The genomics of blood pressure regulation and its target organs from association studies in 342,415 individuals

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ABSTRACT

To dissect the genetic architecture of blood pressure (BP) and assess how its elevation promotes downstream cardiovascular diseases, we analyzed 128,272 SNPs from targeted and genome-wide arrays in 201,529 individuals of European ancestry. Genotypes from an additional 140,886 individuals of European ancestry were used as validation for loci reaching genome-wide significance but without prior support in the literature. We identified 66 BP loci, of which 17 were novel and 15 harbored multiple distinct association signals, and which together explain up to 3.5% of BP variation. The 66 index SNPs were enriched for *cis*-regulatory elements, particularly in vascular endothelial cells, consistent with a primary role in BP control through modulating blood vessel tone and fluid filtration across multiple tissues, not solely the kidney. Importantly, the 66 index SNPs combined in a risk score showed comparable effects in 64,421 individuals of non-European descent (South-Asian, East-Asian and African), confirming that these are ancestral physiological effects that arose prior to human migration out of Africa. The 66-SNP BP risk score was significantly associated with target-organ damage in multiple tissues, with minor effects in the kidney. Our data expand current knowledge of BP pathways, and also, highlight that BP regulation and its effects may occur in multiple organs and tissues beyond the classic renal system.

There are considerable physiological, clinical and genetic data that implicate the kidney as the major regulator of BP through maintaining salt-water balance and that renal damage is consequent to long-term BP elevation. However, alternative hypotheses, such as increasing systemic vascular resistance, are also serious contenders to explain the rise of BP with increasing age. The genetic basis of elevated blood pressure or hypertension (HTN) involves many loci that have been identified using large-scale analyses of candidate genes[1,2], linkage studies, and genome-wide association studies (GWAS)[3-12]. The genes underlying BP regulation can help resolve many of the open questions regarding BP (patho-) physiology. While ~40-50% of BP variability is heritable[13,14], the identified genetic variation explains only ~2%[1-12]. This is considerably less than that observed for other cardiovascular disease (CVD) risk factors, such as plasma lipid fractions, despite the fact that they have comparable heritability[15]. The sources of this discrepancy could be many, but the major reasons are likely to be the constraints on physiological variation of BP and contributions from diverse organs and tissues, potentially resulting in hundreds or thousands of genetic variants of weak effects. Consequently, the fundamental causes of hypertension susceptibility also remain unknown.

The Cardio-MetaboChip is a custom genotyping microarray designed to facilitate cost-effective follow-up of nominal associations for metabolic and cardiovascular traits, including BP. This array comprises 196,725 variants, including ~5,000 SNPs with nominal (P <0.016) evidence of BP association in our previous GWAS meta-analysis[5]. Furthermore, the array includes several dense scaffolds for fine mapping of selected loci spanning, on average, genomic regions of 350 kilobases[5,16], of which 24 include genome-wide significant BP association in the current study[5,16]. Here we performed BP GWAS meta-analysis of both systolic (SBP) and diastolic (DBP) BP using data from 109,096 individuals directly genotyped using the Cardio-MetaboChip array, in combination with imputed data from an additional 92,433 individuals with genome-wide genotyping, all of European (EUR) ancestry. Validation of loci reaching genome-wide significance but without previous support in the literature was sought using association results from an additional 140,886 individuals of European ancestry from the UK Biobank. We assessed whether the genome-wide significant BP SNPs identified, which are largely in non-coding DNA, were associated with expression levels of nearby genes, and tested for enrichment of BP SNPs in *cis*-regulatory sequences. Signal refinement and analyses of associated variants were performed in 64,421 individuals of South-Asian (SAS), East-Asian (EAS), and African (AFR) ancestry to assess their global distribution. Finally, a genotype risk score was constructed to examine the impact of the BP SNPs on cardiovascular and other end-organ outcomes.

RESULTS

Novel genetic loci associated with SBP and DBP

We performed meta-analyses of association summary statistics from a total of 201,529 individuals of EUR ancestry from 74 studies: (i) 109,096 individuals from 46 studies genotyped on Cardio-MetaboChip; and (ii) 92,433 individuals from 28 studies with imputed genotype data from genome-wide genotyping at SNPs overlapping the variants on Cardio-MetaboChip. Twenty-four of the 28 studies with genome-wide genotyping data had contributed to previous analyses (**Supplementary Tables 1-3**)[5,7].

BP was measured using standardized protocols in all studies (**Supplementary Table 1**), regardless of whether the primary focus was BP or another trait. We initially analyzed affected and unaffected individuals from samples selected as cases (e.g. type 2 diabetes) or controls, separately. However, because sensitivity analyses did not reveal any significant difference in BP effect size estimates between case and control samples (data not shown), we analyzed all samples combined. When available, the average of two BP measurements was used for association analyses (**Supplementary Table 1**). If an individual was taking a BP-lowering treatment, the underlying SBP and DBP were estimated by adding 15 mmHg and 10 mmHg, respectively, to the measured values, as done in prior analyses[5,17]. Association statistics, in models adjusting for age, age^2, sex, and body mass index (BMI), were obtained for each study separately, with genomic control applied to correct for study-specific population structure. Fixed-effects meta-analysis proceeded in 4 stages, separately for the following associations: Stage 1, using results based on 46 studies using Cardio-MetaboChip genotypes of 109,096 participants; Stage 2, using additional results based on imputed genotypes from genome-wide genotyping arrays in 4 previously unpublished studies; Stage 3 using imputed genotypes from genome-wide genotyping arrays in 24 previously published studies[5]; and Stage 4, the joint meta-analysis of Stages 1-3 including a total of 201,529 independent individuals (**Supplementary Figure 1, Supplementary Tables 2-3, Supplementary Note**). To account for population structure between studies in Stages 1-3 of our meta-analysis, genomic control correction was applied in each of these stages. The "double" genomic control correction applied is the same approach as other published large-scale studies of quantitative cardio-metabolic traits that combine genotype data from GWAS and Cardio-MetaboChip [18,19].

At stage 4, 67 loci attained genome-wide significance ($P < 5 \times 10^{-8}$), 18 of which without prior support in the literature (**Supplementary Table 4**). Quantile-quantile plots (**Supplementary Figure 2**) of

the stage 4 meta-analysis showed an excess of small *P* values, with an elevated genomic control lambda estimate that were persistent, albeit attenuated, after excluding all 66 loci. This observation is compatible with either residual uncorrected population stratification or the presence of a large number of variants that are truly associated with BP but fail to achieve genome-wide significance in the current meta-analysis. The Cardio-MetaboChip array's inclusion of SNPs from a prior BP GWAS[5] does not appear to be the sole explanation, as we did not observe a significant decrease of the excess of small *P* values when we excluded all SNPs that were selected based on BP for the Cardio-MetaboChip. Given that the quantile-quantile plots continued to show deviation from the null expectation even after removing new, known, and additional variants related to BP (**Supplementary Figures 3 and 4**), we sought additional validation to support variants (N=18) attaining genome-wide significance, but without prior support in the literature, in up to 140,886 individuals of European ancestry from UK Biobank[20]. For these SNPs, stage 5 meta-analysis combined association summary statistics from stage 4 and UK Biobank, in a total of 342,415 individuals (**Supplementary Table 5**).

Upon stage 5 meta-analysis, 17 of 18 variants retained genome-wide significance for the primary trait (SBP or DBP result with lower *P* value). The one variant that was not genome-wide significant had a borderline *P* value of 4.49×10^{-8} at stage 4. These findings are consistent with appropriate calibration of the association test statistics at stage 4 such that observing one failure among 18 validation tests is consistent with the use of a threshold designed ($P < 5 \times 10^{-8}$) to have a 1 in 20 chance of a result as or more extreme solely due to chance.

In total, 66 loci attained genome-wide significance: 13 loci for SBP only, 12 loci for DBP only, and 41 for both traits. Of these, 17 BP loci were novel, while 49 were previously reported at genome-wide significance (**Table 1**). The new loci were defined based on mapping >1Mb from any previously established locus, with the exception of one region characterized by long-range LD spanning several mega-bases, which was considered a single locus. Plots of association results across the genome show the genomic features of each locus and SNP *P* values, with loci labeled arbitrarily according to the gene(s) nearest the lead SNP (**Figure 1**).

Compared with previous BP variants[5,7,21], the average absolute effect size of the newly discovered variants is smaller, although the minor allele frequency (MAF) is comparable, presumably owing to the increased power of a larger sample size (**Figure 2**). As expected from the high correlation between SBP and DBP values, the observed directions of effects for the two traits were generally concordant (**Supplementary Figure 5**), and the absolute effect sizes were inversely correlated with MAF (**Table 1** and **Supplementary Figure 6**). The 66 BP SNPs explained 3.46% and 3.36% of SBP and DBP

variance, respectively, an increase from 2.95% and 2.78% for SBP and DBP for the 49 previously reported SNPs alone (**Supplementary Note**). The low percent of variance explained is consistent with earlier estimates of large numbers of common variants of weak effects and a large number of genes influencing BP levels[5].

Signal refinement at the 66 BP loci

Quantitative trait associations are often reported in the literature based on a single index SNP, despite the fact that linkage disequilibrium (LD) to the causal variant can implicate many nearby variants. To identify distinct signals of association at the 66 BP loci and the variants most likely to be causal for each, we started with an approximate conditional analysis using a model selection procedure implemented in the GCTA-COJO package[22,23] as well as a detailed literature review of all published BP association studies. GCTA-COJO analysis was performed using the association summary statistics for SBP and DBP from the Stage 4 EUR ancestry meta-analyses, with the LD between variants estimated on the basis of Cardio-MetaboChip genotype data from 7,006 individuals of EUR ancestry from the GoDARTS cohort[24]. More than one distinct BP association signal was identified at 13 loci at $P < 5 \times 10^{-8}$ (**Supplementary Table 6**, **Supplementary Figures 7, and Supplementary Note**). At six loci, the distinct signals were identified in separate analyses of both SBP and DBP; these trait-specific associations were represented by the same or highly correlated ($r^2 > 0.8$) SNPs at 5 of the 6 loci (**Supplementary Tables 7-8**). We repeated GCTA-COJO analyses using the same summary association results, but with a different reference sample for LD estimates (WTCCC1-T2D/58BC, N = 2,947, **Supplementary Note**) and observed minimal differences arising from minor fluctuations in the association *P* value in the joint regression models (**Supplementary Table 7-8**). LD-based comparisons of published association signals at established BP loci, and the current study's findings suggested that at 10 loci, the signals identified by the single-SNP and the GCTA-COJO analyses were distinct from those in the literature (**Supplementary Table 9**).

We then performed multivariable regression modeling in a single large cohort (Women's Genome Health Study, WGHS, N = 23,047) with simultaneous adjustment for 1) all combinations of putative index SNPs for each distinct signal from the GCTA-COJO conditional analyses, and 2) all index SNPs for all potential distinct signals identified by our literature review (**Supplementary Table 9, Supplementary Note**). Although WGHS is very large as a single study, power is reduced in a single sample compared to that in the overall meta-analysis (23k vs. 201k individuals) and consequently the failure to reach significance does not represent non-replication for individual SNPs. The WGHS analysis

supported two distinct signals of association from the GCTA-COJO analysis at eight of 13 loci, but could not provide support for the remaining five loci (**Supplementary Table 10**). The joint SNP modeling in WGHS, however, indicated two distinct signals of association at three additional loci (*GUCY1A3-GUCY1B3*, *SYNPO2L* and *TBX5-TBX3*), at which the SNP identified in the current study is distinct from that previously reported in the literature[5,11].

Established loci often extend over hundreds of kilobases and contain many genes that could plausibly underlie the BP association. We sought to refine the localization of likely functional variants at loci with high-density coverage on the Cardio-MetaboChip. We followed a Bayesian approach and used the association summary statistics from the EUR ancestry meta-analyses to define, for each signal, credible sets of variants that have 99% probability of containing or tagging the causal variant (**Supplementary Note**). To improve the resolution of the method, the analyses were restricted to 24 regions selected to fine-map (FM) genetic associations, and that included at least one SNP reaching genome-wide significance in the current meta-analyses (**Supplementary Table 11**). Twenty-one of the Cardio-MetaboChip FM regions were BP loci in the original design, with three of the newly discovered BP loci in FM regions that were originally selected for other traits. We observed that the 99% credible sets at five BP loci spanned a small region, <10 kb (*PLCE1* and *SLC39A8* for SBP and DBP; *FGF5* for SBP, with <20kb for DBP; *JAG1* and *ZC3HC1* for DBP, with <20kb for SBP). The greatest refinement was observed at the *SLC39A8* locus for SBP and DBP, and at the *ZC3HC1* and *PLCE1* loci for DBP, where the 99% credible sets included only the index variants (**Supplementary Table 12**). Although credible sets mapped primarily to non-coding sequence, they included one synonymous and seven non-synonymous variants that attained high posterior probability of driving seven distinct association signals at six BP loci (**Supplementary Table 12**). Of these, three variants alone account for more than 95% of the posterior probability of driving the association signal observed at each of three loci: rs13107325 at the *SLC39A8* locus with posterior probability 99.4% for SBP and nearly 100% for DBP; rs1800562 at the *HFE* locus accounting for 98.1% of the posterior probability for DBP; and rs11556924 at the *ZC3HC1* locus with posterior probability 97.8% for SBP and 99.9% for DBP. Despite reduced statistical power, the analyses restricted to the samples with Cardio-MetaboChip genotypes only (N = 109,096) identified as credible causal SNPs the majority of those identified in the analyses of the GWAS+Cardio-MetaboChip data (**Supplementary Table 12**). Given that the Cardio-MetaboChip-only data included more eligible SNPs, a larger number of credible causal SNPs were identified. The full list of SNPs in the 99% credible sets are listed in **Supplementary Table 13**.

What do the BP SNPs do?

Index SNPs or their proxies ($r^2 > 0.8$) altered amino acid sequence at 11 of 66 BP loci (**Table 1**). Thus, the majority of BP-association signals are likely driven by non-coding variants hypothesized to regulate expression of some nearby gene in *cis*. To identify their effects we first sought SNPs associated with gene expression (eSNPs) from a range of available expression data which included hypertension target end organs and cells of the circulatory system (heart tissue, kidney tissue, brain tissue, aortic endothelial cells, blood vessels) and other tissue/cell types ($CD4^+$ macrophages, monocytes lymphoblastoid cell lines, skin tissue, fat tissue, and liver tissue). Fourteen BP SNPs at the *MTHFR-NPPB*, *MDM4*, *ULK4*, *CYP1A1-ULK3*, *ADM, FURIN-FES, FIGN,* and *PSMD5* loci were eSNPs across different tissues (**Supplementary Table 14)**. Of these 14 eSNPs, three were predicted to alter the amino acid sequence at the *MTHFR-NPPB*, *MAP4* and *ULK4* loci, providing two potential mechanisms to explore in functional studies. Second, we used gene expression levels measured in whole blood in two different samples each including >5,000 individuals of EUR descent. We tested whether the lead BP SNP was associated with expression of any transcript in *cis* (<1Mb from the lead SNP at each locus) at a false discovery rate (FDR) of < 0.05, accounting for all possible *cis*-transcript association tests genome-wide. It is likely that we did not genotype the causal genetic variant underlying a BP association signal. A nearby SNP-transcript association, due to LD, may therefore reflect an independent genetic effect on expression that is unrelated to the BP effect. Consequently, we assumed that the lead BP SNP and the most significant eSNP for a given transcript should be highly correlated ($r^2 > 0.7$). Furthermore, we assumed that the significance of the transcript association with the lead BP SNP should be substantially reduced in a conditional model adjusting for the best eSNP for a given transcript. Eighteen SNPs at 15 loci were associated with 22 different transcripts, with a total of 23 independent SNP-transcript associations (three SNPs were associated with two transcripts each, **Supplementary Table 15, Supplementary Note**). The genes expressed in a BP SNP allele-specific manner are clearly high-priority candidates to mediate the BP association. In whole blood, these genes included obvious biological candidates such as *GUCY1A3*, encoding the alpha subunit of the soluble guanylate cyclase protein, and *ADM*, encoding adrenomedullin, both of which are known to induce vasodilation[25,26]. There was some overlap of eSNPs between the whole blood and other tissue datasets at the *MTHFR-NPPB*, *MDM4*, *PSMD5*, *ULK4* and *CYP1A1-ULK3* loci, illustrating additional potentially causal genes for further study (*MTHFR* and *CLCN6*, *MDM4*, *PSMD5*, *ULK4*, *CYP1A1*, and *ULK3*).

An alternative method for understanding the effect on BP of non-coding variants is to determine whether they fall within DNaseI hypersensitivity sites (DHSs). DHSs represent open regions of chromatin

that are accessible to protein binding and can indicate transcriptional activity. We performed two analyses to investigate whether BP SNPs or their LD proxies ($r^2 > 0.8$) were enriched in DHSs in a cell-type-specific manner (**Supplementary Note**). First, we used Epigenomics Roadmap and ENCODE DHS data from 123 adult cell lines or tissues[27-29] to estimate the fold increase in the proportion of BP SNPs mapping to DHSs compared to SNPs associated at genome-wide significance with non-BP phenotypes from the NHGRI GWAS catalog[30]. We observed that 7 out of the 10 cell types with the greatest relative enrichment of BP SNPs mapping to DHSs were from blood vessels (vascular or micro-vascular endothelial cell-lines or cells) and 11 of the 12 endothelial cells were among the top quarter most enriched among the 123 cell types (**Figure 3** and **Supplementary Table 16**). In a second analysis of an expanded set of tissues and cell lines, in which cell types were grouped into tissues (**Supplementary Table 17**), BP-associated SNP enrichment in DHSs in blood vessels was again observed ($P = 1.2 \times 10^{-9}$), as well as in heart samples ($P = 5.3 \times 10^{-8}$; **Supplementary Table 18**).

We next tested whether there was enrichment of BP SNPs in H3K4me3[31] sites, a methylation mark associated with both promoter and enhancer DNA. We observed significant enrichment in a range of cell types including CD34 primary cells, adult kidney cells, and muscle satellite cultured cells (**Supplementary Table 19)**. Enrichment of BP SNPs in predicted strong and weak enhancer states and in active promoters[32] in a range of cell types was also observed (**Supplementary Table 20, Supplementary Figure 8**).

We used Meta-Analysis Gene-set Enrichment of variaNT Associations (MAGENTA)[33] to attempt to identify pathways over-represented in the BP association results. No gene sets meeting experiment-wide significance for enrichment for BP association were identified by MAGENTA after correction for multiple testing, although some attained nominal significance (**Supplementary Table 21**, **Supplementary Note**). We also adapted the DEPICT[34] pathway analysis tool (Data-driven Expression Prioritized Integration for Complex Traits) to identify assembled gene-sets that are enriched for genes near associated variants, and to assess whether genes from associated loci were highly expressed in particular tissues or cell types. Using the extended BP locus list based on genome-wide significant loci from this analysis and previously published SNPs that may not have reached genome-wide significance in the current analysis (**Supplementary Table 9**), we identified six significant (FDR ≤ 5%) gene sets: embryonic growth retardation, abnormal cardiovascular system physiology, abnormal cardiac muscle contractility, SNTB1 protein complex, G Alpha 1213 signaling events, and prolonged QRS complex duration. We also found that suggestive SBP and DBP associations ($P < 1 \times 10^{-5}$) were enriched for reconstituted gene-sets at DBP loci (mainly related to developmental pathways), but not at SBP loci

(**Supplementary Table 22**, **Supplementary Note**). In a final analysis, we assessed Cardio-MetaboChip SNPs at the fine-mapping loci using formaldehyde-assisted isolation of regulatory elements (FAIRE-gen) in lymphoblastoid cell lines[35]. Our results provided support for two SNPs, one of which SNP (rs7961796 at the *TBX5-TBX3* locus) was located in a regulatory site. Although the other SNP (rs3184504 at the *SH2B3* locus) is a non-synonymous variant, there was also a regulatory site indicated by DNaseI and H3K4me1 signatures at the locus, making the SNP a potential regulatory variant (**Supplementary Table 23**)[36]. Both SNPs were included in the list of 99% credible SNPs at each locus.

Asian- and African ancestry BP SNP association

We tested the 66 lead SNPs at the established and novel loci for association with BP in up to 20,875 individuals of South Asian (SAS) ancestry, 9,637 individuals of East Asian (EAS) ancestry, and 33,909 individuals of AFR ancestry. As expected, the effect allele frequencies are very similar across studies of the same ethnicity, but markedly different across different ancestry groups (**Supplementary Figure 9**). Many associations of individual SNPs failed to reach $P < 0.05$ for the BP trait with the lower P value (**Supplementary Table 24**), which could potentially be due to the much lower statistical power at the sample sizes available, different patterns of LD at each locus across ancestries, variability in allele frequency, or true lack of association in individuals of non-European ancestry. The low statistical power for the great majority of SNPs tested is visible considering SNP-by-SNP power calculations using European ancestry effect sizes (**Supplementary Table 24**). However, concordant directions of allelic effects for both SBP and DBP were observed for 45/66 SNPs in SAS, 36/60 SNPs in EAS, and 42/66 SNPs in AFR samples: the strongest concordance with SAS is not surprising because South Asians are more closely related to Europeans than are East Asians or Africans. Moreover, strong correlation of effect sizes was observed between EUR samples with SAS, EAS, or AFR samples (r = 0.55, 0.60, and 0.48, respectively). To test the overall effect of ancestry, where the BP effect may be detectable at only a subset of SNPs, a more powerful test is to construct a combined risk score weighted by allele-specific effects across 66 index SNPs, separately for SBP and DBP, as a predictor of BP in each population sample. A shortcoming of the use of a score test aggregating effects across multiple variants is that they obscure the subset of variants that does not show reliable association in multiple ethnicities. The score represents the predicted mm Hg change for an individual based on their genotype at all 66 SNPs. The SBP and DBP risk scores were significant predictors of SBP and DBP, respectively, in all samples. The change in risk score associated with a 1 mm Hg higher SBP/DBP in EUR samples was associated with a 0.58/0.50 mm Hg higher SBP/DBP in SAS samples (SBP $P = 1.5 \times 10^{-19}$, DBP $P = 3.2 \times 10^{-15}$), 0.49/0.50 mm

Hg SBP/DBP in EAS samples (SBP $P = 1.9 \times 10^{-10}$, DBP $P = 1.3 \times 10^{-7}$), and 0.51/0.47 mm Hg SBP/DBP in AFR samples (SBP $P = 2.2 \times 10^{-21}$, DBP $P = 6.5 \times 10^{-19}$). The attenuation of the genetic risk score estimates in non-European ancestries is presumably due to inclusion of a subset of variants that lack association in the non-European samples. In the admixed populations tested (mainly African ancestry studies), the degree of European admixture influences the extent of association. We subsequently performed a trans-ethnic meta-analysis of the 66 SNPs in all 64,421 samples across the three non-European ancestries. After correcting for 66 tests, 12/66 SNPs were significantly associated with either SBP or DBP ($P < 7.6 \times 10^{-4}$), with a correlation of EUR and non-EUR effect estimates of 0.77 for SBP and 0.67 for DBP; the European-ancestry SBP or DBP risk score was associated with 0.53/0.48 mm Hg higher BP per predicted mm Hg SBP/DBP respectively (SBP $P < 6.6 \times 10^{-48}$, DBP $P < 1.3 \times 10^{-38}$). For 7 of the 12 significant SNPs, no association has previously been reported in genome-wide studies of non-European ancestry. While some heterogeneity of effects was observed between European and non-European effect estimates (Cochran's Q p-value <0.05 for 30/132 tests), these were not distinguishable from chance effects when considering a multiple test correction (**Supplementary Table 24**). Taken together, these findings suggest that, in aggregate, BP loci identified using data from individuals of EUR ancestry are also predictive of BP in non-EUR samples, but larger non-European sample sizes will be needed to establish precisely which individual SNPs are associated in a given ethnic group.

Impact on hypertensive target organ damage

Long-term elevated BP causes target organ damage, especially in the heart, kidney, brain, large blood vessels, and the retinal vessels[37]. Consequently, the genetic effect of the 66 SBP and DBP SNPs on end-organ outcomes can be directly tested using the risk score, although some outcomes lacked results for a small number of SNPs. Interestingly, BP risk scores significantly predicted (**Supplementary Note**) coronary artery disease risk, left ventricular mass and wall thickness, stroke, urinary albumin/creatinine ratio, carotid intima-medial thickness and central retinal artery caliber, but not heart failure or other kidney phenotypes, after accounting for the number of outcomes examined (**Table 2**). Some SNPs could contribute to the risk score with effects that are stronger or weaker than their BP effects would suggest when considering all BP variants collectively. We sought to test the robustness of our risk scores to removal of SNPs with such outlier effects. We therefore repeated the risk score analysis removing iteratively SNPs that contributed to statistical heterogeneity (SNP trait effects relative to SNP BP effects). Heterogeneity was defined based on a multiple testing adjusted significance threshold for Cochran's Q test of homogeneity of effects (**Supplementary Note**). The risk score analyses restricted to the subset of

SNPs showing no heterogeneity of effect revealed essentially identical results, with the exception that urinary albumin/creatinine ratio was no longer significant. The per-SNP results are provided in **Supplementary Table 25** and **Supplementary Figures 10.** Because large-scale GWAS of non-BP cardiovascular risk factors are available, we examined the BP risk scores as predictors of other cardiovascular risk factors: LDL-cholesterol, HDL-cholesterol, triglycerides, type 2 diabetes, BMI, and height. We observed nominal (P <0.05) associations of the BP risk scores with risk factors, although mostly in the opposite direction to the risk factor-CVD association (**Supplementary Table 26**). The failure to demonstrate an effect of hypertension on heart failure may reflect power from a modest sample size, but the lack of significant effects on renal measures suggests that the epidemiologic relationship of higher BP and worse renal function may not reflect direct consequences of BP elevation.

DISCUSSION

The study reported here is the largest to date to investigate the genomics of BP in multiple continental ancestries. Our results highlight four major features of inter-individual variation in BP: (1) we identified 66 (17 novel) genome-wide significant loci for SBP and DBP by targeted genotyping of up to 342,415 individuals of European ancestry that cumulatively explain ~3.5% of the trait variance (novel loci validated using data from additional 140,886 individuals); (2) the variants were enriched for *cis*-regulatory elements, particularly in vascular endothelial cells; (3) the variants had broadly comparable BP effects in South Asians, East Asian and Africans, albeit in smaller sample sizes; and, (4) a 66 SNP risk-score predicted target organ damage in the heart, cerebral vessels, carotid artery and the eye with little evidence for an effect in kidneys. Overall, there was no enrichment of a single genetic pathway in our data; rather, our results are consistent with the effects of BP arising from multiple tissues and organs.

Genetic and molecular analyses of Mendelian syndromes of hypertension and hypotension point to a renal origin, involving multiple rare deleterious mutations in proteins that regulate salt-water balance[38]. This is strong support for Guyton's hypothesis that the regulation of sodium excretion by the kidney and its effects on extracellular volume is the main pathway determining intra-arterial pressure[39]. However, our genetic data from unselected individuals in the general community argues against a single dominant renal effect.

First, the 66 SNPs we identified are not chance effects, but have a global distribution and impact on BP that are consistent as measured by their effects across the many studies meta-analyzed. That they are polymorphic across all continental ancestries argues for their origin and functional effects prior to human continental differentiation.

The adrenergic autonomic system has been considered an important mediator of BP regulation, and is targeted by beta-adrenergic antagonists for the treatment of hypertension. The SNP rs6271 lies within the coding sequence of the dopamine beta hydroxylase gene (*DBH*), encoding the enzyme that catalyzes the conversion of dopamine to norepinephrine, a critical neurotransmitter and effector of sympathetic control of BP. The variant results in an arginine to cysteine amino acid change at the highly conserved position 549 (R549C) and is predicted to be potentially damaging by Polyphen2. Rare loss-of-function mutations in this gene are associated with low plasma dopamine beta hydroxylase activity, low plasma norepinephrine and high plasma dopamine, and a clinical syndrome including orthostatic hypotension[40,41]. Several of the 17 novel loci contain other strong biological candidates; these are described in greater detail in **Supplementary Table 27 and** the **Supplementary Note**.

The single most common feature we identified was the enrichment of regulatory elements for gene expression in vascular endothelial cells. The broad distribution of these cells across both large and small vessels and across all tissues and organs suggest that functional variation in these cells affect endothelial permeability or vascular smooth muscle cell contractility via multiple pathways. These hypotheses will need to be rigorously tested, in appropriate models, to assess the contribution of these pathways to BP control, and these pathways could be targets for systemic anti-hypertensive therapy as they are for the pulmonary circulation[42]. In summary, the genetic observations will contribute to a new and improved understanding of BP biology and a re-evaluation of the pathways considered relevant for therapeutic BP control.

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SUPPLEMENTARY NOTE

Supplementary Note is available in the online version of the paper.

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AUTHOR CONTRIBUTIONS

See Supplementary Note for Author Contributions.

AUTHOR INFORMATION

The authors declare competing financial interests (see corresponding section in the **Supplementary Note).**

TABLE LEGENDS

Table 1. SBP and DBP association at 66 loci.

Meta-analysis results of up to 342,415 individuals of European ancestry for SBP and DBP: Established and new loci are grouped separately. Nearest genes are shown as locus labels but this should not be interpreted as support that the causal gene is the nearest gene. The lead SNP with the lowest *P* value for either BP trait is shown as the lead SNP and both SBP and DBP results are presented even if both are not genome-wide significant. The SNP effects are shown according to the effect in mm Hg per copy of the coded allele (that is the allele coded 0, 1, 2) under an additive genetic model. "*" in the lead SNP column indicates a non-synonymous coding SNP (either the SNP itself or another SNP in r^2 >0.8). # Established loci have smaller total sample sizes relative to novel loci (see **Supplementary Note**).

Table 2. Prediction of hypertensive target organ damage by a multi-BP SNP score.

Shown are the estimated effects of a BP risk score comprised of up to 66 SNPs (see column "Total #SNPs") on risk of dichotomous outcome (as odds ratios) or increment in continuous measures per predicted mmHg of the SBP or DBP score. The effect sizes are expressed as incremental change in the phenotype for quantitative traits and natural logarithm of the odds ratio for binary traits, per 1 mmHg predicted increase in SBP or DBP. *P* values are bolded if they meet an analysis-wide significance threshold (< 0.05/18 = 0.0028). Results for all SNPs ("all") and for pruned results ("p") are shown. The pruned results were obtained by iterative removal of SNPs from the risk score starting with the SNP with lowest heterogeneity *P* value. Iterations to remove SNPs were continued until the heterogeneity *P* value was < 0.0028 (see **Supplementary Note**). The number of SNPs removed when calculating the pruned results is indicated by "# SNPs rem.". The results per individual SNP can be found in **Supplementary Table 15**. CAD: coronary artery disease, LV: left ventricle, CKD: chronic kidney disease, eGFR: estimated glomerular filtration rate, cr: creatinine, cIMT: carotid intima: media thickness. Var. type denotes the variable type and cont. for continuous, or dic. for dichotomous. Eth. = Ethnicity, Consort. = Consortium, EUR = European ancestry, EAS = East Asian ancestry.

1 Table 1. New and known BP loci.

Locus no.	Locus name	Lead SNP	Chr	Position (hg19)	CA /NC	Coded allele freq	Traits	SBP				DBP			
								Effect	SE	*P* value	Total N	Effect	SE	*P* value	Total N#
NEW 1	***HIVEP3***	rs7515635	1	42,408,070	T/C	0.468	**SBP**	**0.307**	**0.0444**	**4.81E-12**	**340,969**	0.1365	0.0263	2.05E-07	340,934
NEW 2	***PNPT1***	rs1975487	2	55,809,054	A/G	0.464	**DBP**	-0.2107	0.045	2.81E-06	337,522	**-0.1602**	**0.0266**	**1.75E-09**	**337,517**
NEW 3	***FGD5***	rs11128722	3	14,958,126	A/G	0.563	**SBP** & DBP	**-0.3103**	**0.0469**	**3.61E-11**	**310,430**	**-0.1732**	**0.0279**	**5.16E-10**	**310,429**
NEW 4	***ADAMTS9***	rs918466	3	64,710,253	A/G	0.406	**DBP**	-0.0865	0.0459	5.94E-02	336,671	**-0.1819**	**0.027**	**1.73E-11**	**336,653**
NEW 5	***TBC1D1-FLJ13197***	rs2291435	4	38,387,395	T/C	0.524	**SBP** & DBP	**-0.3441**	**0.0449**	**1.90E-14**	**331,382**	**-0.156**	**0.0266**	**4.26E-09**	**331,389**
NEW 6	***TRIM36***	rs10077885	5	114,390,121	A/C	0.501	SBP & **DBP**	**-0.284**	**0.0444**	**1.64E-10**	**338,328**	**-0.1735**	**0.0263**	**3.99E-11**	**338,323**
NEW 7	***CSNK1G3***	rs6891344	5	123,136,656	A/G	0.819	**DBP**	0.2811	0.058	1.24E-06	338,688	**0.2311**	**0.0343**	**1.58E-11**	**338,678**
NEW 8	***CHST12-LFNG***	rs2969070	7	2,512,545	A/G	0.639	SBP & **DBP**	**-0.2975**	**0.0464**	**1.44E-10**	**335,991**	**-0.1821**	**0.0274**	**2.92E-11**	**335,972**
NEW 9	***ZC3HC1***	rs11556924	7	129,663,496	T/C	0.384	SBP & **DBP**	**-0.2705**	**0.0468**	**7.64E-09**	**325,929**	**-0.2141**	**0.0276**	**8.15E-15**	**325,963**
NEW 10	***PSMD5***	rs10760117	9	123,586,737	T/G	0.415	**SBP**	**0.283**	**0.0457**	**6.10E-10**	**333,377**	0.0999	0.0269	2.08E-04	333,377
NEW 11	***DBH***	rs6271*	9	136,522,274	T/C	0.072	SBP & **DBP**	**-0.5911**	**0.0899**	**4.89E-11**	**306,394**	**-0.4646**	**0.0532**	**2.42E-18**	**306,463**
NEW 12	***RAPSN, PSMC3, SLC39A13***	rs7103648	11	47,461,783	A/G	0.614	SBP & **DBP**	**-0.3349**	**0.0462**	**4.43E-13**	**335,614**	**-0.2409**	**0.0272**	**9.03E-19**	**335,592**
NEW 13	***LRRC10B***	rs751984	11	61,278,246	T/C	0.879	SBP & **DBP**	**0.4074**	**0.0691**	**3.80E-09**	**334,583**	**0.3755**	**0.0409**	**4.20E-20**	**334,586**
NEW 14	***SETBP1***	rs12958173	18	42,141,977	A/C	0.306	**SBP** & DBP	**0.3614**	**0.0489**	**1.43E-13**	**331,007**	**0.1789**	**0.0289**	**5.87E-10**	**331,010**
NEW 15	***INSR***	rs4247374	19	7,252,756	T/C	0.143	SBP & **DBP**	**-0.5933**	**0.0673**	**1.23E-18**	**302,458**	**-0.3852**	**0.0396**	**2.08E-22**	**302,459**
NEW 16	***ELAVL3***	rs17638167	19	11,584,818	T/C	0.047	**DBP**	-0.4784	0.1066	7.13E-06	333,137	**-0.3479**	**0.0632**	**3.71E-08**	**333,107**
NEW 17	***CRYAA-SIK1***	rs12627651	21	44,760,603	A/G	0.288	**SBP** & DBP	**0.3905**	**0.0513**	**2.69E-14**	**310,738**	**0.2037**	**0.0301**	**1.36E-11**	**310,722**
EST 1	***CASZ1***	rs880315	1	10,796,866	T/C	0.641	**SBP** & DBP	**-0.475**	**0.062**	**2.09E-14**	**184,226**	**-0.257**	**0.038**	**1.34E-11**	**184,212**
EST 2	***MTHFR-NPPB***	rs17037390	1	11,860,843	A/G	0.155	**SBP** & DBP	**-0.908**	**0.081**	**5.95E-29**	**195,493**	**-0.499**	**0.05**	**1.20E-23**	**195,481**
EST 3	***ST7L-CAPZA1-MOV10***	rs1620668	1	113,023,980	A/G	0.822	**SBP** & DBP	**-0.535**	**0.076**	**1.45E-12**	**197,966**	**-0.285**	**0.047**	**9.00E-10**	**197,948**
EST 4	***MDM4***	rs4245739	1	204,518,842	A/C	0.737	**DBP**	0.326	0.068	1.37E-06	191,594	**0.243**	**0.041**	**4.63E-09**	**191,578**
EST 5	***AGT***	rs2493134*	1	230,849,359	T/C	0.579	SBP & **DBP**	**-0.413**	**0.058**	**9.65E-13**	**199,505**	**-0.275**	**0.036**	**9.53E-15**	**199,502**
EST 6	***KCNK3***	rs2586886	2	26,932,031	T/C	0.599	SBP & **DBP**	**-0.404**	**0.059**	**5.94E-12**	**197,269**	**-0.254**	**0.036**	**1.92E-12**	**197,272**
EST 7	***NCAPH***	rs772178	2	96,963,684	A/G	0.64	**DBP**	-0.072	0.061	2.39E-01	192,513	**-0.208**	**0.038**	**3.58E-08**	**192,501**
EST 8	***FIGN-GRB14***	rs1371182	2	165,099,215	T/C	0.443	**SBP** & DBP	**-0.444**	**0.058**	**1.89E-14**	**196,262**	**-0.252**	**0.036**	**1.50E-12**	**196,240**
EST 9	***HRH1-ATG7***	rs2594992	3	11,360,997	A/C	0.607	**SBP**	**-0.334**	**0.06**	**2.31E-08**	**189,895**	-0.136	0.037	2.20E-04	189,854
EST 10	***SLC4A7***	rs711737	3	27,543,655	A/C	0.604	**SBP**	**0.334**	**0.058**	**9.93E-09**	**200,282**	**0.17**	0.036	2.24E-06	200,260
EST 11	***ULK4***	rs2272007*	3	41,996,136	T/C	0.18	**DBP**	-0.11	0.077	1.52E-01	193,915	**0.328**	**0.047**	**3.94E-12**	**193,900**
EST 12	***MAP4***	rs6442101*	3	48,130,893	T/C	0.692	SBP & **DBP**	**0.396**	**0.062**	**1.62E-10**	**200,543**	**0.303**	**0.038**	**1.60E-15**	**200,534**
EST 13	***MECOM***	rs6779380	3	169,111,915	T/C	0.539	**SBP** & DBP	**-0.439**	**0.06**	**1.85E-13**	**186,535**	**-0.239**	**0.037**	**6.87E-11**	**186,521**
EST 14	***FGF5***	rs1458038	4	81,164,723	T/C	0.3	**SBP** & DBP	**0.659**	**0.065**	**5.36E-24**	**188,136**	**0.392**	**0.04**	**7.36E-23**	**188,088**
EST 15	***ARHGAP24***	rs17010957	4	86,719,165	T/C	0.857	**SBP**	**-0.498**	**0.082**	**1.51E-09**	**196,325**	-0.173	0.051	6.63E-04	196,292
EST 16	***SLC39A8***	rs13107325	4	103,188,709	T/C	0.07	SBP & **DBP**	**-0.837**	**0.127**	**4.69E-11**	**175,292**	**-0.602**	**0.078**	**1.63E-14**	**175,372**
EST 17	***GUCY1A3-GUCY1B3***	rs4691707	4	156,441,314	A/G	0.652	**SBP**	**-0.349**	**0.06**	**7.10E-09**	**198,246**	-0.163	0.037	1.08E-05	198,226
EST 18	***NPR3-C5orf23***	rs12656497	5	32,831,939	T/C	0.403	**SBP** & DBP	**-0.487**	**0.06**	**3.85E-16**	**194,831**	**-0.228**	**0.037**	**4.73E-10**	**194,829**
EST 19	***EBF1***	rs11953630	5	157,845,402	T/C	0.366	**SBP** & DBP	**-0.38**	**0.065**	**3.91E-09**	**167,698**	**-0.23**	**0.04**	**8.07E-09**	**167,708**
EST 20	***HFE***	rs1799945*	6	26,091,179	C/G	0.857	SBP & **DBP**	**-0.598**	**0.086**	**3.28E-12**	**185,306**	**-0.43**	**0.053**	**3.10E-16**	**185,273**
EST 21	***BAT2-BAT5***	rs2187668	6	32,605,884	T/C	0.126	**DBP**	-0.291	0.092	1.60E-03	189,806	**-0.372**	**0.057**	**4.31E-11**	**189,810**
EST 22	***ZNF318-ABCC10***	rs6919440	6	43,352,898	A/G	0.57	**SBP**	**-0.337**	**0.058**	**4.92E-09**	**200,733**	-0.125	0.035	4.25E-04	200,730
EST 23	***RSPO3***	rs1361831	6	127,181,089	T/C	0.541	**SBP** & DBP	**-0.482**	**0.058**	**7.38E-17**	**197,027**	**-0.271**	**0.036**	**2.34E-14**	**197,012**
EST 24	***PLEKHG1***	rs17080093	6	150,997,440	T/C	0.075	**DBP**	-0.564	0.111	3.83E-07	194,728	**-0.411**	**0.068**	**1.71E-09**	**194,734**
EST 25	***HOTTIP-EVX***	rs3735533	7	27,245,893	T/C	0.081	**SBP** & DBP	**-0.798**	**0.106**	**6.48E-14**	**197,881**	**-0.445**	**0.065**	**1.09E-11**	**197,880**
EST 26	***PIK3CG***	rs12705390	7	106,410,777	A/G	0.227	**SBP**	**0.619**	**0.069**	**2.69E-19**	**198,297**	0.059	0.042	1.63E-01	198,290
EST 27	***BLK-GATA4***	rs2898290	8	11,433,909	T/C	0.491	**SBP**	**0.377**	**0.058**	**8.85E-11**	**197,759**	0.167	0.036	3.17E-06	197,726
EST 28	***CACNB2***	rs12243859	10	18,740,632	T/C	0.326	SBP & **DBP**	**-0.402**	**0.061**	**6.13E-11**	**199,136**	**-0.335**	**0.038**	**8.11E-19**	**199,124**
EST 29	***C10orf107***	rs7076398	10	63,533,663	A/T	0.188	SBP & **DBP**	**-0.563**	**0.076**	**1.72E-13**	**187,013**	**-0.409**	**0.047**	**2.55E-18**	**187,024**
EST 30	***SYNPO2L***	rs12247028	10	75,410,052	A/G	0.611	**SBP**	**-0.364**	**0.063**	**8.16E-09**	**180,194**	-0.159	0.039	3.89E-05	180,094
EST 31	***PLCE1***	rs932764*	10	95,895,940	A/G	0.554	**SBP** & DBP	**-0.495**	**0.059**	**6.88E-17**	**195,577**	**-0.224**	**0.036**	**6.28E-10**	**195,547**
EST 32	***CYP17A1-NT5C2***	rs943037	10	104,835,919	T/C	0.087	**SBP** & DBP	**-1.133**	**0.105**	**2.35E-27**	**193,818**	**-0.482**	**0.064**	**4.48E-14**	**193,799**
EST 33	***ADRB1***	rs740746	10	115,792,787	A/G	0.73	SBP & **DBP**	**0.486**	**0.067**	**4.59E-13**	**184,835**	**0.32**	**0.041**	**8.63E-15**	**184,868**
EST 34	***LSP1-TNNT3***	rs592373	11	1,890,990	A/G	0.64	**SBP** & DBP	**0.484**	**0.063**	**2.02E-14**	**177,149**	**0.282**	**0.039**	**3.61E-13**	**177,134**
EST 35	***ADM***	rs1450271	11	10,356,115	T/C	0.468	**SBP** & DBP	**0.413**	**0.059**	**3.40E-12**	**191,246**	**0.199**	**0.036**	**4.11E-08**	**191,221**
EST 36	***PLEKHA7***	rs1156725	11	16,307,700	T/C	0.804	SBP & **DBP**	**-0.447**	**0.072**	**5.65E-10**	**200,889**	**-0.292**	**0.044**	**3.67E-11**	**200,899**
EST 37	***SIPA1***	rs3741378*	11	65,408,937	T/C	0.137	**SBP**	**-0.486**	**0.084**	**8.04E-09**	**194,563**	-0.183	0.052	4.17E-04	194,551
EST 38	***FLJ32810-TMEM133***	rs633185	11	100,593,538	C/G	0.715	**SBP** & DBP	**0.522**	**0.067**	**6.97E-15**	**183,845**	**0.288**	**0.041**	**2.38E-12**	**183,825**
EST 39	***PDE3A***	rs3752728	12	20,192,972	A/G	0.737	**DBP**	0.331	0.066	4.32E-07	200,440	**0.319**	**0.04**	**2.35E-15**	**200,408**
EST 40	***ATP2B1***	rs11105354	12	90,026,523	A/G	0.84	**SBP** & DBP	**0.909**	**0.081**	**3.88E-29**	**195,206**	**0.459**	**0.05**	**2.61E-20**	**195,195**
EST 41	***SH2B3***	rs3184504*	12	111,884,608	T/C	0.475	SBP & **DBP**	**0.498**	**0.062**	**9.97E-16**	**177,067**	**0.362**	**0.038**	**1.28E-21**	**177,122**
EST 42	***TBX5-TBX3***	rs2891546	12	115,552,499	A/G	0.11	**DBP**	-0.529	0.1	1.36E-07	172,012	**-0.38**	**0.061**	**4.71E-10**	**171,980**
EST 43	***CYP1A1-ULK3***	rs936226	15	75,069,282	T/C	0.722	SBP & **DBP**	**-0.549**	**0.067**	**3.06E-16**	**187,238**	**-0.363**	**0.041**	**1.03E-18**	**187,221**
EST 44	***FURIN-FES***	rs2521501	15	91,437,388	A/T	0.684	**SBP** & DBP	**-0.639**	**0.069**	**3.35E-20**	**164,272**	**-0.358**	**0.042**	**1.85E-17**	**164,255**
EST 45	***PLCD3***	rs7213273	17	43,155,914	A/G	0.658	**SBP**	**-0.413**	**0.066**	**4.71E-10**	**164,795**	**-0.185**	0.041	7.23E-06	164,788
EST 46	***GOSR2***	rs17608766	17	45,013,271	T/C	0.854	**SBP**	**-0.658**	**0.083**	**2.27E-15**	**188,895**	-0.218	0.051	1.95E-05	188,928
EST 47	***ZNF652***	rs12940887	17	47,402,807	T/C	0.38	**DBP**	0.321	0.06	7.06E-08	192,546	**0.261**	**0.037**	**1.07E-12**	**192,524**
EST 48	***JAG1***	rs1327235	20	10,969,030	A/G	0.542	SBP & **DBP**	**-0.395**	**0.059**	**2.23E-11**	**192,680**	**-0.308**	**0.036**	**1.78E-17**	**192,659**
EST 49	***GNAS-EDN3***	rs6026748	20	57,745,815	A/G	**0.125**	SBP & **DBP**	**0.867**	**0.089**	**3.15E-22**	**192,338**	**0.552**	**0.055**	**4.86E-24**	**192,327**

Table 2. BP risk score effects on disease outcomes.

Phenotype	Var. type (cont./ dic.)	Eth.	Consort.	Total N or no. ca/co	Total #SNPs	SBP_score					DBP_score				
						effect (all)	*P* value (all)	het. *P* value (all)	*P* value (p)	# SNPs rem.	effect (all)	*P* value (all)	het. *P* value (all)	*P* value (p)	# SNPs rem.
HEART															
CAD	dich.	EUR SAS	CARDIoGRAMplusC4D	63,746 /130,681	61	1.042	**1.72E-44**	1.75E-25	**4.08E-32**	10	1.069	**1.19E-42**	6.63E-27	**2.2E-38**	10
heart failure	dich.	EUR	CHARGE	2,526 /18,400	66	1.021	2.77E-02	1.63E-01	2.77E-02	0	1.035	2.31E-02	1.70E-01	2.31E-02	0
LV mass	cont.	EUR	CHARGE	11,273	66	0.480	**6.43E-04**	3.58E-01	**6.43E-04**	0	0.754	**1.23E-03**	3.21E-01	**1.23E-03**	0
LV wall thickness	cont.	EUR	CHARGE	11,311	66	0.004	**4.45E-06**	5.83E-02	**4.45E-06**	0	0.007	**3.19E-06**	6.40E-02	**3.19E-06**	0
KIDNEY															
CKD	dich.	EUR	CHARGE	6,271 /68,083	65	1.010	1.37E-01	1.77E-03	2.65E-01	1	1.008	4.49E-01	1.25E-03	7.69E-01	1
eGFR (based on cr)	cont.	EUR	CHARGE	74,354	65	0.000	7.07E-01	3.12E-05	3.22E-01	2	0.000	9.41E-01	3.02E-05	9.65E-01	2
eGFR (based on cystatin)	cont.	EUR	CHARGE	74,354	65	0.001	9.05E-02	9.28E-06	4.11E-01	1	0.001	3.30E-01	5.64E-06	6.9E-01	1
creatinine	cont.	EUR	KidneyGEN	23,812	66	0.000	9.42E-01	6.31E-03	9.42E-01	0	0.000	4.11E-01	7.16E-03	4.11E-01	0
microalbuminuria	dich.	EUR	CHARGE	2,499 /29,081	65	0.011	2.10E-01	4.79E-02	2.1E-01	0	0.023	1.02E-01	5.66E-02	1.02E-02	0
urinary albumin/cr ratio	cont.	EUR	CHARGE	31,580	65	0.009	**2.52E-03**	3.02E-04	0.53E-03	1	0.015	**2.40E-03**	3.08E-04	8.31E-03	1
STROKE															
stroke, all subtypes	dich.	EUR	CHARGE	1,544 /18,058	66	0.056	**6.11E-06**	8.26E-02	**6.11E-06**	0	0.085	**3.79E-05**	4.98E-02	**3.79E-05**	0
stroke, ischemic subtype	dich.	EUR	CHARGE	1,164 /18,438	66	0.067	**3.33E-06**	1.75E-01	**3.33E-06**	0	0.096	**5.63E-05**	8.82E-02	**5.63E-05**	0
stroke, ischemic subtype	dich.	EUR	MetaStroke	11,012 /40,824	66	0.036	**1.69E-10**	4.72E-02	**1.69E-10**	0	0.056	**1.29E-09**	2.51E-02	**1.29E-09**	0
VASCULATURE															
cIMT	cont.	EUR	CHARGE	27,610	66	0.004	**4.80E-15**	5.06E-08	**7.32E-10**	4	0.005	**4.15E-11**	3.84E-10	**6.2E-07**	5
EYE															
mild retinop.	dich.	EUR	CHARGE	1,122 /18,289	66	1.021	1.37E-01	6.01E-03	1.37E-01	0	1.046	5.78E-02	7.81E-03	5.78E-02	0
central retinal artery caliber	cont.	EUR	CHARGE	18,576	66	0.343	**3.29E-14**	2.56E-06	**2.06E-13**	2	0.570	**3.61E-14**	2.44E-06	**7.05E-13**	3
mild retinop.	dich.	EAS	SEED	289 /5,419	66	1.033	2.55E-01	2.42E-01	2.55E-01	0	1.087	8.55E-02	2.87E-01	8.55E-02	0
central retinal artery caliber	cont.	EAS	SEED	6,976	63	0.320	**1.39E-04**	9.07E-01	**1.39E-04**	0	0.533	**2.19E-04**	8.91E-01	**2.19E-04**	0

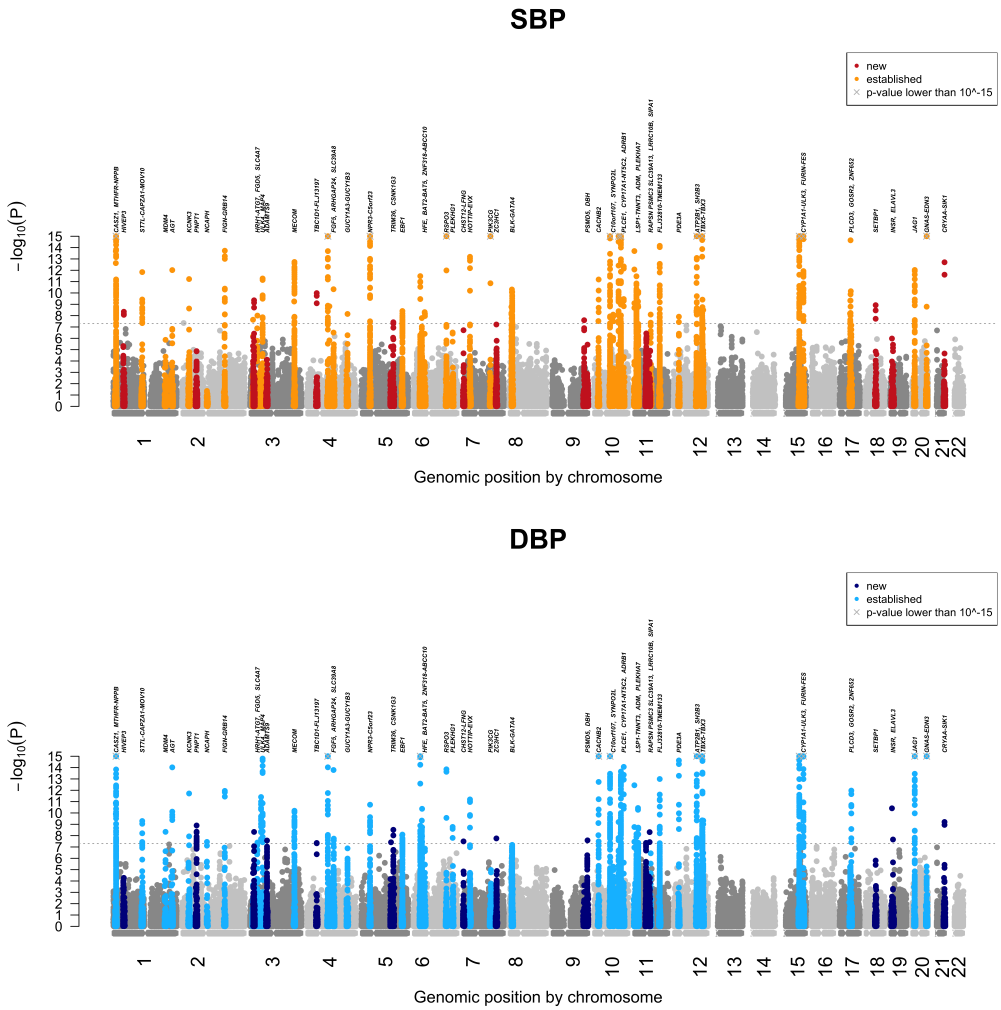

Figure 1. Manhattan plots for SBP and DBP from the stage 4 Cardio-MetaboChip-wide meta-analysis. P values (expressed as $-log_{10}P$) are plotted by physical genomic position labeled by chromosome. SNPs in new loci (3.5MB window around the index SNP), identified in this study, are labeled in dark red (SBP) or dark blue (DBP); SNPs in previously known loci are labeled in orange (SBP) or light blue (DBP). The locus names are indicated. The grey crosses indicate genomic positions at which the y-axis was truncated (SNPs with $P < 10^{-15}$).

	17 new loci	49 established loci	all 66 loci
Minor allele frequency, (mean, range)	32.1% [5%-50%]	28.9% [7%-49%]	29.8% [5%-50%]
Effect size SBP [mmHg], (range, mean)	0.09-0.59 0.34	0.07-1.13 0.5	0.07-1.13 0.46
Effect size DBP [mmHg] (range, mean)	0.1-0.46 0.23	0.06-0.6 0.3	0.06-0.6 0.28
Variance explained SBP	0.52%	2.95%	3.46%
Variance explained DBP	0.58%	2.78%	3.36%
Previously known for BP	5/20	-	-

Figure 2. Overview of novel and known BP variant properties. Key characteristics of the novel and established BP loci are shown. MAF and effect size estimates are derived from the Cardio-MetaboChip data. Variance explained estimates are estimated from one large study (**Supplementary Note**). Novel loci are classified as previously unknown to be linked to BP by a systematic PubMed review of all genes in a 200kb window (**Supplementary Note**).

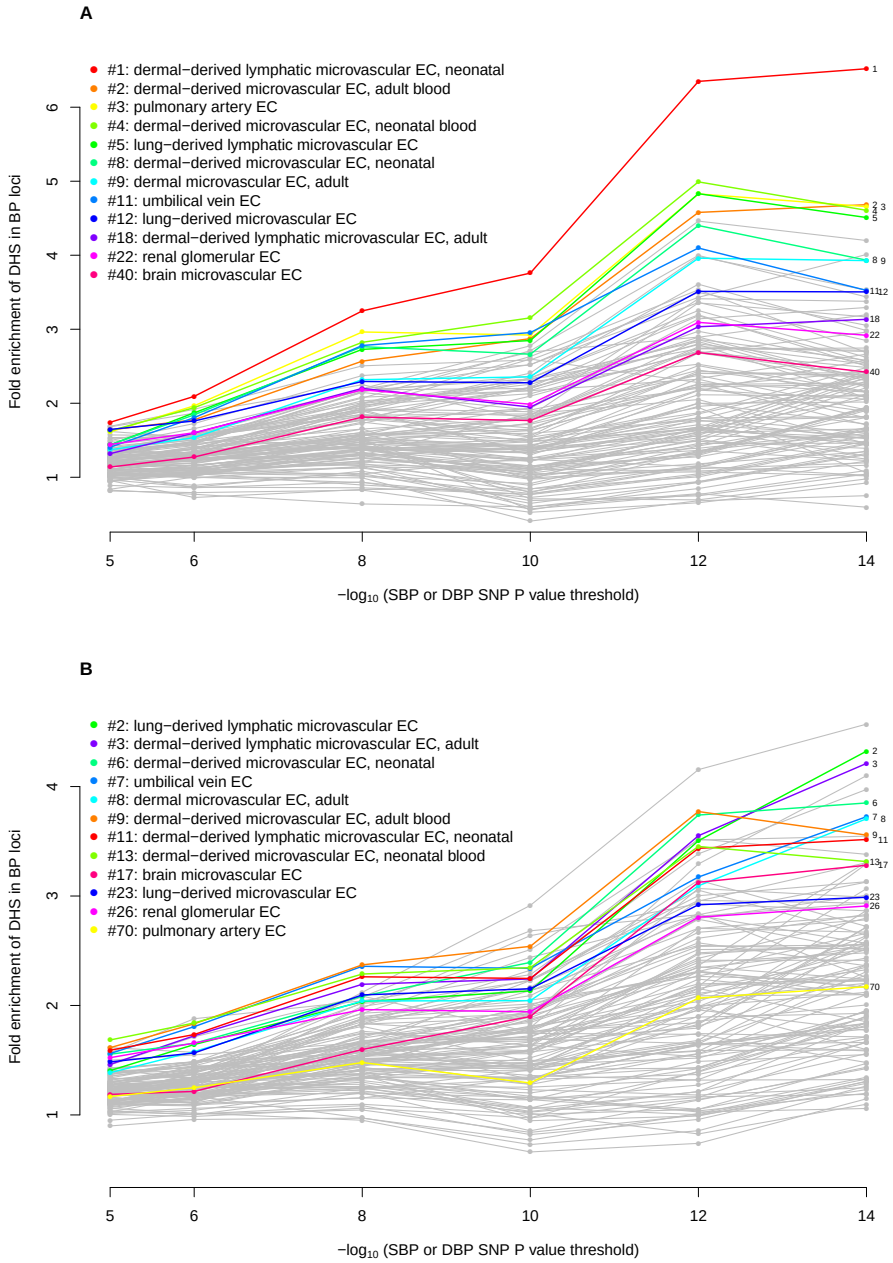

Figure 3. Enrichment of DNAse hypersensitive sites among BP loci in different cell-types. Enrichment analyses of SBP or DBP associated loci according to discovery *P* value using narrow peaks (panel A) or broad peaks (panel B). SNPs were selected according to different *P* value cutoffs (x-axis) and a fold enrichment of overlap with DNAse hypersensitive sites compared to unrelated GWAS SNPs was calculated (y-axis) (see **Supplementary Note**). The 12 endothelial cell-lines are indicated in color and for each endothelial cell-type the rank using the 10^{-14} *P* value cutoff is indicated. EC denotes endothelial cells.

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