Genome-wide Association Analysis of Blood-Pressure Traits in African-Ancestry Individuals Reveals Common Associated Genes in African and Non-African Populations

Nora Franceschini,[1,75,*] Ervin Fox,[2,75] Zhaogong Zhang,[3,4,75] Todd L. Edwards,[5,75] Michael A. Nalls,[6,75] Yun Ju Sung,[7] Bamidele O. Tayo,[8] Yan V. Sun,[9] Omri Gottesman,[10] Adebawole Adeyemo,[11] Andrew D. Johnson,[12] J. Hunter Young,[13] Ken Rice,[14] Qing Duan,[15] Fang Chen,[16] Yun Li,[17,18] Hua Tang,[19] Myriam Fornage,[20] Keith L. Keene,[21] Jeanette S. Andrews,[22] Jennifer A. Smith,[23] Jessica D. Faul,[24] Zhang Guangfa,[25] Wei Guo,[3] Yu Liu,[26] Sarah S. Murray,[27] Solomon K. Musani,[2] Sathanur Srinivasan,[27] Digna R. Velez Edwards,[28] Heming Wang,[3] Lewis C. Becker,[29] Pascal Bovet,[30,31] Murielle Bochud,[30] Ulrich Broeckel,[32] Michel Burnier,[33] Cara Carty,[34] Daniel I. Chasman,[35] Georg Ehret,[36,37] Wei-Min Chen,[16] Guanjie Chen,[11] Wei Chen,[27] Jingzhong Ding,[38] Albert W. Dreisbach,[2] Michele K. Evans,[39] Xiuqing Guo,[40] Melissa E. Garcia,[41] Rich Jensen,[42] Margaux F. Keller,[6,43] Guillaume Lettre,[44] Vaneet Lotay,[10] Lisa W. Martin,[45] Jason H. Moore,[46] Alanna C. Morrison,[47] Thomas H. Mosley,[2] Adesola Ogunniyi,[48] Walter Palmas,[49] George Papanicolaou,[50] Alan Penman,[2] Joseph F. Polak,[51] Paul M. Ridker,[35] Babatunde Salako,[47] Andrew B. Singleton,[6] Daniel Shriner,[11] Kent D. Taylor,[40] Ramachandran Vasan,[52] Kerri Wiggins,[42] Scott M. Williams,[5] Lisa R. Yanek,[13] Wei Zhao,[23] Alan B. Zonderman,[53] Diane M. Becker,[13] Gerald Berenson,[27] Eric Boerwinkle,[47] Erwin Bottinger,[10] Mary Cushman,[54] Charles Eaton,[55] Fredrik Nyberg,[56] Gerardo Heiss,[1] Joel N. Hirschhron,[57,58,59] Virginia J. Howard,[60] Konrad J. Karczewsk,[19] Matthew B. Lanktree,[61] Kiang Liu,[62] Yongmei Liu,[63] Ruth Loos,[10] Karen Margolis,[64] Michael Snyder,[19] the Asian Genetic Epidemiology Network Consortium,[76] Bruce M. Psaty,[42,65] Nicholas J. Schork,[25] David R. Weir,[24] Charles N. Rotimi,[11] Michele M. Sale,[66] Tamara Harris,[67] Sharon L.R. Kardia,[23] Steven C. Hunt,[68] Donna Arnett,[60] Susan Redline,[69] Richard S. Cooper,[8] Neil J. Risch,[70] D.C. Rao,[7] Jerome I. Rotter,[40] Aravinda Chakravarti,[37,75] Alex P. Reiner,[71,75] Daniel Levy,[12,72,75] Brendan J. Keating,[73,74,75] and Xiaofeng Zhu[3,75,*]

[1]Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA; [2]Department of Medicine, University of Mississippi Medical Center, Jackson, MS 39126, USA; [3]Department of Epidemiology & Biostatistics, School of Medicine, Case Western Reserve University, Cleveland, OH 44106, USA; [4]School of Computer Science and Technology, Heilongjiang University, Harbin 150080, China; [5]Center for Human Genetics Research, Vanderbilt Epidemiology Center, Department of Medicine, Vanderbilt University, Nashville, TN 37212, USA; [6]Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD 20892, USA; [7]Division of Biostatistics, Washington University School of Medicine, St. Louis, MO 63110, USA; [8]Department of Preventive Medicine and Epidemiology, Loyola University Chicago Stritch School of Medicine, Maywood, IL 60153, USA; [9]Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA 30322, USA; [10]The Charles Bronfman Institute for Personalized Medicine, Mount Sinai School of Medicine, New York, NY 10029, USA; [11]Center for Research on Genomics and Global Health, National Human Genome Research Institute, Bethesda, MD 20892, USA; [12]Center for Population Studies, National Heart, Lung, and Blood Institute, Framingham, MA 01702, USA; [13]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA; [14]Department of Biostatistics, University of Washington, Seattle, WA 98101, USA; [15]Bioinformatics and Computational Biology Program, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA; [16]Center for Public Health Genomics, University of Virginia, Charlottesville, VA 22908, USA; [17]Department of Biostatistics, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA; [18]Department of Genetics, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA; [19]Department of Genetics, Stanford University School of Medicine, Stanford, CA 94305, USA; [20]Division of Epidemiology, School of Public Health, University of Texas Health Science Center at Houston, Houston, TX 77030, USA; [21]Department of Public Health Science, School of Medicine, University of Virginia, Charlottesville, VA 22908, USA; [22]Department of Biostatistical Science, Public Health Sciences, Wake Forest School of Medicine, Winston-Salem, NC 27157, USA; [23]Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, MI 48109, USA; [24]Survey Research Center, Institute for Social Research, University of Michigan, Ann Arbor, MI 48104, USA; [25]The Scripps Translational Science Institute and The Scripps Research Institute, La Jolla, CA 92037, USA; [26]Center for Proteomics and Bioinformatics, Case Western Reserve University, Cleveland, OH 44106, USA; [27]Tulane Center for Cardiovascular Health, Tulane University, New Orleans, LA 70112, USA; [28]Center for Human Genetics Research, Vanderbilt Epidemiology Center, Department of Obstetrics and Gynecology, Vanderbilt University, Nashville, TN 37212, USA; [29]Department of Medicine, The Johns Hopkins University, Baltimore, MD 21205, USA; [30]Institute of Social and Preventive Medicine, Lausanne University Hospital, Lausanne 1010, Switzerland; [31]Ministry of Health, Victoria, Republic of Seychelles; [32]Department of Pediatrics, Medical College of Wisconsin, Milwaukee, WI 53226, USA; [33]Service of Nephrology and Hypertension, Lausanne University Hospital, Lausanne 1010, Switzerland; [34]Department of Biostatistics and Biomathematics, Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA; [35]Division of Preventive Medicine, Brigham and Women's Hospital, 900 Commonwealth Avenue, Boston, MA 02115, USA; [36]Cardiology, Department of Specialties of Internal Medicine, Geneva University Hospital, Rue Gabrielle-Perret-Gentil 4, 1211 Geneva 14, Switzerland; [37]Center for Complex Disease Genomics, McKusick-Nathans Institute of Genetic Medicine, The Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA; [38]Section on Gerontology and Geriatric Medicine, Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, NC 27157, USA; [39]Health Disparities Unit, National Institute on Aging, National Institutes of Health, Bethesda, MD 20892, USA; [40]Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA; [41]Laboratory of Cellular and Molecular Biology, Intramural Research Program, National Institute on Aging, Bethesda, MD 20892, USA; [42]Cardiovascular Health Research Unit, Department of Medicine, Epidemiology and Health Services, University of Washington, Seattle, WA 98101, USA; [43]Department of Biological Anthropology, Temple University, Philadelphia, PA 19122, USA; [44]Montreal Heart Institute and Université de Montréal, Montréal, QC H1T 1C8, Canada; [45]Cardiovascular Institute, The George Washington University, Washington DC 20037, USA; [46]Institute for Quantitative Biomedical Sciences, Departments of Genetics and Community

High blood pressure (BP) is more prevalent and contributes to more severe manifestations of cardiovascular disease (CVD) in African Americans than in any other United States ethnic group. Several small African-ancestry (AA) BP genome-wide association studies (GWASs) have been published, but their findings have failed to replicate to date. We report on a large AA BP GWAS meta-analysis that includes 29,378 individuals from 19 discovery cohorts and subsequent replication in additional samples of AA (n = 10,386), European ancestry (EA) (n = 69,395), and East Asian ancestry (n = 19,601). Five loci (*EVX1-HOXA*, *ULK4*, *RSPO3*, *PLEKHG1*, and *SOX6*) reached genome-wide significance ($p < 1.0 \times 10^{-8}$) for either systolic or diastolic BP in a transethnic meta-analysis after correction for multiple testing. Three of these BP loci (*EVX1-HOXA*, *RSPO3*, and *PLEKHG1*) lack previous associations with BP. We also identified one independent signal in a known BP locus (*SOX6*) and provide evidence for fine mapping in four additional validated BP loci. We also demonstrate that validated EA BP GWAS loci, considered jointly, show significant effects in AA samples. Consequently, these findings suggest that BP loci might have universal effects across studied populations, demonstrating that multiethnic samples are an essential component in identifying, fine mapping, and understanding their trait variability.

Hypertension (HTN [MIM 145500]) disproportionally affects African Americans, who generally have higher mean blood pressure (BP) and an earlier age of HTN diagnosis than other United States ethnicities.[1–3] Increased severity of HTN contributes to a greater risk of stroke, coronary heart disease, and end-stage renal disease in African Americans than in United States European-ancestry (EA) individuals.[4,5] Several factors are known to be associated with HTN risk, and they include genetic susceptibility and behavioral factors such as lifestyle, diet, and obesity,[6–10] which vary across racial and ethnic groups. Several BP genome-wide association studies (GWASs) in EA individuals have been reported,[11–13] including the International Consortium for Blood Pressure (ICBP) GWAS, which identified 28 loci with a combined genetic effect explaining 0.9% of BP variability.[11] BP GWASs performed in African-ancestry (AA) individuals, however, have involved relatively smaller sample sizes[14,15] and to date have failed to identify replicable loci. In contrast, admixture-mapping analysis has successfully identified *NPR3* (MIM 108962) as a BP-associated locus in AA individuals;[16] this region has also been identified in EA individuals and East Asians.[11,17,18] Unfortunately, there have only been limited large-scale BP GWASs in African Americans, despite their higher risk of HTN and greater burden from BP disease. This communication reports findings from a large GWAS of 29,378 AA subjects for BP traits.

The overall study design is presented in Figure 1. We performed a meta-analyses of 19 studies (n = 29,378 subjects) from the Continental Origins and Genetic Epidemiology Network (COGENT) GWAS of AA samples for BP traits (Table 1). All individuals were at least 20 years old and were from 18 United States African American cohorts and a study from Yoruba, Nigeria. For individuals reporting use of antihypertensive medications, BP was imputed by the addition of 10 and 5 mmHg for systolic BP (SBP) and diastolic BP (DBP), respectively. Outliers defined as >4 SDs from the mean were excluded. Each study received institutional-review-board approval of its consent procedures, examination and surveillance components, data security measures, and DNA collection and use for genetic research. All participants in each study gave written informed consent for their participation in the study and genetic research.

After stringent quality control of genotyped and imputed data (Table S1, available online), ~2.42 million SNPs were available for analyses. Prespecified analyses of SBP, DBP, and clinically treated HTN were performed for each cohort according to standardized protocols. SNP associations for SBP or DBP were assessed by linear regression or the generalized linear mixed-effects model for family data[19] under the assumption of an additive model and after adjustment for age,[2] body mass index, and gender. Each study also adjusted for the first ten principal

and Family Medicine, The Geisel School of Medicine, Dartmouth College, Lebanon, NH 03756, USA; [47]Human Genetics Center, School of Public Health, University of Texas Health Science Center at Houston, Houston TX 77030, USA; [48]Department of Medicine, University of Ibadan, Ibadan, Oyo, Nigeria; [49]Department of Medicine, Columbia University, New York, NY 10032, USA; [50]Division of Prevention and Population Sciences, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD 20892, USA; [51]Tufts Medical Center, Tufts University School of Medicine, Boston, MA 02111, USA; [52]Boston University School of Medicine, Boston, MA 02118, USA; [53]Laboratory of Personality and Cognition, National Institute on Aging, National Institutes of Health, MD 20892, USA; [54]University of Vermont College of Medicine, Burlington, VT 05446, USA; [55]Departments of Family Medicine and Epidemiology, Alpert Medical School, Brown University, Providence, RI 02912, USA; [56]Global Epidemiology, AstraZeneca Research and Development, SE-431 83 Mölndal, Sweden; [57]Program in Medical and Population Genetics, Broad Institute of Harvard and MIT, Cambridge, MA 02141, USA; [58]Divisions of Genetics and Endocrinology, Boston Children's Hospital, Boston, MA 02115, USA; [59]Department of Genetics, Harvard Medical School, Boston, MA 02115, USA; [60]Department of Epidemiology, University of Alabama at Birmingham, Birmingham, AL 35294, USA; [61]Schulich School of Medicine and Dentistry, University of Western Ontario, London, ON N6A 5C1, Canada; [62]Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL 60611, USA; [63]Department of Epidemiology & Prevention, Public Health Sciences, Wake Forest School of Medicine, Winston-Salem, NC 27157, USA; [64]Division of Clinical Epidemiology, Hennepin County Medical Center, Minneapolis, MN 55415, USA; [65]Group Health Research Institute, Group Health Cooperative, Seattle, WA 98101, USA; [66]University of Virginia Center for Public Health Genomics, Charlottesville, VA 22908, USA; [67]Laboratory of Epidemiology, Demography, and Biometry, National Institutes on Aging, Gateway Building, 3C309, 7201 Wisconsin Avenue, Bethesda, MD 22892, USA; [68]Cardiovascular Genetics, University of Utah, Salt Lake City, UT 84132, USA; [69]Department of Medicine, Harvard Medical School, Boston, MA 02115, USA; [70]Institute for Human Genetics, Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA 94143, USA; [71]Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA; [72]Framingham Heart Study, National Heart, Lung, and Blood Institute, Framingham, MA 01702, USA; [73]Center for Applied Genomics, Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA; [74]Department of Pediatrics, University of Pennsylvania, Philadelphia, PA 19104, USA;
[75]These authors contributed equally to this work
[76]A full list of Asian Genetic Epidemiology Network Consortium members can be found in the Supplemental Data
*Correspondence: xiaofeng.zhu@case.edu (X.Z.), noraf@unc.edu (N.F.)
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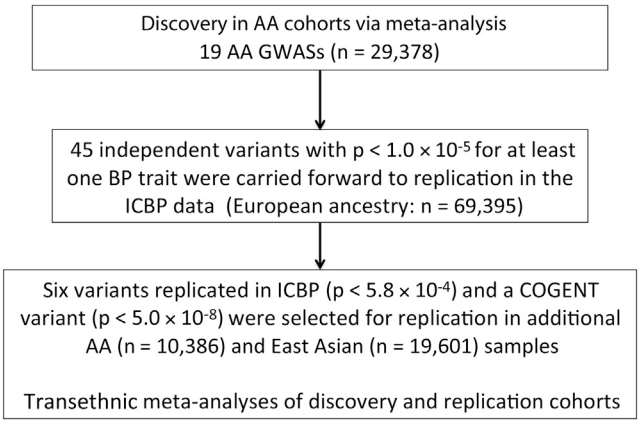

Figure 1. Overview of GWAS Meta-analysis for the COGENT Discovery and Replication Cohorts

components[20,21] in regression analysis. For HTN, we used logistic regression models and adjusted the covariates appropriately. The genomic-control inflation factors showed little evidence of residual confounding by ancestry (λ_{GC} 0.97–1.12), indicating that population structure was well controlled in each cohort (Table S2). For each trait (SBP, DBP, and HTN), we combined results across studies by using the inverse-variance-weighted meta-analysis method. The quantile-quantile and Manhattan plots for discovery analyses are shown in Figure S1. In these analyses, only one SNP (rs11041530) located 10 kb downstream of cytochrome b5 reductase 2 (*CYB5R2* [MIM 608342]) reached genome-wide significance for SBP ($p = 4.0 \times 10^{-8}$) (Table 2).

In addition to including *CYB5R2*, we carried forward all SNPs with $p < 1.0 \times 10^{-5}$ for SBP or DBP from the COGENT discovery AA analyses for replication in each of three replication samples: EA, AA, and Asian. We first attempted replication in the EA ICBP data,[11] which have the largest replication sample size. There were 45 independent SNPs with $p < 1.0 \times 10^{-5}$ for at least one trait (Table S3, pairwise $r^2 < 0.076$ in AA samples). Two SNPs monomorphic in HapMap CEU (Utah residents with ancestry from northern and western Europe from the CEPH collection) data were excluded from further analysis (Table S3). Among the 43 independent SNPs evaluated, we calculated the expected number of SNPs in EA ICBP samples across a range of significance levels under the assumption that the number of variants observed in the ICBP samples follows a binomial distribution when none of these variants are associated with BP. We observed significant enrichment of BP-associated SNPs in the EA ICBP samples across the range of significance levels (the largest $p < 2.2 \times 10^{-7}$, Table S4). After correction for multiple testing (Bonferroni cutoff $p = 5.8 \times 10^{-4}$ for two traits and 43 independent SNPs), six additional SNPs in six BP loci reached the significance threshold for SBP or DBP; these SNPs were located on chromosomes 3, 6, 7, and 11 (Table 2). However, rs11041530 (*CYB5R2*), which reached genome-wide significance in the COGENT discovery AA samples, did not replicate in ICBP samples after adjustment for multiple tests ($p = 0.029$).

We then carried these six SNPs and rs11041530 forward for further replication in additional AA (n = 10,386) and East Asian (n = 19,601) samples. The characteristics of the AA replication sample are shown in Table 1. Power estimates for AA samples are described in Table S5. Three SNPs (rs13209747, rs17428471, and rs1401454) across three independent loci replicated in AA samples (Bonferroni cutoff $p = 0.0037$ for 14 tests, i.e., two traits and seven SNPs, Table 2). Three SNPs (rs13209747, rs17080102 and rs6924906) were also significantly associated with BP traits in East Asians ($p < 0.0037$, Table 2). However, the beta estimate of rs6924906 was the opposite of the COGENT AA beta estimate, and this SNP association was not considered to be replicated (Table 2).

We next conducted transethnic meta-analyses by combining discovery AA samples and replication samples from all three ethnicities. In these analyses, in five independent loci we identified five SNPs associated with BP traits at $p < 1.67 \times 10^{-8}$; they included rs1717027, rs13209747, rs17080102, rs17428471, and rs1401454, which are consistent with the replication analyses of AA and East Asian samples. The threshold $p = 1.67 \times 10^{-8}$, which represents the genome-wide significance after correction for the three traits (SBP, DBP, and HTN) we analyzed, is relatively conservative because of the correlation among the BP traits. Two SNPs, rs6924906 and rs11041530, did not reach genome-wide significance and might indicate false-positive findings.

Three of the five SNPs in the identified loci lack previous associations with BP. SNP rs13209747 is located near R-spondin family member 3 (*RSPO3* [MIM 610574]) in chromosomal region 6q22 ($p = 2.56 \times 10^{-10}$ for SBP and 2.43×10^{-11} for DBP) (Table 2). rs17080102 is an intronic SNP in pleckstrin-homology-domain-containing, family G (with RhoGef domain) member 1 (*PLEKHG1)* in chromosomal region 6q25.1 ($p = 4.75 \times 10^{-8}$ for SBP and 1.90×10^{-11} for DBP) (Table 2). Previous admixture-mapping studies have suggested evidence of local association with HTN at the 6q22–25 region in AA populations.[16,22,23] RSPO3 activates the Wnt/beta-catenin signaling pathway, and variants therein are associated with blood urea nitrogen (a kidney trait) in East Asians,[24] waist-to-hip ratio, and bone mineral density.[25,26] Studies of knockout mice have shown that *RSPO3* is required for *Vegf* expression and endothelial cell proliferation.[27]

The third BP variant, rs17428471, is located at 7p15–14, which contains several homeobox genes (*EVX1-HOXA* locus [MIM 142996 and MIM 142955], transethnic meta-analysis $p = 2.1 \times 10^{-12}$ for SBP and $p = 1.6 \times 10^{-9}$ for DBP) (Table 2). Linkage disequilibrium (LD) in COGENT AA samples at 7p15–14 suggested three LD blocks represented by three independent SNPs—rs17428471, rs17471520, and rs11564022—with maximum pairwise $r^2 = 0.04$. The three SNPs showed evidence

Table 1. Descriptive Characteristics of the AA Studies

Study	Total Subjects	Age in Years (Mean ± SD)	No. of Males (%)	BMI (Mean ± SD)	No. with HTN (%)	SBP in mmHg (Mean ± SD)	DBP in mmHg (Mean ± SD)	Hypertensive Medication (%)
BioVu	942	44.3 ± 16.5	269 (28.6)	32.2 ± 10.0	673 (67.1)	131.4 ± 21.1	79.3 ± 12.6	57.3
ARIC	2,511	53.3 ± 5.8	1,045 (36.9)	29.7 ± 6.0	1,612 (58.7)	128.3 ± 20.8	79.7 ± 12.1	44.0
CARDIA	833	24.4 ± 3.8	366 (38.6)	25.4 ± 6.1	210 (25.2)	116.9 ± 16.4	76.9 ± 12.1	13.0
CFS	489	45.7 ± 16.2	213 (40.9)	34.3 ± 9.7	209 (44.6)	128.2 ± 16.0	76.5 ± 10.7	38.9
JHS	2,017	50.0 ± 12.2	213 (39.3)	32.3 ± 7.8	1,193 (56.5)	124.9 ± 18.0	80.0 ± 10.6	46.3
MESA	1,623	62.2 ± 10.1	745 (45.3)	30.2 ± 5.9	1,019 (62.0)	131.4 ± 21.7	74.5 ± 10.2	50.5
CHS	815	72.7 ± 5.7	305 (37.4)	28.5 ± 5.5	598 (73.4)	148.1 ± 23.9	78.3 ± 11.6	62.7
GeneSTAR	1,132	46.5 ± 12.3	432 (38.2)	32.0 ± 7.8	613 (54.2)	127.7 ± 19.7	80.7 ± 11.4	37.9
GENOA	996	56.4 ± 11.1	295 (29.6)	31.1 ± 6.8	688 (69.1)	135.6 ± 22.5	78.3 ± 12.3	56.9
HANDLS	950	48.5 ± 9.0	424 (44.6)	29.9 ± 8.0	437 (46.0)	126.3 ± 19.8	75.4 ± 12.1	35.5
Health ABC	1,139	73.4 ± 2.9	488 (42.8)	28.6 ± 5.4	871 (76.8)	138.7 ± 21.4	72.5 ± 11.3	62.7
HyperGEN	1,252	45.2 ± 13.3	407 (32.5)	32.5 ± 7.8	780 (54.2)	134.4 ± 23.5	76.5 ± 12.0	37.7
Maywood-Loyola	743	42.3 ± 7.8	467 (62.9)	26.7 ± 7.7	158 (21.3)	120.6 ± 19.9	77.0 ± 13.4	0.7
Nigeria-Loyola	1,188	47.8 ± 15.5	510 (42.9)	23.3 ± 5.1	443 (37.3)	127.9 ± 26.4	77.8 ± 14.9	3.8
Mt. Sinai Study	873	59.3 ± 12.5	364 (41.7)	30.7 ± 7.8	803 (92.0)	134.2 ± 19.6	76.7 ± 10.5	88.3
WHI-SHARe	8,094	61.6 ± 7.0	0 (0.0)	31.0 ± 6.4	4,780 (59.0)	132.2 ± 17.9	78.1 ± 9.4	46.2
HUFS	1,017	48.4 ± 13.2	419 (41.2)	30.5 ± 8.3	509 (50.0)	131.3 ± 21.9	81.4 ± 13.3	13.3
BHS	368	37.6 ± 4.9	142 (38.6)	31.4 ± 8.7	105 (28.5)	125.8 ± 19.5	83.7 ± 13.0	16.2
SIGNET	2,396	63. 5 ± 8.6	870 (36.3)	31.5 ± 6.9	585 (24.4)	137.3 ± 18.8	81.4 ± 10.8	71.4
AA Replication Cohorts								
JUPITER	1,688	66.4 ± 8.1	850 (50.3)	28.2 ± 7.3	1,067 (63.7)	140.7 ± 17.7	84.3 ± 9.4	53.3
Ghana	3,420	43.0 ± 13.6	1,452 (42.5)	24.7 ± 5.0	784 (22.9)	127.3 ± 19.9	76.8 ± 12.0	0.0
FBPP-AXIOM	872	48.9 ± 13.1	372 (42.6)	31.1 ± 7.0	604 (69.2)	128.8 ± 21.6	74.6 ± 11.9	65.4
HRS	1,337	66.5 ± 10.2	483 (36.1)	30.5 ± 6.5	1,073 (80.3)	137.3 ± 23.2	82.2 ± 13.0	66.9
Mt. Sinai IPM Biobank Program	3,057	50.2 ± 14.7	1,018 (33.3)	30.7 ± 8.2	1,999 (65.4)	136.0 ± 23.0	80.0 ± 21.0	65.2
The Seychelles TANDEM	483	48.1 ± 13.6	203 (42.0)	27.8 ± 5.4	310 (64.2)	135.6 ± 22.6	84.5 ± 12.5	44.3
The Seychelles Heart Study III	906	44.9 ± 11.2	401 (44.3)	27.2 ± 5.7	396 (43.7)	129.5 ± 20.0	84.2 ± 12.3	27.9

Characteristics of studies contributing to the COGENT BP meta-analyses. Abbreviations are as follows: BMI, body mass index; BioVU, DNA databank of Vanderbilt University; ARIC, Atherosclerosis Risk in Communities; CARDIA, Coronary Artery Risk Development in Young Adults; CFS, Cleveland Family Study; JHS, Jackson Heart Study; MESA, Multi-Ethnic Study of Atherosclerosis; CHS, Cardiovascular Health Study; GeneSTAR, Genetic Study of Atherosclerosis Risk; GENOA, Genetic Epidemiology Network of Arteriopathy; HANDLS, The Healthy Aging in Neighborhoods of Diversity across the Life Span study; Health ABC, Health, Aging, and Body Composition study; HyperGEN, Hypertension Genetic Epidemiology Network; Maywood-Loyola, Maywood study at Loyola University Medical Center; Nigeria-Loyola, Nigeria study at Loyola University Medical Center; Mt. Sinai Study, Mount Sinai, New York City, USA, study; WHI-SHARe, Women's Health Initiative SNP Health Association Resource; HUFS, Howard University Family Study; BHS, Bogalusa Heart Study; SIGNET, Sea Islands Genetic Network; JUPITER, Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin; Ghana, Ghana study at Vanderbilt University; FBPP-AXIOM, Family Blood Pressure Program-AXIOM; HRS, Health and Retirement Study; and Mt. Sinai IPM Biobank, Mount Sinai Institute for Personalized Medicine Biobank Program.

of association with BP. We then performed conditional analysis by including the three SNPs in linear regression models by using the summary statistics[28] and observed little change in significance (Table S6). These results are consistent with the regional SBP, DBP, and HTN plots, where three independent SNPs are present (Figures 2A–2C). Two of these SNPs replicated in additional AA samples for SBP ($p = 0.011$ for rs11564022 and $p = 1.4 \times 10^{-4}$ for rs17428471). rs17428471 also replicated in EA ICBP samples for both SBP and DBP ($p < 2.8 \times 10^{-5}$). This variant was not associated with BP traits in East Asians, although the allele is of lower frequency in Asians (minor allele frequency < 0.05). rs17428471 also reached genome-wide significance in transethnic meta-analyses ($p = 2.1 \times 10^{-12}$ and no evidence of heterogeneity between ancestry samples) (Table 2 and Table S7).

Table 2. Meta-analyses of COGENT Discovery AA Samples and Replication in EA, East Asian, and Additional AA Data Sets

Chr	SNP	Gene	Effect Allele/ Other Allele	Discovery COGENT				Transethnic Replication			Transethnic Meta-analysis p[b,c]
				Effect Allele Frequency	Trait	Beta (SE)	COGENT p[a]	EA ICBP p[a]	AA p[a]	East Asian p[a]	
6	rs13209747	*RSPO3*	T/C	0.19	SBP	0.85 (0.21)	5.9×10^{-5}	5.4×10^{-4}	5.0×10^{-4}	2.6×10^{-3}	$\mathbf{2.6 \times 10^{-10}}$
					DBP	0.56 (0.12)	8.8×10^{-6}	1.5×10^{-3}	2.2×10^{-2}	1.2×10^{-4}	$\mathbf{2.4 \times 10^{-11}}$
6	rs17080102	*PLEKHG1*	C/G	0.1	SBP	−1.02 (0.25)	3.4×10^{-5}	9.2×10^{-4}	2.3×10^{-1}	3.4×10^{-2}	$\mathbf{4.8 \times 10^{-8}}$
					DBP	−0.74 (0.15)	5.4×10^{-7}	1.5×10^{-4}	4.1×10^{-1}	8.5×10^{-4}	$\mathbf{1.9 \times 10^{-11}}$
6	rs6924906	*C6orf37* (*FAM46A*)	T/C	0.71	SBP	−0.41 (0.17)	1.7×10^{-2}	5.6×10^{-4}	4.7×10^{-1}	2.0×10^{-3}	6.2×10^{-5}
					DBP	−0.51 (0.10)	5.6×10^{-7}	4.9×10^{-2}	9.8×10^{-1}	8.8×10^{-3}	5.5×10^{-7}
7	rs17428471	*EVX1-HOXA*	T/G	0.14	SBP	1.20 (0.24)	4.0×10^{-7}	8.0×10^{-6}	1.4×10^{-4}	3.4×10^{-1}	$\mathbf{2.1 \times 10^{-12}}$
					DBP	0.61 (0.14)	1.2×10^{-5}	2.8×10^{-5}	1.1×10^{-2}	4.4×10^{-1}	$\mathbf{1.6 \times 10^{-9}}$
3	rs1717027	*ULK4*[d]	T/C	0.64	SBP	0.18 (0.16)	2.6×10^{-1}	5.0×10^{-1}	6.0×10^{-1}	5.6×10^{-1}	3.0×10^{-1}
					DBP	0.49 (0.10)	5.1×10^{-7}	2.5×10^{-7}	2.2×10^{-2}	1.5×10^{-1}	$\mathbf{4.6 \times 10^{-13}}$
11	rs1401454	*SOX6*[d]	T/C	0.46	SBP	0.55 (0.16)	5.7×10^{-4}	2.2×10^{-4}	9.7×10^{-4}	6.7×10^{-1}	9.5×10^{-7}
					DBP	0.45 (0.10)	2.1×10^{-6}	3.1×10^{-5}	5.0×10^{-3}	5.5×10^{-1}	$\mathbf{5.1 \times 10^{-10}}$
11	rs11041530	*CYB5R2*	C/G	0.11	SBP	−1.35 (0.25)	$\mathbf{4.0 \times 10^{-8}}$	0.029	8.0×10^{-1}	9.3×10^{-1}	5.6×10^{-6}
					DBP	−0.54 (0.15)	2.6×10^{-4}	0.119	6.5×10^{-1}	6.6×10^{-1}	7.6×10^{-4}

Boldface indicates genome-wide significance after correction for the number of SNPs and traits. The following abbreviation is used: Chr, chromosome.
[a]Significant thresholds: COGENT discovery, $p < 5.0 \times 10^{-8}$; replication in ICBP, $p = 5.8 \times 10^{-4}$; further replication in AA and East Asians, $p = 0.0037$.
[b]Final significant variants were defined with the significance threshold of $p < 1.67 \times 10^{-8}$ after adjustment for the three traits.
[c]p values were combined for the analysis of the ICBP meta-analysis of EA samples. The replication sample size and power for each SNP in the AA studies are presented in Table S5.
[d]These genes were reported by Ehret et al.[11] and Johnson et al.[18]

The fourth variant identified, rs1401454 in *SOX6* (transcription factor SRY-Box6 [MIM 607257]) (Table 2 and Figure 2D), replicated in the additional AA samples. This SNP is 151 kb from rs2014408, a SNP which was previously reported in a GWAS of mean arterial pressure[18] in EA individuals, but the two SNPs are in low LD ($r^2 \leq 0.08$ in our AA data). Furthermore, rs1401454 is 652 kb away from *PLEKHA7* (MIM 612686) rs381815, a BP-associated SNP reported in EA samples,[11] and LD between these SNPs was weak in our data ($r^2 \leq 0.05$). rs2014408 and rs381815 were only nominally associated with DBP in COGENT discovery AA samples ($p = 0.05$ and 0.02, respectively). We then performed conditional analysis for DBP in the COGENT AA cohorts by including rs2014408 and rs381815 as covariates in linear regression models by using the summary-statistic method. The association between rs1401454 and DBP was largely unchanged (Table S8), suggesting that rs1401454 is independent of the two reported SNPs identified in EA subjects.

The fifth identified variant, rs1717027, is located in *ULK4* ($p = 4.6 \times 10^{-13}$ in the transethnic DBP meta-analysis) (Table 2). This locus was previously reported to be associated with DBP in EA individuals.[12] rs1717027 is in strong LD with two nonsynonymous SNPs (nsSNPs) (rs1716975 and rs2272007, pairwise $r^2 > 0.93$ in HapMap YRI [Yoruba in Ibadan, Nigeria]). Another *ULK4* nsSNP, rs3774372, previously reported to be associated with DBP[11] (Figure 2E), was not associated with BP traits in our AA samples ($p = 0.75$), nor was it in LD with rs1717027, rs1716975, or rs2272007 (all pairwise $r^2 < 0.14$ in COGENT AA subjects). We phased haplotypes by using these four SNPs and observed two common haplotypes in the HapMap CEU sample and evidence of a historical recombination event in a haplotype in AA samples (Figure 2F). Both the recombinant haplotype and one original haplotype (blue haplotype in Figure 2F) in AA populations have similar effects on DBP, suggesting that rs3774372 or variants that are in LD with it are unlikely to be the causal variant(s). Because rs1716975 and rs2272007 are in strong LD in the AA population, further conditional fine mapping would be uninformative.

Because of the high correlation among BP traits, we also examined evidence of SNP associations with SBP, DBP, and HTN in COGENT GWAS samples by using a "sign flipping" multitrait test, based on available summary statistics. In brief, let β_{ij}^{SBP} and s_{ij}^{SBP}, β_{ij}^{DBP} and s_{ij}^{DBP}, and β_{ij}^{HTN} and s_{ij}^{HTN} be the estimated regression coefficients and SEs for SBP, DBP, and HTN, respectively, for the ith SNP and the jth cohort, where $i = 1, 2, \ldots, 2{,}415{,}958$ and $j = 1, 2, \ldots, 19$. Let p_i^{SBP}, p_i^{DBP}, and p_i^{HTN} be the meta-analysis p values of the ith SNP for the three traits. We used Fisher's method for combining p values to summarize the total association evidence of the ith SNP for each trait, i.e., $x_i = -\log(p_i^{SBP} p_i^{DBP} p_i^{HTN})$. Because no original genotype and phenotype information is available for the cohorts, we were not able to evaluate the distribution of x_i under

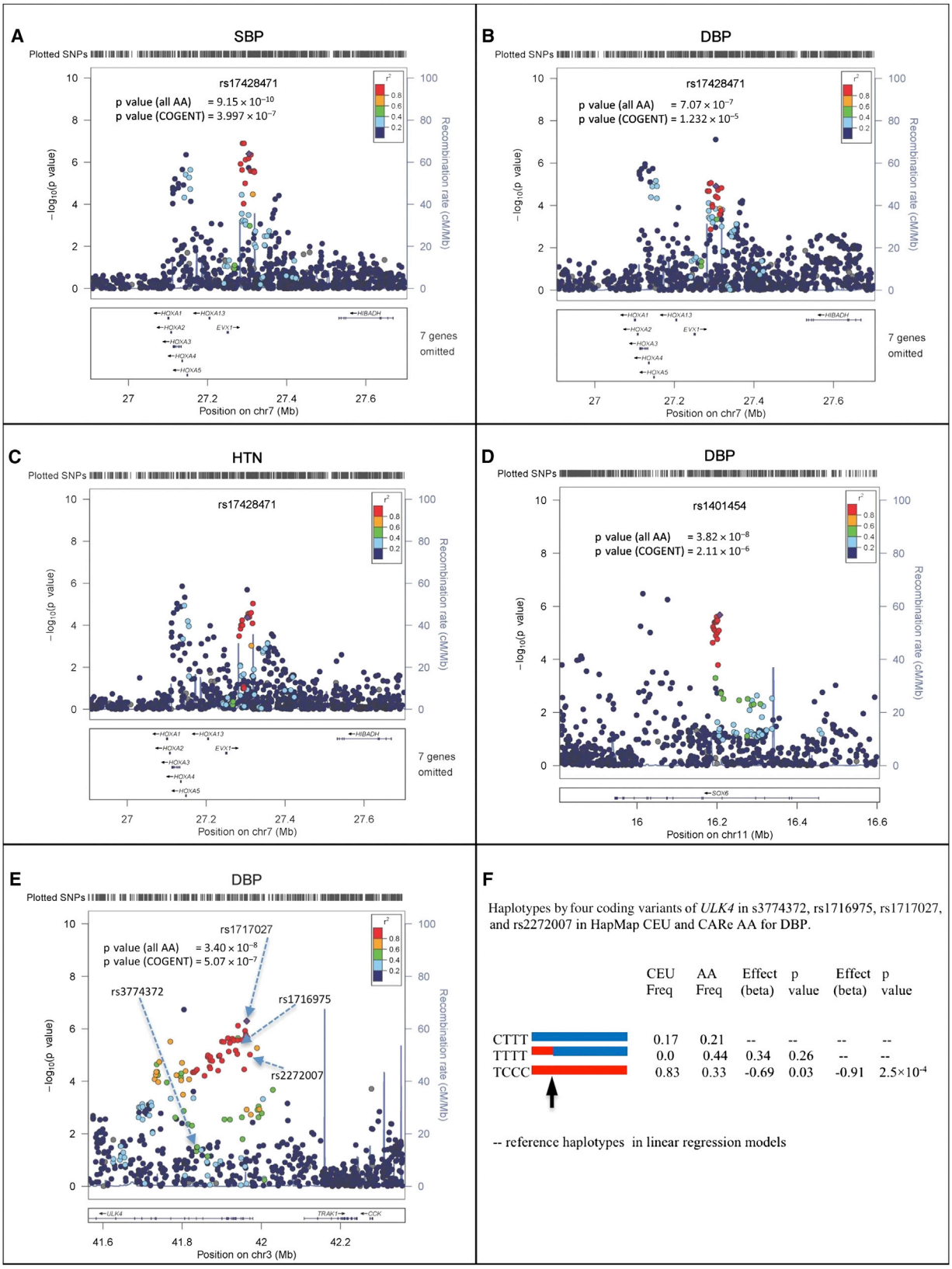

Figure 2. Regional Interrogation of the *EVX1-HOXA*, *SOX6*, and *ULK4* Loci

(A–C) Associations between SBP, DBP, and HTN and homeobox genes on chromosome 7. Note the three independent SNPs (purple diamonds) in this region with multiple homeobox genes and *EVX1* (Table 2). SNP rs17428471 is located in the middle peak.

(D) Association between DBP and *SOX6* on chromosome 11. p values of rs1401454 in both COGENT and all combined AA samples are shown.

(legend continued on next page)

the null hypothesis by a conventional permutation approach, i.e., by permuting the original phenotypes while holding the genotypes constant. Instead, we randomly flipped the sign of regression coefficients. To preserve the correlations among the three traits, as well as the LD patterns among SNPs, we flipped the signs of regression coefficients simultaneously for one cohort and three traits. We performed this procedure 10,000 times. That is, at the kth time for the jth cohort, we generated $\omega_j = 1$ or -1 with equal probability and let $\omega_j\beta_{ij}^{\text{SBP}}$, $\omega_j\beta_{ij}^{\text{DBP}}$, and $\omega_j\beta_{ij}^{\text{HTN}}$ be the estimated regression coefficients. We then performed an inverse-variance-weighted meta-analysis by using the flipped regression coefficients and the original SEs to calculate $p_i^{\text{SBP}(k)}$, $p_i^{\text{DBP}(k)}$, and $p_i^{\text{HTN}(k)}$ and hence $x_i^{(k)} = -\log(p_i^{\text{SBP}(k)} p_i^{\text{DBP}(k)} p_i^{\text{HTN}(k)})$. We recorded $x^{(k)} = \max_i(x_i^{(k)})$, where $k = 1, 2, \ldots, 10{,}000$, which is the empirical distribution of the most extreme summary statistic, genome-wide, under the null hypothesis that a SNP is not associated with any of the three traits. For the ith SNP, we computed the genome-wide p value as $(1 + \sum_k I(x_i < x^{(k)}))/10{,}001$. Any SNP with $p < 0.05$ was considered genome-wide significant. Our simulations suggested that this method has valid type I error and is more powerful than a single SNP analysis (data not shown). With the "sign flipping" test, SNP rs17428471 reached genome-wide significance ($p = 0.002$), suggesting that this variant contributes to SBP, DBP, and HTN traits. These findings also provide further evidence of a role for the *EVX1-HOXA* locus for BP traits.

We also assessed whether BP loci previously identified in EA subjects have a broad role across ancestries. We tested the 29 ICBP-reported BP-associated SNPs from EA individuals;[11] three loci were significantly associated with BP in COGENT AA individuals (Table S9, $p < 0.00086$), and ten additional loci showed nominal replication ($p < 0.05$). We then examined the correlations between effect sizes and $\log_{10}$(p values) and the 29 EA-derived SNPs in our AA and East Asian samples. Although the p values were generally weakly correlated across different ancestries, the effect sizes were strongly correlated (Figure 3), suggesting consistent contribution of these common variants to BP across ancestries.

To fine map the genomic regions of reported ICBP variants, we further examined the 500 kb surrounding region at each of the loci in the COGENT AA samples. In four loci, we noted more significant SNPs than the ICBP index (published) SNPs identified in EA individuals. The index SNPs were not significant when conditioned on the most significant SNPs in the COGENT sample (Table S10 and Figures S2–S5). We calculated the sizes of LD blocks surrounding the most significant SNPs in the COGENT AA sample and observed shorter LD blocks. Therefore, in this data set, AA samples provided further fine mapping of these signals within these BP-associated loci.

We then estimated composite genetic-risk scores, as defined by ICBP, and observed highly significant associations for both SBP and DBP in the COGENT AA sample ($p = 1.5 \times 10^{-10}$ for SBP and $p = 1.3 \times 10^{-7}$ for DBP). A composite genetic-risk score using the five variants identified in this study accounted for 0.44% and 0.54% of the variability of SBP and DBP, respectively. The addition of these SNPs to the known variants from ICBP in the composite genetic-risk score substantially improved the explained variability to 0.80% and 1.42% for SBP and DBP, respectively. These findings provide evidence that many common variants at BP loci have broad effects across EA, AA, and East Asian populations rather than being population specific.

By examining a large number of genome-wide gene-expression data sets primarily from EA populations with significant index SNPs or proxies in high LD ($r^2 > 0.8$ in HapMap CEU and YRI),[29] we identified two loci as expression quantitative trait loci (eQTL). The BP-associated *SOX6* index signal (rs1401454) was also independently associated with gene-expression levels of *SOX6* in liver tissue in two studies ($p < 5.8 \times 10^{-54}$ and $p < 1.0 \times 10^{-16}$).[30,31] The strongest eQTL SNP for *SOX6* in each data set was rs1401454, indicating strong concordance between the BP and expression association signals. Several correlated SNPs at 3p22.1, including the index SNP rs1717027, were associated with gene-expression levels of both *ULK4* and *CTNNB1* (MIM 116806) in multiple tissues, including blood cells, adipose tissue, and brain tissue (*ULK4* strongest $p = 1.0 \times 10^{-19}$ in the prefrontal cortex, *CTNNB1* strongest $p = 3.8 \times 10^{-56}$ in the prefrontal cortex).

Pathway analyses applied to the genes (*EVX1-HOXA*, *SOX6*, *RSPO3*, *PLEKHG1*, and *ULK4*) with Ingenuity Pathway Analysis identified five canonical pathways (Figures S6A and S6B, $p < 0.05$), including nitric oxide signaling, which influences many processes related to BP, such as effects on vessel caliber (vasodilation), endothelial function, and cardiac contraction[32] (Table S11). The genes identified in this study (*EVX1*, *SOX6*, and *HOXA* family genes) were present in a network connecting with *CTNNB1*, which is also a gene identified in expression analysis. CTNNB1 is a key player in Wnt signaling pathway.[33]

(E) Association between DBP and *ULK4* on chromosome 3. One arrow points to the ICBP SNP rs3774372, which does not show evidence of association in COGENT samples. The most significant SNP is rs1717027.
(F) Haplotype analysis of coding variants rs3774372, rs1716975, rs1717027, and rs2272007 in *ULK4*. The red and blue lines indicate haplotypes. The arrow points to a historical recombination breakpoint observed in AA, but not in EA (HapMap CEU), populations. The best model fitting the National Heart, Lung, and Blood Institute Candidate-gene Association Resource ("CARe") data is TCCC versus (CTTT and TTTT), indicating that SNP rs3774372 reported in ICBP[11] is unlikely to be a causal variant.
In (A)–(E), the x axes show chromosomal positions, the left y axes show the p values, and the right y axes show the recombination rates across the region.

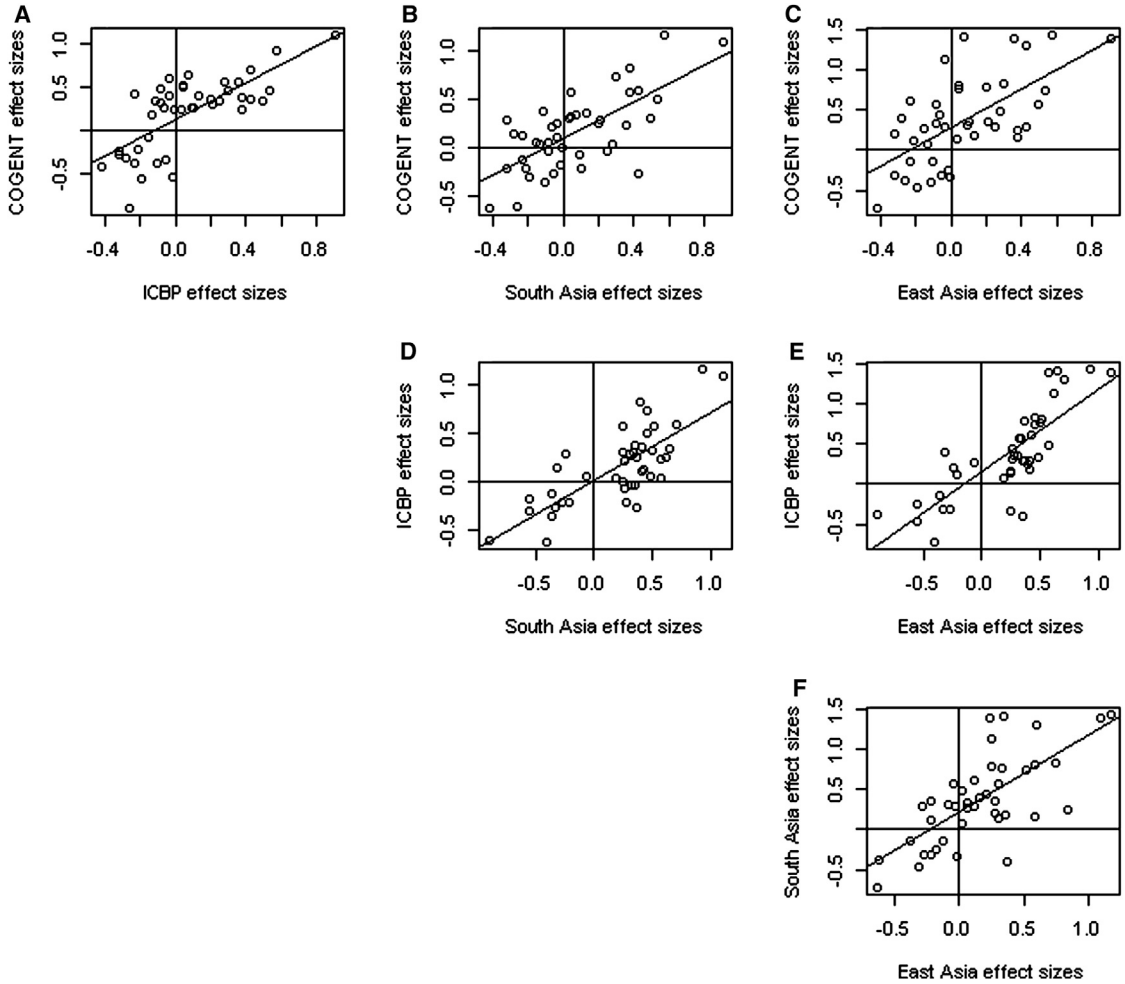

Figure 3. Pairwise Scatter Plots of the Effect Sizes of the 21 ICBP-Reported Variants among the COGENT, ICBP, South Asian, and East Asian Data Sets

The figure is plotted on the basis of the variants after exclusion of eight monomorphic variants in HapMap CHB (Han Chinese in Beijing, China) and JPT (Japanese in Tokyo, Japan) samples. The Pearson correlation coefficients and the corresponding p values are $r = 0.72$ and $p = 8.6 \times 10^{-11}$ (A), $r = 0.69$ and $p = 2.1 \times 10^{-9}$ (B), $r = 0.64$ and $p = 8.6 \times 10^{-7}$ (C), $r = 0.76$ and $p = 1.4 \times 10^{-13}$ (D), $r = 0.8$ and $p = 3.2 \times 10^{-17}$ (E), and $r = 0.7$ and $p = 3.2 \times 10^{-10}$ (F). We observed that the effect sizes are highly correlated across the different ethnic populations. These results strongly suggest that many common variants consistently contribute to BP variation across ethnicities, although replication is challenging because of variation in LD, sample size, and allele frequency.

We further investigated the functional significance of the SNP signals in our association analysis by using the publically available ENCODE Project Consortium resources.[34–36] We primarily used RegulomeDB and HaploReg for functional annotation of our COGENT BP findings.[35,36] The rs17428471 variant in *HOXA3* was observed to be in a Pax-4 motif. rs11564022 (*HOXA3*) is in perfect LD with rs11564023, which is in a DNase site (in NB4 cells) and marked by a number of histone marks and PEBP, Osf2, and Evi-1 motifs. rs17080102 resides in a DNase hypersensitive site marked by H3K27Ac and is in a region shown to bind c-Fos, GATA-2, and Pol2. Furthermore, this variant is in perfect LD with rs17080069, located in a DNase hypersensitive site that demonstrates binding to a number of cardiovascular regulators, including ESR1, TCF4, and NR3C1 (glucocorticoid receptor).

We then evaluated the evidence of recent positive selection near the BP signals identified in our association analysis by using several statistical techniques and the BioVU GWAS data, as well as population reference data sets (HapMap Phase III and the Human Genome Diversity Project). We compared adjusted allele frequencies among the BioVU African Americans and HapMap Phase III LWK (Luhya in Webuye, Kenya) and YRI individuals by using the method Treeselect[37] and detected genome-wide-significant evidence of local differentiation between East and West African populations at nsSNP rs2301721 ($p = 6.73 \times 10^{-9}$) in homeobox A7 (*HOXA7*) in the chromosome 7 region near our SBP signal at *EVX1*. We detected modest signatures of recent positive selection in the region of *EVX1-HOXA* (near *HOXA7*) by using a number of conventional metrics[38–40] (Figures S7–S13). Similar signatures of selection have been previously noted in East Asian

populations at the *ALDH2* locus, where an ethnicity-specific association with BP traits was also observed.[17] These observations are consistent with the notion that BP-regulation mechanisms have been subjected to natural selection during human history.[41]

In summary, using AA samples and transethnic meta-analyses, we identified three BP loci (*EVX1-HOXA*, *RSPO3*, and *PLEKHG1*) and one independent SNP in a known BP locus (*SOX6*) and further fine mapped four previously identified loci. Overall, we observed that common variants discovered in EA subjects also have broad effects in our AA data sets. Cumulatively, these analyses signify that a largely common set of genes regulate BP across the studied human populations.

Supplemental Data

Supplemental Data include descriptions of study samples, Supplemental Acknowledgments, 13 figures, and 11 tables and can be found with this article at http://www.cell.com/AJHG/.

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Web Resources

The URLs for data presented herein are as follows:

ENCODE Pilot Project: Common Consortium Resources, www.genome.gov/12513455
Ingenuity Pathway Analysis, http://www.ingenuity.com
Online Mendelian Inheritance in Man (OMIM), http://www/omim.org/

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Supplemental Data

Genome-wide Association Analysis of Blood-Pressure Traits in African-Ancestry Individuals Reveals Common Associated Genes in African and Non-African Populations

Nora Franceschini, Ervin Fox, Zhaogong Zhang, Todd L. Edwards, Michael A. Nalls, Yun Ju Sung, Bamidele O. Tayo, Yan V. Sun, Omri Gottesman, Adebawole Adeyemo, Andrew D. Johnson, J. Hunter Young, Ken Rice, Qing Duan, Fang Chen, Yun Li, Hua Tang, Myriam Fornage, Keith L. Keene, Jeanette S. Andrews, Jennifer A. Smith, Jessica D. Faul, Zhang Guangfa, Wei Guo, Yu Liu, Sarah S. Murray, Solomon K. Musani, Sathanur Srinivasan, Digna R. Velez Edwards, Heming Wang, Lewis C. Becker, Pascal Bovet, Murielle Bochud Ulrich Broeckel, Michel Burnier, Cara Carty, Daniel I. Chasman, Georg Ehret, Wei-Min Chen, Guanjie Chen, Wei Chen, Jingzhong Ding, Albert W. Dreisbach, Michele K. Evans, Xiuqing Guo, Melissa E. Garcia, Rich Jensen, Margaux F. Keller, Guillaume Lettre, Vaneet Lotay, Lisa W. Martin, Jason H. Moore, Alanna C. Morrison, Thomas H. Mosley, Adesola Ogunniyi, Walter Palmas, George Papanicolaou, Alan Penman, Joseph F. Polak, Paul M. Ridker, Babatunde Salako, Andrew B. Singleton, Daniel Shriner, Kent D. Taylor, Ramachandran Vasan, Kerri Wiggins, Scott M. Williams, Lisa R. Yanek, Wei Zhao, Alan B. Zonderman, Diane M. Becker, Gerald Berenson, Eric Boerwinkle, Erwin Bottinger, Mary Cushman, Charles Eaton, Fredrik Nyberg, Gerardo Heiss, Joel N. Hirschhron, Virginia J. Howard, Konrad J. Karczewsk, Matthew B. Lanktree, Kiang Liu, Yongmei Liu, Ruth Loos, Karen Margolis, Michael Snyder, the Asian Genetic Epidemiology Network Consortium, Bruce M. Psaty, Nicholas J. Schork, David R. Weir, Charles N. Rotimi, Michele M. Sale, Tamara Harris, Sharon L.R. Kardia, Steven C. Hunt, Donna Arnett, Susan Redline, Richard S. Cooper, Neil J. Risch, D.C. Rao, Jerome I. Rotter, Aravinda Chakravarti, Alex P. Reiner, Daniel Levy, Brendan J. Keating, and Xiaofeng Zhu

AGEN Consortium Members

Min Jin Go, Young Jin Kim, Jong-Young Lee, Jae-Pil Jeon, Sung Soo Kim, Bok-Ghee Han, Yoon Shin Cho, Xueling Sim, Wan Ting Tay, Rick Twee Hee Ong, Mark Seielstad, Jian Jun Liu, Tin Aung, Tien Yin Wong, Yik Ying Teo, E Shyong Tai, Chien-Hsiun Chen, Li-ching Chang, Yuan-Tsong Chen, Jer-Yuarn Wu, Tanika N. Kelly, Dongfeng Gu, James E. Hixson, Yun Ju Sung, Jiang He, Yasuharu Tabara, Yoshihiro Kokubo, Tetsuro Miki, Naoharu Iwai, Norihiro Kato, Fumihiko Takeuchi, Tomohiro Katsuya , Toru Nabika, Takao Sugiyama, Yi Zhang, Wei Huang, Xuegong Zhang, Xueya Zhou, Li Jin, Dingliang Zhu

Study Description and Populations

1. Discovery COGENT BP studies

BioVU: BioVU is a DNA biorepository linked to a database of de-identified electronic medical records (EMR), designed and implemented to support genetic association studies at Vanderbilt University (VU). BioVU is an ongoing study with rapid accrual of DNA specimen, accumulating ~26,000 participants per year, and with a current size of over 130,000. Studies in BioVU have demonstrated the validity of EMR-based phenotypes [1], clinical assessment of ancestry [2], investigated pharmacogenetic traits [3-5], and cardiovascular traits [6-8]. A detailed description of the human subjects protection applied to BioVU is described by Pulley *et al.* (2010)[9] The program is under continuous oversight by the institutional review board (IRB) and was reviewed in detail by the federal Office for Human Research Protections (OHRP). The BioVU DNA Repository is housed within the Center for Human Genetics Research DNA Resources Core (DNARC). Program planning for BioVU started in 2004, and sample accrual started in February 2007. Sample accrual is ongoing; there are over 126,676 DNA samples from adult clinic patients.

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 1.7 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, gender, race), text from clinical care including discharge summaries, nursing notes, progress notes, history and physical, problem lists and multi-disciplinary assessments, laboratory values, echocardiogram (ECG) diagnoses, imaging reports, clinical text and electronically derived trace values, and inpatient medication orders.

For this blood pressure (BP) study, we used adult (age ≥ 21) African American BioVU participants with GWAS data. We used the first non-Emergency Department measured BP in the EMR, and excluded participants if there was a diagnosis of secondary hypertension (ICD-9 405), HIV infection (ICD-9 042), any cancer (ICD-9 140-239), end-stage renal disease (ICD-9 585.6), or heart failure (ICD-9 428) prior to, or on the date, of BP measurement. To define hypertension cases, participants' measured systolic BP (SBP) or diastolic BP (DBP) ≥ 140mmHg or 90 mmHg respectively, have a diagnosis of hypertension (ICD-9 401-404), or a prescription for antihypertensive medication prior to, or on the date, of BP measurement (57.3% of eligible participants). For hypertension controls, participants' measured SBP and DBP ≤ 125 mmHg and 80 mmHg, and no prior diagnoses of hypertension, or prescriptions for antihypertensive medications.

Bogalusa Heart Study: The Bogalusa Heart Study is an epidemiologic survey of cardiovascular disease risk factors from birth through mid-adulthood. Participants (n = 1,420, ~40% male, ~70% European ancestry, 18–38 years of age) were previously examined as children in this long-term survey. Details of screening and examination procedures, followed in the Bogalusa Heart

Study since its inception, are reported elsewhere [10 11]. All data were collected after obtaining informed consent.

The BP levels were measured from the right arm of the subjects, with the subjects in a sitting position by two trained observers (three replicates each). The SBP and DBP were recorded at the first and fifth Korotkoff phases, respectively, using a mercury sphygmomanometer. The average of the six BP readings was used for this analysis.

Candidate Gene Association Resource (CARe): 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).

Atherosclerosis Risk Communities Study (ARIC): 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) [12]. 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 examination. 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 use 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.

The Coronary Artery Risk Development in Young Adults (CARDIA) 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 [13]. The CARDIA study initial enrollment consisted of 5,115 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[13]. 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. Hypertension was defined if SBP ≥140 mmHg, DBP ≥90 mmHg, or reported use of antihypertensive medication.

The Cleveland Family Study (CFS): 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 basis of genetic informativness, including multigenerational data or individuals from the extremes of the distribution of apnea phenotype[14]. 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 P.M.) and upon awakening (7:00 A.M.), and another three sitting at 11 am, following standardized guidelines using a calibrated sphygmomanometer. Cuff size was determined by the circumference of the upper arm and the appropriate bladder size from a standard chart. BP phenotypes were determined from the average of the nine measurements.

Jackson Heart Study (JHS): JHS was initiated in 2000 to investigate prospectively the epidemiology and determinants of cardiovascular disease in African Americans [15]. JHS recruited 5,302 participants after completion of data adjustment, representing more than 5% of African Americans 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[16]. 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.

The Multi-Ethnic Study of Atherosclerosis (MESA): 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. Thirty-eight % 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[17]. This manuscript utilizes data from African-American MESA participants, genotyped through the CARe project.

BP was measured three times at 1 minute intervals 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.

Cardiovascular Health Study (CHS): The CHS is a population-based cohort study of risk factors for CHD and stroke in adults ≥65 years conducted across four field centers[18]. 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)[19]. Means of the repeated BP measurements from the baseline examination were used for the analyses.

Genetic Study of Atherosclerosis Risk (GeneSTAR): 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 [20]. The genotyped sample size is 3,200, with ~35 % African American (n= 1,132). 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[21]. BP was measured using a standard mercury sphygmomanometer, following the American Heart Association [22] and JNC guidelines

[23]. 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 ≥140 mmHg, a mean DBP of ≥90 mmHg, and/or currently taking an antihypertensive medication.

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 [24]. 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 =90 mmHg 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.

The Healthy Aging in Neighborhoods of Diversity across the Life Span study (HANDLS): 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 [25]. The HANDLS design is an area probability sample of Baltimore based on the 2000 Census. The study protocol facilitated our ability to recruit 3,722 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 three designed as a re-examination wave of all participants seen between 2004-2009. This wave began in July of 2009 and will conclude in 2012. 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.

BP was measured using a non-invasively using the brachial artery auscultation method with an aneroid manometer, a stethoscope, and an inflatable cuff in individuals resting for 5 minutes. The average of right and left sitting BP values was taken to represent each of SBP and DBP, respectively for analyses.

The Health, Aging and Body Composition (Health ABC) study: HealthABC is a prospective cohort study of 3,075 community-dwelling men and women of African American and American European ancestry living in Memphis, Tennessee, USA and Pittsburgh, Pennsylvania, USA, aged 70–79 years at recruitment in 1997 [26]. To identify potential participants, a random sample of European ancestry and African American Medicare-eligible elders, within designated zip code areas, were contacted. To be eligible, participants had to report no difficulty with activities of daily living, walking a quarter of a mile, or climbing ten steps without resting. They also had to be free of life-threatening cancer diagnoses and have no plans to move out of the study area for at least three years. The sample was approximately balanced for sex (51% women) and 42% of participants were African American. Participants self-designated race/ethnicity from a fixed set of options (Asian/Pacific Islander, black/African American, white/Caucasian, Latino/Hispanic, do not know, other). The study was designed to have sufficient numbers of African Americans to allow separate estimates of the relationship of body composition to functional decline. All eligible participants signed a written informed consent, approved by the IRBs at the clinical sites. This study was approved by the IRBs of the clinical sites and the coordinating center (University of California, San Francisco).

The baseline clinic visit included a drug inventory to assess pharmacological treatment, evaluation of body composition using dual energy x-ray absorptiometry (DEXA), BP measurements, electrocardiogram, physical performance tests, and strength measures. BP was calculated as the average of two seated measurements.

The Hypertension Genetic Epidemiology Network (HyperGEN): HyperGEN is a multicenter family-based study to research the genetic causes of hypertension and related conditions [27]. 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.

Loyola-Maywood 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 [28]. 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[28; 29]. 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 [29]. Three measurements were taken three minutes apart and the average of the final two was used in the analysis. Individuals with SBP ≥140 mmHg, DBP ≥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.

Loyola-Nigeria study: The sampling frame for the Nigeria cohort was also provided by the (International Collaborative Study on Hypertension in Blacks) ICSHIB. 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 [30]. 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. 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. Protocols for BP measurement are described under the Loyola-Maywood study.

Mount Sinai IPM Biobank Program: The Charles Bronfman Institute for Personalized Medicine (IPM) Biobank Program is a consented, Electronic Medical Record (EMR)-linked medical care setting biorepository of the Mount Sinai Medical Center (MSMC), drawing from a population of over 70,000 inpatients and 800,000 outpatient visits annually. The study design is described in detail elsewhere [31]. MSMC serves the diverse local communities of upper Manhattan, including Central Harlem (86% African American), East Harlem (88% Hispanic Latino), and Upper East Side (88% Americans of European ancestry) with broad health disparities. IPM Biobank populations include 28% African American, 38% Hispanic Latino predominantly of Caribbean origin, 23% of European ancestry. IPM Biobank disease burden is reflective of health disparities with broad public health impact. Since 2007, over 21,000 Mount Sinai patients have enrolled in the IPM Biobank program. Biobank operations are fully integrated in clinical care processes, including direct recruitment from clinical sites waiting areas and phlebotomy stations by dedicated Biobank 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

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.

SIGNET/ Reasons for Geographic and Racial Differences in Stroke (REGARDS): The Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study is a national, population-based, longitudinal study of ~30,000 adult individuals of African American or European descent. Participants were randomly sampled with recruitment by mail then telephone. Individuals aged 45 years old and older were eligible for inclusion in the REGARDS cohort, for which enrollment began in February 2003. Exclusion criteria for REGARDS participation included active treatment for cancer; any serious medical condition which would prevent long-term participation; cognitive impairment as judged by the interviewer; living in a nursing home or on the waiting list for a nursing home; and a language barrier (speaks other than English). Samples from 2,398 SIGNET individuals with measures of BP and with GWAS data respectively were available for this study.

SBP and DBP were defined as the average of two measurements taken by a trained technician using a standard protocol and regularly tested aneroid sphygmomanometer (American Diagnostic Corporation, Hauppauge, NY), measured after the participant was seated for 5 minutes [32]. Briefly, BPs measurements were taken in the left arm (when possible) and a large size cuff was used if the arm circumference was greater than 13 inches. Both the cuff bladder width and pulse obliteration level were recorded. The cuff was inflated to 20 mmHg above the pulse obliteration level and slowly deflated (~ 2 mmHg/second) to obtain the BPs. This process was repeated to obtain the second BP on the same arm.

Women's Health Initiative SNP Health Association Resource (WHI-SHARe): Women's Health Initiative (WHI) is a long-term national health study that focuses on strategies for preventing common diseases such as heart disease, cancer and fracture in postmenopausal women. A total of 161,838 women aged 50–79 years old were recruited from 40 clinical centers in the US between 1993 and 1998. WHI consists of an observational study, two clinical trials of postmenopausal hormone therapy (estrogen alone or estrogen plus progestin), a calcium and vitamin D supplement trial, and a dietary modification trial [33]. Study recruitment and exclusion criteria have been described previously [33]. Study protocols and consent forms were approved by the IRB at all participating institutions. Medical history was updated annually (for women in the observational study) or semiannually (for women in the clinical trials) by mail and/or telephone questionnaires.

BP was measured by certified staff using standardized procedures and instruments [34]. 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. 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. Demographic data, medical history and anthropometric measures were obtained at a baseline clinical visit.

The Howard University Family Study (HUFS): is a population-based family study of African Americans in the Washington DC metropolitan area [35]. 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 1,016 individuals were included in this analysis.

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.

Replication African ancestry studies

Ghana study:

Participants, of homogeneous Gahanna ancestry were enrolled into the Ghana study between May 2002 and October 2003 through community recruitment in Sunyani, Ghana. Exclusion criteria were age less than 18, prior enrollment of a first or second degree relative, and any acute illness such as malaria that might affect levels of tissue-type plasminogen activator (t-PA) or plasminogen activator inhibitor-1 (PAI-1). Participants were examined at the Regional Hospital, Sunyani after a 10-hour fast. All participants provided written informed consent or fingerprint consent, and all forms were approved by the IRBs at Vanderbilt University and Regional Hospital, Sunyani. All participants provided medical history and standard demographic data including age, sex, education, smoking status, alcohol consumption, current medications, cardiovascular disease, diabetes, and cancers. Height, weight and BP were measured. Three tubes of blood were taken from each participant, stored in liquid nitrogen, and shipped to VU. Genotyping for this project was conducted using the Sequenom genotyping system at the Vanderbilt DNA Resources Core. A total of seven candidate SNPs were genotyped and analyzed according to the analytic protocol for the discovery GWAS analysis, with the exception that principal components summarizing ancestry were not adjusted for due to the fact that these participants are not admixed. Concordance rates among candidate SNP genotypes for duplicate QC samples from the HapMap were all 100%.

BPs measurements were measured using an Omron HEM-705c instrument (Omron Healthcare Corp., Bannockburn, Ill., USA). Participants were seated in a quiet room and two measures of BP were taken from the left arm. The average of the two measures was used in the analysis. All BP measures were taken prior to blood draws.

Family Blood Pressure Program-AXIOM. These 872 African-American subjects were included from the **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 include 808,558 SNPs. SNPs were called using Affymetrix Genotyping Console (GTC) by analyzing CEL files from Affymetrix AXIOM arrays

(www.affymetrix.com). Samples with Dish QC(DQC)<=0.82 were excluded. Samples with call Rate <=0.97 were also dropped. Imputation was performed using MaCH 1.0.17 with parameter "--round 50 –greedy". Reference haplotypes were downloaded from (http://www.sph.umich.edu/csg/abecasis/MACH/download/HapMap-r21.html, with ratio of CEU and YRI 1:1). All the replication SNPs have Rsq>0.76.

The Health and Retirement Study (HRS): 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 a 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, adjusted for anti-hypertensive medication use (+10 mmHg for SBP, +5 mmHg for DBP) were used as the final quantitative outcome variables. Hypertension was defined as having a mean SBP ≥140 mmHg, a mean DBP≥90 mmHg, or self-reported hypertension medication use. Mean SBP was 143.96 mmHg, mean DBP was 85.53 mmHg, and 1073 (80.25%) participants had hypertension. 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.

Mt Sinai IPM Biobank Program: The Institute for Personalized Medicine (IPM) Biobank Program is a consented, Electronic Medical Record (EMR)-linked medical care setting biorepository of the Mount Sinai Medical Center (MSMC), drawing from a population of over 70,000 inpatients and 800,000 outpatient visits annually. MSMC serves the diverse local communities of upper Manhattan, including Central Harlem (86% African American), East Harlem (88% Hispanic Latino), and Upper East Side (88% Caucasian/white) with broad health disparities. IPM Biobank populations include 28% African American, 38% Hispanic Latino predominantly of Caribbean origin, 23% Caucasian/White. IPM Biobank disease burden is reflective of health disparities with broad public health impact. Since 2007, over 23,000 Mount Sinai patients have enrolled in the IPM Biobank program. Biobank operations are fully integrated in clinical care processes, including direct recruitment from clinical sites waiting areas and phlebotomy stations by dedicated Biobank 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. For the discovery analysis, participants genotyped on Affymerix 6.0 in 2010 were included. For the replication analysis, participants genotyped on Illumina OmniExpress in 2012 were included. Information on anthropometrics, demographics, blood pressure and use of antihypertensive medication was derived from participants EMR. The Mount Sinai Biobank Project (IRB # 07-0529 0001 02 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.

The Seychelles TANDEM study: The TANDEM study is a family-based study conducted in the Republic of Seychelles between 1999 and 2002. The Seychelles islands are located in the Indian Ocean, approximately 2000 km east to Kenya; the majority of the population is of African descent. The study was approved by the ethical committee in Seychelles and at the University of Lausanne, Switzerland and participants provided written informed consent, including for genetic analyses. Methods and main findings have been published in a number of publications. Families were selected from a national hypertension register if the family was from predominantly African descent and one could identify ≥2 full siblings with hypertension (≥140/90 mm Hg, average of 3 office measures or on current antihypertensive treatment) and ≥2 other first-degree relatives (full siblings or parents) with or without hypertension [36; 37]. Seventy-six of the 135 screened families were found to be eligible. Only persons aged 18 years or older have been included. Three BP measurements were taken at the study center in the morning between 7:00 and 10:30 AM, for participants who had been sitting quietly for at least 10 minutes, by trained health professionals, using a standard mercury sphygmomanometer with a triple-bladder cuff (Tricuff) that automatically adjusts bladder width to arm circumference.

The Seychelles Heart Study III (2004): The Seychelles Heart Study III is a population-based survey conducted in 2004 under the auspices of the Ministry of Health of the Republic of Seychelles. The Seychelles islands are located in the Indian Ocean, approximately 2000 km east to Kenya; the majority of the population is of African descent. The survey was approved by the Ministry of Health after technical and ethical reviews. Participants were free to participate and gave written informed consent. Survey methods have been described elsewhere [38]and findings published in over 20 publications. The sampling frame consisted of a sex and age stratified random sample of the entire population aged 25-64 years, using computerized data of a national population census in 2002 thereafter updated by civil status authorities. The survey was attended by 1255 individuals, corresponding to a participation rate of 81% [39]. BP was measured 3 times, at a survey center, in the morning, at intervals of more than 2 minutes, after a participant had been seated for at least 15 minutes, by trained nurses, using a mercury sphygmomanometer and a cuff that automatically adapts width to the arm circumference (Tricuff). BP was based on the average of the last two of three readings.

Genotyping for both **TANDEM** and **Heart Study III** samples from the Seychelles was performed on an Illumina iSelect platform (CardioMetaboChip - http://www.sph.umich.edu/csg/kang/MetaboChip) according to standard protocols. Data was cleaned using completeness parameters per individual and per SNP, principal components calculated in the presence of HapMap genotypes, sex mismatch, cryptic family relationships, Mendelian error, and similar parameters as appropriate.

Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER). The study population was derived from JUPITER, an international, randomized, placebo-controlled trial of rosuvastatin (20mg/day) in the primary prevention of cardiovascular disease conducted among apparently healthy men 50 year or older and women 60 years or older with LDL-C < 130 mg/dL and hsCRP > 2 mg/L [40]. Blood pressure measures were made by a

healthcare professional at baseline. Approximately 70% of JUPITER participants provided blood for DNA extraction at baseline and consent for genetic analysis, among whom approximate 13.7% were self-reported blacks from South Africa. A single BP measure was obtained at time of enrollment.

Genotyping was performed using the Omni 1M Quad platform (Illumina, San Diego). Briefly, raw genotype intensity data were reduced to genotype calls using the Illumina Genome Studio (v. 1.6.2) software (Illumina, San Diego)[41]. SNP clusters were initially defined automatically using data from the JUPITER sample. SNPs with poor automatically defined clusters, ~1%, were visually inspected, and annotated, removed, or clustered again with manual intervention. After these procedures, 99.71% of the loci yielded successful genotype information. All samples had successful genotyping for >98.5% of the final SNPs. Identity-by-state clustering in PLINK [42] applied to 1,435 JUPITER ancestry informative SNPs confirmed of a cluster of JUPITER participants who were strongly correlated with self-reported South African ancestry. In total, over 97.4% or 1,688 of the South African black JUPITER participants with consent for genetic analysis remained after successful genotyping and exclusions requiring that no pair of individuals was related more closely than second degree using identity-by-descent clustering procedures in PLINK. EIGENSTRAT [43] was applied on the South African black population to compute covariates for population sub-structure to adjust for potential confounding in association analysis. Analyses followed the standard protocol and included adjustments for age, sex, BMI and markers for population stratification

Multi-ethnic samples

ICBP European samples

Summary *P*-values results for ICBP European ancestry were obtained from www.igm.jhmi.edu/~gehret/icbp32413ahsfd134/icbp_088023401234-9812599.html.

East Asian samples: AGEN

The Asian Genetic Epidemiology Network (AGEN) is a consortium of genetic epidemiology studies of cardiovascular disease related phenotypes, including BP, diabetes, and obesity, conducted among Asian populations. AGEN-BP consists of 19,608 East Asian participants who underwent standardized collection of BP measurements in eight population-and family-based GWAS, including: the Cardio-metabolic Genome Epidemiology (CAGE) Network, Genetic Epidemiology Network of Salt-Sensitivity (GenSalt), Korean Association Resource (KARE) Project, Shanghai Hypertension Study, Singapore Malay Eye Survey (SiMES), Singapore Prospective Study (SP2) Program, Suita Study, and Taiwan Super Control Study. Each study established a consensus on phenotype harmonization and analytical plan for within-study GWAS and meta-analysis of results across studies. Each study received an approval from the IRB and all participants in each study provided written informed consent for participation in the study. Our study utilized results from selected SNPs from Stage 1, which was a meta-analysis of directly genotyped and imputed SNPs from individuals of East Asian descent, drawn from the population-based or control samples in case-control studies in AGEN-BP, described above. The

BP measures and quality control (QC) criteria for genetic data have been previously described by He *et al.* [44]. All BP measures were taken at least two times, and the average of measures was used for analysis.

Briefly, studies each performed genotyping QC separately, and removed participants that had missing data between 2% and 10%, SNPs with missing data between 5% and 2%, HWE *P*-values between 1×10^{-4} and 1×10^{-6}, and SSNP with MAF ≤ 1%. Ungenotyped SNPs were imputed to phased haplotypes from the International HapMap Consortium CHB (Chinese from Beijing) and JPT (Japanese from Tokyo) reference data using MACH, IMPUTE, or BEAGLE. Association between SNPs and measured quantitative BP traits was assessed with linear regression with adjustment for age, age^2, sex, BMI, and any study-specific covariates within each study. All within-study genomic control lambdas (λ) for tests of association with BP outcomes were between 1 and 1.05. Evidence across studies for associations between SNPs and BP was evaluated by inverse-variance weighted fixed-effects meta-analysis using METAL.

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Bogalusa Heart Study (BHS): NJS is supported in part by NIH/NCRR Grant Number UL1 RR025774. The BHS was supported by grants HD-061437 and HD-062783 from the National Institute of Child Health and Human Development, and AG-16592 from the National Institute on Aging**.**

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Atherosclerotic Risk in Communities (ARIC): University of North Carolina at Chapel Hill (N01-HC-55015), Baylor Medical College (N01-HC-55016), University of Mississippi Medical Center (N01-HC-55021), University of Minnesota (N01-HC-55019), Johns Hopkins University (N01-HC-55020), University of Texas, Houston (N01-HC-55017), University of North Carolina, Forsyth County (N01-HC-55018);

Cardiovascular Health Study (CHS): University of Washington (N01-HC-85079), Wake Forest University (N01-HC-85080), Johns Hopkins University (N01-HC-85081), University of Pittsburgh (N01-HC-85082), University of California, Davis (N01-HC-85083), University of California, Irvine (N01-HC-85084), New England Medical Center (N01-HC-85085), University of Vermont (N01-HC-85086), Georgetown University (N01-HC-35129), Johns Hopkins University (N01 HC-15103), University of Wisconsin (N01-HC-75150), Geisinger Clinic (N01-HC-45133), University of Washington (N01 HC-55222, U01 HL080295); **Cleveland Family Study (CFS)**: Case Western Reserve University (RO1 HL46380-01-16);

Coronary Artery Risk in Young Adults (CARDIA): University of Alabama at Birmingham (N01-HC-48047), University of Minnesota (N01-HC-48048), Northwestern University (N01-HC-48049), Kaiser Foundation Research Institute (N01-HC-48050), University of Alabama at Birmingham (N01-HC-95095), Tufts-New England Medical Center (N01-HC-45204), Wake Forest University (N01-HC-45205), Harbor-UCLA Research and Education Institute (N01-HC-05187), University of California, Irvine (N01-HC-45134, N01-HC-95100);

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Loyola-Nigeria: The Loyola-Nigeria study was supported by NIH grant numbers R01-HL053353. The authors acknowledge the assistance of the research staff and participants in Ibadan and Igbo-Ora, Oyo State, Nigeria.

Loyola-Maywood: Maywood African-American study is supported by the National Institutes of Health grant number HL074166 from National Heart, Lung, Blood Institute.

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JUPITER: Genetic analysis in the JUPITER study was funded by AstraZeneca.

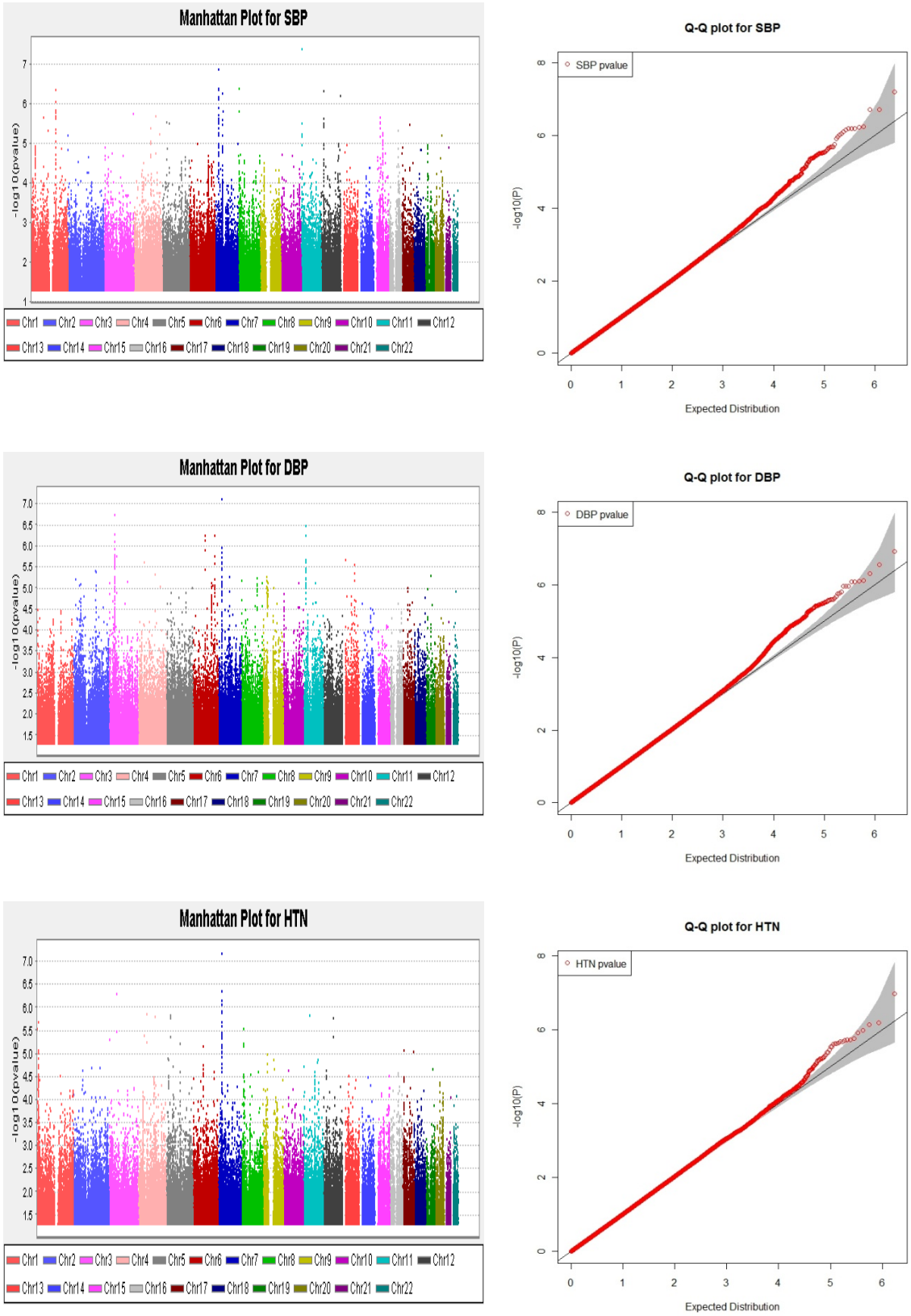

Figure S1. Genome-wide association Manhattan plots and Q-Q plots of SBP, DBP and HTN in the Continental Origins and Genetic Epidemiology Network (COGENT). GWAS Manhattan and Q-Q plots are illustrated for SBP, DBP and hypertension (HTN) in COGENT.

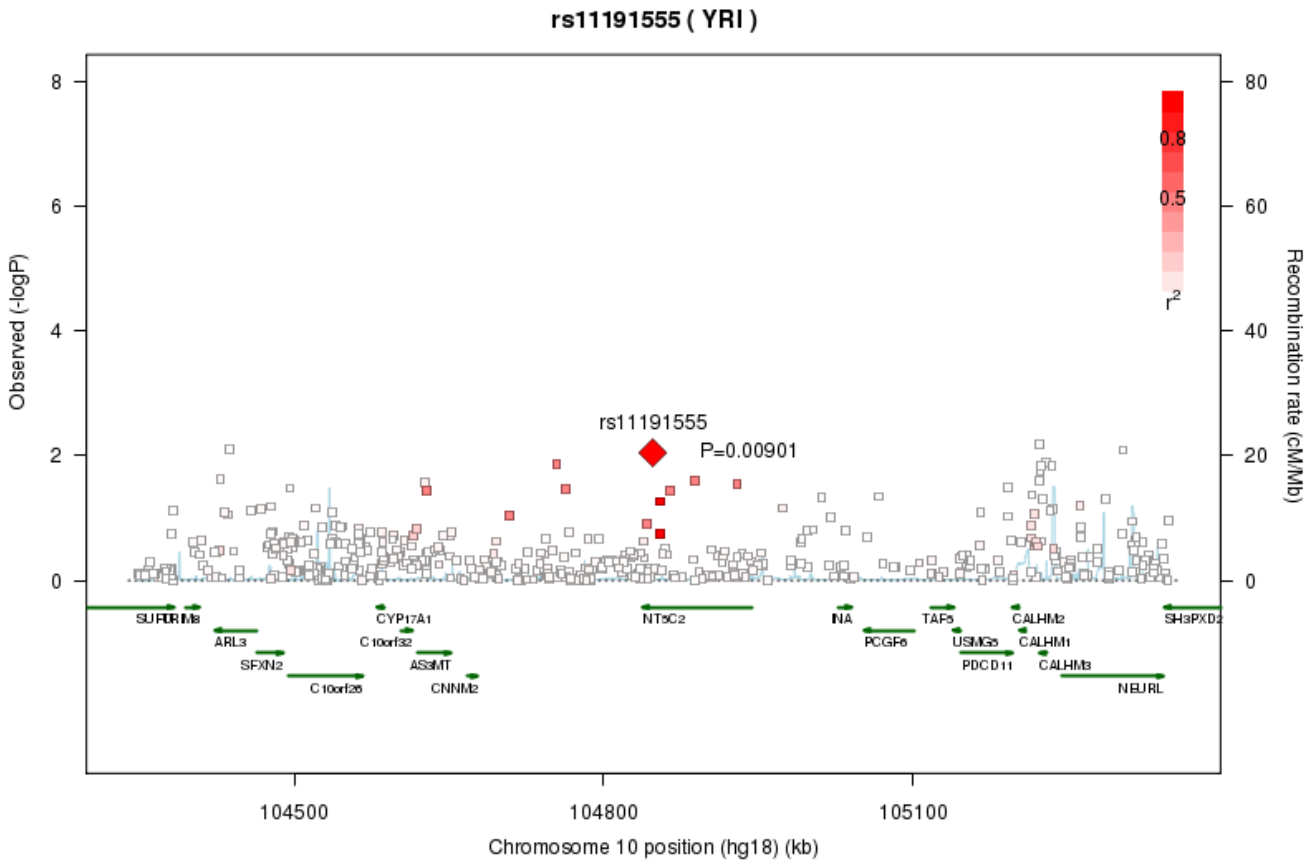

Figure S2. Regional plot of –log10(*P*-value) of *NT5C2* and SBP. The LD is based on YRI 1000G data. rs11191555 is the most significant SNP in this locus in COGENT AA data.

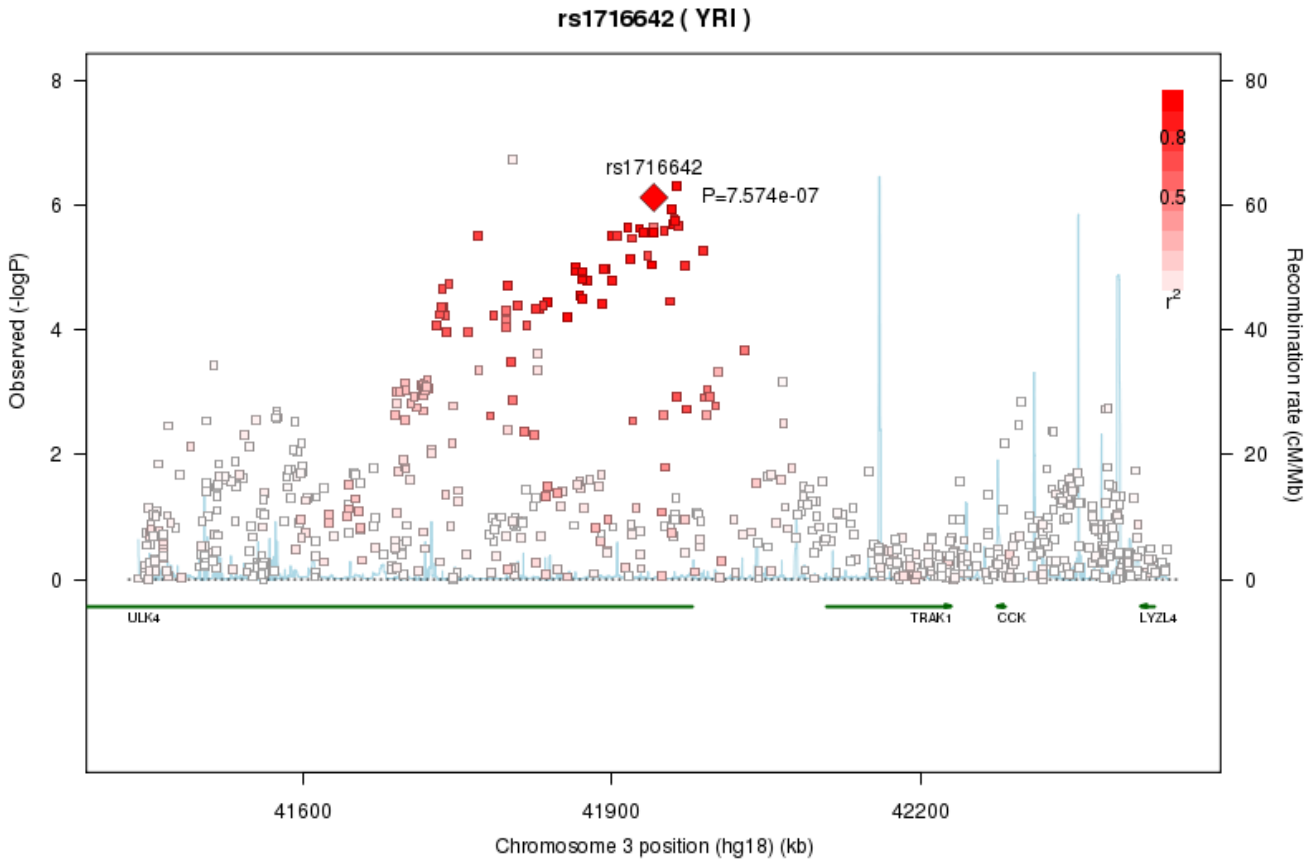

Figure S3. Regional plot of –log10(*P*-value) of *ULK4* and DBP. The LD is based on YRI 1000G data. rs1716642 is the most significant SNP in this locus in COGENT AA data.

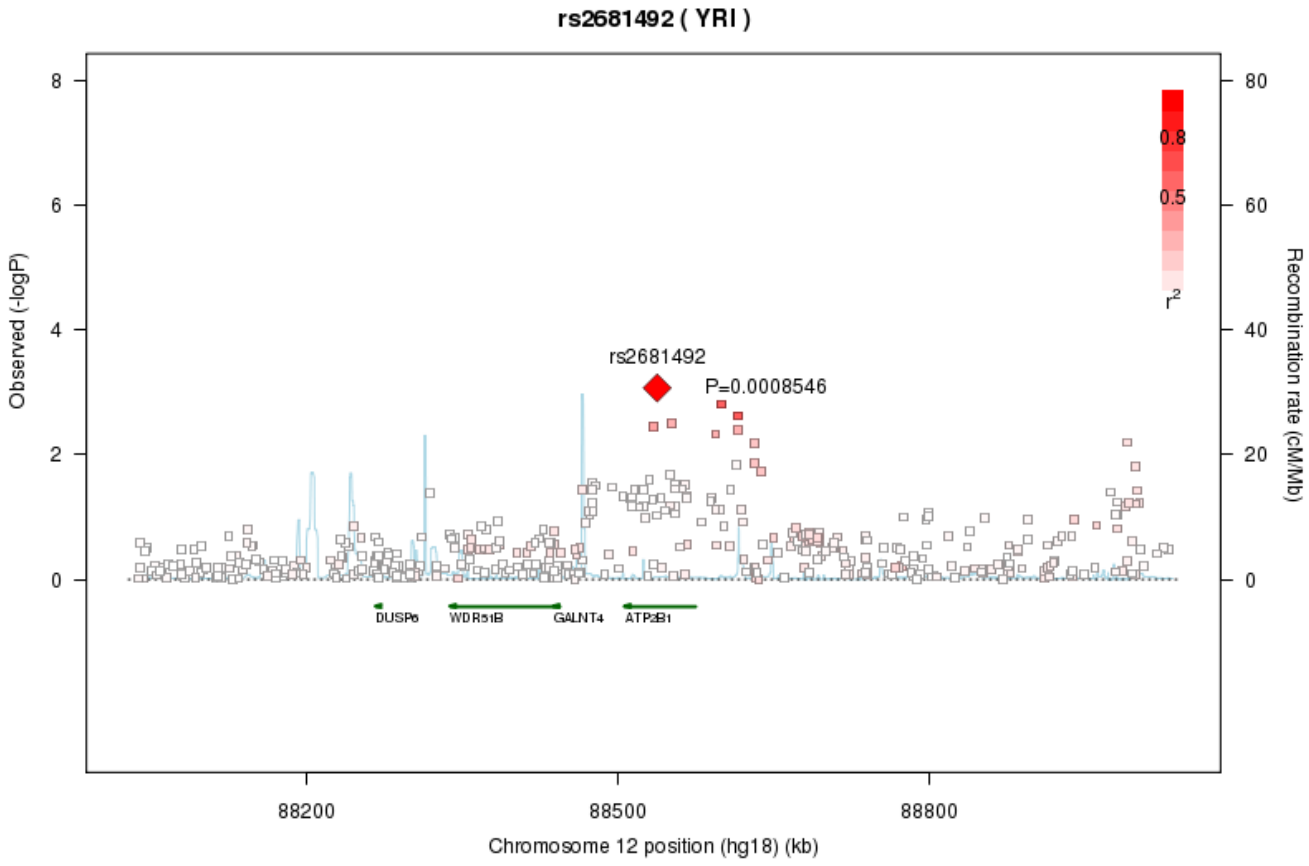

Figure S4. Regional plot of –log10(*P*-value) of *ATP2B1* and HTN. The LD is based on YRI 1000G data. rs2681492 is the most significant SNP in this locus in COGENT AA data.

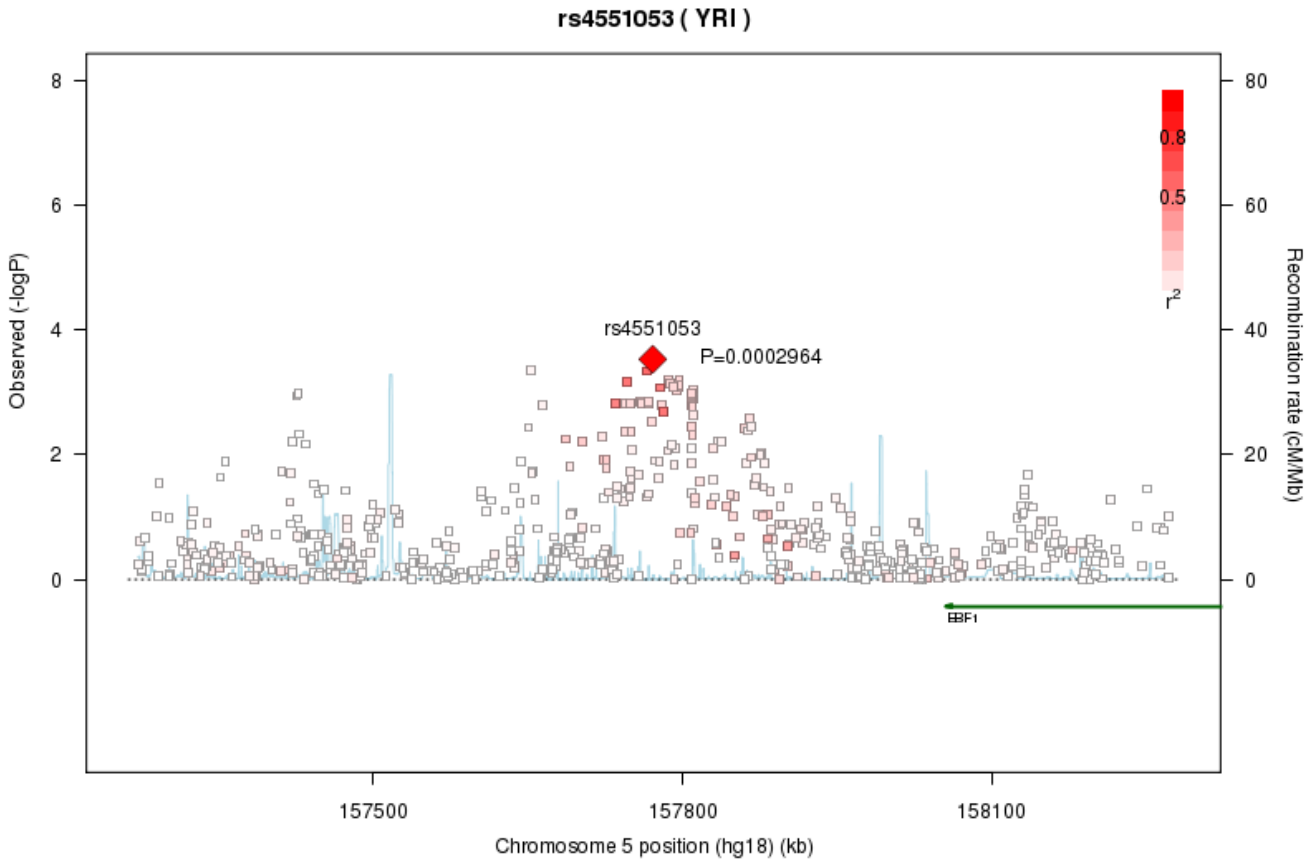

Figure S5. Regional plot of –log10(*P*-value) of *EBF1* and HTN. The LD is based on YRI 1000G data. rs4551053 is the most significant SNP in this locus in COGENT AA data.

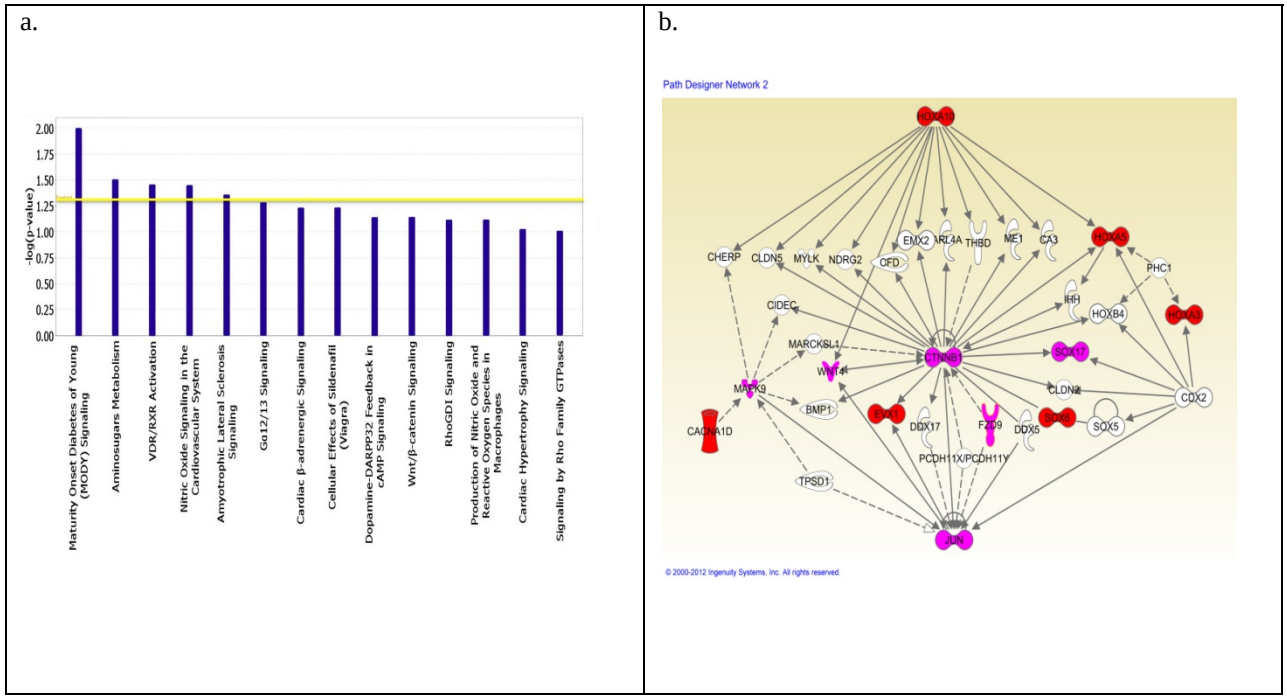

Figure S6. A. Canonical pathways and associated *p* -values identified by ingenuity pathway analysis (IPA). The yellow horizontal line is the threshold for *P* =0.05 with the names of the imputed genes shaded in red. B. Network constructed using the identified genes in GWAS by IPA. *CTNNB1* has the most connections in the network. Multiple genes including *SOX6*, *EVX1*, *HOXA* family genes and *CACNA1D* are present in this network.

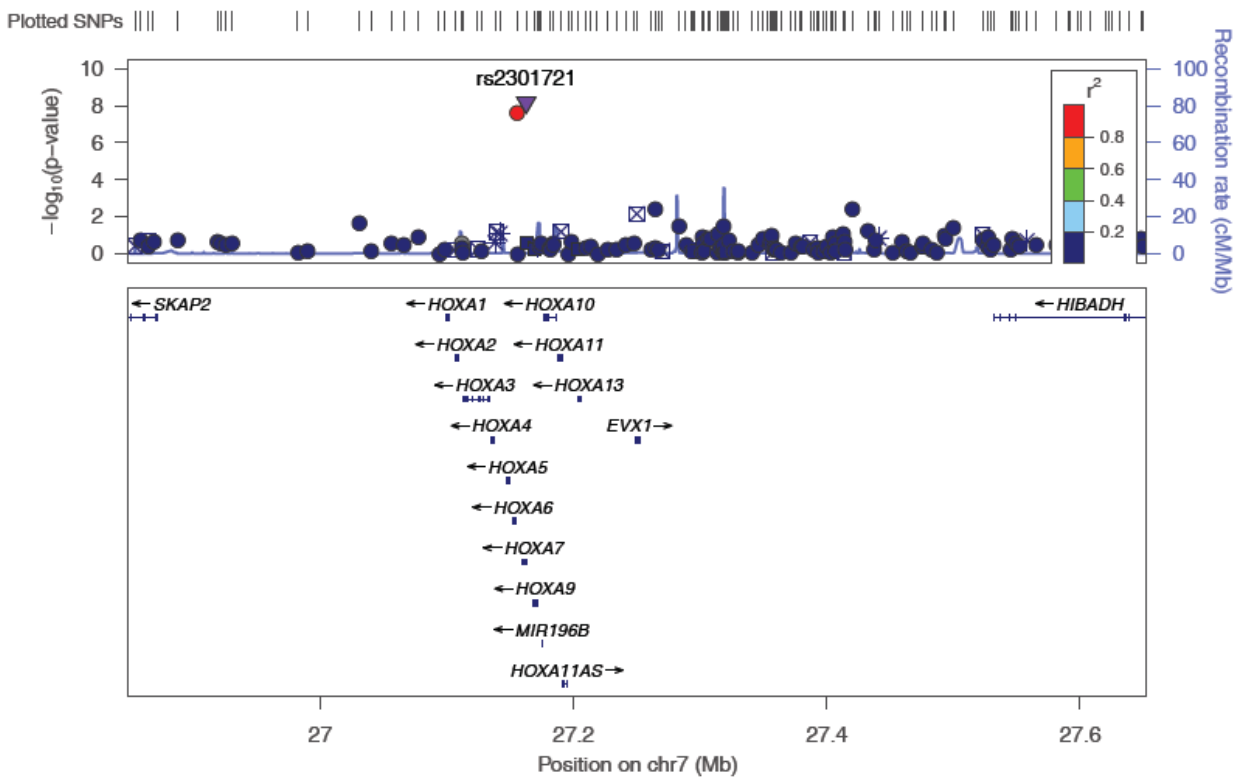

Figure S7. Regional plot of –log(*P*-values) from Treeselect analysis along the LWK branch of an unrooted tree with LWK, YRI and AA samples.

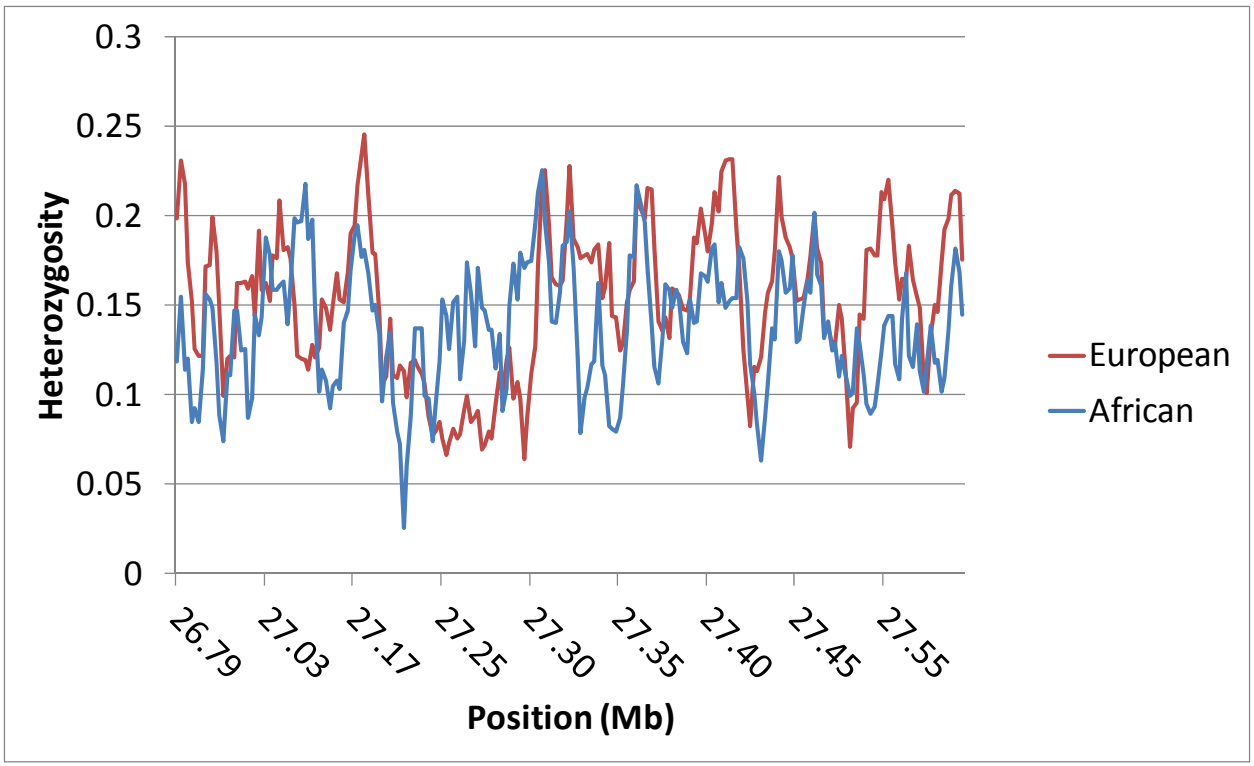

Figure S8. Regional heterozygosity in European and African Human Genome Diversity Project (HGDP) participants, with a decrease in heterozygosity in Europeans at the *HOX* gene cluster on chromosome 7 from 27.18 to 27.3 Mb.

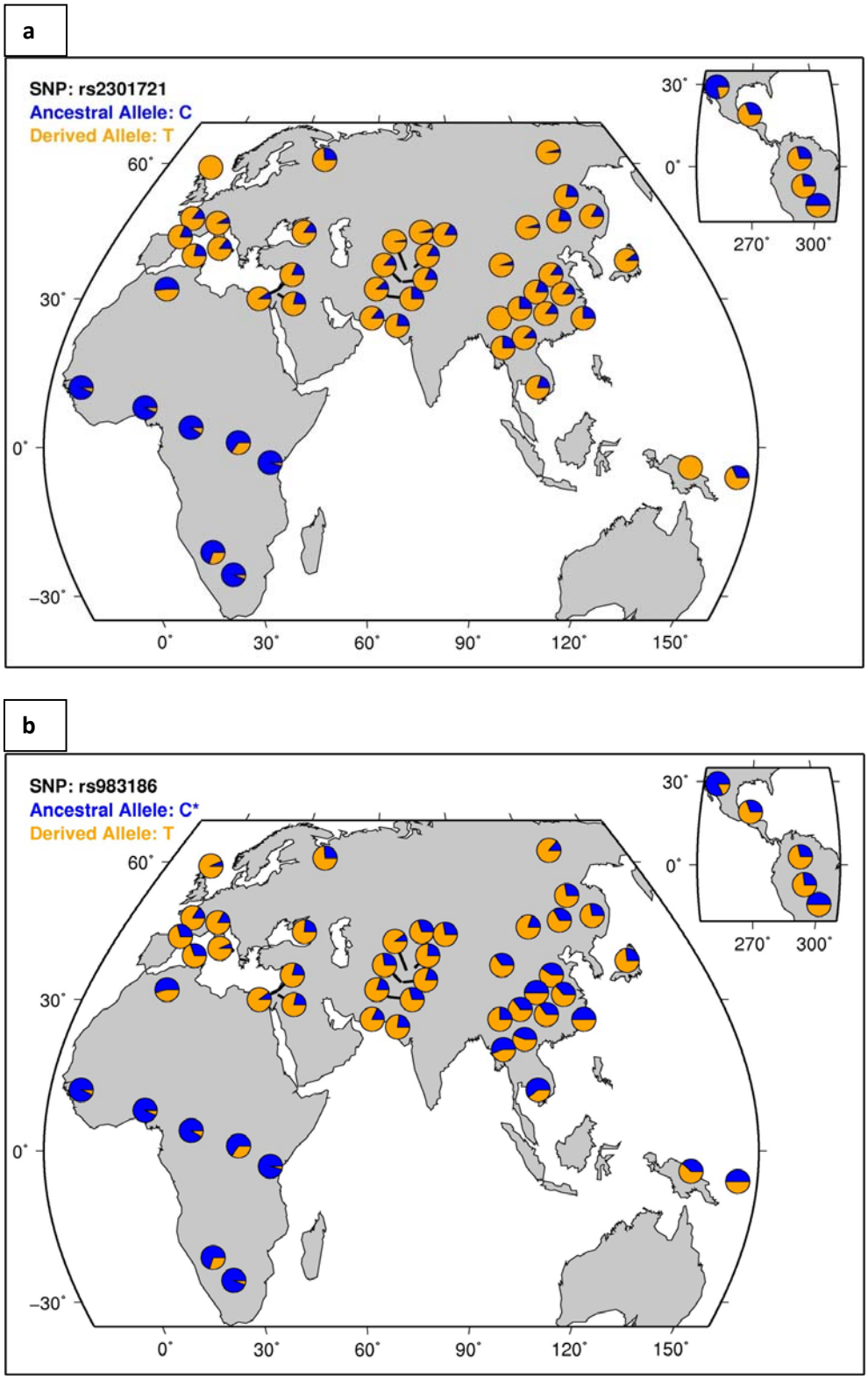

Figure S9.

(A) Map of allele frequencies from the Human Genome Diversity Project (HGDP) for the non-synonymous SNP rs2301721 in *HOXA7;*

(B) Map of allele frequencies from the HGDP for rs983186 near *EVX1.*

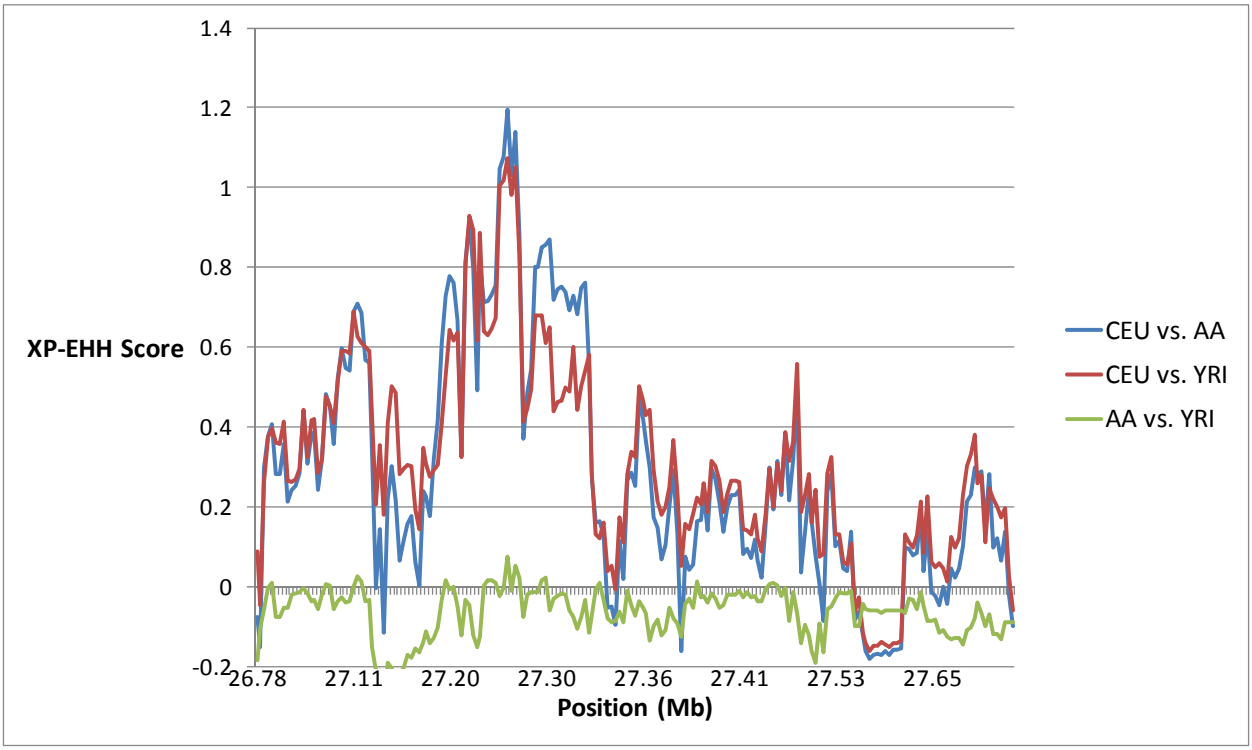

Figure S10. XP-EHH Scores for the *EVX1*/*HOXA* region for HapMap and African Ancestry samples. Signatures of recent positive selection across the *EVX1*/*HOXA* region in HapMap Phase III Yoruba (YRI) and European CEPH (CEU), and BioVU African Americans (AA) using the cross-population extended haplotype homozygosity statistic (XP-EHH).

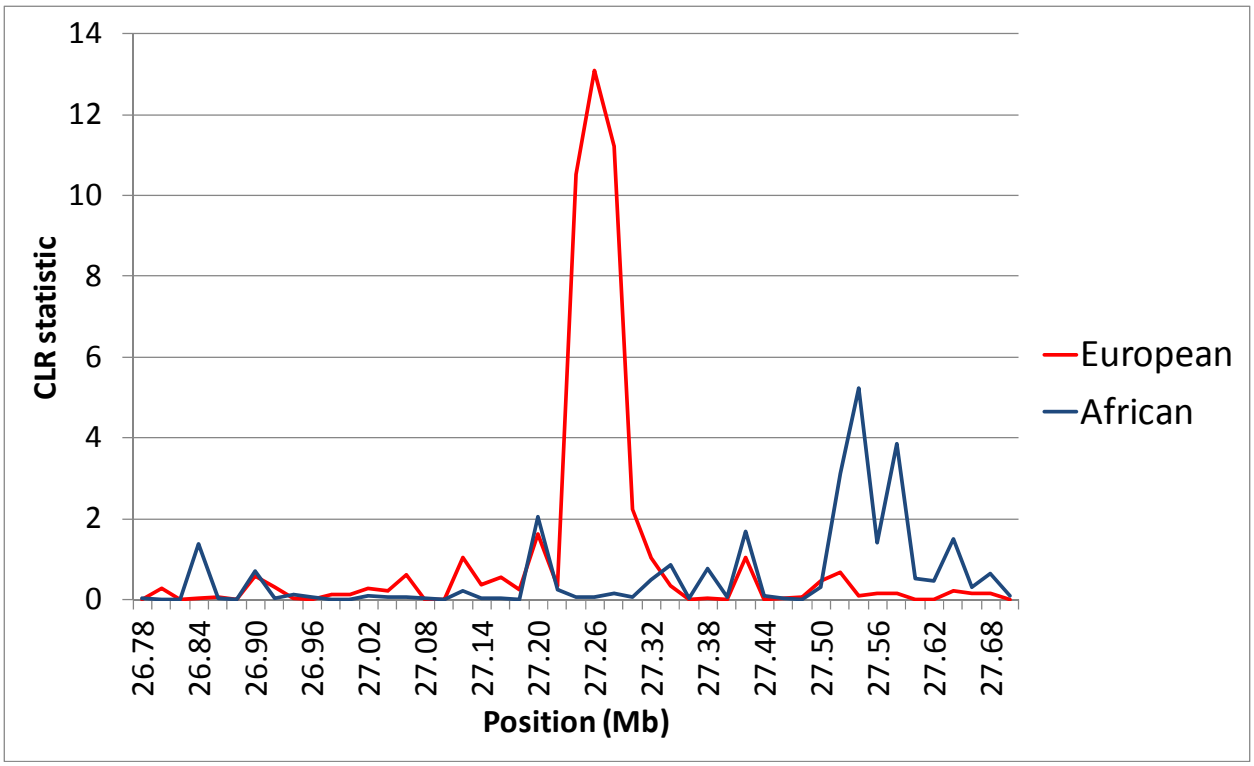

Figure S11. CLR statistics for Human Genome Diversity Project (HGDP) participants from Europe and Bantu-speaking Africans in the *HOXA*/*EVX1* region.

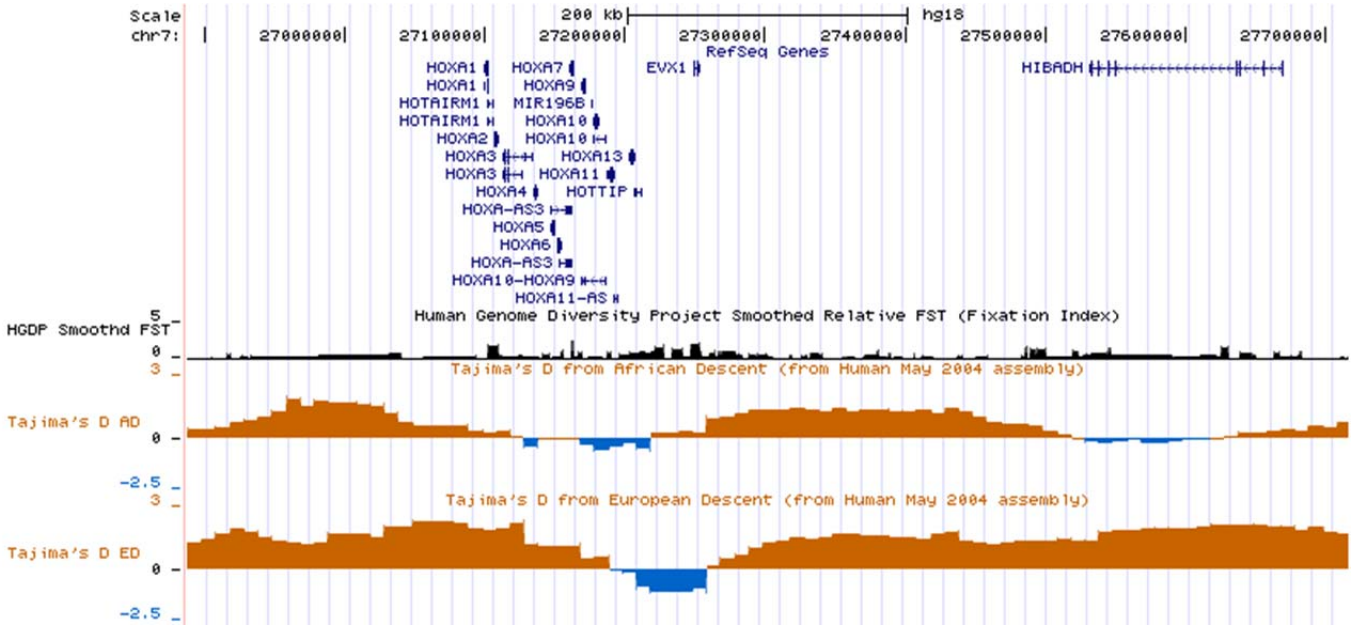

Figure S12. Calculations of Tajima's D from HapMap European (CEU) and African (YRI) participants, with negative values near the *HOX* gene cluster supporting recent positive selection at this locus.

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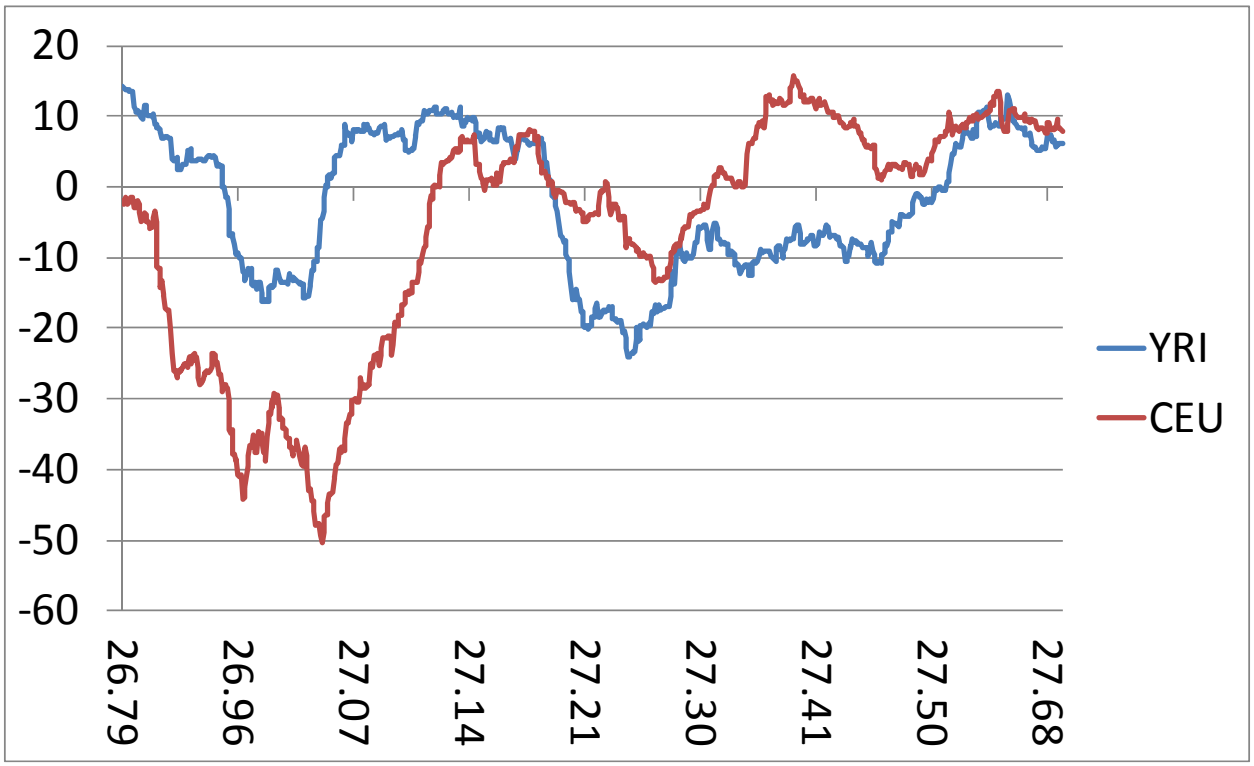

Figure S13. Calculation of Fay and Wu's H from European (CEU) and African HapMap (YRI) participants, with negative values nearby the *HOX* gene cluster.

Table S1. Genome-wide Genotyping and Imputation Information by Study

Study	Genotyping Platform	Genotyping calling algorithm	Genotype filter	Imputation	Imputation HapMap reference	Imputation NCBI version
BioVu	Illumina Human 1M-DuoV3 array	Illumina BeadStudio	No palindromic SNPs, Call rate < 95%, MAF < 0.01, HWE p < 0.0000001,	IMPUTE v2.1.2	YRI/CEU 1:1 ratio	b36
ARIC†	Affymetrix GeneChip SNP Array 6.0	BirdSeed	Call rates<95%, mapped to more than one locus	MACH	YRI/CEU 1:1 ratio	b36
CARDIA†	Affymetrix GeneChip SNP Array 6.0	BirdSeed	Call rates<90%, mapped to more than one locus	MACH	YRI/CEU 1:1 ratio	b36
CFS†	Affymetrix GeneChip SNP Array 6.0	BirdSeed	Call rates<90%, mapped to more than one locus, Mendelian inconsistence	MACH	YRI/CEU 1:1 ratio	b36
JHS†	Affymetrix GeneChip SNP Array 6.0	BirdSeed	Call rates<90%, mapped to more than one locus	MACH	YRI/CEU 1:1 ratio	b36
MESA†	Affymetrix GeneChip SNP Array 6.0	BirdSeed	Call rates<90%, mapped to more than one locus	MACH	YRI/CEU 1:1 ratio	b36
CHS	Illumina HumanOmni1-Quad_v1 BeadChip system	Illumina GenomeStudio software	Call rate < 97%, HWE P < 10-5, > 1 duplicate error or Mendelian inconsistency (for reference CEPH trios), heterozygote frequency = 0	BEAGLE v3.2.1	Imputation in 2 phases: HapMap III from ASW, YRI & CEU & HapMap II using CEU & YRI, & resulting 3 sets merged (final imputed data: 2,770,583 SNPs).	b36
GeneSTAR	Illumina Human 1Mv1_c Array	BeadStudio	Call rates <90%	MACH	YRI/CEU 1:1 ratio	HapMap2_r21_b36
GENOA	Affymetrix GeneChip SNP Array 6.0 & Illumina 1M array	BirdSeed and Beadstudio	Call rates < 95%	MACH	YRI/CEU 1:1 ratio	HapMap2_r22_b36
HANDLS	1M Illumina	Illumina GenomeStudio	Call rates<95%, mapped to more than one locus	MACH	YRI/CEU 1:1 ratio	HapMap2_r22_b36
HealthABC	Genotyping Platform 1M Illumina	Illumina GenomeStudio	Call rates < 97%	MACH	YRI/CEU 1:1 ratio	HapMap2_r22_b37
HyperGEN	Affymetrix GeneChip SNP Array 6.0	BirdSeed	Call rates < 95%	MACH	YRI/CEU 1:1 ratio	HapMap2_r22_b36
Maywood-Loyola	Affymetrix GeneChip SNP Array 6.0	BirdSeed	Call rates < 95%	MACH	YRI/CEU 1:1 ratio	HapMap2_r22_b36
Maywood-Nigeria	Affymetrix GeneChip SNP Array 6.0	BirdSeed	Call rates < 95%	MACH	YRI	HapMap2_r22_b36
Mt Sinai study	Affymetrix GeneChip SNP Array 6.0	BirdSeed	Call rates < 95%	MACH	CEU/YRI/JPT/CHB	HapMap2_r22_b36
WHI-SHARe	Affymetrix GeneChip SNP Array 6.0	Birdseed v2	Call rates < 95%	MACH	YRI/CEU 1:1 ratio	HapMap2_r22_b37

HUFS	Affymetrix GeneChip SNP Array 6.0	BirdSeed v2			Combined HapMap phase II+III YRI/CEU, 2 rounds of imputation, YRI then CEU, followed by merge	HapMap2+3_r28__b36
Bogalusa	Illumina Human 610 + Illumina CVD BeadChip	Illumina BeadStudio	Call rates < 95%, MAF<0.01, HWE ≥1.0×10-3	MACH		
			Call rates <90%	MACH	YRI/CEU 1:1 ratio	HapMap2_r22_b36
SIGNET	Affymetrix GeneChip SNP Array 6.0	BirdSeed v1.33	Call rates < 95%	MACH	YRI/CEU 1:1 ratio	HapMap2_r22_b36

† Members of the NHLBI Candidate gene Association Resource (CARe).

Genome-wide genotyping and imputation information by study within the Continental Origins and Genetic Epidemiology Network (COGENT). Abbreviations: Biological bank of Vanderbilt University (BioVU); Atherosclerosis Risk In Communities (ARIC); Coronary Artery Risk Development in Young Adults (CARDIA); Cleveland Family Study (CFS); Jackson Heart Study (JHS); Multi-Ethnic Study of Atherosclerosis (MESA); Cardiovascular Health Study (CHS); Genetic Study of Atherosclerosis Risk (GeneSTAR); Genetic Epidemiology Network of Arteriopathy (GENOA); The Healthy Aging in Neighborhoods of Diversity Across the Life Span Study (HANDLS); Health, Aging, and Body Composition (Health ABC) Study; The Hypertension Genetic Epidemiology Network (HyperGEN); Mount Sinai, New York City, USA study (Mt Sinai Study); Women's Health Initiative SNP Health Association Resource (WHI-SHARe); Howard University Family Study (HUFS); Bogalusa Heart Study (BHS); Sea Islands Genetic NETwork (SIGNET). MAF, minor allele frequency; HWE, Hardy Weinberg Equilibrium; SNP, single nucleotide polymorphism.

Table S2. Lambda (λ)values for the COGENT discovery genome-wide association studies.

Study	Number	Lambda HTN	Lambda SBP	Lambda DBP
BioVu	941	1.011	0.993	0.978
CARe-ARIC	2,511	1.033	1.027	1.023
CARe-CARDIA	833	1.051	1.003	0.999
CARe-CFS	489	1.048	1.038	1.044
CARe-JHS	2,017	1.022	1.025	1.04
CARe-MESA	1,623	1.004	0.998	1.025
CHS	815	1.025	1.027	1.023
GeneSTAR	1,132	1.052	1.02	1.011
GENOA	996	1.102	1.012	1.007
HANDLS	950	1.013	0.992	0.988
HealthABC	1,139	1.008	0.996	0.996
HyperGEN	1,252	1.058	1.016	1.018
Maywood-Loyola	743	1.031	1.008	1.001
Mt Sinai study	873	1.032	0.966	0.966
Nigeria-Loyola	1,188	1.118	1.107	1.091
WHI-SHARe	8,094	1.020	1.011	1.011
HUFS	1,017	1.031	1.041	1.056
Bogalusa	368	1.018	1.011	1.011
SIGNET-REGARDS	2,394	0.996	1.013	1.013
total	**29,375**			

Abbreviations: Biological bank of Vanderbilt University (BioVU); Atherosclerosis Risk In Communities (ARIC); Coronary Artery Risk Development in Young Adults (CARDIA); Cleveland Family Study (CFS); Jackson Heart Study (JHS); Multi-Ethnic Study of Atherosclerosis (MESA); Cardiovascular Health Study (CHS); Genetic Study of Atherosclerosis Risk (GeneSTAR); Genetic Epidemiology Network of Arteriopathy (GENOA); The Healthy Aging in Neighborhoods of Diversity Across the Life Span Study (HANDLS); Health, Aging, and Body Composition (Health ABC) Study; The Hypertension Genetic Epidemiology Network (HyperGEN); Mount Sinai, New York City, USA study (Mt Sinai Study); Women's Health Initiative SNP Health Association Resource (WHI-SHARe); Howard University Family Study (HUFS); Bogalusa Heart Study (BHS); Sea Islands Genetic NETwork (SIGNET).

Table S3. SNPs with P<1.0 x 10-5 in COGENT for Systolic Blood Pressure, Diastolic Blood Pressure or Hypertension.

						DBP					SBP					Hypertension							HapMap YRI		HapMap CEU	
SNPID	Chr	Position (build 36)	Coded allele	Other allele	Coded allele frequency	beta	SE	*P*	Het PVal	N	beta	SE	*P*	Het PVal	N	beta	SE	*P*	Het PVal	N	Gene nearby	GeneVariant	MAF	MAF	MAF	MAF
rs2745282	1	11552817	t	g	0.22	0.36	0.11	1.69E-03	6.55E-03	29090.9	0.64	0.19	9.22E-04	6.87E-01	29091.9	0.10	0.05	4.33E-02	6.87E-01	10860.9	*N/A*	INTERGENIC	T	0.03	G	0.28
rs351361	1	112844081	t	c	0.20	-0.45	0.14	1.84E-03	4.55E-01	27940.9	-1.11	0.24	4.60E-06	8.72E-01	27941.9	-0.07	0.03	1.75E-02	5.13E-01	27454.9	*WNT2B*	INTRONIC	T	0.14	T	0.19
rs7522390	1	165615309	a	g	0.27	0.25	0.10	1.65E-02	1.55E-01	28906	0.88	0.17	4.41E-07	1.68E-01	28907	0.08	0.04	7.70E-02	2.41E-01	8765	*POU2F1*	INTRONIC	A	0.29	A	0.27
rs10925060	1	245717763	t	c	0.16	0.35	0.13	7.13E-03	5.77E-01	28940	0.49	0.22	2.26E-02	5.00E-01	28941	0.10	0.03	6.91E-04	4.31E-01	27184	*N/A*	UPSTREAM	T	0.22	T	0.04
rs13405738	2	1929865	t	c	0.85	-0.28	0.14	4.71E-02	2.57E-01	29294	-1.05	0.23	5.94E-06	7.16E-01	29295	-0.13	0.03	7.69E-05	3.29E-01	27170	*MYT1L*	INTRONIC	C	0.12	C	0.16
rs17570579	2	50955087	t	c	0.07	0.85	0.19	8.07E-06	3.79E-01	29321	1.02	0.32	1.28E-03	4.07E-01	29322	0.09	0.04	4.35E-02	6.74E-01	27564	*NRXN1*	INTRONIC	T	0.01	T	0.22
rs1534260	2	156602790	t	c	0.36	-0.44	0.10	4.02E-06	1.62E-03	29303.7	-0.49	0.16	2.32E-03	1.30E-03	29304.7	-0.08	0.04	2.72E-02	2.77E-01	11401.7	*N/A*	INTERGENIC	T	0.40	T	0.09
rs234790	3	7055901	c	g	0.18	-0.41	0.13	1.78E-03	8.64E-01	29065.9	-0.96	0.22	1.26E-05	8.71E-01	29066.9	-0.02	0.04	6.55E-01	1.11E-01	13990.9	*GRM7*	INTRONIC	C	0.07	C	0.40
rs1449292	3	29906889	a	g	0.64	0.22	0.10	2.53E-02	3.50E-02	28948	0.49	0.16	2.46E-03	3.52E-02	28949	0.04	0.03	1.88E-01	1.19E-03	16865	*RBMS3*	INTRONIC	G	0.31	A	0.44
rs6802072	3	41002684	t	c	0.45	-0.42	0.09	6.17E-06	4.26E-01	29272.8	-0.43	0.16	6.17E-03	6.68E-01	29273.8	0.00	0.04	9.81E-01	2.29E-01	11035.8	*N/A*	INTERGENIC	T	0.34	C	0.07
rs1717027	3	41962924	t	c	0.64	0.49	0.10	5.07E-07	2.51E-01	29321.9	0.18	0.16	2.64E-01	5.04E-01	29322.9	0.05	0.02	1.15E-02	4.36E-02	29462.9	*ULK4*	INTRONIC	C	0.30	T	0.22
rs10049492	3	53571572	a	g	0.74	0.58	0.12	1.78E-06	5.07E-01	27878.9	0.86	0.20	1.74E-05	9.94E-02	27879.9	0.14	0.03	4.88E-07	1.40E-01	26184.8	*CACNA1D*	INTRONIC	G	0.08	G	0.45
rs7655423	4	112132084	t	c	0.51	-0.15	0.09	1.19E-01	2.98E-01	28955	-0.69	0.16	9.94E-06	4.62E-01	28956	-0.05	0.02	1.06E-02	9.87E-01	27175	*N/A*	INTERGENIC	T	0.40	C	0.03
rs7676999	4	117153528	t	c	0.10	-0.90	0.20	4.62E-06	8.18E-01	28933.7	-1.33	0.33	5.48E-05	6.14E-01	28934.7	-0.15	0.04	9.20E-04	7.17E-01	26173.7	*N/A*	INTERGENIC	T	0.03	T	0.26
rs4383597	4	148225110	a	g	0.51	-0.30	0.09	9.89E-04	7.23E-01	28944	-0.73	0.15	2.04E-06	8.76E-01	28945	-0.03	0.04	5.19E-01	3.19E-01	8747	*N/A*	INTERGENIC	G	0.41	A	0.44
rs12374234	4	150061158	t	c	0.25	0.48	0.11	8.85E-06	2.73E-01	28938	0.55	0.18	2.33E-03	5.49E-02	28939	0.06	0.02	2.10E-02	1.70E-01	27157	*N/A*	INTERGENIC	T	0.21	C	0.49
rs3828634	5	31496959	t	c	0.23	0.46	0.11	3.80E-05	8.80E-01	29131.8	0.88	0.19	2.81E-06	6.69E-01	29132.8	0.00	0.05	9.96E-01	4.62E-01	10862.8	*RNASEN*	INTRONIC	T	0.11	C	0.32
rs11963288	6	56443263	t	c	0.95	0.20	0.21	3.32E-01	2.88E-01	27373	1.55	0.35	9.73E-06	3.54E-01	27375	0.18	0.05	1.36E-04	7.19E-01	27877	*DST*	INTRONIC	C	0.03	C	0.03
rs6924906	6	82277271	t	c	0.71	-0.51	0.10	5.57E-07	5.93E-01	29111	-0.41	0.17	1.74E-02	7.68E-01	29112	-0.02	0.04	5.22E-01	7.57E-01	10860	*N/A*	INTERGENIC	C	0.32	C	0.07
rs13209747	6	127157147	t	c	0.17	0.56	0.12	8.84E-06	4.71E-01	28708	0.85	0.21	5.88E-05	6.10E-01	28709	0.04	0.05	3.25E-01	5.70E-01	12312	*N/A*	INTERGENIC	T	0.13	T	0.46
rs17080102	6	151046463	c	g	0.10	-0.74	0.15	5.45E-07	6.85E-01	29323	-1.02	0.25	3.42E-05	8.21E-01	29324	-0.10	0.03	1.32E-03	5.86E-02	29464	*PLEKHG1*	INTRONIC	C	0.11	C	0.05
rs17471520	7	27145315	t	c	0.69	-0.50	0.10	1.81E-06	6.04E-01	29232.7	-0.88	0.17	4.39E-07	9.54E-01	29233.7	-0.10	0.02	3.97E-06	9.92E-01	29373.7	*N/A*	DOWNSTREAM	C	0.34	C	0.11
rs11564022	7	27303571	t	c	0.23	-0.60	0.11	7.66E-08	7.95E-01	29321.9	-0.89	0.19	1.83E-06	4.99E-01	29322.9	-0.13	0.02	6.78E-08	1.46E-01	29462.9	*N/A*	INTERGENIC	T	0.18	T	0.42
rs17428471	7	27304392	t	g	0.12	0.61	0.14	1.23E-05	7.76E-01	29325.9	1.20	0.24	4.00E-07	7.48E-01	29326.9	0.15	0.03	1.32E-06	4.76E-01	29834.9	*N/A*	INTERGENIC	T	0.14	T	0.06
rs11972761	7	52858144	c	g	0.15	0.40	0.13	1.71E-03	6.99E-01	29321	1.09	0.22	5.39E-07	5.32E-01	29322	0.07	0.03	1.52E-02	7.66E-01	29830	*N/A*	INTERGENIC	C	0.19	C	0.03
rs12718983	7	55692246	t	g	0.85	0.39	0.14	4.58E-03	6.79E-01	29294.8	1.10	0.23	1.46E-06	8.48E-01	29295.8	0.06	0.03	3.81E-02	1.57E-01	29435.8	*N/A*	INTERGENIC	G	0.10	G	0.42

rs11768155	7	80203792	a	g	0.75	-0.48	0.11	5.40E-06	4.09E-01	29072.7	-0.41	0.18	2.13E-02	2.08E-01	29073.7	-0.12	0.04	2.87E-03	4.00E-01	10851.7	*N/A*	INTERGENIC	G	0.37	G	0.02
rs6997487	8	107034687	a	c	0.27	-0.48	0.11	5.62E-06	6.28E-01	29303	-0.31	0.18	8.37E-02	2.09E-01	29304	-0.04	0.02	8.92E-02	3.49E-01	27546	*N/A*	INTERGENIC	A	0.20	A	0.50
rs12339156	9	35905230	c	g	0.17	-0.56	0.12	7.73E-06	7.32E-01	29304.9	-0.61	0.21	3.30E-03	1.55E-01	29305.9	-0.07	0.03	1.42E-02	5.42E-01	29813.9	*N/A*	INTERGENIC	C	0.20	C	0.28
rs7868945	9	72704778	a	g	0.24	0.50	0.11	9.70E-06	7.42E-01	28881	0.53	0.19	5.84E-03	4.68E-01	28882	0.07	0.03	9.39E-03	6.19E-01	27126	*TRPM3*	INTRONIC	A	0.30	A	0.08
rs4918017	10	105234221	c	g	0.73	0.53	0.12	7.31E-06	6.08E-01	28308.9	0.48	0.20	1.45E-02	8.29E-01	28309.9	0.05	0.03	3.24E-02	8.79E-01	28818.8	*N/A*	INTERGENIC	G	0.06	C	0.33
rs11041530	11	7658079	c	g	0.11	-0.54	0.15	2.65E-04	9.21E-01	29173.9	-1.35	0.25	4.04E-08	3.45E-01	29174.9	-0.08	0.05	1.50E-01	4.66E-01	11002.9	*N/A*	INTERGENIC	C	0.09	C	0.01
rs16932474	11	16008731	t	c	0.83	-0.55	0.12	5.61E-06	7.12E-01	29313	-0.49	0.20	1.70E-02	1.89E-02	29314	-0.07	0.03	1.37E-02	9.29E-01	27557	*SOX6*	INTRONIC	C	0.28		monomorphic
rs1401454	11	16206759	t	c	0.46	0.45	0.10	2.11E-06	8.70E-01	27939	0.55	0.16	5.68E-04	8.25E-01	27940	0.05	0.02	1.10E-02	8.96E-01	26185	*SOX6*	INTRONIC	C	0.47	T	0.48
rs17142803	11	81104083	t	c	0.10	0.98	0.22	7.53E-06	6.24E-01	15897	0.58	0.35	9.60E-02	8.69E-01	15894	0.07	0.05	1.72E-01	6.68E-01	14161	*N/A*	INTERGENIC	T	0.13		monomorphic
rs12311091	12	19872394	t	c	0.20	-0.21	0.12	7.23E-02	1.71E-01	28308.9	-0.99	0.20	4.69E-07	8.22E-01	28309.9	-0.08	0.03	1.21E-03	1.98E-01	28818.9	*N/A*	INTERGENIC	T	0.22	T	0.17
rs10848279	12	130139844	a	c	0.10	-0.53	0.16	7.25E-04	6.15E-01	29131	-1.33	0.27	6.18E-07	7.89E-01	29132	-0.05	0.06	4.38E-01	6.30E-01	12691	*GPR133*	INTRONIC	A	0.05	A	0.23
rs9555689	13	109782559	a	g	0.67	0.20	0.10	4.87E-02	1.13E-02	28308.9	0.61	0.17	5.21E-04	5.12E-02	28309.9	0.08	0.02	8.08E-04	7.12E-02	27822.9	*COL4A2*	INTRONIC	G	0.42	G	0.22
rs6575454	14	94215314	t	g	0.14	-0.29	0.13	2.72E-02	1.56E-01	28661	-0.54	0.22	1.68E-02	2.78E-02	28662	-0.10	0.05	3.25E-02	3.00E-04	11335	*N/A*	INTERGENIC	T	0.19	T	0.20
rs11633456	15	62835692	t	c	0.32	0.34	0.10	6.65E-04	6.12E-01	28308.9	0.76	0.17	5.45E-06	8.71E-01	28310	0.07	0.02	9.41E-04	7.56E-01	28818.9	*RBPMS2*	INTRONIC	T	0.36	T	0.04
rs467649	16	64392242	t	g	0.02	0.74	0.31	1.88E-02	4.52E-01	26887	2.41	0.52	4.43E-06	9.21E-01	26889	0.05	0.08	5.19E-01	3.61E-01	26423	*N/A*	INTERGENIC	T	0.02	T	0.09
rs16958138	17	52697608	a	g	0.25	0.24	0.12	3.74E-02	7.24E-01	28308.9	0.90	0.19	3.14E-06	5.86E-01	28309.9	0.08	0.03	1.72E-03	2.33E-02	28818.9	*MSI2*	INTRONIC	A	0.25	A	0.05
rs1786784	18	33252486	a	g	0.31	-0.19	0.15	2.09E-01	1.79E-02	13840	-0.14	0.24	5.58E-01	3.11E-03	13838	-0.10	0.03	1.43E-03	2.19E-02	14343	*BRUNOL4*	INTRONIC	A	0.44	A	monomorphic
rs11084566	19	36049889	t	c	0.71	0.47	0.10	5.13E-06	3.00E-01	28720	0.62	0.17	2.80E-04	7.27E-01	28722	0.01	0.02	5.10E-01	1.44E-01	26964	*N/A*	INTERGENIC	C	0.25	C	0.33
rs2064726	20	50149092	t	c	0.47	-0.24	0.09	8.23E-03	9.58E-01	28599	-0.70	0.15	6.02E-06	9.04E-01	28600	-0.02	0.04	5.65E-01	8.01E-01	8576	*ZFP64*	INTRONIC	C	0.44	T	0.37

SNPs association values with P<1.0 x 10-5 for SBP, DBP and hypertension (HTN) in the Continental Origins and Genetic Epidemiology Network (COGENT). Abbreviations: Chr, chromosome; MAF, minor allele frequency; HetPVal, P for heterogeneity; N/A, not available

Table S4. Comparison of the number of observed and expected signals in ICBP for the 43 independent SNPs in COGENT with P <1.0 x 10-5

Significance level	0.05	0.01	0.001	0.0001
Observed	18	14	11	5
Expected	4.5	0.9	0.09	0.009
P-value	2.2×10^{-7}	2.3×10^{-13}	2.3×10^{-20}	3.5×10^{-13}

Comparison observed and expected SBP or DBP signals in the International Consortium for Blood Pressure (ICBP) for 43 independent SNPs in Continental Origins and Genetic Epidemiology Network (COGENT) with $P < 1.0 \times 10^{-5}$

Table S5. Statistical power of replicating the SNPs in Table 1 and 2 using African ancestry samples only.

SNP	Alleles	Trait	Estimated SNP specific variance	Total sample size in AA available for the SNP	Allele frequency	Sample size required for 80% power at alpha=0.05
rs13209747	T/C	SBP	5.85E-04	8686	0.1854	1.65E+04
		DBP	7.07E-04	8686	0.1854	1.36E+04
rs17080102	C/G	SBP	5.56E-04	10070	0.1016	1.73E+04
		DBP	8.19E-04	10070	0.1016	1.18E+04
rs6924906	T/C	SBP	1.98E-04	11770	0.7145	4.87E+04
		DBP	8.85E-04	11770	0.7145	1.09E+04
rs17428471	T/G	SBP	8.99E-04	6650	0.1432	1.07E+04
		DBP	6.70E-04	6650	0.1432	1.44E+04
rs1717027	T/C	SBP	4.44E-05	10070	0.6447	2.17E+05
		DBP	9.07E-04	10070	0.6447	1.06E+04
rs1401454	T/C	SBP	4.41E-04	10070	0.4615	2.18E+04
		DBP	8.35E-04	10070	0.4615	1.15E+04
rs11041530	C/G	SBP	1.07E-03	8686	0.1134	9000
		DBP	4.78E-04	8686	0.1134	2.02E+04

Table S6. Conditional analysis of SNPs in HOXA locus for SBP and DBP

Systolic blood pressure (SBP)					COGENT single-SNP meta-analysis				Conditional analysis, LD from 5 CARe studies*		
SNP	**Chr**	**Position (build 36)**	**Nearest gene**	**Allele 1**	**allele frequency**	**beta**	**se**	**pvalue**	**beta**	**se**	**pvalue**
rs11564022	7	27303571	*EVX1-HOXA*	T	0.2256	-0.8915	0.1868	1.83E-06	-0.88434	0.185832	1.95E-06
rs17471520	7	27145315	*EVX1-HOXA*	T	0.6945	-0.8786	0.1739	4.39E-07	-0.85691	0.16913	4.05E-07
rs11564022	7	27303571	*EVX1-HOXA*	T	0.2256	-0.8915	0.1868	1.83E-06	-0.89508	0.185545	1.41E-06
rs17428471	7	27304392	*EVX1-HOXA*	T	0.1225	1.1961	0.236	4.00E-07	1.17406	0.235888	6.45E-07
rs17471520	7	27145315	*EVX1-HOXA*	T	0.6945	-0.8786	0.1739	4.39E-07	-0.8851	0.172681	2.97E-07
rs17428471	7	27304392	*EVX1-HOXA*	T	0.1225	1.1961	0.236	4.00E-07	1.19066	0.241156	7.92E-07

Diastolic blood pressure (DBP)					COGENT single-SNP meta-analysis				Conditional analysis, LD from 5 CARe studies*		
SNP	**Chr**	**Position (build 36)**	**Nearest gene**	**Allele 1**	**allele frequency**	**beta**	**se**	**pvalue**	**beta**	**se**	**pvalue**
rs11564022	7	27303571	*EVX1-HOXA*	T	0.2256	-0.5969	0.111	7.66E-08	-0.59355	0.110236	7.27E-08
rs17471520	7	27145315	*EVX1-HOXA*	T	0.6945	-0.496	0.1039	1.81E-06	-0.47971	0.100524	1.82E-06
rs11564022	7	27303571	*EVX1-HOXA*	T	0.2256	-0.5969	0.111	7.66E-08	-0.59901	0.110113	5.33E-08
rs17428471	7	27304392	*EVX1-HOXA*	T	0.1225	0.6143	0.1405	1.23E-05	0.589174	0.140037	2.58E-05
rs17471520	7	27145315	*EVX1-HOXA*	T	0.6945	-0.496	0.1039	1.81E-06	-0.49819	0.103024	1.33E-06
rs17428471	7	27304392	*EVX1-HOXA*	T	0.1225	0.6143	0.1405	1.23E-05	0.609722	0.143636	2.19E-05

Conditional analysis of SNPs in the HOXA region performed for systolic blood pressure (SBP) and diastolic blood pressure (DBP) in the Continental Origins and Genetic Epidemiology Network (COGENT). *Estimates and p-values
Abbreviations: Chr, chromosome; LD, linkage disequilibrium; SNP, single nucleotide polymorphism

Table S7. Heterogeneity P-values for the top SNPs in main text Table 1

					Replication *P*								
		Effect	Effect		COGENT	COGENT	ICBP	African	East	Phase III+replication	All African	All African	All samples
Chr	SNP	Other Allele	Allele Freq	Trait	*P*	P_{HET}	*P*	Ancestry	Asian		*P*	P_{HET}	P_{HET}
				SBP	$2.6x10^{-1}$	0.5	$5.0x10^{-1}$	$6.0x10^{-1}$	$5.6x10^{-1}$	$3.00x10^{-1}$	0.218	0.3577	0.4657
3	rs1717027	T/C	0.64	DBP	$5.1x10^{-7}$	0.25	$2.5x10^{-7}$	**$2.2x10^{-2}$**	$1.5x10^{-1}$	**$4.62x10^{-13**}$**	**$3.40x10^{-8}$**	**0.9375**	0.6815
				SBP	1.7x10-2	0.77	5.6x10-4	4.7x10-1	2.0x10-3*	6.16x10-5	9.61x10-2	0.2483	0.07095
6	rs6924906	T/C	0.71	DBP	5.6x10-7	0.59	4.9x10-2	9.8x10-1	8.8x10-3	5.50x10-7	1.31x10-5	0.2013	0.215
				SBP	$5.9x10^{-5}$	0.61	$5.4x10^{-4}$	**$5.0x10^{-4*}$**	**$2.6x10^{-3*}$**	**$2.56x10^{-10**}$**	$3.32x10^{-7}$	**0.366**	0.1698
6	rs13209747	T/C	0.19	DBP	$8.8x10^{-6}$	0.47	$1.5x10^{-3}$	**$2.2x10^{-2}$**	**$1.2x10^{-4*}$**	**$2.43x10^{-11**}$**	$6.37x10^{-7}$	**0.2151**	0.2296
				SBP	3.4x10-5	0.82	9.2x10-4	2.3x10-1	3.4x10-2	4.75x10-8	2.54x10-5	0.7246	0.8165
6	rs17080102	C/G	0.1	DBP	5.4x10-7	0.69	1.5x10-4	4.1x10-1	8.5x10-4*	1.90x10-11**	1.15x10-6	0.294	0.3656
				SBP	$4.0x10^{-7}$	0.75	$8.0x10^{-6*}$	$1.4x10^{-4*}$	$3.4x10^{-1}$	$2.1x10^{-12**}$	$9.15x10^{-10}$	0.2651	0.07015
7	rs17428471	T/G	0.14	DBP	$1.2x10^{-5}$	0.78	$2.8x10^{-5*}$	$1.1x10^{-2}$	$4.4x10^{-1}$	$1.6x10^{-9**}$	$7.07x10^{-7}$	0.7819	0.4949
				SBP	5.7x10-4	0.83	2.2x10-4	9.7x10-4*	6.7x10-1	9.50x10-7	3.79x10-6	0.4655	0.05645
11	rs1401454	T/C	0.46	DBP	2.1x10-6	0.87	3.1x10-5	5.0x10-3	5.5x10-1	5.12x10-10**	3.82x10-8	0.5955	0.1655
				SBP	$4.0x10^{-8}$	0.34	$2.9x10^{-2}$	$8.0x10^{-1}$	$9.3x10^{-1}$	$5.6x10^{-6}$	$2.89x10^{-6}$	0.03584	0.02305
11	rs11041530	C/G	0.11	DBP	2.6**$x10^{-4}$**	0.47	0.119	$6.5x10^{-1}$	$6.6x10^{-1}$	$7.6x10^{-4}$	$2.30x10^{-3}$	0.1446	0.2073

Abbreviations: SNP, single nucleotide polymorphisms; PHET, p for heterogeneity

Table S8. Conditional analysis of SNPs in SOX6 for SBP and DBP

Systolic blood pressure (SBP)

					COGENT single-SNP meta-analysis				Conditional analysis, LD from 5 CARe studies*		
SNP	**Chr**	**Position (build 36)**	**Nearest gene**	**Allele 1**	**allele frequency**	**beta**	**se**	**pvalue**	**beta**	**se**	**pvalue**
rs1401454	11	16206759	*SOX6*	T	0.46	0.5512	0.1599	5.68E-04	0.550958	0.158859	5.24E-04
rs381815	11	16858844	*SOX6*	T	0.2225	0.2765	0.1886	0.1427	0.301567	0.190844	1.14E-01
rs1401454	11	16206759	*SOX6*	T	0.46	0.5512	0.1599	5.68E-04	0.528509	0.159365	9.12E-04
rs2014408	11	16321858	*SOX6*	T	0.0718	0.5363	0.3106	0.08423	0.527856	0.307876	8.64E-02

Diastolic blood pressure (DBP)

					COGENT single-SNP meta-analysis				Conditional analysis, LD from 5 CARe cohorts*		
SNP	**Chr**	**Position (build 36)**	**Nearest gene**	**Allele 1**	**allele frequency**	**beta**	**se**	**pvalue**	**beta**	**se**	**pvalue**
rs1401454	11	16206759	*SOX6*	T	0.46	0.451	0.0951	2.11E-06	0.450111	0.094335	1.83E-06
rs381815	11	16858844	*SOX6*	T	0.2225	0.2517	0.1122	0.0249	0.303716	0.113146	7.27E-03
rs1401454	11	16206759	*SOX6*	T	0.46	0.451	0.0951	2.11E-06	0.434742	0.094648	4.36E-06
rs2014408	11	16321858	*SOX6*	T	0.0718	0.3731	0.1873	0.04636	0.388407	0.184351	3.51E-02

*Conditional analysis estimates and p-values were obtained when using two SNPs (marked in the same color) in a linear regresion models

We performed conditional analysis using summary statistics methods previously described by Yang et al (2012, Nat Genet) for SBP and DBP signals in the NHLBI Candidate gene Association Resource (CARe) GWAS data using rs1401454, rs381815, rs2014408 from the SOX6 locus. The CARe cohorts used were as follows: Atherosclerosis Risk In Communities (ARIC); Coronary Artery Risk Development in Young Adults (CARDIA); Cleveland Family Study (CFS); Jackson Heart Study (JHS); Multi-Ethnic Study of Atherosclerosis (MESA).

Table S9. Replication analysis in COGENT of 29 identified SNPs by ICBP

							Allele frequencies					COGENT Results		
trait	Chr	Position (build 36)	SNP	Nearby gene	Coded Allele	Other allele	EUR	AA	Asia	YRI	CEU	Beta	SE	pvalue
DBP	chr12	113872179	rs10850411	*TBX5–TBX3*	T	C	0.70	0.657782	0.408	0.653	0.683	-0.0087	0.1052	0.9344
SBP	chr12	113872179	rs10850411	*TBX5–TBX3*	T	C	0.70	0.657782	0.408	0.653	0.683	-0.114	0.1748	0.5142
DBP	chr10	104836168	rs11191548	CYP17A1	T	C	0.91	0.950721	0.808		0.917	0.2967	0.2065	0.1507
SBP	chr10	104836168	rs11191548	CYP17A1	T	C	0.91	0.950721	0.808		0.917	0.9017	0.3457	0.009086
DBP	chr5	32850785	rs1173771	*NPR3–*	G	A	0.60	0.772235	0.658	0.805	0.525	-0.0741	0.109	0.4966
SBP	chr5	32850785	rs1173771	*NPR3–*	G	A	0.60	0.772235	0.658	0.805	0.525	0.0369	0.1824	0.8397
DBP	chr5	157777980	rs11953630	EBF1	T	C	0.37	0.185074	0.058	0.127	0.342	-0.3209	0.1188	0.0069
SBP	chr5	157777980	rs11953630	EBF1	T	C	0.37	0.185074	0.058	0.127	0.342	-0.4194	0.1992	0.03523
DBP	chr17	44757806	rs12940887	*ZNF652*	T	C	0.38	0.103031	0.1	0.008	0.375	0.0985	0.1491	0.5089
SBP	chr17	44757806	rs12940887	*ZNF652*	T	C	0.38	0.103031	0.1	0.008	0.375	0.4184	0.2501	0.0944
DBP	chr3	27512913	rs13082711	SLC4A7	T	C	0.78	0.925671	0.942	0.958	0.775	-0.3236	0.1775	0.06822
SBP	chr3	27512913	rs13082711	SLC4A7	T	C	0.78	0.925671	0.942	0.958	0.775	-0.2767	0.2988	0.3544
DBP	chr4	103407732	rs13107325	*SLC39A8*	T	C	0.05	0.018869			0.092	-1.1784	0.5385	0.02865
SBP	chr4	103407732	rs13107325	*SLC39A8*	T	C	0.05	0.018869			0.092	-1.589	0.8346	0.05692
DBP	chr4	156864963	rs13139571	GUCY1A3–	C	A	0.76	0.839506	0.733	0.915	0.717	0.0889	0.1298	0.4933
SBP	chr4	156864963	rs13139571	GUCY1A3–	C	A	0.76	0.839506	0.733	0.915	0.717	-0.0929	0.2169	0.6684
DBP	chr20	10917030	rs1327235	*JAG1*	G	A	0.46	0.506287	0.492	0.551	0.508	0.2137	0.0919	0.0201
SBP	chr20	10917030	rs1327235	*JAG1*	G	A	0.46	0.506287	0.492	0.551	0.508	0.4864	0.1543	0.001621
DBP	chr15	72864420	rs1378942	CYP1A1–	C	A	0.35	0.882267	0.808		0.3	-0.2289	0.1472	0.12
SBP	chr15	72864420	rs1378942	CYP1A1–	C	A	0.35	0.882267	0.808		0.3	-0.042	0.2482	0.8655
DBP	chr4	81383747	rs1458038	*FGF5*	T	C	0.29	0.087862	0.283	0.059	0.267	0.5318	0.1821	0.003494
SBP	chr4	81383747	rs1458038	*FGF5*	T	C	0.29	0.087862	0.283	0.059	0.267	0.4195	0.305	0.169
DBP	chr12	88584717	rs17249754	ATP2B1	G	A	0.84	0.865644	0.667	0.873	0.9	0.039	0.1378	0.7773
SBP	chr12	88584717	rs17249754	ATP2B1	G	A	0.84	0.865644	0.667	0.873	0.9	0.5724	0.2306	0.01306
DBP	chr1	11785365	rs17367504	*MTHFR–*	G	A	0.15	0.108908	0.108	0.085	0.183	-0.0199	0.1465	0.8922
SBP	chr1	11785365	rs17367504	*MTHFR–*	G	A	0.15	0.108908	0.108	0.085	0.183	-0.2578	0.2472	0.2971
DBP	chr17	42368270	rs17608766	GOSR2	T	C	0.86	0.972944			0.908	0.0986	0.3985	0.8046
SBP	chr17	42368270	rs17608766	GOSR2	T	C	0.86	0.972944			0.908	-0.4198	0.6375	0.5102

DBP	chr6	26199158	rs1799945	*HFE*	G	C	0.14	0.028593				0.3771	0.3892	0.3326
SBP	chr6	26199158	rs1799945	*HFE*	G	C	0.14	0.028593				0.3962	0.6193	0.5223
DBP	chr10	18747454	rs1813353	CACNB2(39)	T	C	0.68	0.872536	0.833	0.856	0.633	-0.0392	0.1241	0.7523
SBP	chr10	18747454	rs1813353	CACNB2(39)	T	C	0.68	0.872536	0.833	0.856	0.633	0.3615	0.2072	0.08101
DBP	chr15	89238392	rs2521501	*FURIN–FES*	T	A	0.31	0.269298	0.075	0.169	0.383	0.1965	0.1276	0.1235
SBP	chr15	89238392	rs2521501	*FURIN–FES*	T	A	0.31	0.269298	0.075	0.169	0.383	0.0656	0.2113	0.7564
DBP	chr1	113018066	rs2932538	MOV10	G	A	0.75	0.821123	0.842	0.831	0.7	0.3786	0.1197	0.001561
SBP	chr1	113018066	rs2932538	MOV10	G	A	0.75	0.821123	0.842	0.831	0.7	0.3793	0.2008	0.05883
DBP	chr12	110368991	rs3184504	*SH2B3*	T	C	0.47	0.082043			0.45	0.5759	0.2384	0.01571
SBP	chr12	110368991	rs3184504	*SH2B3*	T	C	0.47	0.082043			0.45	1.29E+00	3.70E-01	5.05E-04
DBP	chr3	41852418	rs3774372	ULK4	T	C	0.83	0.796856	0.842	0.805	0.783	-0.2336	0.1126	0.03805
SBP	chr3	41852418	rs3774372	ULK4	T	C	0.83	0.796856	0.842	0.805	0.783	-0.1484	0.1883	0.4305
DBP	chr11	16858844	rs381815	*PLEKHA7*	T	C	0.26	0.218154	0.175	0.203	0.317	0.2517	0.1122	0.0249
SBP	chr11	16858844	rs381815	*PLEKHA7*	T	C	0.26	0.218154	0.175	0.203	0.317	0.2765	0.1886	0.1427
DBP	chr3	170583580	rs419076	MECOM	T	C	0.47	0.507554	0.133	0.593	0.467	0.0268	0.0915	0.7699
SBP	chr3	170583580	rs419076	MECOM	T	C	0.47	0.507554	0.133	0.593	0.467	0.1333	0.154	0.3868
DBP	chr10	18459978	rs4373814	*CACNB2(59)*	G	C	0.55	0.441108	0.508	0.415	0.667	-0.2097	0.0989	0.03399
SBP	chr10	18459978	rs4373814	*CACNB2(59)*	G	C	0.55	0.441108	0.508	0.415	0.667	-0.1033	0.1661	0.5342
DBP	chr10	63137559	rs4590817	C10orf107	G	C	0.84	0.83826		0.797	0.817	-0.2224	0.1266	0.07897
SBP	chr10	63137559	rs4590817	C10orf107	G	C	0.84	0.83826		0.797	0.817	0.1496	0.2134	0.4833
DBP	chr20	57184512	rs6015450	*GNAS–EDN3*	G	A	0.12	0.186073		0.178	0.058	0.3083	0.1231	0.01225
SBP	chr20	57184512	rs6015450	*GNAS–EDN3*	G	A	0.12	0.186073		0.178	0.058	0.1621	0.2059	0.4311
DBP	chr11	100098748	rs633185	FLJ32810–	G	C	0.28	0.210992	0.525	0.144	0.292	-0.0559	0.1164	0.6311
SBP	chr11	100098748	rs633185	FLJ32810–	G	C	0.28	0.210992	0.525	0.144	0.292	-0.1942	0.1937	0.3161
DBP	chr11	10307114	rs7129220	*ADM*	G	A	0.89	0.927608		0.941	0.883	-0.3187	0.1728	0.0651
SBP	chr11	10307114	rs7129220	*ADM*	G	A	0.89	0.927608		0.941	0.883	-0.9915	0.2879	0.000573
DBP	chr6	31724345	rs805303	BAT2–BAT5	G	A	0.61	0.401722				-0.0285	0.0945	0.7634
SBP	chr6	31724345	rs805303	BAT2–BAT5	G	A	0.61	0.401722				0.095	0.1588	0.5495
DBP	chr10	95885930	rs932764	*PLCE1*	G	A	0.44	0.193873	0.542	0.195	0.425	-0.1295	0.1157	0.2627
SBP	chr10	95885930	rs932764	*PLCE1*	G	A	0.44	0.193873	0.542	0.195	0.425	-0.0855	0.1944	0.6599

Replication analysis of the 29 genome-wide significant SNPs identified by the International Consortium for Blood Pressure (ICBP) study in the in Continental Origins and Genetic Epidemiology Network (COGENT). Significant associations (P < 0.05) are shown in red.

Table S10. Fine-mapping of four loci identified by ICBP

								European ancestry (EA)			African ancestry (AA)				Conditional analysis	Conditional SNP	
Gene/Chr	Trait	SNP	r^2 EUR	r^2 AFR	Alleles (effect/other)	Effect allele frequency (EA, AA)	Position (Build 36)	N	Beta	P-value	N	Beta (SE)	P-value	Explained variance (%)	P-value		HapMap CEU and YRI block sizes (bp) defined by r2>0.7
EBF1/chr5	DBP	rs11953630	0.928	0.499	T/C	0.342,0.127	157777980	203056	-0.281	3.80E-13	28308.9	-0.3209(0.1188)	0.0069	0.0189%	0.431005	rs4551053	CEU 75,779
	DBP	rs4551053			A/G	0.325,0.068	157771120	203056		2.37E-05	28309	-0.4973(0.14)	0.000384	0.0259%			YRI 24,249
	SBP	rs11953630			T/C	0.342,0.127	157777980	203056	-0.412	3.00E-11	28308.9	-0.4194(0.1992)	0.03523	0.0114%	0.804633	rs4551053	
	SBP	rs4551053			A/G	0.325,0.068	157771120	203056		2.72E-06	28309	-0.754(0.2321)	0.001161	0.0211%			
	HTN	rs11953630			T/C	0.342,0.127	157777980	203056	-0.052	1.70E-07	28308.9	-0.0867(0.026)	0.000847	0.0111%	0.115087	rs4551053	
	HTN	rs4551053			A/G	0.325,0.068	157771120	203056			28309	-0.1148(0.0317)	0.000296	0.0111%			
ATP2B1/chr12	DBP	rs17249754	0.915	0.703	A/G	0.1,0.1298	88584717	203056	0.522	1.20E-14	28925	-0.039(0.1378)	0.7773	0.0003%	0.617033	rs2681492	CEU 150,233
	DBP	rs2681492			T/C	0.892,0.87	88537220	203056		6.12E-08	29247.9	0.0853(0.1403)	0.5433	0.0014%			YRI 58,987
	SBP	rs17249754			A/G	0.1,0.1298	88584717	203056	0.928	1.80E-18	28925	-0.5724(0.2306)	0.01306	0.0216%	0.574338	rs2681492	
	SBP	rs2681492			T/C	0.892,0.87	88537220	203056		2.06E-11	29247.9	0.745(0.2349)	0.001517	0.0367%			
	HTN	rs17249754			A/G	0.1,0.1298	88584717	203056	0.126	1.10E-14	28925	-0.1159(0.0522)	0.02642	0.0202%	0.574623	rs2681492	
	HTN	rs2681492			T/C	0.892,0.87	88537220	203056			29247.9	0.1034(0.031)	0.000855	0.0161%			
NT5C2/chr10	DBP	rs11191548	1	0.496	T/C	0.917,0.949	104836168	203056	0.464	9.40E-13	28675	0.2967(0.2065)	0.1507	0.0070%	0.774123	rs11191555	CEU 422,828
	DBP	rs11191555			A/C	0.917,0.956	104847513	203056		3.74E-06	27823	0.4455(0.2292)	0.05192	0.0138%			YRI 400,148
	SBP	rs11191548			T/C	0.917,0.949	104836168	203056	1.095	6.90E-26	28675	0.9017(0.3457)	0.009086	0.0230%	0.418126	rs11191555	
	SBP	rs11191555			A/C	0.917,0.956	104847513	203056		9.49E-10	27823	1.0032(0.3841)	0.00901	0.0247%			
	HTN	rs11191548			T/C	0.917,0.949	104836168	203056	0.097	1.40E-05	28675	0.1199(0.0777)	0.1226	0.0093%	0.568881	rs11191555	
	HTN	rs11191555			A/C	0.917,0.956	104847513	203056			27823	0.1045(0.0525)	0.04634	0.0061%			
ULK4/chr3	DBP	rs3774372	1	0.098	T/C	0.783,0.797	41852418	203056	-0.367	9.00E-14	29317	-0.2336(0.1126)	0.03805	0.0146%	0.613398	rs1716642	CEU 314,745
	DBP	rs1716642			A/C	0.783,0.648	41940869	203056		2.60E-07	24185	0.5359(0.1084)	7.57E-07	0.1083%			YRI 221,195
	SBP	rs3774372			T/C	0.783,0.797	41852418	203056	-0.067	0.39	29317	-0.1484(0.1883)	0.4305	0.0021%	0.573685	rs1716642	
	SBP	rs1716642			A/C	0.783,0.648	41940869	203056		0.497	24185	0.1424(0.1805)	0.4301	0.0027%			
	HTN	rs3774372			T/C	0.783,0.797	41852418	203056	-0.017	0.18	29317	0.0487(0.0476)	0.3069	0.0051%	0.0741162	rs1716642	
	HTN	rs1716642			A/C	0.783,0.648	41940869	203056			24185	0.0781(0.0238)	0.001047	0.0186%			

Table S11. Cardiotoxicity and associated molecules and p-values from toxicology function analysis of IPA

Cardiotoxicity	Molecules	Pvalue
Cardiac stenosis	*HOXA3*	4.54×10^{-3}
Congenital heart anomaly	*HOXA3*	1.31×10^{-2}
Cardiac congestive cardiac failure	*CACNA1D*	4.16×10^{-2}
Heart failure	*CACNA1D*	4.16×10^{-2}

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