Discovery of rare variants associated with blood pressure regulation through meta-analysis of 1.3 million individuals

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Genetic studies of blood pressure (BP) to date have mainly analyzed common variants (minor allele frequency, MAF > 0.05). In a meta-analysis of up to >1.3 million participants, we discovered 106 new BP-associated genomic regions and 87 rare (MAF ≤ 0.01) variant BP associations ($P < 5 \times 10^{-8}$), of which 32 were in new BP-associated loci and 55 were independent BP-associated SNVs within known BP-associated regions. Average effects of rare variants (44% coding) were ~8 times larger than common variant effects and indicate potential candidate causal genes at new and known loci (*e.g. GATA5*, *PLCB3*). BP-associated variants (including rare and common) were enriched in regions of active chromatin in fetal tissues, potentially linking fetal development with BP regulation in later life. Multivariable Mendelian randomization suggested possible inverse effects of elevated systolic and diastolic BP on large artery stroke. Our study demonstrates the utility of rare variant analyses for identifying candidate genes and the results highlight potential therapeutic targets.

Increased blood pressure (BP) is a major risk factor for cardiovascular disease (CVD) and related disability worldwide[1]. Its complications are estimated to account for ~10.7 million premature deaths annually[1]. Genome-wide association studies (GWAS) and exome array-wide association studies (EAWAS) have identified over 1,000 BP-associated single nucleotide variants (SNVs)[2-19] for this complex, heritable, polygenic trait. The majority of these are common SNVs (MAF > 0.05) with small effects on BP. Most reported associations involve non-coding SNVs, and due to linkage disequilibrium (LD) between common variants, these studies provide limited insights into the specific causal genes through which their effects are mediated. The exome array was designed to facilitate analyses of rare coding variants (MAF ≤ 0.01) with potential functional consequences. Over 80% of SNVs on the array are rare, ~6% are low frequency (0.01 < MAF ≤ 0.05), and ~80% are missense, *i.e.* the variants implicate a candidate causal gene through changes to the amino acid sequence. Previously, using the exome array, we identified four BP loci with rare variant associations (*RBM47*, *COL21A1*, *RRAS*, *DBH*)[13,14] and a rare nonsense BP variant in *ENPEP*, encoding an aminopeptidase with a known role in BP regulation[13]. These findings confirmed the utility of rare variant studies for identifying potential causal genes. These rare variant associations had larger effects on BP (typically ~1.5 mmHg per minor allele) than common variants identified by previous studies (typically ~0.5 mmHg per minor allele), many of which had power to detect common variants with large effects. Here, we combine the studies from our previous two exome array reports with additional studies, including the UK Biobank (UKBB) study, to analyze up to ~1.319 million participants and investigate the role of rare SNVs in BP regulation.

Results

We performed an EAWAS and a rare variant GWAS (RV-GWAS) of imputed and genotyped SNVs to identify variants associated with BP traits, hypertension (HTN), and inverse normal transformed systolic BP (SBP), diastolic BP (DBP), and pulse pressure (PP) using (i) single variant analysis and (ii) a gene-based test approach. An overview of our study design for both the EAWAS and for the RV-GWAS is provided in Figure 1.

Blood pressure associations in the EAWAS. We performed a discovery meta-analysis to identify genetic variants associated with BP in up to ~1.32 million individuals. To achieve this, we first performed a meta-analysis of 247,315 exome array variants in up to 92 studies (870,217 participants, including UKBB) for association with BP, Stage 1 (Fig. 1, Methods, and Supplementary Information). There were 362 BP loci known at the time of the analysis (Supplementary Table 1), 240 of which were covered on the exome array. To improve statistical power for discovery for a subset of variants significant in Stage 1 at $P < 5 \times 10^{-8}$ outside of the known BP regions (Supplementary Table 1a), we requested summary association statistics from three additional studies (Million Veteran Program (MVP), deCODE, and GENOA). We then performed meta-analyses of the three data request studies and Stage 1 results to discover novel variants associated with BP. In total, 343 SNVs (200 genomic regions; Methods) were associated ($P < 5 \times 10^{-8}$) with one or more BP traits in the Stage 2 single variant European (EUR) EAWAS meta-analyses involving up to ~1.168 million individuals (Table 1, Fig. 2, Supplementary Table 2, and Supplementary Information). A further seven SNVs (seven genomic regions) were only associated ($P < 5 \times 10^{-8}$) in the pan-ancestry (PA) meta-analyses of ~1.319 million individuals (Supplementary Table 2). All 350 SNV-BP associations were novel at the time of analysis (204 loci), 220 have subsequently been reported[20,21], and 130 SNVs (99 loci) remain novel, including nine rare and 13 low-frequency SNVs (Fig. 2, Supplementary Table 2, Supplementary Fig. 1).

All nine novel rare BP-associated SNVs identified in the EAWAS were conditionally independent of common variant associations within the respective regions (Supplementary Table 3) using the multi-SNP-based conditional and joint association analysis (GCTA v1.91.4)[22] with the Stage 1 EUR EAWAS results

(Methods and Supplementary Table 4). In addition to the rare variants, there were 147 additional distinct ($P < 1 \times 10^{-6}$) common SNV-BP associations (46% were missense variants), and 18 distinct low-frequency SNVs (89% were missense). Approximately 59% of the distinct BP-associated SNVs were coding or in strong LD ($r^2 > 0.8$) with coding SNVs. In total, 42 of the 99 novel loci had two or more distinct BP-associated SNVs in the conditional analyses. Of the 50 loci that were previously identified using UKBB[16,17] and were on the exome array, 43 replicated at $P < 0.001$ (Bonferroni correction for 50 known variants) in samples independent of the original discovery (Supplementary Table 5).

Blood pressure associations from EUR RV-GWAS. We tested a further 29,454,346 (29,404,959 imputed and 49,387 genotyped) rare SNVs for association with BP in 445,360 UKBB participants[23] using BOLT-LMM[24] (Fig. 1 and Methods). The SNVs analyzed as part of the EAWAS were not included in the RV-GWAS. Similar to EAWAS, within RV-GWAS we performed a single discovery meta-analyses to identify rare SNVs associated with BP. In Stage 1 (UKBB), 84 rare SNVs outside of the known BP loci (at the time of our analyses) were associated with one or more BP traits at $P < 1 \times 10^{-7}$ (Supplementary Table 6). Additional data were requested from MVP for the 84 BP-associated SNVs in up to 225,112 EUR from the MVP, and 66 were available. Meta-analyses of Stage 1 (UKBB) and results obtained from MVP were performed for novel rare variant discovery. We identified 23 unique rare SNVs associated with one or more BP traits ($P < 5 \times 10^{-8}$) with consistent direction of effects in a meta-analysis of UKBB and MVP (min $P_{\text{heterogeneity}} = 0.02$) (Table 1, Fig. 2, Supplementary Table 7, and Supplementary Fig. 1). Two of the SNVs, rs55833332 (p.Arg35Gly) in *NEK7* and rs200383755 (p.Ser19Trp) in *GATA5*, were missense. Eleven rare SNVs were genome-wide significant in UKBB alone but were not available in MVP and await further support in independent studies (Supplementary Table 7).

Rare and low frequency variant associations at established BP loci. It is difficult to prioritize candidate genes at common variant loci for functional follow up. We believe analysis of rare (MAF < 0.01) and very low frequency coding variants (MAF ≤ 0.02) in known loci may provide further support for or identify a candidate causal gene at a locus. Twelve of the 240 BP-associated regions had one or more conditionally

565 independent rare variant associations ($P < 10^{-6}$ in the GCTA joint model of the EUR Stage 1 EAWAS;
566 Methods, Table 2, and Supplementary Table 3). A further nine loci had one or more conditionally
567 independent BP-associated SNVs with MAF ≤ 0.02 (Table 2 and Supplementary Table 8). In total, 183
568 SNVs (rare and common) across 110 known loci were not identified previously.
569 We used FINEMAP[25] to fine-map 315 loci known at the time of our analysis and available in UKBB
570 GWAS, which provides dense coverage of genomic variation not available on the exome array. Of these, 36
571 loci had one or more conditionally independent rare variant associations (Supplementary Table 8), and 251
572 loci had multiple common variants associations. We also replicated rare variant associations that we
573 reported previously[13,14] at *RBM47*, *COL21A1*, *RRAS*, and *DBH* ($P < 5 \times 10^{-5}$) in UKBB (independent of
574 prior studies). Overall, from both FINEMAP and GCTA, we identified 40 loci with one or more rare SNV
575 associations, independent of previously reported common variant associations (Table 3, Fig. 2,
576 Supplementary Table 8, and Supplementary Information).
577 We note that, of 256 known variants identified without UKBB participants (Supplementary Table
578 1a), 229 replicated at $P < 1.95 \times 10^{-4}$ (Bonferroni adjusted for 256 variants) in UKBB.
579
580 **Gene-based tests to identify BP-associated genes.** To test whether rare variants in aggregate affect BP
581 regulation, we performed gene-based tests for SBP, DBP, and PP using SKAT[26]
582 (https://genome.sph.umich.edu/wiki/RareMETALS), including SNVs with MAF ≤ 0.01 that were predicted
583 by VEP[27] to have high or moderate impact (Methods). We performed separate analyses within the Stage 1
584 EAWAS and the UKBB RV-GWAS. Six genes in the EAWAS (*FASTKD2*, *CPXM2*, *CENPJ*, *CDC42EP4*,
585 *OTOP2*, *SCARF2*) and two in the RV-GWAS (*FRY*, *CENPJ*) were associated with BP ($P < 2.5 \times 10^{-6}$,
586 Bonferroni adjusted for ~20,000 genes) and were outside known and new BP loci (Supplementary Tables 1
587 and 9). To ensure these associations were not attributable to a single (sub-genome-wide significant) rare
588 variant, we also performed SKAT tests conditioning on the variant with the smallest *P*-value in the gene
589 (Methods and Supplementary Table 9). *FRY* had the smallest conditional *P*-value ($P = 0.0004$), but did not
590 pass our pre-determined conditional significance threshold (conditional SKAT $P \leq 0.0001$; Methods),

suggesting that all gene associations are due to single (sub-genome-wide significant) rare variants and not due to the aggregation of multiple rare variants.

Amongst the known loci, five genes (*NPR1*, *DBH*, *COL21A1*, *NOX4*, *GEM*) were associated with BP due to multiple rare SNVs independent of the known common variant associations (conditional $P \leq 1 \times 10^{-5}$; Methods, Supplementary Information, and Supplementary Table 9) confirming the findings in the single variant conditional analyses above (Supplementary Table 8).

We also performed gene-based tests using a MAF ≤ 0.05 threshold to assess sensitivity to the MAF ≤ 0.01 threshold. The results were concordant with the MAF ≤ 0.01 threshold findings, and two new genes (*PLCB3* and *CEP120*) were associated with BP due to multiple SNVs and were robust to conditioning on the top SNV in each gene (Supplementary Information and Supplementary Table 9).

Rare variant BP associations. In total, across the EAWAS and the RV-GWAS, there were 32 new BP-associated rare variants spanning 18 new loci (Table 1 and Fig. 2). Of these 32, five (representing five loci) were genome-wide significant for HTN, 22 (ten loci) for SBP, 14 (six loci) for DBP, and 15 (ten loci) for PP (Supplementary Tables 1, 2, 3, 6, and 7). Ten of the new rare variants were missense. Within previously reported loci, there were 55 independent rare-variant associations (representing 40 loci) from either the EAWAS or RV-GWAS, making a total of 87 independent rare BP-associated SNVs. We identified 45 BP-associated genes, eight of which were due to multiple rare variants and independent of common variant associations ($P < 1 \times 10^{-4}$, Methods). Twenty-one rare variants were located within regulatory elements (e.g. enhancers), highlighting genetic influence on BP levels through gene expression (Fig. 2). The rare variants contributed to BP variance explained (Supplementary Information).

Power calculations are provided in the Supplementary Information and show that our study had 80% power to detect an effect of 0.039 SD for a MAF = 0.01 (Extended Data Fig. 1). As anticipated, given statistical power, some rare variants displayed larger effects on BP regulation than common variants (Fig. 2 and Supplementary Tables 3, 7, and 8); mean effects of rare SNVs for SBP and DBP were ~7.5 times larger than common variants (mean effect ~0.12 SD/minor allele for rare SNVs, ~0.035 SD/minor allele for low-frequency and ~0.016 SD/minor allele for common SNVs) and for PP were 8.5 times larger for rare variants

compared to common (mean effect ~0.135 SD/minor allele for rare SNVs, ~0.04 SD/minor allele for low-frequency and ~0.016 SD/minor allele for common SNVs). Our study was exceptionally well-powered to detect common variants (MAF > 0.05) with similarly large effects but found none, consistent with earlier BP GWAS and genetic studies of some other common complex traits[28,29,36].

Overlap of rare BP associations with monogenic BP genes. Twenty-four genes are reported in ClinVar to cause monogenic conditions with hypertension or hypotension as a primary phenotype. Of these, three (*NR3C2*, *AGT*, *PDE3A*) were associated with BP in SKAT tests in the EAWAS ($P < 0.002$, Bonferroni adjusted for 24 tests; Supplementary Table 10). These genes also had genome-wide significant SNV-BP associations in the EAWAS and/or RV-GWAS (Supplementary Table 10).

Functional annotation of rare BP-associated SNVs. None of the BP-associated rare SNVs (from known or novel loci) had been previously reported as expression quantitative trait loci (eQTL) in any tissue ($P > 5 \times 10^{-8}$; Supplementary Table 11 and Methods). We used GTEx v7 data to examine in which tissues the genes closest to the rare BP-SNVs were expressed (Extended Data Fig. 2 and Supplementary Table 4). Many of the eQTL gene transcripts were expressed in BP-relevant tissues (e.g. kidney, heart, and arteries). We observed significant enrichment (Bonferroni adjusted $P < 0.05$) in liver, kidney, heart left ventricle, pancreas, and brain tissues, where the BP genes were down-regulated. In contrast, the BP genes were up-regulated in tibial artery, coronary artery, and aorta (Extended Data Fig. 3). There were 33 genes at 30 known loci with novel BP rare variants (from Supplementary Table 12); distinct known common BP variants at these known loci were eQTLs for 52% of these genes, providing additional evidence that the rare variants implicate plausible candidate genes (Supplementary Table 12).

We tested whether genes near rare BP-associated SNVs were enriched in gene sets from Gene Ontology (GO), KEGG, Mouse Genome Informatics (MGI), and Orphanet (Methods and Supplementary Table 4). These (rare variant) genes from both known and novel loci were enriched in BP-related pathways (Bonferroni adjusted $P < 0.05$; Methods and Supplementary Table 13), including “regulation of blood vessel size” (GO) and “renin secretion” (KEGG). Genes implicated by rare SNVs at known loci were enriched in

"tissue remodeling" and "artery aorta" (GO). Genes implicated by rare SNVs at new BP-loci were enriched in rare circulatory system diseases (that include hypertension and rare renal diseases) in Orphanet.

Potential therapeutic insights from the rare BP-associated SNVs. Twenty-three of the genes near rare or low-frequency BP-associated variants in novel and known loci were potentially druggable as suggested by the "druggable genome"[30] (Supplementary Information and Supplementary Tables 4 and 14). Six genes (four with rare variants) are already drug targets for CVD conditions, while 15 others are in development or used for other conditions. As an example, the renin-angiotensin-aldosterone system (RAAS) is one of the principal homeostatic mechanisms for BP control, and aldosterone is the main mineralocorticoid (secreted by adrenal glands) and binds receptors, including *NR3C2*, resulting in sodium retention by the kidney and increased potassium excretion. Spironolactone is an aldosterone antagonist widely used in heart failure and as a potassium-sparing anti-hypertensive medication that targets NR3C2 (Open targets: https://www.opentargets.org).

Overlap of new BP-associations with metabolites. To identify novel BP variants that are metabolite QTLs, we performed *in silico* lookups of new sentinel and conditionally independent BP variants for association with 913 plasma metabolites measured using the Metabolon HD4 platform in ~14,000 individuals (Methods and Supplementary Table 4). Nine BP-associated variants were associated with 25 metabolites ($P < 5 \times 10^{-8}$) involved in carbohydrate, lipids, cofactors and vitamins, nucleotide (cysteine), and amino acid metabolism (Supplementary Table 15), while 11 were unknown.

We performed MR analyses to assess the influence of the 14 known metabolites (Supplementary Table 15) on BP. Lower levels of 3-methylglutarylcarnitine(2) (acyl carnitines involved in long-chain fatty acid metabolism in mitochondria and in leucine metabolism) were significantly associated with increased DBP ($P < 0.003$, 0.05/14 metabolites; Supplementary Table 16). There was no suggestion of reverse causation, i.e. BP did not affect 3-methylglutarylcarnitine(2) ($P > 0.04$; Supplementary Table 16). We further tested whether the association with 3-methylglutarylcarnitine(2) was due to pleiotropic effects of

other metabolites in a multivariable MR framework, but found it was still causally associated with DBP (Supplementary Information and Supplementary Table 16).

New BP-associated SNVs are gene eQTLs across tissues. Sentinel variants from 66 new BP loci were associated ($P < 5 \times 10^{-8}$) with gene expression (or had $r^2 > 0.8$ in 1000G EUR with eQTLs) in publicly available databases (Methods and Supplementary Tables 4 and 11). We performed colocalization for 49 of the 66 BP loci (169 genes) with significant eQTLs available in GTEx v7, jointly across all 48 tissues and the BP traits using HyPrColoc[31] (Methods), to verify that the eQTL and BP-SNV associations were due to the same SNVs and not due to LD or spurious pleiotropy[32]. The BP associations and eQTL colocalized at 17 BP loci with a single variant (posterior probability, PPa > 0.6), i.e. the expression and BP associations were due to the same underlying causal SNV (Fig. 3 and Supplementary Table 17). A further 10 loci had PPa > 0.6 for colocalization of BP associations and eQTL for multiple nearby genes (Fig. 3). Colocalization analyses were also performed for the 35 eQTLs in whole blood from the Framingham Heart Study, and five additional loci were consistent with a shared SNV between BP and gene expression (Supplementary Table 17).

Given the central role of the kidney in BP regulation, we investigated if BP-associated SNVs from the EAWAS were kidney eQTLs using TRANScriptome of renaL humAn TissuE study and The Cancer Genome Atlas study (n = 285; Methods[33,34]). We observed significant eQTL associations ($P < 5 \times 10^{-8}$) at three newly identified BP loci (*MFAP2*, *NFU1*, and *AAMDC*, which were also identified in GTEx) and six at previously published loci (*ERAP1*, *ERAP2*, *KIAA0141*, *NUDT13*, *RP11-582E3.6*, and *ZNF100*; Supplementary Table 18).

New BP-associated SNVs are pQTLs. Eighteen BP loci had sentinel variants (or were in LD with BP SNVs, $r^2 > 0.8$ in 1000G EUR) that were also protein QTL (pQTL) in plasma. Across the 18 loci, BP-SNVs were pQTLs for 318 proteins (Supplementary Table 19). Low-frequency SNVs in *MCL1* and *LAMA5* were cis-pQTL for MCL1 and LAMA5, respectively. The BP-associated SNV, rs4660253, is a cis-pQTL and cis-eQTL for *TIE1* across eight tissues in GTEx including heart (Fig. 3 and Supplementary Table 17). The DBP-

associated SNV, rs7776054, is in strong LD with rs9373124, which is a trans-pQTL for erythropoietin, a hormone mainly synthesized by the kidneys, which has links to hypertension.

Pathway and enrichment analyses. The over-representation of rare and common BP SNVs in DNaseI-hypersensitive sites (DHS), which mark open chromatin, was tested using GARFIELD (Methods and Supplementary Table 4). The most significant enrichment in DHS hotspots for SBP-associated SNVs was in fetal heart tissues, with an ~3-fold enrichment compared to ~2-fold in adult heart (Fig. 3 and Supplementary Information). This difference in enrichment was also reflected in fetal muscle compared to adult muscle for SBP-associated SNVs. The most significant enrichment for DBP- and PP-associated SNVs (~3-fold) was in blood vessels (Fig. 3 and Supplementary Information). There was also enrichment across SBP, DBP and PP in fetal and adult kidney and fetal adrenal gland. In support, complementary enrichment analyses with FORGE (Methods) showed similar enrichments including in fetal kidney and fetal lung tissues (*Z*-score = 300; Supplementary Table 13 and Supplementary Information).

Mendelian randomization with CVD. Twenty-six new BP loci were also associated with cardiometabolic diseases and risk factors in PhenoScanner[35] (http://www.phenoscanner.medschl.cam.ac.uk) (Methods, Fig. 3, Supplementary Information, and Supplementary Tables 4, 20, and 21). Given that BP is a key risk factor for CVD, we performed Mendelian randomization (MR) analyses to assess the causal relationship of BP with any stroke (AS), ischemic stroke (IS), large artery stroke (LAS), cardio-embolic stroke (CE), small vessel stroke (SVS), and coronary artery disease (CAD) using all the distinct BP-associated SNVs from our study (both known and new; Supplementary Table 4 and Methods). BP was a predictor of all stroke types analyzed and CAD (Fig. 4 and Supplementary Fig. 4). Notably, SBP had the strongest effect on all CVD phenotypes, with the most profound effect on LAS, increasing risk by >2-fold per SD (Supplementary Table 22). BP had weakest effect on CE, which may reflect the greater role of atrial fibrillation versus BP in CE risk. Multi-variable MR analyses, including both SBP and DBP, showed that the effect of DBP attenuated to zero once SBP was accounted for (consistent with observational studies[37]), except for LAS (Fig. 4, Supplementary Table 22, and Methods), where SBP/DBP had a suggestive inverse relationship, perhaps

reflecting arterial stiffening. An inverse relationship between DBP and stroke above age 50 years has also been reported[37].

Discussion

Unlike most previous BP studies that focused primarily on common variant associations, the novelty of this investigation is the extensive analysis of rare variants, both individually and in aggregate within a gene. Many of the new rare variants are located in genes that potentially have a role in BP regulation, as evidenced by support from existing mouse models (21 genes) and/or have previously been implicated in monogenic disorders (11 genes) whose symptoms include hyper-/hypotension or impaired cardiac function/development (Supplementary Table 12). For example, rs139600783 (p.Pro274Ser) was associated with increased DBP and is located in the *ARHGAP31* gene that causes Adams-Oliver syndrome, which can be accompanied by pulmonary hypertension and heart defects. A further three (of the six) genes that cause Adams-Oliver syndrome are located in BP-associated loci (*DLL4*[16], *DOCK6*[13,15], and *NOTCH1*, a new BP locus). A missense variant rs200383755 (p.Ser19Trp, predicted deleterious by SIFT), located in the *GATA5*, encoding a transcription factor, is associated with increased SBP and DBP. *GATA5* mutations cause congenital heart defects, including bicuspid aortic valve and atrial fibrillation, while a *Gata5*-null mouse model had increased SBP and DBP at 90 days[38].

Within the known loci, we detected new rare variant associations at several candidate genes, e.g. a rare missense SNV rs1805090 (MAF = 0.0023) in the angiotensinogen (*AGT*) gene was associated with increased BP independently of the known common variant association. *AGT* is known to have an important role in BP regulation, and the variant is predicted to be among the top 1% of most deleterious substitutions[39]. The established common variant at *FOXS1* was not associated with BP in the conditional analysis, but new rare variants in *FOXS1* (rs45499294, p.Glu74Lys; MAF = 0.0037) and *MYLK2* (rs149972827; MAF = 0.0036; Supplementary Information) were associated with BP. Two BP-associated SNVs (rs145502455, p.Ile806Val; rs117874826, p.Glu564Ala) highlight *PLCB3* as a candidate gene. Phospholipase C is a key enzyme in phosphoinositide metabolism, with PLCB3 as the major isoform in macrophages[40], and a negative regulator of VEGF-mediated vascular permeability, a key process in ischemic disease and cancer[41].

PLCβ3 deficiency is associated with decreased atherogenesis, increased macrophage apoptosis in atherosclerotic lesions, and increased sensitivity to apoptotic induction *in vitro*[40]. Variants in *SOS2* have previously been linked to kidney development/function[42] and also cause Noonan syndromes 1 and 9, which are rare inherited conditions characterized by craniofacial dysmorphic features and congenital heart defects, including hypertrophic cardiomyopathy[43]. Here we report the rare variant rs72681869 (p.Arg191Pro) in *SOS2* as associated with SBP, DBP, PP, and HTN, highlighting *SOS2* as a candidate gene. Previously, we identified a rare missense BP-associated variant in *RRAS*, a gene causing Noonan syndrome[13]. Our discoveries of rare missense variants at known BP loci provide additional support for candidate genes at these loci.

We report new low-frequency variant associations, such as the missense variant rs45573936 (T>C, Ile216Thr) in *SLC29A1*. The minor allele is associated with both decreased SBP and DBP (Table 1), and the SNV has been shown to affect the function of the encoded protein, equilibrative nucleoside transporter (ENT1)[44]. Best et al.[45] showed that loss of function of ENT1 caused an (~2.75-fold) increase in plasma adenosine and (~15%) lower BP in mice. Drugs, including dipyridamole and S-(4-Nitrobenzyl)-6-thioinosine (NBTI, NBMPR), are currently used as ENT1 inhibitors for their anti-cancer, anti-cardio, and neuro-protective properties, and our results provide the genetic evidence to indicate that ENT1 inhibition might lower BP in humans.

We found greater enrichment of SBP-associated SNVs in DHS hotspots in fetal vs. adult heart muscle tissue. These results suggest that BP-associated SNVs may influence the expression of genes that are critical for fetal development of the heart. This is consistent with our finding that some BP-associated genes also cause congenial heart defects (see above). Furthermore, *de novo* mutations in genes with high expression in the developing heart, as well as in genes that encode chromatin marks that regulate key developmental genes, have previously been shown to be enriched in congenital heart disease patients[46,47]. A recent study of atrial fibrillation genetics, for which BP is a risk factor, described enrichment in DHS in fetal heart[48]. The authors hypothesized that the corresponding genes acting during fetal development increase risk of atrial fibrillation[48]. Together, these data suggest that early development and/or remodeling of cardiac tissues may be an important driver of BP regulation later in life.

The BP measures we have investigated here are correlated; amongst the 107 new genetic BP loci, only two are genome-wide significant across all four BP traits (*RP11-284M14.1* and *VTN*; Fig. 2). None of the new loci were unique to HTN (Fig. 2), perhaps as HTN is derived from SBP and DBP, or perhaps due to reduced statistical power for a binary trait. The results from our study indicate rare BP-associated variants contribute to BP variability in the general population, and their identification has provided information on new candidate genes and potential causal pathways. We have primarily focused on the exome array, which is limited. Future studies using both exome and whole genome sequencing in population cohorts (e.g. UKBB and TOPMed) will lead to identification of further rare variant associations and may advance the identification of causal BP genes across the ~1,000 reported BP loci.

CONSORTIA

LifeLines Cohort Study

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AUTHOR CONTRIBUTIONS

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COMPETING INTERESTS

The following authors affiliated with deCODE genetics/Amgen Inc. are employed by the company: Vinicius Tragante, Gudmar Thorleifsson, Anna Helgadottir, Patrick Sulem, Gudmundur Thorgeirsson, Hilma Holm, Daniel F. Gudbjartsson, Unnur Thorsteinsdottir, Kari Stefansson. Bruce Psaty serves on the Steering Committee of the Yale Open Data Access Project funded by Johnson & Johnson. John Danesh reports grants, personal fees and non-financial support from Merck Sharp & Dohme (MSD), grants, personal fees and non-financial support from Novartis, grants from Pfizer, and grants from AstraZeneca outside the submitted work. Adam Butterworth reports grants outside of this work from AstraZeneca, Biogen, Merck, Novartis, and Pfizer and personal fees from Novartis. Veikko Salomaa has participated in a conference trip sponsored by Novo Nordisk and received an honorarium for participating in an advisor board meeting, outside the present study. He also has ongoing research collaboration with Bayer Ltd, outside the present study. Dennis Mook-Kanamori is a part-time clinical research consultant for Metabolon, Inc. Mark I. McCarthy has served on advisory panels for Pfizer, Novo Nordisk, Zoe Global, has received honoraria from Merck, Pfizer, Novo Nordisk and Eli Lilly, and research funding from Abbvie, Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, NovoNordisk, Pfizer, Roche, Sanofi Aventis, Servier, and Takeda. As of June 2019, he is an employee of Genentech, and a holder of Roche stock. Eric B. Fauman is an employee of and owns stock in Pfizer, Inc. Mark J. Caulfield is Chief Scientist for Genomics England, a UK Government company. Joanna M. M. Howson became a full-time employee of Novo Nordisk, and I.N. became a full-time employee of Gilead during revision of the manuscript.

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FIGURE LEGENDS

Figure 1 | Study design for single variant discovery. a, Exome array-wide association study (EAWAS) of SBP, DBP, PP and HTN. In Stage 1, we performed two fixed effect meta-analyses for each of the blood pressure (BP) phenotypes SBP, DBP, PP and HTN: one meta-analysis including 810,865 individuals of European (EUR) ancestry and a second pan-ancestry (PA) meta-analysis including 870,217 individuals of EUR, South Asians (SAS), East Asians (EAS), African Ancestry (AA), Hispanics (HIS) and Native Americans (NAm) (Supplementary Tables 23 and 24; Methods). Summary association statistics for SNVs with $P < 5 \times 10^{-8}$ in Stage 1 that were outside of previously reported BP loci (Methods, Supplementary Tables 1 and 25) were requested in independent studies (up to 448,667 participants; Supplementary Table 24). In Stage 2, we performed both a EUR and a PA meta-analyses for each trait of Stage 1 results and summary statistics from the additional studies. Only SNVs that were associated with a BP trait at $P < 5 \times 10^{-8}$ in the combined Stage 2 EUR or PA meta-analyses and had concordant directions of effect across studies ($P_{\text{heterogeneity}} > 1 \times 10^{-4}$; Methods) were considered significant. Further details are provided in the Methods and Supplementary Information. **b**, Rare variant GWAS (RV-GWAS) of SBP, DBP and PP. For SNVs outside of the previously reported BP loci (Methods, Supplementary Tables 1 and 6) with $P < 1 \times 10^{-7}$ in Stage 1, summary association statistics were requested from MVP (up to 225,112 participants; Supplementary Table 24). In Stage 2, we performed meta-analyses of Stage 1 and MVP for SBP, DBP and PP in EUR. SNVs that were associated with a BP trait at $P < 5 \times 10^{-8}$ in the combined Stage 2 EUR with concordant directions of effect across UKBB and MVP ($P_{\text{heterogeneity}} > 1 \times 10^{-4}$; Methods) were considered significant. Justification of the significance thresholds used and further information on the statistical methods are detailed in the Methods and Supplementary Information. *Total number of participants analyzed within each study that provided single variant association summaries following the data request—EAWAS EUR: Million Veterans Program (MVP: 225,113), deCODE (127,478) and GENOA (1,505); EAWAS PA: Million Veterans Program (MVP: 225,113 EUR; 63,490 AA; 22,802 HIS; 2,695 Nam; 4,792 EAS), deCODE (127,478 participants from Iceland) and GENOA (1,505 EUR; 792 AA); RV-GWAS EUR: Million Veterans Program (MVP: 225,112 EUR).

Figure 2 | New BP associations. a, Fuji plot of the genome-wide significant BP-associated SNVs from the Stage 2 EAWAS and Stage 2 rare variant GWAS. The first four circles (from inside-out) and the last circle (locus annotation) summarize pleiotropic effects, while circles 5 to 8 summarize the genome-wide significant associations. Every dot or square represents a BP-associated locus, and large dots represent novel BP-associated loci, while small dots represent loci containing novel

variants identified in this study, which are in linkage disequilibrium with a variant reported by Evangelou et al.[20] and/or Giri et al.[21]. All loci are independent of each other, but due to the scale of the plot, dots for loci in close proximity overlap. *Loci with rare variant associations. **b**, Venn diagram showing the overlap of the 107 new BP loci across the analyzed BP traits. **c**, Functional annotation from VEP of all the identified rare variants in known and novel regions. **d**, Plots of minor allele frequency against effect estimate on the transformed scale for the BP-associated SNVs. Blue squares are new BP-associated SNVs, black dots represent SNVs at known loci, and red dots are newly identified distinct BP-associated SNVs at known loci. Effect estimates and SEs for the novel loci are taken from the Stage 2 EUR analyses (up to 1,164,961 participants), while for the known are from the Stage 1 analyses (up to 810,865 participants). Results are from the EAWAS where available and the GWAS (up to 670,472 participants) if the known variants were not on the exome array (data from Supplementary Tables 1, 3, 7, 8, and 25 were used).

Figure 3 | Annotation of BP loci. a, BP associations shared with eQTL from GTEx through multi-trait colocalization analyses. Expressed gene and the colocalized SNV are provided on the *y*-axis. BP trait and eQTL tissues are provided on the *x*-axis. The color indicates whether the candidate SNV increases BP and gene expression (brown), decreases BP and gene expression (orange), or has the inverse effects on BP and gene expression (blue). **b**, Enrichment of BP-associated SNVs in DNase I hypersensitivity hot spots (active chromatin). The top plot is for SBP, middle is for DBP, and bottom represents PP. Height of the bar indicates the fold enrichment in the listed tissues, with error bars representing the 95% confidence intervals. The colors represent the enrichment *P*-value.

Figure 4 | Phenome-wide associations of the new BP loci. a, Modified Fuji plot of the genome-wide significant associated SNVs from the Stage 2 EAWAS and Stage 2 rare variant GWAS (novel loci only). Each dot resents a novel locus where a conditionally independent variant or a variant in LD with the conditionally independent variant has been previously associated with one or more traits unrelated to blood pressure, and each circle represents different trait category (Supplementary Table 20). Locus annotation is plotted in the outer circle, and * sign denotes loci where the conditionally independent signal maps to a gene which is different to the one closest to the sentinel variant. **b**, Bar chart showing the distribution of traits (*x*-axis) and number of distinct BP-associated variants per trait (*y*-axis) that the SNVs in **a** are associated with. **c**, Bar chart of the number of traits included in **b** (*y*-axis) by trait category (*x*-axis). The color coding for **a** and **b** is relative to **c**.

Figure 5 | Causal association of BP with stroke and coronary artery disease. Mendelian randomization analyses of the effect of blood pressure on stroke and coronary artery disease. **a**, Univariable analyses. **b**, Multivariable analyses (Methods). Analyses were performed using summary association statistics (Methods). The causal estimates are on the odds ratio (OR) scale (the square in the plot). The whiskers on the plots are the 95% confidence intervals for these ORs. Results on the standard deviation scale are provided in Supplementary Table 22. The genetic variants for the estimation of the causal effects in this plot are sets of SNVs after removing the confounding SNVs and invalid instrumental variant. OR, odds ratio (*P*-value from the inverse variance weighted two sample Mendelian randomization method). *n*, number of disease cases.

Table 1 | Rare and low-frequency SNV-blood pressure associations in participants of European ancestry from the (Stage 2) EAWAS and (Stage 2) RV-GWAS that map to new BP loci

Locus	rsID	Chr:Pos	Gene	EA/OA	Amino acids	Consequence	Trait	EAF	β	*P*	Het *P*	*n*
Exome array-wide association study (EAWAS)												
10	rs11580946	1:150,551,327	*MCL1*	A/G	p.Val227Ala	missense	PP	0.016	-0.37	2.74×10^{-9}	0.24	1,159,900
11	rs61747728†	1:179,526,214	*NPHS2*	T/C	p.Gln229Arg	missense	DBP	0.040	0.26	8.74×10^{-13}	0.22	1,160,530
16	rs4149909	1:242,023,898	*EXO1*	G/A	p.Ser279Asn	missense	SBP	0.033	0.36	2.46×10^{-8}	0.09	1,158,190
32	rs3821033†	2:219,507,302	*ZNF142*	T/C	p.Thr1313Ala	missense	DBP	0.033	-0.29	1.42×10^{-13}	0.75	1,160,530
	rs16859180†	2:219,553,468	*STK36*	T/C	p.Trp477Arg	missense	DBP	0.049	-0.26	1.11×10^{-16}	0.34	1,160,530
44	**rs145072852**	**3:101,476,645**	***CEP97***	**T/C**	p.Phe399Leu	**missense**	**PP**	**0.004**	**1.05**	$\mathbf{1.42 \times 10^{-13}}$	**0.01**	**1,158,820**
46	**rs139600783**	**3:119,109,769**	***ARHGAP31***	**T/C**	p.Ser274Pro	**missense**	**HTN**	**0.008**	**5.85**	$\mathbf{5.05 \times 10^{-9}}$	**0.19**	**975,381**
50	**rs73181210**	**3:169,831,268**	***PHC3***	**C/T**	p.Glu692Lys	**missense**	**DBP**	**0.009**	**-0.66**	$\mathbf{9.14 \times 10^{-15}}$	**0.04**	**1,159,580**
52	rs11937432†	4: 2,233,709	*HAUS3*	G/A	p.Thr586Ile	missense	DBP	0.046	0.21	9.56×10^{-10}	0.26	1,160,520
58	rs1229984	4:100,239,319	*ADH1B*	T/C	p.His48Arg	missense	PP	0.026	-0.75	2.97×10^{-25}	0.54	686,104
63	**rs143057152**	**4:149,075,755**	***NR3C2***	**T/C**	p.His771Arg	**missense**	**SBP**	**0.003**	**1.75**	$\mathbf{4.14 \times 10^{-14}}$	**0.22**	**1,128,880**
71	rs61755724	5:132,408,967	*HSPA4*	A/G	p.Thr159Ala	missense	DBP	0.024	0.26	9.75×10^{-9}	0.36	1,160,530
72	rs33956817	5:137,278,682	*FAM13B*	C/T	p.Met802Val	missense	SBP	0.044	0.31	1.76×10^{-8}	0.27	1,158,190
77	rs34471628†	5:172,196,752	*DUSP1*	G/A	p.His187Tyr	missense	DBP	0.039	-0.23	3.00×10^{-10}	0.42	1,153,300
85	rs45573936	6: 44,198,362	*SLC29A1*	C/T	p.Ile295Thr	missense	DBP	0.027	-0.38	3.70×10^{-19}	0.59	1,160,530
100	rs144867634	7:111,580,166	*DOCK4*	C/T	p.Val326Met	missense/splice region	DBP	0.025	-0.26	2.62×10^{-8}	0.04	1,160,530
109	rs56335308†	8: 17,419,461	*SLC7A2*	A/G	p.Met545Val	missense	DBP	0.025	0.31	1.40×10^{-10}	0.26	1,160,530
114	rs76767219	8: 81,426,196	*ZBTB10*	A/C	p.Glu346Ala	missense	SBP	0.034	-0.44	4.41×10^{-13}	0.18	1,160,830
119	rs61732533†	8:145,108,151	*OPLAH*	A/G	-	synonymous	DBP	0.049	-0.21	2.05×10^{-10}	0.86	1,085,170
	rs34674752†	8:145,154,222	*SHARPIN*	A/G	p.Ser294Pro	missense	DBP	0.049	-0.19	5.89×10^{-10}	0.91	1,132,350
146	rs117874826	11: 64,027,666	*PLCB3*	C/A	p.Ala564Glu	missense	SBP	0.014	0.71	4.67×10^{-12}	0.42	1,153,360
	rs145502455	**11: 64,031,030**	***PLCB3***	**A/G**	p.Ile806Val	**missense**	**SBP**	**0.005**	**0.90**	$\mathbf{5.01 \times 10^{-9}}$	**0.04**	**1,156,310**
154	**rs141325069**	**12: 20,769,270**	***PDE3A***	**A/G**	p.Gln459Arg	**missense**	**SBP**	**0.003**	**1.45**	$\mathbf{6.25 \times 10^{-11}}$	**0.82**	**1,134,260**
158	**rs77357563**	**12:114,837,349**	***TBX5***	**A/C**	p.Tyr111Asp	**missense**	**PP**	**0.005**	**-1.01**	$\mathbf{7.72 \times 10^{-22}}$	**0.22**	**1,152,080**
159	rs13141	12:121,756,084	*ANAPC5*	A/G	p.Val630Ala	missense	DBP	0.011	0.52	1.98×10^{-12}	0.63	1,156,950

168	rs17880989†	14: 23,313,633	*MMP14*	A/G	p.Ile355Met	missense	DBP	0.027	0.32	2.02×10^{-14}	0.95	1,160,530
169	**rs61754158**	**14: 31,774,324**	***HEATR5A***	**T/C**	p.Arg1670Gly p.Arg191Pro	**missense**	**SBP**	**0.009**	**-0.70**	$\mathbf{6.28 \times 10^{-9}}$	**0.04**	**1,119,230**
170	**rs72681869**	**14: 50,655,357**	***SOS2***	**C/G**		**missense**	**SBP**	**0.010**	**-1.22**	$\mathbf{2.25 \times 10^{-22}}$	**0.25**	**1,144,040**
177	rs150843673	15: 81,624,929	*TMC3*	T/G	p.Ser1045Ter	stop/lost	DBP	0.021	0.36	1.43×10^{-12}	0.14	1,154,000
181	rs61739285	16: 27,480,797	*GTF3C1*	T/C	p.His1630Arg	missense	DBP	0.035	0.24	4.71×10^{-10}	0.04	1,155,020
186	rs62051555	16: 72,830,539	*ZFHX3*	G/C	p.His2014Gln	missense	PP	0.048	0.47	1.19×10^{-25}	0.43	797,332
206	rs11699758	20: 60,901,762	*LAMA5*	T/C	p.Ile1757Val	missense	PP	0.034	-0.26	6.68×10^{-11}	0.54	1,154,410
	rs13039398	20: 60,902,402	*LAMA5*	A/G	p.Trp1667Arg	missense	PP	0.033	-0.26	1.89×10^{-10}	0.44	1,133,830
Rare variant – genome-wide association study (RV-GWAS)												
215	**rs55833332**	**1:198,222,215**	***NEK7***	**G/C**	p.Gly35Arg	**missense**	**PP**	**0.008**	**0.62**	$\mathbf{4.58 \times 10^{-8}}$	**0.08**	**670,129**
	rs143554274	1:198,455,391	*ATP6V1G3*	T/C	-	intergenic	PP	0.008	0.71	1.26×10^{-9}	0.14	670,128
216	rs12135454	1:219,310,461	*LYPLAL1-AS1*	T/C	-	intron	PP	0.010	-0.62	1.61×10^{-8}	0.22	665,523
	rs12128471	1:219,534,485	*RP11-392O17.1*	A/G	-	intergenic	PP	0.010	-0.68	2.99×10^{-9}	0.19	670,130
217	rs114026228	4: 99,567,918	*TSPAN5*	C/T	-	intron	PP	0.008	-0.65	5.20×10^{-9}	0.03	670,128
	rs145441283	4: 99,751,794	*EIF4E*	G/A	-	intergenic	PP	0.010	-0.71	2.01×10^{-11}	0.08	670,128
219	rs187207161	6:122,339,304	*HMGB3P18*	C/T	-	intergenic	PP	0.009	-0.63	2.16×10^{-10}	0.02	670,130
221	rs149165710	8:121,002,676	*DEPTOR*	A/G	-	intron	PP	0.003	1.32	2.78×10^{-12}	0.03	665,523
222	rs184289122	10:106,191,229	*CFAP58*	G/A	-	intron	SBP	0.008	1.31	1.66×10^{-13}	0.53	670,472
	rs7076147	10:106,250,394	*RP11-127O4.3*	G/A	-	intergenic	SBP	0.010	1.11	1.71×10^{-14}	0.75	670,472
	rs75337836	10:106,272,188	*RP11-127O4.3*	T/G	-	intergenic	SBP	0.010	1.12	2.67×10^{-15}	0.54	670,472
	rs142760284	10:106,272,601	*RP11-127O4.3*	A/C	-	intergenic	SBP	0.009	1.22	2.19×10^{-15}	0.92	670,472
	rs576629818	10:106,291,923	*RP11-127O4.3*	T/C	-	intergenic	SBP	0.009	1.24	1.02×10^{-15}	0.71	670,472
	rs556058784	10:106,322,283	*RP11-127O4.2*	G/A	-	intergenic	SBP	0.009	1.26	4.54×10^{-16}	0.57	665,861
	rs535313355†	10:106,399,140	*SORCS3*	C/T	-	upstream gene	SBP	0.009	1.36	1.04×10^{-17}	0.22	670,472
	rs181200083†	10:106,520,975	*SORCS3*	C/A	-	intron	SBP	0.009	1.60	1.08×10^{-21}	0.58	665,861
	rs540369678†	10:106,805,351	*SORCS3*	T/A	-	intron	SBP	0.010	1.18	2.29×10^{-14}	0.16	670,472
	rs117627418	10:107,370,555	*RP11-45P22.2*	T/C	-	intergenic	SBP	0.009	1.11	1.98×10^{-11}	0.1	665,861
224	rs138656258	14: 31,541,910	*AP4S1*	G/T	-	intron	SBP	0.007	-0.93	1.15×10^{-8}	0.13	665,861
228	rs6061911	20: 60,508,289	*CDH4*	C/T	-	intron	SBP	0.010	-0.85	4.67×10^{-8}	0.09	665,861

rs114580352	20: 60,529,963	*TAF4*	A/G	-		intron	SBP	0.009	-0.84	1.99×10^{-8}	0.04	665,860
rs11907239	20: 60,531,853	*TAF4*	A/G	-		intron	SBP	0.009	-0.82	4.99×10^{-8}	0.05	670,472
rs200383755	**20: 61,050,522**	***GATA5***	**C/G**	p.Trp19Ser		**missense**	**DBP**	**0.006**	**1.00**	**1.01×10^{-13}**	**0.49**	**670,172**

Newly identified rare and low-frequency SNV-inverse normal transformed blood pressure associations are reported from Stage 2 of the exome array study and genome-wide association study. The reported associations are for the trait with the smallest *P*-value in the Stage 1 meta-analysis; the full results are provided in Supplementary Tables 2 and 7. SNVs are ordered by trait, chromosome, and position. Gene, gene containing the SNV or the nearest gene; rsID, dbSNP rsID; Chr:Pos, Chromosome:NCBI Build 37 position; EA/OA, effect allele (also the minor allele) and other allele; EAF, effect allele frequency based on Stage 1; Consequence, consequence of the SNV to the transcript as annotated by VEP; Amino acids, reference and variant amino acids from VEP; Trait, blood pressure trait for which association is reported; β, effect estimate, in mmHg, from the Stage 2 meta-analysis of the *untransformed* BP trait or the *Z*-score from the HTN analyses in Stage 2 ; *P*, *P*-value for association with the listed inverse normal transformed blood pressure trait from the Stage 2 meta-analyses; Het_*P*, *P*-value for heterogeneity; *n*, sample size. Bold type indicates rare missense variants.

†Novel variants identified in this study that are in linkage disequilibrium (LD: $r^2 > 0.6$ rare SNVs and $r^2 > 0.1$ common SNVs) with a variant that has been reported by Evangelou et al.[20] and/or Giri et al.[21] within +/- 500 kb of the novel variant.

Table 2 | Conditionally independent rare and very low-frequency SNV (MAF < 0.02) associations from exome array at known loci in Stage 1 EUR studies

Locus ID	rsID	Chr:bp	Gene	EA/OA	AA	Consequence	Trait	EAF	β_joint	*P*_joint	*n*	Ref
18	**rs116245325**	**1: 153665650**	***NPR1*** [+]	**T/C**	**p.Phe1034Leu**	**Missense**	**SBP**	**0.001**	**0.1660**	**7.49×10^{-9}**	**758,252**	[14]
	rs61757359	**1: 153658297**		**A/G**	**p.Ser541Gly**	**Missense**		**0.003**	**-0.0812**	**6.10×10^{-9}**	**794,698**	
	rs35479618 **	1: 153662423		A/G	p.Lys967Glu	Missense		0.017	0.0694	1.19×10^{-28}	774,862	
28	**rs1805090**	**1: 230840034**	***AGT*** [+]	**T/G**	**p.Met392Leu**	**Missense**	**DBP**	**0.002**	**0.1070**	**6.00×10^{-10}**	**759,349**	[8]
	rs699	1: 230845794		G/A	p.Thr268Met	Missense	DBP	0.408	0.0225	2.12×10^{-45}	806,731	
94	**rs111620813**	**4: 8293193**	***HTRA3*** [+]	**A/G**	**p.Met269Val**	**Missense**	**PP**	**0.011**	**-0.0432**	**1.38×10^{-8}**	**798,063**	[18]
	rs7437940 **	4: 7887500	*AFAP1*	T/C	-	Intron	PP	0.406	-0.0131	1.62×10^{-16}	806,708	
102	**rs112519623**	**4: 103184239**	***SLC39A8*** [+]	**A/G**	**p.Phe449Leu**	**Missense**	**DBP**	**0.016**	**-0.0391**	**3.02×10^{-10}**	**803,151**	[6]
	rs13107325 **	4: 103188709		T/C	p.Thr391Ala	Missense	DBP	0.072	-0.0615	9.69×10^{-88}	806,731	
	rs4699052	4: 104137790	*CENPE*	T/C	-	Intergenic	DBP	0.388	-0.0121	7.31×10^{-14}	806,731	
105	rs6825911	4: 111381638	***ENPEP***	T/C	-	Intron	DBP	0.205	-0.0215	1.47×10^{-28}	801,965	
	rs33966350	**4: 111431444**		**A/G**	p.Ter413Trp	**Stop/lost**	**DBP**	**0.013**	**0.0735**	**2.40×10^{-25}**	**798,385**	
144	rs4712056 **	6: 53989526	*MLIP*	G/A	p.Val159Il	Missense	PP	0.360	0.0091	1.86×10^{-8}	806,708	[14,16,13]
	rs115079907	**6: 55924005**	***COL21A1*** [+]	**T/C**	p.Arg882Gly	Missense	**PP**	**0.003**	**0.2060**	**8.33×10^{-17}**	**783,546**	
	rs12209452	6: 55924962		G/A	p.Pro821Leu	Missense	PP	0.049	0.0411	5.49×10^{-26}	743,036	
	rs200999181 **	**6: 55935568**		**A/C**	p.Val665Gly	Missense	**PP**	**0.001**	**0.3350**	**4.74×10^{-43}**	**764,864**	
	rs35471617	6: 56033094		A/G	p.Met343Thr	Missense/splice region	PP	0.073	0.0249	1.03×10^{-15}	806,708	
	rs2764043	**6: 56035643**		**G/A**	**p.Pro277Leu**	**Missense**	**PP**	**0.002**	**0.1530**	**5.11×10^{-14}**	**785,643**	
	rs1925153 **	6: 56102780		T/C	-	Intron	PP	0.448	-0.0096	1.03×10^{-8}	786,734	
	rs4294007	6: 57512510	*PRIM2*	T/G	-	Splice acceptor	PP	0.379	0.0096	1.13×10^{-7}	632,625	
208	rs507666	9:136149399	*ABO*	A/G	-	Intron	DBP	0.189	-0.0293	7.53×10^{-47}	796,103	[13,15]
	rs3025343	9:136478355	*LL09NC01-254D11.1*	A/G	-	Exon (noncoding transcript)	DBP	0.112	-0.0126	4.91×10^{-7}	806,731	
	rs77273740	9:136501728	*DBH*	T/C	p.Trp65Arg	Missense	DBP	0.027	-0.0846	3.85×10^{-11}	790,500	
	rs3025380	**9:136501756**	***DBH***	**C/G**	**p.Ala74Gly**	**Missense**	**DBP**	**0.005**	**-0.1030**	**5.37×10^{-18}**	**795,263**	
	rs74853476	**9:136501834**	***DBH***	**T/C**	**-**	**Splice donor**	**DBP**	**0.002**	**0.1000**	**3.69×10^{-8}**	**775,793**	
223	**rs201422605**	**10: 95993887**	***PLCE1***	**G/A**	**p.Val678Met**	**Missense**	**SBP**	**0.003**	**-0.0837**	**1.41×10^{-7}**	**795,009**	[7,14]
	rs11187837	10: 96035980		C/T	-	Intron	SBP	0.110	-0.0198	4.23×10^{-14}	801,969	
	rs17417407	10: 95931087		T/G	p.Leu548Arg	Missense	SBP	0.167	-0.0122	9.97×10^{-9}	806,735	
	rs9419788	10: 96013705		G/A	-	Intron	SBP	0.387	0.0137	9.63×10^{-16}	806,735	
229	**rs60889456**	**11: 723311**	***EPS8L2*** [+]	**T/C**	**p.Leu471Pro**	**Missense**	**PP**	**0.017**	**0.0303**	**6.37×10^{-7}**	**799,021**	[17]
	rs7126805 **	11: 828916	*CRACR2B*	G/A	p.Gln77Arg	Missense	PP	0.271	-0.0134	1.43×10^{-13}	752,026	
246*	**rs56061986**	**11: 89182686**	***NOX4*** [+]	**C/T**	**p.Gly67Ser**	**Missense**	**PP**	**0.003**	**-0.1080**	**2.25×10^{-11}**	**798,273**	[17 16]

	rs139341533	**11: 89182666**		**A/C**	**p.Phe97Leu**	**Missense**	**PP**	**0.004**	**-0.0947**	**$6.82x10^{-14}$**	**785,947**	
	rs10765211	11: 89228425		A/G	-	Intron	PP	0.342	-0.0176	$8.77x10^{-27}$	806,708	
250	**rs117249984**	**11: 107375422**	***ALKBH8***	**A/C**	**p.Tyr653Asp**	**Missense**	**SBP**	**0.019**	**-0.0304**	**$2.90x10^{-7}$**	**805,695**	16
	rs3758911	11: 107197640	*CWF19L2*	C/T	p.Cys894Tyr	Missense	SBP	0.341	0.0113	$1.54x10^{-11}$	806,735	
304	**rs61738491**	**16: 30958481**	***FBXL19*** +	**A/G**	**p.Gln652Arg**	**Missense**	**PP**	**0.010**	**-0.0460**	**$1.25x10^{-8}$**	**796,459**	17,16
	rs35675346 **	16: 30936081		A/G	p.Lys10Glu	Missense	PP	0.241	-0.0125	$1.06x10^{-11}$	802,932	
130 *	**rs114280473**	**5: 122714092**	***CEP120*** +	**A/G**	**p.Phe712Leu**	**Missense**	**PP**	**0.006**	**-0.0584**	**$9.98x10^{-8}$**	**805,632**	13, 12, 14, 15
	rs2303720	5: 122682334		T/C	p.His947Arg	Missense	PP	0.029	-0.0419	$3.44x10^{-18}$	806,708	
	rs1644318	5: 122471989	*PRDM6*	C/T	-	Intron	PP	0.387	0.0192	$2.43x10^{-32}$	790,025	
179 *	rs3735080	7: 150217309	*GIMAP7*	T/C	p.Cys83Arg	Missense	DBP	0.237	-0.0092	$6.56x10^{-7}$	806,731	9, 14, 10
	rs3807375	7: 150667210	*KCNH2*	T/C	-	Intron	DBP	0.364	-0.0084	$3.94x10^{-7}$	806,731	
	rs3918234	**7: 150708035**	***NOS3*** +	**T/A**	**p.Leu982Gln**	**Missense**	**DBP**	**0.004**	**-0.0727**	**$1.33x10^{-7}$**	**786,541**	
	rs891511 **	7: 150704843		A/G	-	Intron	DBP	0.331	-0.0231	$1.56x10^{-40}$	778,271	
	rs10224002 **	7: 151415041	*PRKAG2*	G/A	-	Intron	DBP	0.286	0.0186	$7.41x10^{-27}$	806,731	
190 *	**rs138582164**	**8: 95264265**	***GEM*** +	**A/G**	p.Ter199Arg	**Stop lost**	**PP**	**0.001**	**0.2810**	**$1.90x10^{-17}$**	**735,507**	16, 78
195 *	**rs112892337**	**8: 135614553**	***ZFAT*** +	**C/G**	**p.Cys470Ser**	**Missense**	**SBP**	**0.005**	**-0.0831**	**$4.39x10^{-12}$**	**792,203**	17
	rs12680655	8: 135637337		G/C	-	Intron	SBP	0.398	0.0118	$1.81x10^{-13}$	797,982	
259 *	**rs145878042**	**12: 48143315**	***RAPGEF3*** +	**G/A**	**p.Pro258Leu**	**Missense**	**SBP**	**0.012**	**-0.0453**	**$9.28x10^{-10}$**	**805,791**	16, 13
	rs148755202	**12: 48191247**	***HDAC7***	**T/C**	**p.His166Arg**	**Missense**	**SBP**	**0.016**	**0.0310**	**$9.07x10^{-7}$**	**806,735**	
	rs1471997	12: 48723595	*H1FNT*	A/G	p.Gln174Arg	Missense	SBP	0.216	0.0130	$1.15x10^{-11}$	806,735	
	rs1126930 **	12: 49399132	*PRKAG1*	C/G	p.Ser98Thr	Missense	SBP	0.035	0.0408	$1.45x10^{-21}$	793,216	
	rs52824916 **	12: 49993678	*FAM186B*	T/C	p.Gln582Arg	Missense	SBP	0.088	-0.0155	$1.70x10^{-8}$	806,735	
	rs7302981 **	12: 50537815	*CERS5*	A/G	p.Cys75Arg	Missense	SBP	0.375	0.0219	$1.52x10^{-41}$	806,735	
312 *	**rs61753655**	**17: 1372839**	***MYO1C*** +	**T/C**	p.Lys866Glu	Missense	**SBP**	**0.011**	**0.0653**	**$6.48x10^{-18}$**	**806,735**	17, 16
	rs1885987	17: 2203025	*SMG6*	G/T	p.Thr341Asn	Missense	SBP	0.371	-0.0127	$3.94x10^{-15}$	806,735	
339 *	**rs34093919**	**19: 41117300**	***LTBP4*** +	**A/G**	**p.Asn715Asp**	**Missense/splice region**	**PP**	**0.014**	**-0.0631**	**$4.18x10^{-20}$**	**805,764**	19
	rs814501	19: 41038574	*SPTBN4*	G/A	p.Gly1331Ser	Missense	PP	0.482	-0.0115	$2.40x10^{-13}$	806,708	
346	**rs45499294**	**20: 30433126**	***FOXS1*** +	**T/C**	**p.Lys74Glu**	**Missense**	**SBP**	**0.004**	**-0.0732**	**$2.36x10^{-8}$**	**801,284**	16

GCTA was used to perform conditional analyses of the meta-analysis results from the exome array study from the Stage 1 meta-analysis of EUR studies in known blood pressure regions (defined in Supplementary Table 1). All SNVs had $P < 0.0001$ for heterogeneity. The trait selected in this table is the trait for which the rare variant had the smallest *P*-value. We provide all conditionally independent variants at these loci, i.e. rare, very low frequency (MAF < 0.02), low frequency, and common. The full detailed listing of results is provided in Supplementary Table 8. Bold font highlights variants with MAF < 0.02. Locus ID, the known locus identifier used in Supplementary Table 1; Chr:Position,

chromosome and NCBI Build 37 physical position; EA/OA, Effect allele/other allele; AA, amino acid change; Effect, predicted consequence of the SNV from VEP; EAF, effect allele frequency; β_joint, effect estimate for the SNV in the joint analysis from GCTA; *P*_joint, the *P*-value for association of the rare variant from the joint analysis in GCTA; Gene, nearest gene; Trait, blood pressure trait analyzed; Ref, reference of the first reports of association in the listed region.
*Indicates that one or more of the previously reported variants in the locus were not on exome array.
**Indicates that the listed variant is the known variant or its proxy ($r^2 > 0.8$ in 1000G EUR).
+Indicates that the listed gene had an unconditional SKAT *P*-value < 2×10^{-6} (see Supplementary Table 9).

Table 3 | Newly identified independent BP-associated rare SNVs (MAF ≤ 0.01) at known loci in UK Biobank only

Locus ID	rsID	Chr:Position	Gene	Info	EA/ OA	Consequence	Trait	Unconditional SNV analysis			FINEMAP output			Ref
								EAF	β	*P*-value	Common SNVs in top configuration	PP of n SNVs	log_{10}BF	
5	rs41300100	1:11908146	*NPPA*	0.82	G/C	5' UTR	SBP	0.010	-0.10	$4.70x10^{-21}$	rs2982373, rs5066, rs55892892	0.55	122.50	9,2,79
18	rs756799918	1:153464738	*RN7SL44P*	0.89	T/C	intergenic	SBP	0.0004	0.26	$4.30x10^{-7}$	rs12030242	0.36	27.49	14
28	rs1805090	1:230840034	*AGT*	NA	T/G	missense	SBP	0.0025	0.11	$6.80x10^{-8}$	rs3889728, rs2493135	0.79	26.23	8
28	rs539645495	1:230860071	*RP11-99J16__A.2*	0.97	G/A	intron, non-coding transcript	DBP	0.0024	0.13	$3.20x10^{-9}$	rs2493135, rs3889728	0.83	30.97	8
33	rs56152193	2:20925891	*LDAH*	0.76	C/G	intron	PP	0.0006	-0.23	$8.10x10^{-7}$	rs7255	0.36	17.95	17, 16
55	rs759606582	2:178325956	*AGPS*	0.96	G/A	intron	PP	0.0003	0.29	$1.90x10^{-7}$	rs56726187	0.57	7.48	16
72	rs555934473	3:48899332	*SLC25A20*	0.74	T/G	intron	DBP	0.0012	-0.17	$2.50x10^{-6}$	rs36022378, rs6442105, rs6787229	0.25	35.71	17, 16, 6, 11
73	rs76920163	3:53857055	*CHDH*	0.96	G/T	intron	SBP	0.0059	0.10	$3.80x10^{-13}$	rs3821843, rs7340705, rs11707607	0.58	29.45	18, 16
	rs144980716	3:53776904	*CACNA1D*	0.91	A/G	intron	PP	0.0065	0.07	$2.60x10^{-8}$	rs36031811, rs77347777	0.57	18.42	
85	rs547947160	3:141607335	*ATP1B3*	0.75	G/A	intron	PP	0.0008	0.20	$6.00x10^{-6}$	rs6773662	0.54	7.040	13
86	rs545513277	3:143113550	*SLC9A9*	0.70	A/G	intron	PP	0.0006	-0.24	$6.90x10^{-6}$	rs1470121	0.56	11.97	16
92	rs186525102	3:185539249	*IGF2BP2*	0.85	A/G	intron	SBP	0.0086	-0.06	$6.70x10^{-7}$	rs4687477	0.56	8.08	17
94	rs111620813	4:8293193	*HTRA3*	NA	A/G	missense	PP	0.0100	-0.05	$2.00x10^{-6}$	rs28734123	0.53	12.54	18

132	rs181585444	5:129963509	*AC005741.2*	0.83	C/T	intergenic	DBP	0.0003	-0.30	3.80×10^{-6}	rs274555	0.55	10.70	14, 13
137	rs546907130	6:8156072	*EEF1E1*	0.90	T/C	intergenic	SBP	0.0017	-0.14	1.90×10^{-7}	rs3812163	0.70	8.57	16
141	rs72854120	6:39248533	*KCNK17*	0.91	C/T	intergenic	SBP	0.0073	-0.08	3.10×10^{-9}	rs2561396	0.76	10.49	16
141	rs72854118	6:39248092	*KCNK17*	0.91	G/A	intergenic	DBP	0.0072	-0.07	2.70×10^{-7}	rs1155349	0.85	11.12	16
164	rs138890991	7:40804309	*SUGCT*	0.94	C/T	intron	PP	0.0100	0.06	1.60×10^{-7}	rs17171703	0.77	19.08	17
179	rs561912039	7:150682950	*NOS3*	0.74	T/C	intergenic	DBP	0.0017	-0.13	6.40×10^{-6}	rs3793341, rs3918226, rs6464165, rs7788497, rs891511	0.34	81.75	9,14,10
183	rs570342886	8:23380012	*SLC25A37*	0.85	C/G	intergenic	DBP	0.0001	-0.48	9.80×10^{-7}	rs7842120	0.58	15.74	16
190	rs201196388	8:95265263	*GEM*	NA	T/C	splice donor	PP	0.0005	0.26	2.40×10^{-9}	rs2170363	0.34	31.80	16, 78
193	rs532252660	8:120587297	*ENPP2*	0.79	T/C	intron	DBP	0.0025	-0.11	4.10×10^{-7}	rs7017173	0.81	26.53	6
193	rs181416549	8:120678125	*ENPP2*	0.84	A/G	intron	PP	0.0026	0.20	5.10×10^{-21}	rs35362581, rs80309268	0.95	113.21	6
212	rs138765972	10:20554597	*PLXDC2*	0.94	C/T	intron	DBP	0.0075	-0.07	4.40×10^{-8}	rs61841505	0.49	9.06	16
219	rs192036851	10:64085523	*RP11-120C12.3*	0.92	C/T	intergenic	SBP	0.0062	0.06	6.40×10^{-6}	rs10995311	0.28	19.55	16, 13
234	rs150090666	11:14865399	*PDE3B*	NA	T/C	stop gained	DBP	0.0010	-0.16	5.20×10^{-7}	rs11023147, rs2597194	0.55	12.93	16
242	rs139620213	11:61444612	*DAGLA*	0.89	T/C	upstream gene	PP	0.0019	0.11	5.90×10^{-6}	rs2524299	0.48	6.64	15
246	rs540659338	11:89183302	*NOX4*	0.85	C/T	intron	PP	0.0027	-0.14	2.60×10^{-10}	rs2289125, rs494144	0.62	58.09	17, 16
260	rs186600986	12:53769106	*SP1*	0.91	A/G	upstream gene	PP	0.0030	-0.09	1.10×10^{-6}	rs73099903	0.48	12.91	19
266	rs137937061	12:111001886	*PPTC7*	0.74	A/G	intron	SBP	0.0048	-0.09	1.30×10^{-6}	rs9739637, rs35160901, rs10849937, rs3184504	0.34	55.74	16, 4, 5
268	rs190870203	12:123997554	*RILPL1*	0.85	T/G	intron	PP	0.0020	0.12	1.70×10^{-7}	rs4759375	0.72	9.50	13
270	rs541261920	13:30571753	*RP11-629E24.2*	0.79	G/C	intergenic	SBP	0.0005	0.24	9.20×10^{-6}	rs7338758	0.54	10.09	16
281	rs149250178	14:100143685	*HHIPL1*	0.75	A/G	3' UTR	DBP	0.0004	-0.29	2.30×10^{-6}	rs7151887	0.51	7.93	16

299	rs139491786	16:2086421	*SLC9A3r2*	NA	T/C	missense	DBP	0.0068	-0.12	1.60×10^{-20}	rs28590346, rs34165865, rs62036942, rs8061324	0.57	50.80	16
304	rs2234710	16:30907835	*BCL7C*	0.79	T/G	upstream gene	SBP	0.0075	-0.08	2.30×10^{-9}	-	0.52	6.29	17, 16
304*	rs148753960	16:31047822	*STX4*	0.89	T/C	intron	PP	0.0099	-0.07	1.80×10^{-9}	rs7500719	0.42	12.21	17, 16
317	rs756906294	17:42323081	*SLC4A1*	0.73	T/C	downstream gene	PP	0.0030	0.01	8.30×10^{-6}	rs66838809	0.27	18.94	17
322	rs16946721	17:61106371	*TANC2*	0.91	G/A	intron	DBP	0.0100	-0.07	1.40×10^{-11}	rs1867624, rs4291	0.51	20.91	17, 16
333	rs55670943	19:11441374	*RAB3D*	0.87	C/T	intron	SBP	0.0085	-0.10	2.10×10^{-17}	rs12976810, rs4804157, rs160838, rs167479	0.78	85.45	13-15
346*	rs149972827	20:30413439	*MYLK2*	0.98	A/G	intron	SBP	0.0036	-0.10	6.20×10^{-9}	-	0.85	9.86	16
362	rs115089782	22:42329632	*CENPM*	0.93	T/C	intergenic	SBP	0.0001	0.53	4.20×10^{-6}	rs139919	0.44	14.12	17, 13

FINEMAP[25] was used to identify the most likely causal variants within the known loci (defined in Supplementary Table 1) using the BOLT-LMM results in UKBB, the full detailed listing of results is provided in Supplementary Table 8. Locus ID, the known locus identifier provided in Supplementary Table 1; Chr:Position, chromosome and physical position in Build 37; Info, imputation information score, NA indicates that the SNV was genotyped and not imputed; EA/OA, Effect allele and other allele, respectively; AA, amino acid change; Effect, predicted effect of the listed SNV; EAF, effect allele frequency; β, single variant effect estimate for the rare variant in the BOLT-LMM analysis; *P*-value, the single variant *P*-value from the mixed model in the BOLT-LMM analysis; PP of n SNVs, the posterior probability of the number of causal variants; $Log_{10}BF$, log_{10} Bayes factor for the top configuration; Gene, nearest gene; Trait, blood pressure trait analyzed; Ref, reference of the first reports of association in the listed region.

rs540659338 identified in UK Biobank in *NOX4* has $r^2 = 1$ in 1000G EUR with rs56061986 identified in the GCTA analysis in Table 4.

*Variants at these loci are in LD with GCTA variants (Table 2): at locus 304, $r^2 = 0.876$ between rs148753960 and rs61738491; at locus 346, $r^2 = 0.952$ between rs149972827 and rs45499294.

Online Methods

The statistical methods used and analytical packages used are further detailed in the Life Sciences Reporting Summary.

Participants. The cohorts contributing to Stage 1 of the EAWAS comprised 92 studies from four consortia (CHARGE, CHD Exome+, GoT2D:T2DGenes, ExomeBP), and UK Biobank (UKBB) totalling 870,217 individuals of European (EUR, *n* = 810,865), African Ancestry (AA, *n* = 21,077), South Asian (SAS, *n* = 33,689), and Hispanic (HIS, *n* = 4,586) ancestries. Study-specific characteristics, sample quality control and descriptive statistics for the new studies are provided in Supplementary Tables 23 and 24 (and in Supplementary Table 1 and 2 of Surendran *et al.*[13] (https://media.nature.com/original/nature-assets/ng/journal/v48/n10/extref/ng.3654-S2.xlsx) and Supplementary Table 20 of Liu *et al.*[14] (https://media.nature.com/original/nature-assets/ng/journal/v48/n10/extref/ng.3660-S1.pdf) for the previously published studies).

For EAWAS, summary association statistics were requested (for the SNVs with $P < 5 \times 10^{-8}$, outside of known BP loci) from the following cohorts: 127,478 Icelanders from deCODE; 225,113 EUR, 63,490 AA, 22,802 HIS, 2,695 NAm (Native Americans), and 4,792 EAS (East Asians) from the Million Veterans Program (MVP); and 1,505 EUR and 792 AA individuals from the Genetic Epidemiology Network of Arteriopathy (GENOA). In total, following the data request, 448,667 individuals of EUR (*n* = 354,096), AA (*n* = 63,282), HIS (*n* = 22,802), NAm (*n* = 2,695), and EAS (*n* = 4,792) ancestries were available for meta-analyses with Stage 1. Study specific characteristics are provided in Supplementary Tables 23 and 24.

Stage 1 of the RV-GWAS used data from 445,360 EUR individuals from UKBB (Supplementary Tables 23 and 24, Supplementary Information), and rare variants were followed up in a data request involving 225,112 EUR individuals from MVP.

All participants provided written informed consent, and the studies were approved by their local research ethics committees and/or institutional review boards. The BioVU biorepository performed DNA extraction on discarded blood collected during routine clinical testing, and linked to de-identified medical records.

Phenotypes. SBP, DBP, PP and HTN were analyzed. Details of the phenotype measures for the previously published studies can be found in the Supplementary Information of the Surendran *et al.* and Liu *et al.* papers (https://media.nature.com/original/nature-assets/ng/journal/v48/n10/extref/ng.3654-S2.xlsx; https://media.nature.com/original/nature-assets/ng/journal/v48/n10/extref/ng.3660-S1.pdf), and further details of the additional studies are provided in Supplementary Table 24 and Supplementary Information. Typically, the average of two baseline measurements of SBP and DBP were used. For individuals known to be taking BP-lowering medication, 15 and 10 mmHg were added to the raw SBP and DBP values, respectively, to obtain medication-adjusted values[49]. PP was defined as SBP minus DBP after medication adjustment. For HTN, individuals were classified as hypertensive cases if they satisfied at least one of the following criteria: (i) SBP $\geq$ 140 mmHg, (ii) DBP $\geq$ 90 mmHg, or (iii) use of antihypertensive or BP-lowering medication. All other individuals were considered controls. Further information on study-specific BP measurements is provided in Supplementary Table 24. Residuals from the null model obtained after regressing the medication-adjusted trait on the covariates (age, age^2, sex, BMI, principal components (PCs) to adjust for population stratification, in addition to any study-specific covariates) within a linear regression model were ranked and inverse normalized (Supplementary Information).

Genotyping. The majority of the studies were genotyped using one of the Illumina HumanExome BeadChip arrays (Supplementary Table 24). An exome chip quality control standard operating procedure (SOP: https://ruderd02.u.hpc.mssm.edu/Exome-chip-QC.pdf) developed by A. Mahajan,

N.R.R. and N.W.R. at the Wellcome Trust Centre for Human Genetics, University of Oxford was used by some studies for genotype calling and quality control, while the CHARGE implemented an alternative approach[50] (Supplementary Table 24 and Supplementary Tables 3 and 21, respectively, of Surendran et al.[13] and Liu et al.[14]). All genotypes were aligned to the plus strand of the human genome reference sequence (build 37) before any analyses and any unresolved mappings were removed. UKBB, MVP, and deCODE were genotyped using GWAS arrays (Supplementary Table 24).

Exome array meta-analyses. Study-specific analyses were performed to test for the association of 247,315 SNVs with SBP, DBP, PP and HTN in 810,865 individuals of European ancestry (75 EUR studies) and additionally in 59,352 individuals of non-European ancestry comprising of SAS (5 studies), AA (10 studies), and HIS (2 studies) individuals (Supplementary Information). Study-specific association summaries were meta-analyzed in Stage 1 using an inverse-variance-weighted fixed-effect meta-analyses implemented in METAL[52]. Fixed effect and random effects meta-analyses showed concordant results (Supplementary Table 2). For the binary trait (HTN), we performed sample-size-weighted meta-analysis.

Minimal inflation in the association test statistic, λ, was observed (λ = 1.18 for SBP, 1.20 for DBP, 1.18 for PP, and 1.18 for HTN in the EUR meta-analyses; and λ = 1.19 for SBP, 1.20 for DBP, 1.18 for PP, and 1.16 for HTN in the PA meta-analyses). The meta-analyses were performed independently at three centres, and results were found to be concordant across the centres. Following Stage 1, SNVs outside of known BP-associated regions with $P < 5 \times 10^{-8}$ were looked up in individuals from the MVP, deCODE, and GENOA studies (data request). Two meta-analyses of the three additional studies for each trait were performed by two independent analysts, one involving EUR individuals (354,096 participants) only and one PA (448,667 participants). Likewise, two Stage 2 meta-analyses for each trait were performed by two independent analysts, one EUR (1,167,961

participants) and one PA (1,318,884 participants). SNVs with (a conservative) $P < 5 \times 10^{-8}$ in the Stage 2 meta-analysis, with consistent directions of effect in Stage 1 and data request studies and no evidence of heterogeneity ($P > 0.0001$), were considered potentially novel[53].

RV-GWAS. Rare SNVs with $P < 5 \times 10^{-8}$ (a widely accepted significance threshold[54,55]) in the inverse variance-weighted meta-analysis of UKBB and MVP, with consistent directions of effect in Stage 1 and MVP and no evidence of heterogeneity ($P > 0.0001$), were considered potentially novel.

Quality control. As part of the sample QC, plots comparing inverse of the standard error as a function of the square root of study sample size for all studies were manually reviewed for each trait, and phenotype-specific study outliers were excluded. In addition, inflation of test static was manually reviewed for each study and for each phenotype and confirmed minimal or no inflation prior to Stage 1 meta-analyses. For EAWAS and RV-GWAS, we performed our own QC for genotyped variants as we were specifically interested in rare variants and knew that these were most vulnerable to clustering errors. Full details of UKBB QC are provided in the Supplementary Note. To ensure that the variants we reported are not influenced by technical artefacts and not specific to a certain ancestry, we ensured that there was no heterogeneity and also that the variants had consistent direction of effects between Stage 1 and the data request studies (MVP+deCODE+GENOA). In addition, we ensured that the association was not driven by a single study. For variants reported in RV-GWAS and EAWAS, we reviewed the cluster plots for clustering artefacts and removed poorly clustered variants. Lastly, for RV-GWAS, if the variant was available in UKBB whole exome data (~50K individuals), we ensured that the minor allele frequencies were consistent with the imputed MAF despite restricting the reporting of only variant with a good imputation quality (INFO > 0.8).

Definition of known loci. For each known variant, pairwise LD was calculated between the known variant and all variants within the 4-Mb region in the 1000 Genomes phase 3 data restricted to samples of European (EUR) ancestry. Variants with $r^2 > 0.1$ were used to define a window around the known variant. The region start and end were defined as the minimum position and maximum position of variants in LD within the window ($r^2 > 0.1$), respectively. Twelve variants were not in 1000 Genomes, and for these variants, a ±500-kb window around the known variant was used. The window was extended by a further 50 kb and overlapping regions were merged (Supplementary Table 1).

Conditional analyses. Within the new BP loci, we defined a region based on LD (Supplementary Table 1) within which conditional analysis was performed (five variants were not in the 1000G panel, and for these we established a ±500-kb window definition). Conditional and joint association analysis as implemented in Genome-wide Complex Trait Analysis (GCTA v1.91.4)[22] was performed using the EAWAS results to identify independent genetic variants associated with BP traits within newly identified and known regions available in the exome array. We restricted this analysis to the summary data from Stage 1 EUR EAWAS meta-analyses (n = 810,865) as LD patterns were modelled using individual level genotype data from 57,718 EUR individuals from the CHD Exome+ consortium. Variants with $P_{joint} < 1 \times 10^{-6}$ were considered conditionally independent.

We used the UKBB GWAS results and FINEMAP[25] v1.1 to fine-map the known BP-associated regions in order to identify rare variants that are associated with BP independently of the known common variants (Supplementary Note; due to lack of statistical power, we did not use UKBB GWAS data alone to perform conditional analyses within the new EAWAS loci). For each known region, we calculated pairwise Pearson correlation for all SNVs within a 5-Mb window of the known SNVs using LDstore v1.1. *Z*-scores calculated in the UKBB single-variant association analyses were provided as input to FINEMAP along with the correlation matrix for the region. We

selected the configuration with the largest Bayes Factor (BF) and largest posterior probability as the most likely causal SNVs. We considered causal SNVs to be significant if the configuration cleared a threshold of $\log_{10}BF > 5$ and if the variants in the configuration had an unconditional association of $P \leq 1 \times 10^{-6}$. We examined the validity of the SNVs identified for the most likely configuration by checking marginal association *P*-values and LD (r^2) within UKBB between the selected variants. For loci that included rare variants identified by FINEMAP, we validated the selected configuration using a linear regression model in R.

Gene-based tests. Gene-based tests were performed using the sequence kernel association test (SKAT)[26] as implemented in the rareMETALS package version 7.1 (https://genome.sph.umich.edu/wiki/RareMETALS) (which allows for the variants to have different directions and magnitudes of effect) to test whether rare variants in aggregate within a gene are associated with BP traits. For the EAWAS, two gene-based meta-analyses were performed for inverse-normal transformed DBP, SBP, and PP, one of EUR and a second PA including all studies with single-variant association results and genotype covariance matrices (up to 691,476 and 749,563 individuals from 71 and 88 studies were included in the EUR and PA gene-based meta-analyses, respectively).

In UKBB, we considered summary association results from 364,510 unrelated individuals only. We annotated all SNVs on the exome array using VEP[27]. A total of 15,884 (EUR) and 15,997 genes (PA) with two or more variants with MAF ≤ 0.01 annotated with VEP as high or moderate effects were tested. The significance threshold was set at $P < 2.5 \times 10^{-6}$ (Bonferroni adjusted for ~20,000 genes).

A series of conditional gene-based tests were performed for each significant gene. To verify the gene association was due to more than one variant (and not due to a single sub-genome-wide significance threshold variant), gene tests were conditioned on the variant with the smallest *P*-value

in the gene (top variant). Genes with $P_{conditional} < 1 \times 10^{-4}$ were considered significant, which is in line with locus-specific conditional analyses used in other studies[56]. In order to ensure that gene associations located in known or newly identified BP regions (Supplementary Note and Supplementary Table 1) were not attributable to common BP-associated variants, analyses were conditioned on the conditionally independent known/novel common variants identified using GCTA within the known or novel regions, respectively, for the EAWAS (or identified using FINEMAP for the GWAS). Genes mapping to either known or novel loci with $P_{conditional} < 1 \times 10^{-5}$, were considered significant. The *P*-value to identify gene-based association not driven by a single variant was set in advance of performing gene-based tests and was based on an estimation of the potential number of genes that could be associated with BP.

Mendelian randomization with CVDs. We used two-sample MR to test for causal associations between BP traits and any stroke (AS), any ischemic stroke (IS), large artery stroke (LAS), cardioembolic stroke (CE), small vessel stroke (SVS), and coronary artery disease (CAD). All the new and known BP-associated SNVs (including conditionally independent SNVs) listed in Supplementary Tables 2, 3, 5, 7 and 8, were used as instrumental variables (IVs). In addition to trait specific analyses, we performed an analysis of "generic" BP, in which we used the SNVs associated with any of the traits. Where variants were associated with multiple BP traits, we extracted the association statistics for the trait with the smallest *P*-value (or the largest posterior probability for the known loci). To exclude potentially invalid (pleiotropic) genetic instruments, we used PhenoScanner[35] to identify SNVs associated with CVD risk factors, cholesterol (LDL/HDL/triglycerides (TG)), smoking, type 2 diabetes (T2D) and atrial fibrillation (AF) (Supplementary Table 22) and removed these from the list of IVs. We extracted estimates for the associations of the selected instruments with each of the stroke subtypes from the MEGASTROKE

PA GWAS results (67,162 cases; 454,450 controls)[63] and from a recent GWAS for CAD[64]. We applied a Bonferroni correction ($P < 0.05/6 = 0.0083$) to account for the number of CVD traits. We used the inverse-variance weighting method with a multiplicative random-effects because we had hundreds of IVs for BP[65]. We performed MR-Egger regression, which generates valid estimates even if not all the genetic instruments are valid, as long as the Instrument Strength Independent of Direct Effect assumption holds[66]. We note that MR-Egger has been shown to be conservative[66], but has the useful property that the MR-Egger-intercept can give an indication of (unbalanced) pleiotropy, which allowed us to test for pleiotropy amongst the IVs. We used MR-PRESSO to detect outlier IVs[67]. To assess instrument strength, we computed the F-statistic[68] for the association of genetic variants with SBP, DBP and PP, respectively (Supplementary Information and Supplementary Table 22). We also assessed heterogeneity using the Q-statistic. Although these methods may have different statistical power, the rationale is that, if these methods give a similar conclusion regarding the association of BP and CVD, then we are more confident in inferring that the positive results are unlikely to be driven by violation of the MR assumptions[69].

Moreover, we used multivariable MR (mvMR) to estimate the effect of multiple variables on the outcome[65,70]. This is useful when two or more correlated risk factors are of interest, e.g. SBP and DBP, and may help to understand whether both risk factors exert a causal effect on the outcome, or whether one exerts a leading effect on the outcome. Thus, we used multiple genetic variants associated with SBP and DBP to simultaneously estimate the causal effect of SBP and DBP on CVDs.

All analyses were performed using R version 3.4.2 with R packages 'TwoSampleMR' and 'MendelianRandomization' and "MRPRESSO".

Metabolite quantitative trait loci and Mendelian randomization analyses. Plasma metabolites were measured in up to 8,455 EUR individuals from the INTERVAL study[71,72] and up to 5,841 EUR

individuals from EPIC-Norfolk[73] using the Metabolon HD4 platform. In both studies, 913 metabolites passed QC and were analyzed for association with ~17 million rare and common genetic variants. Genetic variants were genotyped using the Affymetrix Axiom UK Biobank array and imputed using the UK10K+1000Genomes or the HRC reference panel. Variants with INFO > 0.3 and MAC > 10 were analyzed. Phenotypes were log-transformed within each study, and standardized residuals from a linear model adjusted for study-specific covariates were calculated prior to the genetic analysis. Study-level genetic analysis was performed using linear mixed models implemented in BOLT-LMM to account for relatedness within each study, and the study-level association summaries were meta-analyzed using METAL prior to the lookup of novel BP variants for association with metabolite levels.

The same methodology for MR analyses as implemented for CVDs was also adopted to test the effects of metabolites on BP. Causal analyses were restricted to the list of 14 metabolites that overlapped our BP-associations and were known. We used a Bonferroni significance threshold ($P < 0.05/14 = 0.0036$), adjusting for the number of metabolites being tested. We also tested for a reverse causal effect of BP on metabolite levels. The IVs for the BP traits were the same as those used for MR with CVDs. For the mvMR analysis of metabolites with BP, we included 3-methylglutarylcarnitine(2) and the three metabolites that shared at least one IV with 3-methylglutarylcarnitine(2) in the mvMR model. A union set of genetic IVs for all the metabolites were used in the mvMR model to simultaneously estimate the effect size of each metabolite on DBP.

Colocalization of BP associations with eQTLs. Details of kidney-specific eQTL are provided in Supplementary Information. Using the phenoscanner lookups to prioritize BP regions with eQTLs in GTEx version 7, we performed joint colocalization analysis with the HyPrColoc package in R[31] (https://github.com/jrs95/hyprcoloc; regional colocalization plots, https://github.com/jrs95/gassocplot). HyPrColoc approximates the COLOC method developed by

Giambartolomei et al.[62] and extends it to allow colocalization analyses to be performed jointly across many traits simultaneously and pinpoint candidate shared SNV(s). Analyses were restricted to SNVs present in all the datasets used (for GTEx data this was 1 Mb upstream and downstream of the center of the gene probe), data were aligned to the same human genome build 37 and strand, and a similar prior structure as the colocalization analysis with cardiometabolic traits was used ($P = 0.0001$ and $\gamma = 0.99$).

Gene set enrichment analyses. In total, 4,993 GO biological process, 952 GO molecular function, 678 GO cellular component, 53 GTEx, 301 KEGG, 9537 MGI, and 2645 Orphanet gene sets were used for enrichment analyses (Supplementary Information).

We restricted these analyses to the rare BP-associated SNVs (Supplementary Table 4). For each set of gene sets, the significance of the enrichment of the genetically identified BP genes was assessed as the Fisher's exact test for the over-abundance of BP genes in the designated gene set based on a background of all human protein coding genes or, in the case of the MGI gene sets, a background of all human protein-coding genes with an available knock-out phenotype in the MGI database.

Results were deemed significant if after multiple testing correction for the number of gene sets in the specific set of gene sets the adjusted *P*-value < 0.05. Results were deemed suggestive if the adjusted *P*-value was between 0.05 and 0.1.

Functional enrichment using BP-associated variants. To assess enrichment of GWAS variants associated with the BP traits in regulatory and functional regions in a wide range of cell and tissue types, we used GWAS Analysis of Regulatory or Functional Information Enrichment with LD Correction (GARFIELD). The GARFIELD method has been described extensively elsewhere[76,77]. In brief, GARFIELD takes a non-parametric approach that requires GWAS summary statistics as input.

It performs the following steps: (i) LD-pruning of input variants; (ii) calculation of the fold enrichment of various regulatory/functional elements; and (iii) testing these for statistical significance by permutation testing at various GWAS significance levels, accounting for MAF, the distance to the nearest transcription start site, and the number of LD proxies of the GWAS variants. We used the SNVs from the full UKBB GWAS of BP traits as input to GARFIELD (Supplementary Table 4).

Data availability

Summary association results for all the traits are available for download from:
https://app.box.com/s/1ev9iakptips70k8t4cm8j347if0ef2u
and from the CHARGE dbGaP Summary site, (https://www.ncbi.nlm.nih.gov/gap/) accession number phs000930.

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