	NA	NA	6.41E-07	31970/31967/27922	NA	NA	4.19E-01	38978/38978/39247	NA	NA	3.22E-05	70948/70945/67170		
2:210033781:AT_A	2	210033781	a	at	0.06	SBP	-1.3903	0.3929	4.03E-04	28554	-0.0632	0.2028	7.55E-01	49649	-0.3424	0.1802	5.75E-02	78203			
							DBP	0.0739	0.2321	7.50E-01	28551	-0.0529	0.1233	6.68E-01	49649	-0.025	0.1089	8.18E-01	78200		
							PP	-1.6191	0.2926	3.13E-08	24802	-0.2198	0.1308	9.30E-02	46093	-0.453	0.1194	1.49E-04	70895		
							HTN	-0.1021	0.0475	3.17E-02	20615.5	-0.0153	0.0275	5.79E-01	36192	-0.0371	0.0238	1.19E-01	56807.5		
							CPASSOC (SHom)	NA	NA	4.67E-02	28554/28551/20615	NA	NA	4.25E-01	49649/49649/36192	NA	NA	1.25E-01	78203/78200/56808		
							CPASSOC (SHet)	NA	NA	1.68E-06	28554/28551/20615	NA	NA	7.56E-01	49649/49649/36192	NA	NA	7.61E-05	78203/78200/56808		
rs737126	2	231896779	a	g	0.24	SBP	0.7711	0.2281	7.23E-04	30841	0.1842	0.1775	3.00E-01	35171	0.4056	0.1401	3.79E-03	66012			
							DBP	0.6105	0.1348	5.97E-06	30838	0.0421	0.1087	6.98E-01	35171	0.2661	0.0846	1.66E-03	66009		
							PP	0.1599	0.1628	3.26E-01	28703	0.1227	0.1261	3.30E-01	35171	0.1367	0.0997	1.70E-01	63874		
							HTN	0.1225	0.0263	3.27E-06	26789	0.0207	0.0225	3.58E-01	35399	0.0638	0.0171	1.93E-04	62188		
							CPASSOC (SHom)	NA	NA	7.79E-07	30841/30838/26789	NA	NA	3.30E-01	35171/35171/35399	NA	NA	1.18E-05	66012/66009/62188		
							CPASSOC (SHet)	NA	NA	1.51E-06	30841/30838/26789	NA	NA	6.77E-01	35171/35171/35399	NA	NA	5.76E-05	66012/66009/62188		
rs17042306	3	5381728	a	g	0.88	SBP	-1.2546	0.2849	1.06E-05	31970	0.397	0.254	1.18E-01	35125	-0.3344	0.1896	7.78E-02	67095			
							DBP	-0.7937	0.17	3.05E-06	31967	0.1412	0.1565	3.67E-01	35125	-0.2877	0.1151	1.25E-02	67092		
							PP	-0.538	0.2053	8.77E-03	30918	0.3106	0.1873	9.73E-02	35125	-0.0749	0.1384	5.88E-01	66043		
							HTN	-0.126	0.0329	1.30E-04	27727.9	-0.0011	0.0332	9.74E-01	35383	-0.0641	0.0234	6.08E-03	63110.9		
							CPASSOC (SHom)	NA	NA	6.58E-07	31970/31967/27727	NA	NA	7.03E-01	35125/35125/35383	NA	NA	2.96E-05	67095/67092/63111		
							CPASSOC (SHet)	NA	NA	5.69E-06	31970/31967/27727	NA	NA	4.46E-01	35125/35125/35383	NA	NA	9.94E-05	67095/67092/63111		
rs114821199	3	40965875	a	g	0.01	SBP	4.4192	1.0433	2.28E-05	22648	-1.7438	2.3296	4.54E-01	13817	3.3896	0.9522	3.71E-04	36465			
							DBP	0.2012	0.6004	7.38E-01	22645	-0.569	1.4464	6.94E-01	13817	0.088	0.5545	8.74E-01	36462		
							PP	4.2099	0.7349	1.01E-08	22645	-0.3834	0.8188	6.40E-01	16476	2.1606	0.5469	7.80E-05	39121		
							HTN	0.1781	0.121	1.41E-01	20396	-0.2443	0.1603	1.28E-01	16692	0.0248	0.0966	7.97E-01	37088		
							CPASSOC (SHom)	NA	NA	2.92E-02	22648/22645/20396	NA	NA	5.10E-01	13817/13817/16692	NA	NA	1.10E-01	36465/36462/37088		
							CPASSOC (SHet)	NA	NA	1.87E-04	22648/22645/20396	NA	NA	7.50E-01	13817/13817/16692	NA	NA	4.40E-03	36465/36462/37088		
rs7651190*	3	41765955	a	g	0.35	SBP	0.0447	0.1825	8.07E-01	30356	-0.0501	0.1392	7.19E-01	51662	-0.0152	0.1107	8.91E-01	82018			
							DBP	-0.4501	0.1099	4.20E-05	30353	-0.3808	0.0863	1.02E-05	51662	-0.4072	0.0679	1.97E-09	82015		
							PP	0.4271	0.1323	1.25E-03	30918	0.125	0.099	2.07E-01	51662	0.2335	0.0793	3.23E-03	82580		
							HTN	-0.0563	0.0215	8.79E-03	26905.5	-0.0179	0.0188	3.39E-01	51935	-0.0345	0.0141	1.46E-02	78840.7		
							CPASSOC (SHom)	NA	NA	7.47E-03	30356/30353/2690										



						CPASSOC (SHet)	NA	NA	1.63E-06	31970/31967/27870	NA	NA	4.15E-01	37570/37570/37839	NA	NA	3.03E-05	69540/69537/65910
rs7006531*	8	95110744	a	g	0.85	SBP	-0.8494	0.2372	3.43E-04	31970	-0.7612	0.4429	8.57E-02	40920	-0.8297	0.2091	7.25E-05	72890
						DBP	0.3108	0.1433	3.01E-02	31967	0.457	0.3875	2.38E-01	38254	0.3284	0.1344	1.46E-02	70221
						PP	-1.1601	0.168	5.03E-12	31967	-0.5275	0.3176	9.67E-02	40920	-1.0218	0.1485	5.96E-12	72887
						HTN	-0.0152	0.0274	5.78E-01	27733.8	0.0403	0.0882	6.48E-01	38526	-0.0103	0.0262	6.94E-01	66259.8
						CPASSOC (SHom)	NA	NA	5.63E-01	31970/31967/27733	NA	NA	9.11E-01	40920/38254/38526	NA	NA	9.22E-01	72890/70221/66260
						CPASSOC (SHet)	NA	NA	7.56E-14	31970/31967/27733	NA	NA	6.13E-03	40920/38254/38526	NA	NA	2.19E-13	72890/70221/66260
rs186208701	8	99580116	t	c	0.99	SBP	-0.9056	0.8754	3.01E-01	23777	NA	NA	NA	NA	NA	NA	NA	NA
						DBP	1.291	0.5168	1.25E-02	23774	NA	NA	NA	NA	NA	NA	NA	NA
						PP	-2.117	0.623	6.79E-04	25388	NA	NA	NA	NA	NA	NA	NA	NA
						HTN	-0.1806	0.1002	7.15E-02	21525	NA	NA	NA	NA	NA	NA	NA	NA
						CPASSOC (SHom)	NA	NA	8.82E-01	23777/23774/21525	NA	NA	NA	NA	NA	NA	NA	8.82E-01
						CPASSOC (SHet)	NA	NA	7.77E-07	23777/23774/21525	NA	NA	NA	NA	NA	NA	7.77E-07	NA
rs187821766	8	99741278	t	c	0.02	SBP	0.6681	0.9348	4.75E-01	14176	NA	NA	NA	NA	NA	NA	NA	NA
						DBP	-1.6757	0.5577	2.66E-03	14173	NA	NA	NA	NA	NA	NA	NA	NA
						PP	2.2392	0.6959	1.29E-03	14173	NA	NA	NA	NA	NA	NA	NA	NA
						HTN	0.1939	0.1049	6.45E-02	12891	NA	NA	NA	NA	NA	NA	NA	NA
						CPASSOC (SHom)	NA	NA	8.91E-01	14176/14173/12891	NA	NA	NA	NA	NA	NA	NA	8.91E-01
						CPASSOC (SHet)	NA	NA	9.25E-08	14176/14173/12891	NA	NA	NA	NA	NA	NA	9.25E-08	NA
rs79455834	8	122045324	a	c	0.96	SBP	1.7549	0.4515	1.02E-04	31155	0.1733	1.275	8.92E-01	27691	1.5787	0.4256	2.08E-04	58846
						DBP	1.1009	0.274	5.85E-05	31152	0.8366	0.8333	3.15E-01	27691	1.0751	0.2603	3.62E-05	58843
						PP	0.7324	0.319	2.17E-02	31152	-0.7314	0.9673	4.50E-01	27691	0.5888	0.3029	5.20E-02	58843
						HTN	0.2535	0.0527	1.48E-06	26392.1	0.125	0.1893	5.09E-01	27958	0.2443	0.0508	1.50E-06	54350.1
						CPASSOC (SHom)	NA	NA	6.55E-07	31155/31152/26392	NA	NA	3.26E-01	27691/27691/27958	NA	NA	9.95E-06	58846/58843/54350
						CPASSOC (SHet)	NA	NA	4.93E-06	31155/31152/26392	NA	NA	7.52E-01	27691/27691/27958	NA	NA	1.91E-04	58846/58843/54350
rs3866719	8	134932570	t	c	0.82	SBP	1.084	0.235	3.98E-06	30714	-0.0146	0.1309	9.11E-01	36781	0.2456	0.1144	3.18E-02	67495
						DBP	0.583	0.1423	4.21E-05	30711	0.0827	0.0802	3.03E-01	36781	0.2033	0.0699	3.62E-03	67492
						PP	0.5419	0.1685	1.30E-03	30711	-0.0892	0.0937	3.41E-01	36781	0.06	0.0819	4.64E-01	67492
						HTN	0.1148	0.0271	2.22E-05	18238	-0.0102	0.0172	5.53E-01	37024	0.0256	0.0145	7.71E-02	55262
						CPASSOC (SHom)	NA	NA	5.87E-07	30714/30711/18238	NA	NA	8.24E-01	36781/36781/37024	NA	NA	3.58E-05	67495/67492/55262
						CPASSOC (SHet)	NA	NA	5.08E-06	30714/30711/18238	NA	NA	7.18E-01	36781/36781/37024	NA	NA	1.81E-04	67495/67492/55262
rs78192203*	8	142375073	a	t	0.20	SBP	-0.8242	0.2257	2.61E-04	31970	-2.0961	0.5973	4.50E-04	30714	-0.9831	0.2111	3.22E-06	62684
						DBP	-0.7722	0.1357	1.26E-08	31967	-1.3428	0.3686	2.69E-04	30714	-0.8403	0.1273	4.15E-11	62681
						PP	-0.1477	0.1597	3.55E-01	31967	-1.3663	0.4247	1.29E-03	39423	-0.2987	0.1495	4.57E-02	71390
						HTN	-0.0756	0.026	3.58E-03	27820.6	-0.2519	0.0857	3.28E-03	30714	-0.0905	0.0249	2.77E-04	58534.6
						CPASSOC (SHom)	NA	NA	2.33E-06	31970/31967/27820	NA	NA	1.66E-03	30714/30714/30714	NA	NA	1.42E-07	62684/62681/58535
						CPASSOC (SHet)	NA	NA	1.09E-07	31970/31967/27820	NA	NA	2.85E-03	30714/30714/30714	NA	NA	1.69E-08	62684/62681/58535
rs114334738	9	28165671	t	c	0.94	SBP	1.6453	0.4236	1.03E-04	31970	3.7745	5.6727	5.06E-01	20901	1.6571	0.4224	8.75E-05	52871
						DBP	1.2762	0.2552	5.73E-07	31967	1.7709	3.7499	6.37E-01	20901	1.2785	0.2546	5.13E-07	52868
						PP	0.3841	0.2996	2.00E-01	31967	2.7247	4.3212	5.28E-01	20901	0.3953	0.2989	1.86E-01	52868
						HTN	0.1069	0.0505	3.42E-02	27225.6	-0.2018	0.9575	8.33E-01	21170	0.106	0.0504	3.55E-02	48395.6
						CPASSOC (SHom)	NA	NA	2.88E-05	31970/31967/27225	NA	NA	8.99E-01	20901/20901/21170	NA	NA	1.22E-03	52871/52868/48396
						CPASSOC (SHet)	NA	NA	4.94E-06	31970/31967/27225	NA	NA	7.72E-01	20901/20901/21170	NA	NA	2.01E-04	52871/52868/48396
rs71512425	9	28165694	a	g	0.80	SBP	0.8122	0.225	3.07E-04	31970	0.0033	0.1894	9.86E-01	35538	0.3389	0.1449	1.94E-02	67508
						DBP	0.6974	0.1348	2.32E-07	31967	-0.0322	0.1102	7.70E-01	38168	0.2599	0.0853	2.31E-03	70135
						PP	0.124	0.1605	4.40E-01	31967	-0.0253	0.1422	8.59E-01	35538	0.0403	0.1064	7.05E-01	67505
						HTN	0.0456	0.0262	8.12E-02	27878.6	0.0318	0.0252	2.06E-01	35798	0.0384	0.0182	3.42E-02	63676.6
						CPASSOC (SHom)	NA	NA	6.47E-05	31970/31967/27879	NA	NA	6.75E-01	35538/38168/35798	NA	NA	1.42E-03	67508/70135/63677
						CPASSOC (SHet)	NA	NA	1.99E-06	31970/31967/27879	NA	NA	3.84E-01	35538/38168/35798	NA	NA	3.27E-05	67508/70135/63677
rs115795127 <sup>bc</sup>	9	85993901	t	c	0.89	SBP	0.9906	0.2847	5.03E-04	31970	8.7717	9.0475	3.32E-01	4473	0.9983	0.2846	4.51E-04	36443
						DBP	0.4763	0.1716	5.52E-03	31967	0.7026	6.6522	9.16E-01	4473	0.4765	0.1715	5.48E-03	36440
						PP	0.5871	0.2022	3.69E-03	31967	9.2572	8.6147	2.83E-01	4473	0.5919	0.2021	3.41E-03	36440
						HTN	0.172	0.0325	1.23E-07	27675.5	4.4894	1.6767	7.42E-03	4473	0.1736	0.0325	1.13E-08	32148.5
						CPASSOC (SHom)	NA	NA	5.10E-06	31970/31967/27675	NA	NA	1.07E-01	4473/4473/4473	NA	NA	8.42E-06	36443/36440/32149
						CPASSOC (SHet)	NA	NA	1.05E-06	31970/31967/27675	NA	NA	8.41E-06	4473/4473/4473	NA	NA	7.30E-09	36443/36440/32149
rs190531342	9	114719568	t	c	0.92	SBP	-1.5414	0.4156	2.09E-04	30356	3.5014	1.4213	1.38E-02	28014	-1.1442	0.3989	4.13E-03	58370
						DBP	-1.0192	0.2484	4.09E-05	30353	1.8065	0.8716	3.82E-02	28014	-0.807	0.2389	7.30E-04	58367
						PP	-0.5053	0.2939	8.55E-02	31967	1.6605	1.151	1.49E-01	28014	-0.372	0.2848	1.91E-01	59981
						HTN	-0.2325	0.0495	2.65E-06	25877.2	0.2763	0.171	1.06E-01	28286	-0.1927	0.0475	4.86E-05	54163.2
						CPASSOC (SHom)	NA	NA	9.63E-07	30356/30353/25877	NA	NA	6.07E-02	28014/28014/28286	NA	NA	1.99E-06	58370/58367/54163
						CPASSOC (SHet)	NA	NA	5.19E-06	30356/30353/25877	NA	NA	2.10E-01	28014/28014/28286	NA	NA	3.61E-05	58370/58367/54163
rs10123054	9	128452054	t	c	0.65	SBP	-0.6921	0.182	1.43E-04	31003	-0.2167	0.1298	9.51E-02	37754	-0.377	0.1057	3.61E-04	68757
						DBP	-0.5706	0.11	2.13E-07	31000	-0.0705	0.0798	3.77E-01	37754	-0.2428	0.0646	1.70E-04	68754
						PP	-0.0933	0.1302	4.74E-01	31000	-0.159	0.0927	8.61E-02	37754	-0.1369	0.0755	6.97E-02	68754
						HTN	-0.0667	0.021	1.48E-03	27582.1	-0.0131	0.0173	4.50E-01	38026	-0.0348	0.0134	9.22E-03	65608.1
						CPASSOC (SHom)	NA	NA	2.70E-06	31003/31000/27582	NA	NA	3.23E-01	37754/37754/38026	NA	NA	3.42E-05	68757/68754/65608
						CPASSOC (SHet)	NA	NA	1.85E-06	31003/31000/27582	NA	NA	6.78E-01	37754/37754/38026	NA	NA	6.89E-05	68757/68754/65608
rs28687694	9	128483092	t	c	0.26	SBP	0.8674	0.2036	2.05E-05	28472	-0.146	0.142	3.04E-01	37494	0.1856	0.1165	1.11E-01	65966
						DBP	0.5658	0.1233	4.43E-06	28469	-0.1233	0.0877	1.60E-01	37494	0.1081	0.0715	1.30E-01	65963
						PP	0.296	0.1461	4.28E-02	30083	0.026	0.0996	7.94E-01	37494	0.1117	0.082		

rs10842715	12	26487183	t	g	0.46	PP	-0.1279	0.1228	2.98E-01	30838	-0.0402	0.0926	6.64E-01	38701	-0.072	0.0739	3.30E-01	69539
						HTN	-0.1026	0.0204	4.79E-07	26649	-0.0133	0.0171	4.37E-01	38971	-0.0502	0.0131	1.29E-04	65620
						CPASSOC (SHom)	NA	NA	2.50E-04	30841/30838/26649	NA	NA	7.30E-01	38701/38701/38971	NA	NA	9.63E-03	69542/69539/65620
						CPASSOC (SHet)	NA	NA	4.26E-06	30841/30838/26649	NA	NA	4.64E-01	38701/38701/38971	NA	NA	1.81E-04	69542/69539/65620
12:53049050:AC_A	12	53049050	a	ac	0.86	SBP	-1.7032	0.4322	8.11E-05	17426	0.6576	0.2759	1.72E-02	28247	-0.0259	0.2326	9.11E-01	45673
						DBP	-1.1805	0.2708	1.30E-05	17426	0.0525	0.1626	7.47E-01	28247	-0.2741	0.1394	4.92E-02	45673
						PP	-0.46	0.3141	1.43E-01	15812	0.6155	0.1932	1.45E-03	28247	0.3202	0.1646	5.17E-02	44059
						HTN	-0.2433	0.0554	1.15E-05	11700	-0.0151	0.0431	7.26E-01	19441	-0.1011	0.034	2.95E-03	31141
rs113866309 <sup>b,c</sup>	12	66516948	t	c	0.98	CPASSOC (SHom)	NA	NA	7.67E-07	17426/17426/11700	NA	NA	9.72E-01	28247/28247/19441	NA	NA	1.13E-05	45673/45673/31141
						CPASSOC (SHet)	NA	NA	5.49E-06	17426/17426/11700	NA	NA	1.21E-01	28247/28247/19441	NA	NA	1.01E-05	45673/45673/31141
						SBP	-3.7312	0.8675	1.70E-05	23760	-12.0824	10.7806	2.60E-01	10729	-3.7821	0.8633	1.24E-05	34489
						DBP	-0.6665	0.5167	1.97E-01	23757	8.3116	7.3912	2.63E-01	10729	-0.2559	0.4539	2.33E-01	34486
rs144058433	13	73013077	t	c	0.14	PP	-3.2809	0.6275	1.71E-07	23757	<b>-9.7833</b>	<b>3.3063</b>	<b>1.50E-03</b>	<b>9684</b>	<b>-2.2172</b>	<b>0.5424</b>	<b>8.24E-09</b>	<b>33441</b>
						HTN	-0.2244	0.1033	2.99E-02	22043	-3.5217	3.3044	2.83E-01	10729	-0.1475	0.0943	2.74E-02	32772
						CPASSOC (SHom)	NA	NA	3.91E-03	23760/23757/22043	NA	NA	3.50E-01	10729/10729/10729	NA	NA	1.87E-02	34489/34486/32772
						CPASSOC (SHet)	NA	NA	1.40E-04	23760/23757/22043	NA	NA	1.60E-02	10729/10729/10729	NA	NA	4.78E-05	34489/34486/32772
rs2414856	15	65072461	a	g	0.51	SBP	1.1947	0.2826	2.37E-05	31969.9	-0.1628	0.255	5.23E-01	36119	0.4465	0.1893	1.84E-02	68088.9
						DBP	0.8518	0.1695	5.03E-07	31966.9	0.023	0.1622	8.87E-01	36119	0.4192	0.1172	3.48E-04	68085.9
						PP	0.3197	0.2002	1.10E-01	31966.9	-0.1381	0.1718	4.21E-01	36119	0.0561	0.1304	6.67E-01	68085.9
						HTN	0.1119	0.0327	6.29E-04	27732.3	-0.0032	0.0337	9.24E-01	36364	0.056	0.0235	1.69E-02	64096.3
rs12445099	16	57890233	a	g	0.67	CPASSOC (SHom)	NA	NA	1.08E-06	31969/31966/27732	NA	NA	5.35E-01	36119/36119/36364	NA	NA	3.00E-05	68089/68086/64096
						CPASSOC (SHet)	NA	NA	4.35E-06	31969/31966/27732	NA	NA	9.11E-01	36119/36119/36364	NA	NA	2.55E-04	68089/68086/64096
						SBP	0.6013	0.1944	1.98E-03	31970	0.2477	0.2368	2.95E-01	35367	0.4589	0.1502	2.25E-03	67337
						DBP	0.2529	0.117	3.07E-02	31967	0.0723	0.1436	6.14E-01	35367	0.1808	0.0907	4.62E-02	67334
rs12149202	16	85700360	a	g	0.11	PP	0.36	0.1373	8.74E-03	31967	0.2399	0.1813	1.86E-01	35367	0.3162	0.1095	3.86E-03	67334
						HTN	0.1193	0.023	2.16E-07	27573.2	-0.0317	0.0303	2.94E-01	35599	0.064	0.0183	4.74E-04	63172.2
						CPASSOC (SHom)	NA	NA	3.40E-05	31970/31967/27573	NA	NA	7.75E-01	35367/35367/35599	NA	NA	1.04E-03	67337/67334/63172
						CPASSOC (SHet)	NA	NA	1.86E-06	31970/31967/27573	NA	NA	1.89E-01	35367/35367/35599	NA	NA	1.29E-05	67337/67334/63172
rs17721557	17	27260017	t	c	0.21	SBP	-1.3354	0.3011	9.21E-06	31970	0.0767	0.1592	6.30E-01	36873	-0.2319	0.1408	9.94E-02	68843
						DBP	-0.6867	0.1813	1.53E-04	31967	0.0948	0.0976	3.32E-01	36873	-0.0809	0.086	3.47E-01	68840
						PP	-0.7034	0.2168	1.18E-03	31967	-0.0135	0.1142	9.06E-01	36873	-0.1633	0.101	1.06E-01	68840
						HTN	-0.1877	0.0345	5.14E-08	27643.5	-0.0224	0.0205	2.73E-01	37140	-0.0655	0.0176	2.01E-04	64783.5
rs17225706	22	26680705	a	c	0.03	CPASSOC (SHom)	NA	NA	9.24E-08	31970/31967/27643	NA	NA	9.99E-01	36973/36873/37140	NA	NA	1.33E-05	68843/68840/64784
						CPASSOC (SHet)	NA	NA	2.98E-07	31970/31967/27643	NA	NA	4.49E-01	36973/36873/37140	NA	NA	7.52E-06	68843/68840/64784
						SBP	1.0488	0.2099	5.82E-07	30086	0.0711	0.2085	7.33E-01	37483	0.5566	0.1479	1.68E-04	67569
						DBP	0.5784	0.1266	4.87E-06	30083	0.1056	0.1271	4.06E-01	37483	0.343	0.0897	1.32E-04	67566
rs114296860	17	51285996	t	c	0.02	PP	0.5216	0.1497	4.93E-04	30083	-0.063	0.1532	6.81E-01	37483	0.236	0.1071	2.75E-02	67566
						HTN	0.0597	0.0245	1.47E-02	25498.2	0.0076	0.0273	7.81E-01	37756	0.0365	0.0182	4.55E-02	63254.2
						CPASSOC (SHom)	NA	NA	6.13E-06	30086/30083/25498	NA	NA	6.14E-01	37483/37483/37756	NA	NA	1.66E-04	67569/67566/63254
						CPASSOC (SHet)	NA	NA	2.22E-06	30086/30083/25498	NA	NA	5.88E-01	37483/37483/37756	NA	NA	1.24E-04	67569/67566/63254
rs2832976	21	32037484	t	c	0.16	SBP	2.5521	0.6484	8.29E-05	30321	-11.985	14.626	4.13E-01	9684	2.5236	0.6478	9.79E-05	40005
						DBP	1.6074	0.3904	3.84E-05	30318	-5.247	8.863	5.54E-01	9684	1.5941	0.39	4.37E-05	40002
						PP	1.1088	0.4557	1.50E-02	30318	-6.88	10.815	5.25E-01	9684	1.0946	0.4553	1.62E-02	40002
						HTN	-0.042	0.0772	5.86E-01	25456	-0.676	4.305	8.75E-01	9684	-0.0422	0.0772	5.85E-01	35140
rs62225706	22	26680705	a	c	0.03	CPASSOC (SHom)	NA	NA	7.16E-03	30321/30318/25456	NA	NA	5.80E-01	9684/9684/9684	NA	NA	2.69E-02	40005/40002/35140
						CPASSOC (SHet)	NA	NA	2.65E-07	30321/30318/25456	NA	NA	8.47E-01	9684/9684/9684	NA	NA	3.66E-06	40005/40002/35140
						SBP	-1.1975	0.2602	4.19E-06	31969.9	-0.0669	0.1387	6.30E-01	39617	-0.3172	0.1224	9.58E-03	71586.9
						DBP	-0.3333	0.1564	3.31E-02	31966.9	-0.0361	0.0862	6.75E-01	37007	-0.1054	0.0755	1.63E-01	68973.9
rs6006767	22	45927045	t	c	0.94	PP	-0.9467	0.1865	3.86E-07	31966.9	0.038	0.0992	7.02E-01	39617	-0.179	0.0876	4.09E-02	71583.9
						HTN	-0.0719	0.0302	1.72E-02	27732.2	-0.0097	0.0179	5.89E-01	39832	-0.0259	0.0154	9.27E-02	67564.2
						CPASSOC (SHom)	NA	NA	6.57E-04	31969/31969/27732	NA	NA	5.47E-01	39617/37007/39832	NA	NA	6.97E-03	71587/68974/67564
						CPASSOC (SHet)	NA	NA	3.54E-05	31969/31969/27732	NA	NA	8.52E-01	39617/37007/39832	NA	NA	1.29E-03	71587/68974/67564
rs6006767	22	45927045	t	c	0.94	SBP	-3.9669	0.8283	1.68E-06	16221	-0.0782	0.4006	8.45E-01	26143	-0.8154	0.3607	2.38E-02	42364
						DBP	-2.624	0.4943	1.10E-07	15169	-0.028	0.2441	9.09E-01	26143	-0.537	0.2189	1.42E-02	41312
						PP	-1.6075	0.6099	8.40E-03	16218	0.1566	0.3286	6.34E-01	26143	-0.2403	0.2893	4.06E-01	42361
						HTN	-0.2607	0.0964	6.85E-03	12891	-0.0344	0.0464	4.58E-01	26387	-0.077	0.0418	6.55E-02	39278
rs6006767	22	45927045	t	c	0.94	CPASSOC (SHom)	NA	NA	1.17E-06	16221/15169/12891	NA	NA	5.17E-01	26143/26143/26387	NA	NA	3.06E-05	42364/41312/39278
						CPASSOC (SHet)	NA	NA	4.62E-07	16221/15169/12891	NA	NA	7.73E-01	26143/26143/26387	NA	NA	2.57E-05	42364/41312/39278
						SBP	-1.0401	0.3723	5.21E-03	31970	-0.3444	0.2025	8.90E-02	37910	-0.5033	0.1779	4.67E-03	69880
						DBP	-1.1597	0.2295	4.37E-07	30918	-0.2582	0.1245	3.81E-02	38497	-0.4632	0.1094	2.31E-05	69415
rs6006767	22	45927045	t	c	0.94	PP	0.0491	0.2651	8.53E-01	31967	-0.1627	0.1418	2.51E-01	37910	-0.1156	0.125	3.55E-01	69877
						HTN	-0.0763	0.0455	9.35E-02	25742.1	-0.0151	0.0266	5.70E-01	38183	-0.0307	0.023	1.81E-01	63925.1
						CPASSOC (SHom)	NA	NA	2.63E-04	31970/30918/25742	NA	NA	2.63E-01	37910/38497/38183	NA	NA	1.36E-03	69880/69415/63925
						CPASSOC (SHet)	NA	NA	3.76E-06	31970/30918/25742	NA	NA	2.77E-01	37910/38497/38183	NA	NA	3.79E-05	69880/69415/63925

N: sample size for CPASSOC refers the sample sizes of SBP/DBP/HTN

<sup>a</sup> Variants identified reaching genome-wide significant threshold of  $5.0 \times 10^{-8}$  in discovery stage and successfully replicated with experimental significance in replication

<sup>b</sup> Variants identified not reaching genome-wide significant threshold of  $5.0 \times 10^{-8}$  in discovery stage but replicated with experimental significance in replication

<sup>c</sup> Novel blood pressure loci identified in current study

Bold statistics are the corresponding significant statistics for significant of identified variants

**S7 Table. Summary of iHS signals in significant loci with frequency differences across ancestry populations**

SNP	Chr	Pos	Gene	Derived Allele	Ancestry Allele	Derived Allele Frequency				iHS
						African American	African	European	Asian	
rs78192203	8	142375073	<i>GPR20</i>	A	T	0.2	0.21	0	0	-2.678
rs7006531	8	95110744	<i>CDH17</i>	G	T	0.15	0.19	0	0	-1.567
rs113866309	12	66516948	<i>LLPH</i>	C	T	0.02	0.02	0	0	-1.776
rs76987554	6	134080855	<i>TCF21</i>	T	C	0.09	0.09	0	0	-1.723
rs115795127	9	85993901	<i>FRMD3</i>	T	C	0.89	0.86	1	1	2.702

S8 Table. MAGENTA analysis

Rank	Database	Gene Set	Original number of genes	Effective number of genes	Nominal GSEA P value	FDR	Trait
1	BIOCARTA	GSK3_PATHWAY	27	26	0.0012	0.163	SBP
2	BIOCARTA	TH1TH2_PATHWAY	19	16	0.0016	0.157	DBP
3	BIOCARTA	SHH_PATHWAY	16	16	0.0021	0.156	SHOM
4	BIOCARTA	CSK_PATHWAY	24	19	0.0023	0.113	SHOM
5	BIOCARTA	EIF2_PATHWAY	11	10	0.0039	0.116	SHOM
6	BIOCARTA	CTLA4_PATHWAY	21	15	0.0043	0.228	DBP
7	BIOCARTA	VIP_PATHWAY	27	26	0.0044	0.137	SHOM
8	BIOCARTA	MEF2D_PATHWAY	21	18	0.0051	0.279	HTN
1	GOTERM	dendrite	111	107	3.00E-05	0.233	SBP
2	GOTERM	regulation of blood pressure	52	46	1.00E-04	0.200	PP
3	GOTERM	filopodium	25	24	1.00E-04	0.226	PP
4	GOTERM	response to nicotine	12	12	1.00E-04	0.273	SHOM
5	GOTERM	cellular defense response	60	49	3.00E-04	0.201	SHOM
6	GOTERM	nuclear chromosome telomeric region	15	15	4.00E-04	0.220	SHOM
7	GOTERM	recycling endosome membrane	18	15	4.00E-04	0.216	SHOM
8	GOTERM	membrane depolarization	16	15	5.00E-04	0.163	PP
9	GOTERM	histone deacetylation	17	15	6.00E-04	0.168	PP
10	GOTERM	high-density lipoprotein particle	19	15	7.00E-04	0.195	SHET
11	GOTERM	lipid transporter activity	19	18	7.00E-04	0.104	SHET
12	GOTERM	membrane fraction	479	437	9.00E-04	0.152	SHET
13	GOTERM	triglyceride metabolic process	24	23	0.001	0.196	SHET
14	GOTERM	activity	29	26	0.0013	0.224	PP
15	GOTERM	iron ion binding	65	58	0.0015	0.274	PP
16	GOTERM	negative regulation of gene-specific transcription from RNA polymerase II promoter	43	40	0.0017	0.280	PP
17	GOTERM	actin cytoskeleton organization	119	104	0.0018	0.277	PP
18	GOTERM	promoter binding	74	68	0.002	0.262	PP
19	GOTERM	phosphate metabolic process	21	21	0.002	0.202	PP
20	GOTERM	myeloid cell differentiation	15	15	0.0023	0.259	PP
21	GOTERM	Rho GTPase activator activity	22	18	0.0037	0.293	PP
22	GOTERM	DNA damage response signal transduction by p53 class mediator resulting in induction of apoptosis	13	13	0.0051	0.270	PP
23	GOTERM	sarcoplasmic reticulum	21	21	0.0053	0.297	PP
24	GOTERM	transcription repressor binding	12	11	0.0066	0.278	PP
25	GOTERM	polysaccharide binding	11	11	0.007	0.280	PP
26	GOTERM	methylation	12	11	0.0079	0.292	PP
27	GOTERM	heart development	123	120	0.0082	0.141	PP
1	Panther	Pyrimidine_Metabolism	6	6	0.004	0.137	DBP
2	Panther	Apoptosis_signaling_pathway	53	47	0.006	0.186	SBP
3	Panther	B_cell_activation	24	21	0.006	0.210	SBP
4	Panther	T_cell_activation	31	21	0.0064	0.263	SHOM
1	Ingenuity	JAK.Stat.Signaling	10	10	1.00E-04	0.011	DBP
2	Ingenuity	T.Cell.Receptor.Signaling	34	33	0.0021	0.160	SHOM
3	Ingenuity	B.Cell.Receptor.Signaling	35	33	0.0024	0.073	DBP
4	Ingenuity	Aryl.Hydrocarbon.Receptor.Signaling	52	50	0.0029	0.168	HTN
6	Ingenuity	Integrin.Signaling	38	37	0.0098	0.200	PP
1	KEGG	KEGG_CYTOKINE_CYTOKINE_RECEP TOR_INTERACTION	267	192	0.0013	0.263	DBP
2	KEGG	KEGG_VASCULAR_SMOOTH_MUSCLE _CONTRACTION	115	104	0.0015	0.256	PP
3	KEGG	KEGG_CARDIAC_MUSCLE_CONTRAC TION	80	66	0.0018	0.278	PP
4	KEGG	KEGG_BASAL_CELL_CARCINOMA	55	53	0.0023	0.180	SHOM

6	KEGG	KEGG_STARCH_AND_SUCROSE_METABOLISM	52	37	0.0044	0.247	DBP
7	KEGG	KEGG_GLYCEROLIPID_METABOLISM	49	43	0.0047	0.255	SHET
1	PANTHER_BIOLOGICAL_PROCESS	Other_neuronal_activity	136	120	0.001	0.2364	HTN
2	PANTHER_BIOLOGICAL_PROCESS	T-cell_mediated_immunity	138	103	0.0018	0.2359	PP
3	PANTHER_BIOLOGICAL_PROCESS	Tumor_suppressor	102	72	0.0023	0.1611333	PP
4	PANTHER_BIOLOGICAL_PROCESS	DNA_metabolism	32	30	0.0023	0.14215	HTN
5	PANTHER_BIOLOGICAL_PROCESS	Phagocytosis	39	36	0.0026	0.1248	HTN
6	PANTHER_BIOLOGICAL_PROCESS	DNA_repair	169	138	0.0031	0.15365	HTN
8	PANTHER_BIOLOGICAL_PROCESS	Transport	509	384	0.0042	0.18848	HTN
9	PANTHER_BIOLOGICAL_PROCESS	Fatty_acid_beta-oxidation	27	23	0.0044	0.2383	PP
12	PANTHER_BIOLOGICAL_PROCESS	Cytokinesis	115	82	0.0056	0.1951833	HTN
13	PANTHER_BIOLOGICAL_PROCESS	Protein_phosphorylation	660	556	0.0082	0.247925	HTN
1	PANTHER_MOLECULAR_FUNCTION	Non-motor_actin_binding_protein	165	136	5.00E-04	0.150	SHET
2	PANTHER_MOLECULAR_FUNCTION	Transcription_cofactor	168	137	0.002	0.254	SHOM
3	PANTHER_MOLECULAR_FUNCTION	Dehydrogenase	225	183	0.004	0.298	PP

**S9 Table. eQTL analysis of significant SNPs in tissues**

SNP	Proxy	Correlation R2	Gene Symbol	P-Value	Effect Size	Tissue
rs6969780	rs6969780	NA	HOTAIRM1	2.50E-14	0.54	Esophagus - Mucosa
rs6969780	rs6969780	NA	HOXA2	8.10E-13	-0.6	Artery - Tibial
rs6969780	rs6969780	NA	HOTAIRM1	6.30E-12	0.59	Esophagus - Muscularis
rs6969780	rs6969780	NA	HOTAIRM1	1.80E-10	0.33	Lung
rs6969780	rs6969780	NA	HOTAIRM1	5.00E-10	0.58	Artery - Tibial
rs6969780	rs6969780	NA	HOTAIRM1	1.30E-09	0.64	Skin - Sun Exposed (Lower leg)
rs6969780	rs6969780	NA	HOXA2	1.60E-09	-0.62	Nerve - Tibial
rs6969780	rs6969780	NA	HOTAIRM1	5.70E-09	0.66	Cells - Transformed fibroblasts
rs6969780	rs6969780	NA	HOTAIRM1	2.90E-08	0.48	Adipose - Subcutaneous
rs6969780	rs6969780	NA	HOXA2	3.10E-07	-0.49	Adipose - Subcutaneous
rs6969780	rs6969780	NA	HOTAIRM1	4.70E-07	0.46	Muscle - Skeletal
rs6969780	rs6969780	NA	HOXA5	7.50E-07	-0.5	Cells - Transformed fibroblasts
rs6969780	rs6969780	NA	HOTAIRM1	0.0000023	0.53	Skin - Not Sun Exposed (Suprapubic)
rs6969780	rs6969780	NA	HOTAIRM1	0.0000025	0.36	Stomach
rs6969780	rs6969780	NA	HOXA7	0.0000032	-0.4	Artery - Tibial
rs7651190	rs7651190	NA	ULK4	1.10E-44	0.99	Cells - Transformed fibroblasts
rs7651190	rs7651190	NA	ULK4	1.70E-31	0.87	Artery - Aorta
rs7651190	rs7651190	NA	ULK4	1.80E-27	0.68	Whole Blood
rs7651190	rs7651190	NA	ULK4	8.50E-27	0.74	Thyroid
rs7651190	rs7651190	NA	ULK4	8.20E-25	0.67	Nerve - Tibial
rs7651190	rs7651190	NA	ULK4	5.10E-24	0.94	Esophagus - Mucosa
rs7651190	rs7651190	NA	ULK4	2.40E-21	0.62	Artery - Tibial
rs7651190	rs7651190	NA	ULK4	3.00E-19	0.67	Muscle - Skeletal
rs7651190	rs7651190	NA	ULK4	3.10E-18	0.85	Cells - EBV-transformed lymphocytes
rs7651190	rs7651190	NA	ULK4	6.70E-18	0.64	Esophagus - Muscularis
rs7651190	rs7651190	NA	ULK4	2.30E-15	0.59	Skin - Sun Exposed (Lower leg)
rs7651190	rs7651190	NA	ULK4	3.80E-15	1.2	Brain - Cortex
rs7651190	rs7651190	NA	ULK4	7.10E-14	0.76	Stomach
rs7651190	rs7651190	NA	ULK4	1.30E-13	0.45	Adipose - Subcutaneous
rs7651190	rs7651190	NA	ULK4	9.70E-13	1.2	Pituitary
rs7651190	rs7651190	NA	ULK4	1.10E-12	1.2	Brain - Anterior cingulate cortex (BA24)
rs7651190	rs7651190	NA	ULK4	2.30E-12	1.1	Brain - Frontal Cortex (BA9)
rs7651190	rs7651190	NA	ULK4	1.10E-11	0.88	Adrenal Gland
rs7651190	rs7651190	NA	ULK4	1.10E-11	0.64	Adipose - Visceral (Omentum)
rs7651190	rs7651190	NA	ULK4	1.80E-11	0.59	Colon - Transverse
rs7651190	rs7651190	NA	ULK4	6.50E-11	0.44	Lung
rs7651190	rs7651190	NA	ULK4	6.90E-11	1.1	Brain - Putamen (basal ganglia)
rs7651190	rs7651190	NA	ULK4	1.20E-10	0.89	Brain - Nucleus accumbens (basal ganglia)
rs7651190	rs7651190	NA	ULK4	1.30E-10	0.69	Pancreas
rs7651190	rs7651190	NA	RPL36P20	2.30E-09	0.55	Testis
rs7651190	rs7651190	NA	ULK4	1.20E-08	0.71	Colon - Sigmoid
rs7651190	rs7651190	NA	ULK4	2.20E-08	0.8	Spleen
rs7651190	rs7651190	NA	ULK4	2.90E-08	0.73	Brain - Caudate (basal ganglia)
rs7651190	rs7651190	NA	ULK4	8.60E-08	0.63	Brain - Hypothalamus
rs7651190	rs7651190	NA	ULK4	1.20E-07	0.63	Heart - Left Ventricle
rs7651190	rs7651190	NA	ULK4	1.30E-07	0.49	Skin - Not Sun Exposed (Suprapubic)
rs7651190	rs7651190	NA	ULK4	3.70E-07	0.55	Breast - Mammary Tissue
rs7651190	rs7651190	NA	ULK4	4.20E-07	0.91	Brain - Cerebellar Hemisphere
rs7651190	rs7651190	NA	ULK4	0.0000014	0.79	Brain - Cerebellum
rs7651190	rs7651190	NA	ULK4	0.0000031	0.57	Artery - Coronary
rs7651190	rs7651190	NA	ULK4	0.0000032	0.62	Esophagus - Gastroesophageal Junction
rs62434120	rs4869927	0.9	PLEKHG1	0.0000068	-0.27	Testis
rs62434120	rs9480528	0.86	PLEKHG1	0.0000068	-0.27	Testis

**S10 Table. Primers of candidate genes.**

The primers of candidate genes for real-time polymerase chain reaction (RT-PCR) primers were designed based on the latest mouse genome (GRCm38/mm10) using Primer3 (<http://bioinfo.ut.ee/primer3-0.4.0/>) online. Primers were also designed for isoforms of certain candidate genes.

Mouse Genes	Forward Primer	Reverse Primer
<i>Ulk4</i>	TCTTGAAAGCCTCAAGAACA	AAAGGATGGTGTGGGATCTG
<i>Eya4</i>	GCTTTGAGCGAATAATGCAA	GTGCTTGATGTAGAGCCAAGAG
<i>Tcf21</i>	CTCCAAGCTGGACACTCTCA	TCACCACTTCCTTCAGGTCA
<i>Evx1</i>	CTTACCCGGGAGCAGATT	GCTGACGCTTGTCTTCAT
<i>Hoxa1-1</i>	GCAGACCTTTGACTGGATGA	GCGCTCGTGTAAAGTACTTG
<i>Hoxa1-2</i>	CCCAGACGGCTACTTACCAG	GGAGAAGACGTCTCTGAAGCA
<i>Hoxa5</i>	GCGCAAGCTGCACATTAG	GGCATGAGCTATTTCGATCC
<i>Hoxa7</i>	AAGCCAGTTCCGCATCTAC	GCTCTTTCTTCCACTTCATGC
<i>Hoxa9</i>	CCACGCTTGACACTCACACT	AGCGAGCATGTAGCCAGTT
<i>Hoxa10-1</i>	TCCAGCCCCTTCAGAAAACA	GCTACGGCTGATCTCTAGGC
<i>Hoxa10-2</i>	TCAAGGCAGTTCCAAAGG	TCACTTGCTGTCCGTGAGG
<i>Hoxa11</i>	GTCTTCCGGCCACACTGA	CAGTTGCAGACGCTTCTCTTT
<i>Igfbp3</i>	CGCAGAGAAATGGAGGACA	ACTTGTCACACACCAGCAG
<i>Cdh17</i>	CCAGTTACTTTCTGCCAGTGTG	CCAGTTACTTTCTGCCAGTGTG
<i>Gpr20</i>	GCGTGGAGAAGAATTCAAGC	TCCTAGAGCCTTGACCTTGA
<i>Plekhg1</i>	GTCAGCATAGGCCAGTCA	CAGCCATCCTTCTGAGCTTT
<i>Frm3-1</i>	TCAGACACCAGAGTTTGAGCA	TCTTGACAACCTGAAGGCCAAT
<i>Frm3-2</i>	AATCCTGACCGGCCATATC	GGATGTGTCTCCATGTGC
<i>Llph</i>	GAGATAGCAACCGTGGTGGT	TCATCCACACTGGGTACTGG
<i>Tmbim4</i>	TCTGGTTCTGCAAGCGTTTA	ACCAGCTCCATCGTCTCACT
<i>Hprt</i>	CAAACCTTGCTTCCCTGGT	CAAGGGCATATCCAACAACA

# Single-trait and multi-trait genome wide association analyses identify novel loci for blood pressure in African-ancestry populations

## Supplementary Notes

### AUTHOR CONTRIBUTIONS

*Principal investigators (alphabetically for study names)*

*Manuscript writing*

*Phenotyping*

*Genotyping*

*Quality control*

*Software development*

*Statistical analysis*

*GWAS Look-ups in other Consortia*

## DESCRIPTION OF STUDY SAMPLES

### 1. Discovery COGENT BP studies

#### *CARe*

**Candidate Gene Association Resource** CARe samples were collected from five NHLBI-funded cohort studies where GWAS African American samples were available.

(<http://public.nhlbi.nih.gov/GeneticsGenomics/home/care.aspx>)

#### *ARIC*

**Atherosclerosis Risk Communities Study** The ARIC study is a population-based, biracial prospective cohort study of cardiovascular disease and its risk factors sponsored by National Heart, Lung and Blood Institute (NHLBI)<sup>1</sup>. ARIC included 15,792 European ancestry and African American individuals aged 45-64 years at baseline (1987-89), chosen by probability sampling from four US communities. Cohort members completed four clinic examinations, conducted three years apart between 1987 and 1998. Follow-up for clinical events was annual. The current analysis included only African American individuals with BP measures at baseline examinations. The IRB at each of the study sites approved the study protocols, and written informed consent was obtained from all participants.

BP was measured using a standardized Hawksley random-zero mercury column sphygmomanometer with participants in a sitting position after a resting period of 5 minutes. The size of the cuff was chosen according to the arm circumference. Three sequential recordings for SBP and DBP were obtained; the mean of the last two measurements was used in this analysis, discarding the first reading. BP lowering medication used was recorded from the medication history. Outliers (> 4 SDs from the mean) with respect to the SBP and DBP distribution were excluded from the analysis.

#### *CARDIA*

**The Coronary Artery Risk Development in Young Adults Study** The CARDIA study is a population based, prospective cohort examining the development and determinants of clinical and subclinical cardiovascular disease and its risk factors<sup>2</sup>. The CARDIA study initial enrollment consisted of 5,155 European Americans and African American men and women between 18 and 30 years old (52% African American and 55% women). The study is multicenter with recruitment in Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA. The IRB at each of the study sites approved the study protocols, and written informed consent was obtained from all participants. Baseline measurements were repeated, and additional measurements performed, at Years 2, 5, 7, 10, 15 and 20<sup>2</sup>. The current analysis included data measured at Year 15 (2000-2001) and only African American male and females.

Seated BP was measured on the right arm following 5 minutes rest using a random-zero sphygmomanometer. SBP and DBP were recorded as Phase I and Phase V Korotkoff sounds.

Three measurements were taken at 1 minute intervals with the average of the second and third measurements taken for the BP values.

### ***CFS***

**The Cleveland Family Study** CFS participants consist of first or selected second-degree relatives of a proband with either laboratory diagnosed obstructive sleep apnea or neighborhood control of an affected proband. Families were selected for genotyping on the bases of genetic informativness, including multigenerational data or individuals from the extremes of the distribution of apnea phenotype<sup>3</sup>. These families include 59 African-American families with 176 individuals (100 females and 76 males) and 66 European-American families with 262 individuals (120 females and 142 males) with genotype and phenotype information. The IRB approved the study and written informed consent was obtained from all participants.

Participants had three supine BP measurements each performed after lying quietly for 10 minutes, before bed (10:00 PM) and upon awakening (7:00 AM), and another three sitting at 11:00 AM, following standardized guidelines using a calibrated sphygmomanometer. BP phenotypes were determined from the average of the nine measurements.

### ***JHS***

**Jackson Heart Study** JHS was initiated in 2000 to investigate prospectively the epidemiology and determinants of cardiovascular disease in African Americans<sup>4</sup>. JHS recruited 5,302 participants after completion of data adjustment, representing more than 5% of African American 35-84 years old living in the Jackson, Mississippi tri-county area. Of this number, ~30% were prior Jackson participants in the Atherosclerosis Risk in Communities Study. Of the remaining, 23% were recruited by random selection from a commercial listing that represents the overall tri-county population and an additional 23% volunteer sample, in which recruitment was distributed among defined demographic cells in proportions designed to mirror those in the overall population<sup>5</sup>. Those who were overlapping ARIC participants and those with previous MI were excluded from the GWAS. The IRB approved the study protocol, and written informed consent was obtained from all participants.

Seated BP was measured with a random-zero sphygmomanometer three times with the last two measurements averaged.

### ***MESA***

**The Multi-Ethnic Study of Atherosclerosis** The MESA is a multicenter prospective cohort study initiated to study the development of subclinical cardiovascular disease. A total of 6,814 women and men between the age of 45 and 84 year were recruited for the first examination between 2000 and 2002. Participants were recruited in six US cities (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; Northern Manhattan, NY; and St. Paul, MN). 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. 38% are of European ancestry, 28% African-American, 22% Hispanic, and 12% Asian, predominantly of Chinese descent. This study was approved by the IRB of each study site, and written informed consent was obtained from all participants<sup>6</sup>. The manuscript utilizes data from African-American MESA participants, genotyped through the CARE project.

BP was measured three times at 1 minute interval after a 5 minute initial rest using a Dinamap PRO 100 automated oscillometric device (Critikon, Tampa, FL) with the subject in seated, and the average of the second and third BP measurements was used in the analysis.

### ***FBPP***

**Family Blood Pressure Program - AXIOM** These 872 African-American subjects were included from HyperGEN and GENOA studies but whom were not genotyped with conventional GWAS platforms. The sample schemes are the same as HyperGEN and GENOA. For BP measures, see HyperGEN and GENOA descriptions. These African-Americans were genotyped using Affymetrix Axiom chips, which included 808,558 SNPs. SNPs were called using Affymetrix Genotyping Console (GTC) by analyzing CEL files from Affymetrix AXIOM arrays ([www.affymetrix.com](http://www.affymetrix.com)).

### ***HANDLS***

**The Healthy Agin Neighorhoods of Diversity acrossume the Life Span Study** The Healthy Aging in Neighborhoods of Diversity across the Life Span study (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 among socioeconomically diverse African Americans and European ancestry individuals in Baltimore, Maryland, USA<sup>7</sup>. The HANDLS design is an area probability sample of Baltimore based on the 2000 Census. The study protocol facilitated our ability to recruit 3,720 participants from Baltimore. Among those who completed their examinations, there were no age differences associated with sex and poverty status, but African Americans were negligibly younger than individuals of European descent. The study is currently conducting Wave 4 designed as a second re-examination wave of all participants initially recruited at baseline (2004-2009). Wave 4 began in September of 2013 and will conclude in June of 2017. Genotyping was focused on a subset of participants self-reporting as African American was undertaken at the Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health. Genotype Imputation was performed using the 1000 Genomes Project phase 1 version 3 multi-ethnic reference panel, March 2012 release. BP was measured non-invasively using the brachial artery auscultation method with an aneroid manometer, a stethoscope, and an inflatable cuff in individuals resting for 5 minutes. For this analysis, the average of right and left sitting BP values was taken to represent each of SBP and DBP.

### ***CHS***

**Cardiovascular Health Study** The CHS is a population-based cohort study of risk factors for CHD and stroke in adults  $\geq 65$  years conducted across four field centers<sup>8</sup>. The original cohort, predominantly Americans of European Ancestry, comprised 5,201 persons who were recruited in 1989-1990 from random samples of the Medicare eligibility lists. Additional 687 individuals, predominantly African-Americans, were enrolled subsequently for a total sample of 5,888. DNA was extracted from blood samples drawn on all participants at their baseline examination in 1989-90 (original cohort) or 1992-93 (African American cohort). A sample of 823 African-Americans satisfying study design criteria, and with genome-wide association data, were used for analysis. Research staff with central training in BP measurement assessed repeated right-arm seated SBP and DBP levels at baseline with a Hawksley random-zero sphygmomanometer. The reported BP is the average of two measurements, which were taken after the participant had been sitting quietly for five minutes. First the technician determined the correct cuff size by measuring the arm circumference at the midpoint between the acromion and the olecranon. After applying the appropriate cuff, the maximum inflation level was determined by inflating the cuff until the radial pulse was no longer felt. The maximum inflation level was then determined to be the pulse obliteration pressure plus 30 mmHg plus the maximum zero level of the instrument. BP was measured by inflating the cuff to the maximum inflation level, waiting 5 seconds, then lowering by 2-3 mmHg per second. The first and fifth Korotkoff sounds were recorded. At least 30 seconds elapsed between each cuff inflation. Medication use was collected by interview. Information on prescription medication use in the previous two weeks was collected directly from the medications. A computer program developed by CHS was used to match the medication names with NDC numbers and then to group medications into analytic variables (e.g. beta blockers, lipid - lowering medications)<sup>9</sup>. Means of the repeated BP measurements from the baseline examination were used for the analyses.

### **GENOA**

**The Genetic Epidemiology Network of Arteriopathy (GENOA)** GENOA is one of four networks in the Family Blood Pressure Program (FBPP) which recruited hypertensive African American and non - Hispanic white sibships for linkage and family - based association studies to investigate genetic contributions to BP in multiple racial groups<sup>10</sup>. Recruitment (Exam 1, 1995-2000 and Exam 2, 2000-2005) was population-based in two geographic locations: Jackson, Mississippi and Rochester, Minnesota. African Americans were recruited solely at the Jackson field center. Hypertensive probands were ascertained from the Jackson cohort of the ARIC study if they were in a sibship with two individuals with essential hypertension (SBP =140 mmHg or DBP =90mmHg on the second and third clinic visit), diagnosed prior to age 60, and consented to participate. Index sib - pairs with possible secondary hypertension, including sib - pairs with previously diagnosed kidney disease (defined by serum creatinine level  $> 2$  mg/dL), were excluded. After quality control procedures, and exclusion of all overlapping participants with ARIC, genotype data from a total of 996 African Americans was available for this study.

SBP and DBPs were measured using an automated oscillometric BP measurement device with a consistent protocol across the FBPP networks. BP was measured three times on each participant by trained and certified technicians and then averaged for use in this analysis.

### ***HRS***

**The Health and Retirement Study** The HRS is a longitudinal survey of a representative sample of Americans over age 50 sponsored by the National Institute on Aging (NIA) and conducted by the University of Michigan's Institute for Social Research. The sample for this analysis includes 1,337 African Americans (N=483 males, 36.1%) interviewed in 2006 or 2008 with BP measured using an Omron HEM-780 Intellisense. Automated BP monitor with ComFit cuff. Participants that had missing values for both SBP and DBP, had missing values for covariates, and one individual that was > 5 SDs from the mean of BMI were excluded. Mean SBP and DBP from three measures. Genotyping was performed by the Center for Inherited Disease Research (CIDR) using Illumina's Human Omni2.5-Quad BeadChip methodology. Genotyping quality control was performed by the Genetics Coordinating Center, Department of Biostatistics, University of Washington, Seattle.

### ***HyperGEN***

**The Hypertension Genetic Epidemiology Network** HyperGEN is a multicenter family-based study to research the genetic causes of hypertension and related conditions<sup>11</sup>. HyperGEN recruited African American and Caucasian participants at five field centers, with recruitment based largely on ongoing population-based studies. Study participants were recruited as one of three main types of subjects: 1) as part of a hypertensive sibship with at least two siblings diagnosed with hypertension; 2) random subjects, who were age-matched with hypertensive sibs; or 3) unmedicated adult offspring of one or more of the hypertensive siblings. Subjects were brought into the clinic for a one day exam, and data were collected from questionnaires, a physical exam, and blood and urine samples. This study obtained informed consent from participants and approval from the appropriate IRBs. SBP and DBPs were measured using an automated oscillometric BP measurement device with a consistent protocol across the FBPP networks. BP was measured three times on each participant by trained and certified technicians and then averaged for use in this analysis.

***Maywood-Loyola Study*** Participants were self-identified African Americans from a working class suburb of Chicago, Illinois, USA who were enrolled in studies of BP at the Loyola University Medical Center in Maywood, Illinois, USA as part of the International Collaborative Study on Hypertension in Blacks (ICSHIB) which is described in detail elsewhere<sup>12</sup>. Briefly, nuclear families were identified through middle-aged probands who were not ascertained based on any phenotype. Thereafter all available first-degree relatives 18 years old and above were enrolled into the study cohort of families. A screening exam was completed by trained and certified research staff using a standardized protocol<sup>12,13</sup>. Information was obtained on medical history, age, body weight and height. Protocols were reviewed and approved by the IRB at the Loyola University Chicago Stritch School of Medicine prior to recruitment activities. This present study included

unrelated adults sampled and for whom information on anthropometrics, BP and use of antihypertensive medication was available. BP measurements were obtained using an oscillometric device, previously evaluated in our field settings<sup>13</sup>. Three measurements were taken three minutes apart and the average of the final two was used in the analysis. Individuals with SBP  $\geq 140$  mmHg, DBP  $\geq 90$  mmHg or on anti-hypertensive medication at time of exam were defined as hypertensive. Participants with hypertension were offered treatment after detection at the screening exam.

***Maywood-Nigeria Cohort-1 & Cohort-2*** The sampling frame for the Nigeria cohort was also provided by the International Collaborative Study on Hypertension in Blacks (ICSHIB) as described in detail elsewhere<sup>12</sup>. Study participants were recruited from Igbo-Ora and Ibadan in southwest Nigeria as part of a long-term study on the environmental and genetic factors underlying hypertension. The base cohort consists of over 15,000 participants with information available on anthropometrics, BP and use of antihypertensive medication. BP measurements followed the same protocol described in the Loyola-Maywood study. This present study included unrelated adults samples from the cohort and some hypertensive participants who were recruited as controls in the Africa-America Diabetes Mellitus (AADM) Study recruited from Ibadan in similar neighborhoods<sup>14</sup>. Both projects were reviewed and approved by the sponsoring US institutions (Loyola University Chicago and Howard University) and the University of Ibadan. All participants signed informed consent administered in either English or Yoruba. BP measurements were obtained using an oscillometric device, previously evaluated in our field settings<sup>13</sup>. Three measurements were taken three minutes apart and the average of the final two was used in the analysis. Individuals with SBP  $\geq 140$  mmHg, DBP  $\geq 90$  mmHg or on anti-hypertensive medication at time of exam were defined as hypertensive. Participants with hypertension were offered treatment after detection at the screening exam.

### ***HUFS***

**The Howard University Family Study** HUFS is population based family study of African Americans in the Washington metropolitan area. Investigators enrolled a randomly recruited set of families in addition to a set of unrelated individuals to study genetic and environmental factors of common complex diseases including hypertension. The IRB approved the study protocol, and written informed consent was obtained from all participants. A total of 1,192 unrelated individuals were included in this analysis. Blood pressure (BP) was measured in the sitting position using an oscillometric device (Omron). Three BP readings were taken with a 10 minute interval between readings. The reported SBP and DBP readings were the average of the second and third readings.

### ***WHI***

**Women's Health Initiative SNP Health Association Resource** WHI is a study of postmenopausal women (aged 50-79 years), comprising 161,808 women recruited from 40 U.S. clinical centers to participate in an observational study (WHI-OS) or in clinical trials (WHI-CT). Details of recruitment and follow-up are described elsewhere<sup>15,16</sup>. BP was measured by certified

staff using standardized procedures and instruments. Two BP measures were recorded after 5 minutes rest using a mercury sphygmomanometer. Appropriate cuff bladder size was determined at each visit based on arm circumference. Diastolic BP was taken from the phase V Korotkoff measures. The average of the two measurements, obtained 30 seconds apart, was used in analyses. Women were asked to bring all of their current prescription and over-the-counter medications to each visit. Demographic data, medical history and anthropometric measures were obtained at a baseline clinical visit.

The WHI SNP Health Association Resource (SHARe) minority cohort includes 8,515 self-identified African American women from WHI who provided written informed consent for study participation and DNA analysis. WHI GARNET (Genome-wide Association Research Network into Effects of Treatment) is a nested case-control genetic study of gene-by-hormone therapy interaction on the risk of CVD events and incident diabetes, where CHD, stroke, venous thromboembolic (VTE) and diabetes cases were matched to controls based on age, race, hysterectomy, enrollment date, and length of follow-up. WHI\_WHIMS+ (Women's Health Initiative Memory Study) is composed of hormone therapy trial participants aged  $\geq 65$  years at randomization and free of dementia at baseline. The Long Life Study is composed of 7,875 women aged 62 or older from the WHI Extension II, who participated in the Hormone Therapy Clinical Trials, and is focused on aging and health/disease conditions. Genotyping was performed using HumanOmniExpress Exome-8v1\_B.

### ***GeneSTAR***

**Genetic Study of Atherosclerosis Risk** GeneSTAR is a 27 year prospective family-based study of incident CAD, diabetes, stroke, and other vascular diseases in initially healthy African American and European American adult relatives of probands with angiographically documented coronary disease prior to 60 years of age at the time of hospitalization for an acute CAD event in any of 10 Baltimore area hospitals<sup>17</sup>. The genotyped sample size is 3,200, with ~35 % African American (n=1,129). Participants are siblings of the probands, offspring of the siblings and probands, and coparents of the offspring. All participants were under 60 years of age at the time of enrollment (from 1983 to 2006). Demographic information, self-reported medical history, medication use, and smoking information were obtained from a standardized interview<sup>18</sup>. BP was measured using a standard mercury sphygmomanometer, following the American Heart Association<sup>19</sup> and JNC 6 guidelines<sup>20</sup>. The mean of three resting BP readings, taken early morning, midday, and late afternoon during the screening day was used to characterize BP measurements. Hypertension was defined as the subject having a mean SBP of  $\geq 140$  mmHg, a mean DBP of  $\geq 90$  mmHg, and/or currently taking an antihypertensive medication.

### ***IPM***

**Mount Sinai IPM Biobank** The BioMe Biobank is an ongoing, prospective, hospital- and outpatient- based population research program operated by The Charles Bronfman Institute for Personalized Medicine (IPM) at Mount Sinai and has enrolled over 33,000 participants since September 2007. BioMe is an Electronic Medical Record (EMR)-linked biobank that integrates

research data and clinical care information for consented patients at The Mount Sinai Medical Center, which serves diverse local communities of upper Manhattan with broad health disparities. BioMe populations include 25% of African ancestry (AA), 36% of Hispanic Latino ancestry (HL), 30% of white European ancestry (EA), and 9% of other ancestry. The BioMe disease burden is reflective of health disparities in the local communities.

BioMe operations are fully integrated in clinical care processes, including direct recruitment from clinical sites waiting areas and phlebotomy stations by dedicated recruiters independent of clinical care providers, prior to or following a clinician standard of care visit. Recruitment currently occurs at a broad spectrum of over 30 clinical care sites. This present study included only unrelated, adult, self-reported African Americans. Information on anthropometrics, demographics, BP and use of antihypertensive medication was derived from participants EMR. The Mount Sinai Biobank Project (IRB # 07-0529 0001 02 9 ME) operates under an IRB-approved research protocol with IRB-approved informed consent forms. All study participants provided written informed consent. The Mount Sinai IPM Biobank Program is supported by The Andrea and Charles Bronfman Philanthropies.

**BioVU** BioVU is a DNA biorepository linked to a database of de-identified EMRs (electronic medical records), designed and implemented with the goal of supporting genetic association studies at Vanderbilt University, including the identification of factors that affect disease susceptibility, disease progression, and/or drug response. BioVU is an ongoing study with rapid accrual of DNA specimens, accumulating approximately 27,000 participants per year, and with a current size of over 200,000. The DNA samples were obtained from patients at the Vanderbilt University Hospital, including all clinics that are part of the hospital system. A detailed description of the human subjects protection applied to BioVU is described by Pulley *et al*<sup>21</sup>. The program is under continuous oversight by the IRB and was reviewed in detail by the federal Office for Human Research Protections (OHRP). Program planning for BioVU started in 2004, and sample accrual started in February 2007. Traits are constructed for BioVU using the Synthetic Derivative (SD) database. This database is only accessible to Vanderbilt investigators and available by IRB approval. The SD database is a research tool developed to enable studies with de-identified clinical data. The SD collection includes information extracted from the EMR systems, and indexed by the same one-way Research Unique Identifier (RUI) used to track samples. The SD contains 2.4 million total records, with highly detailed longitudinal clinical data for approximately one million subjects. The database incorporates data from multiple sources and includes diagnostic and procedure codes (ICD-9 and CPT), basic demographics (age, sex, race), text from clinical care including discharge summaries, nursing notes, progress notes, history and physical examination, problem lists and multi-disciplinary assessments, laboratory values, echocardiogram (ECG) diagnoses, imaging reports, electronically derived trace values, and inpatient medication orders. All clinical data are updated regularly to include new patients and append new data to clinical records of existing patients. BioVU uses discarded blood samples collected during routine patient care, linked to de-identified data extracted and continuously updated from the EMR.

For this blood pressure (BP) study, we used adult (age  $\geq 18$ ) BioVU participants with GWAS data. We used the first eligible outpatient measured BP in the EMR, and excluded measures at or after a diagnosis of secondary hypertension (ICD-9 405), chronic kidney or end-stage renal disease (ICD-9 group 585), thyroid disease (ICD-9 groups 240-246), diabetes (ICD-9 group 250), mental disorders (ICD-9 groups 290-319) or heart failure (ICD-9 group 428). We also excluded BP measures when they occurred at the same time as a diagnosis of atrial fibrillation (ICD-9 group 427), stroke (ICD-9 V17.1, 997.0, 992.0, V12.54), migraine (ICD-9 group 346), shock (ICD-9 group 785), myocardial infarction (ICD-9 group 410), poisoning (ICD-9 groups 960-989), and cancer (ICD-9 groups 140-239). We also censored measures taken within 1 year of death for any cause and measures taken in the inpatient clinical setting. To define hypertension cases, participants' measured systolic BP (SBP) or diastolic BP (DBP)  $\geq 140$ mmHg or 90 mmHg respectively, have a diagnosis of hypertension (ICD-9 groups 401-404), or a prescription for antihypertensive medication prior to, or on the date, of BP measurement. Hypertension controls were defined by the absence of case criteria. BP measures were taken in outpatient clinics by sphygmomanometer for sitting patients.

## **2. Replication multi-ethnic studies**

**East Asian Samples.** Three independent dataset from Korea were used for replication studies. They are called as KARE, HEXA and NC, respectively, and collected from population-based cohorts. The Korea Association Resource (KARE) cohort has 8,842 subjects with 352,228 SNPs genotyped by the Affymetrix Genome-Wide Human SNP Array 5.0. 3,703 subjects were recruited in Health Examinee (HEXA) cohort and genotyped for 646,062 SNPs with Affymetrix Genome-Wide Human SNP Array 6.0. Nong-Chon (NC) cohorts has collected 1,816 subjects who have 606,875 SNPs genotyped by Affymetrix Genome-Wide Human SNP Array 6.0.

In our imputation study for 72 variants, we excluded variants which the HWE p-values were less than  $10^{-5}$ , the minor allele frequencies (MAF) were less than 0.05 or the genotype missing rate were greater than 5% from the study panel. We also discarded subjects whose reported gender were discordant with sex chromosome, call rates were less than 95% or identity by state (IBS) was more than 0.8. We extracted only variants within +/- 500kb of 72 variants to construct study panel. Finally, we used 8,773 subjects with 3,865 SNPs for KARE, 3,702 subjects with 4,228 SNPs for HEXA and 1,814 subjects with 6,569 SNPs for NC as study panels, respectively. We utilized the 1000G Phase I Integrated Release Version 3 for reference panel.

By definition, there are 2,284 HTN patients in KARE, 665 HTN patients in HEXA and 858 HTN patients in NC. The mean and standard deviation (SD) of SBP, DBP and PP in KARE were 121.64 mmHg (18.62), 80.24 mmHg (11.46), and 41.41 mmHg (11.54), respectively. Similarly, HEXA showed 121.68 mmHg (14.37) of SBP, 80.24 mmHg (11.46) of DBP and 44.63 mmHg (9.26) of PP. Finally, the mean and SD of SBP, DBP and PP in NC were 133.81 mmHg (18.03), 83.88 mmHg (10.77) and 49.93 mm Hg (12.89), respectively.

## **European American Samples**

**The Atherosclerosis Risk In Communities (ARIC).** The Atherosclerosis Risk In Communities Study is a population-based prospective cohort study of cardiovascular disease sponsored by the National Heart, Lung, and Blood Institute (NHLBI). ARIC included 15,792 individuals aged 45-64 years at baseline (1987-89), chosen by probability sampling from four US communities<sup>11</sup>. Cohort members completed four clinic examinations each spread over about three years, conducted approximately three years apart between 1987 and 1998. The data used in this study are from the first visit in 1987-1989. A detailed study protocol is available on the ARIC study website (<http://www.csc.unc.edu/aric>). Blood pressure was measured using a standardized Hawksley random-zero mercury column sphygmomanometer with participants in a sitting position after a resting period of 5 minutes. The size of the cuff was chosen according to the arm circumference. Three sequential recordings for systolic and diastolic blood pressure were obtained; the mean of the last two measurements was used in this analysis, discarding the first reading. Blood pressure lowering medication use was recorded from the medication history. Outliers (>4 SD from the mean) with respect to the systolic or diastolic blood pressure distributions were excluded from the analysis. For this study the sample was restricted to individuals of European descent by self-report and principal component analysis using genome-wide genotypes.

### **African Samples**

**Uganda Study** The Uganda study sought to determine whether a set of genetic loci significantly associated with blood pressure traits could be replicated among samples from the Medical Education Partnership Initiative for Cardiovascular Disease (MEPI-CVD) survey in Uganda, East Africa. The methods of the MEPI-CVD Survey have been described elsewhere<sup>22</sup>. In brief, MEPI-CVD Survey was a cross-sectional study conducted between September 2012 and May, 2013 in Wakiso district of central Uganda among men and women aged 18 years and older. Data on CVD risk factors of interest was collected by trained research nurses using the World Health Organisation (WHO) modified expanded STEPs questionnaire. Subjects were asked to provide information on their age, sex, address, dietary habits, tobacco and alcohol consumption, exercise, smoke exposure, socio-economic status (housing characteristics), family history and symptoms of heart disease including angina. Self-reported history of hypertension diagnosis, diabetes, dyslipidaemia and the treatment for these conditions was also recorded. Anthropometric measurements collected included height, weight, and waist circumference. Blood pressure, fasting cholesterol and blood sugar measurements were also collected.

Participants were requested beforehand to refrain from smoking, drinking alcohol or caffeinated beverage a half an hour prior to blood pressure measurement. Blood pressure and heart rate was measured with an Omron automated sphygmomanometer model HEM-907. The BP was measured on the left arm after the participant had sat for at least five minutes. The blood pressure was taken in the sitting position, legs uncrossed, the arm resting on a table and the ante-cubital fossa at the level of the lower sternum. Two arm cuffs that fitted arm circumferences 9-13 inches and 13-17 inches were used in the process. Three readings were taken three minutes apart and

the mean of the closest two values were used to describe the blood pressure of the subject. Additional measurements included height which was measured to the nearest 0.1 cm as the perpendicular distance between the top of the head (the vertex) and the bottom of the feet by a SECA 214 portable stadiometer. The weight was measured to the nearest 0.1 kg using a SECA 762 weighing scale with the subjects putting on loose clothing. The waist circumference was measured to the nearest 0.1 cm at the level of the midpoint between the inferior margin of the last rib and the crest of the ilium in the mid-axillary plane using a non-stretchable tape measure. Thirty SNPs were selected for genotyping and association analysis with BP. These SNPs were selected based on the previous association evidence with BP from GWASs or admixture mapping analysis<sup>23-28</sup>.

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