87 rare variants associated with blood pressure regulation in meta-analysis of ~1.3 million individuals

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Abstract

Genetic studies of blood pressure (BP) to date have mainly analysed 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 ($P<5x10^{-8}$) of which, 32 were in new BP-associated loci and 55 were independent BP-associated SNVs within known BP-associated regions. Rare variants, 44% of which were coding, on average had effects ~8 times larger than the mean effects of common variants 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 foetal tissues, potentially linking foetal development with BP regulation in later life. Multivariable Mendelian randomisation highlighted 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.

Introduction

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 1000 BP-associated single nucleotide variants (SNVs)[2-19] for this complex, heritable, polygenic trait. The majority of these were common SNVs (minor allele frequency [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*, an aminopeptidase with a known role in BP regulation[13]. These findings confirmed the utility of rare variant studies for identification of potential causal genes. These rare variant associations had larger effects on BP (typically ~1.5mmHg per minor allele) than common variants identified by previous studies (typically ~0.5mmHg 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 analyse up to ~1.319 million participants to 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 1) single variant analysis and 2) 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 (Figure 1, Methods). Known at the time of the analysis were 362 BP loci (Supplementary Table 4), 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 $P<5x10^{-8}$ and outside of the known BP regions (Supplementary Table 4a), summary association statistics were requested from three additional studies (Million Veteran Program [MVP], deCODE, and GENOA). Meta-analyses of the three data request studies and Stage 1 results were then performed (Supplementary Table 5) to discover novel variants associated with BP. Three hundred and forty-three SNVs (200 genomic regions; Methods) were associated ($P<5x10^{-8}$) 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, Supplementary Table 5, Figure 2, Supplementary Information). A further seven SNVs (seven genomic regions) were only associated ($P<5x10^{-8}$) in the pan-ancestry (PA) meta-analyses of ~1.319 million individuals (Supplementary Table 5). 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 (Supplementary Table 5, Figure 2, Supplementary Figure 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 6) using the multi-SNP-based conditional and joint association analysis (GCTA v1.91.4)[22] with the Stage 1 EUR EAWAS results

(Methods; Supplementary Table 25). In addition to the rare variants, there were 147 additional distinct ($P<1x10^{-6}$) 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 by UKBB and overlapped the Exome array, 43 replicated at $P<0.001$ (Bonferroni correction for 50 known variants) in samples independent of the original discovery (Supplementary Table 9).

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] (Figure 1; 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), eighty-four rare SNVs outside of the known BP loci (at the time of our analyses) were associated with one or more BP traits at $P<1x10^{-7}$ (Supplementary Table 7). 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 was performed for novel rare variant discovery. We identified 23 unique rare SNVs associated with one or more BP traits ($P<5x10^{-8}$) with consistent direction of effects in a meta-analysis of UKBB and MVP (min $P_{heterogeneity}=0.02$) (Table 1, Supplementary Table 8, Figure 2, Supplementary Figure 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 8).

Rare and low frequency variant associations at established BP loci

It is difficult to prioritise 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 the 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 independent rare variant associations ($P<10^{-6}$ in the GCTA joint model of the EUR Stage 1 EAWAS; Methods; Supplementary Table 25; Table 2). A further nine loci had one or more conditionally independent BP-associated SNVs with MAF≤0.02 (Table 2; Supplementary Table 10). In total, 183 SNVs (rare and common) across 110 known loci were not identified previously.

We used FINEMAP[25] to fine-map 315 loci known at the time of our analysis and available in UKBB GWAS, which provides dense coverage of genomic variation not available on the Exome array. Of these, 36 loci had one or more conditionally independent rare variant associations (Supplementary Table 10) and 251 loci had multiple common variants associations. We also replicated rare variant associations that we reported previously[13,14] at *RBM47*, *COL21A1*, *RRAS* and *DBH* ($P<5x10^{-5}$) in UKBB (independent of prior studies). Overall, from both FINEMAP and GCTA we identified forty loci with one or more rare SNV associations, independent of previously reported common variant associations (Table 3; Supplementary Table 10; Supplementary Information; Figure 2).

We note that of 256 known variants identified without UK Biobank participants (Supplementary Table 4a), 229 replicated at $P<1.95x10^{-4}$ (Bonferroni adjusted for 256 variants) in UK Biobank.

Gene-based tests to identify BP-associated genes

To test whether rare variants in aggregate affect BP regulation, we performed gene-based tests for SBP, DBP and PP using SKAT[26] including SNVs with MAF≤0.01 that were predicted by VEP[27] to have high or moderate impact (Methods). We performed separate analyses within the Stage 1 EAWAS and the UKBB RV-GWAS. Six genes in the EAWAS (*FASTKD2*, *CPXM2*, *CENPJ*, *CDC42EP4*, *OTOP2*, *SCARF2*) and two in the RV-GWAS (*FRY*, *CENPJ*) were associated with BP ($P<2.5x10^{-6}$, Bonferroni adjusted for ~20,000 genes) and were outside known and new BP loci (Supplementary Table 4 and 11). To ensure these associations were not attributable to a single (sub-genome-wide significant) rare variant, SKAT tests conditioning on the variant with the smallest *P*-value in the gene were also performed (Methods; Supplementary Table 11). *FRY* had the smallest conditional *P*-value=0.0004, but did not pass our pre-determined conditional significance threshold (conditional SKAT $P\leq0.0001$; 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, Supplementary Table 11) confirming the findings in the single variant conditional analyses above (Supplementary Table 10).

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 11).

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, Figure 2). Of these 32, five (representing five loci) were genome-wide significant for HTN, 22 (ten loci) for SBP, 14 (six loci) for DBP, 15 (ten loci) for PP (Supplementary Tables 4, 5, 6, 7, 8). 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 (Figure 2).

Power calculations are provided in the Supplementary Information and show our study had 80% power to detect an effect of 0.039 SD for a MAF=0.01 (Supplementary Figure 2). As anticipated, given statistical power, some rare variants displayed larger effects on BP regulation than common variants (Figure 2; Supplementary Table 6, 10); mean effect 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 the genetics of some other common complex traits[28,29].

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 12). These genes also had genome-wide significant SNV-BP associations in the EAWAS and/or RV-GWAS (Supplementary Table 12).

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 ($P>5x10^{-8}$; Supplementary Table 19; Methods). We used GTEx v7 data to examine in which tissues the genes closest to the rare BP-SNVs were expressed (Supplementary Figure 3; Supplementary Table 25). 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-value<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 artery (Supplementary Figure 3). There were 33 genes at 30 known loci with novel BP rare variants (from Supplementary Table 13); 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 13).

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; Supplementary Table 25). These

(rare variant) genes from both known and novel loci were enriched in BP-related pathways (Bonferroni adjusted $P<0.05$, Methods; Supplementary Table 23) 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] (Methods; Supplementary Tables 25 and 24). Six genes (4 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).

Variance explained by BP loci

The estimated percentage of variance in BP explained by all the BP-associated SNVs (known and novel) was: 4.54 for SBP, 3.54 for DBP, and 5.39 for PP. This is consistent with previous reports. Within the novel loci, ~0.6% of the variance is explained by the new independent SNVs, with <0.2% of the variance explained by independent rare variants (although we note only ~ 50% of rare variants were available for this calculation; Supplementary Information).

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; Supplementary Table 25). Nine BP-associated

variants were associated with 25 metabolites ($P<5x10^{-8}$) involved in carbohydrate, lipids, cofactors and vitamins, nucleotide (cysteine) and amino acid metabolism (Supplementary Table 17) while 11 were unknown.

We performed MR analyses to assess the influence of the 14 known metabolites (Supplementary Table 17) on BP. Lower levels of 3-methylglutarylcarnitine(2) were significantly associated with increased DBP ($P<0.003$, 0.05/14 metabolites; Supplementary Table 18). There was no suggestion of reverse causation i.e. BP did not affect 3-methylglutarylcarnitine(2) ($P>0.04$; Supplementary Table 18). 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, Supplementary Table 18).

New BP-associated SNVs are gene eQTLs across tissues

Sentinel variants from 66 new BP-associated loci were associated ($P<5x10^{-8}$) with gene expression (or had $r^2>0.8$ in 1000G EUR with eQTLs) in publicly available databases (Methods, Supplementary Tables 25 and 19). We performed colocalisation 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 colocalised at seventeen 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 (Supplementary Table 20, Figure 5). A further 10 loci had PPa>0.6 for colocalisation of BP associations and eQTL for multiple nearby genes (Figure 5). Colocalisation 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 20).

Kidney is central for BP regulation and the development of hypertension, yet publically available renal tissue is sparse, e.g. there are no significant eQTLs in kidney (n=39 samples) in GTEx[33]. 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 ($P<5x10^{-8}$) at three newly identified BP loci (*MFAP2*, *NFU1* and *AAMDC*, which was also identified in GTEx) and six at previously published loci (*ERAP1*, *ERAP2*, *KIAA0141*, *NUDT13*, *RP11-582E3.6* and *ZNF100*; Supplementary Table 21).

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 22). 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 (Supplementary Table 20, Figure 5). 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) that mark open chromatin, was tested using GARFIELD (Methods; Supplementary Table 25). The most significant enrichment in DHS hotspots for SBP-associated SNVs was in foetal heart tissues with an ~3-fold enrichment compared to ~2-fold in adult heart (Figure 5; Supplementary Information). This difference in enrichment was also reflected in foetal 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 (Figure 5; Supplementary Information). There was also enrichment across SBP, DBP and PP in foetal and adult kidney and foetal adrenal gland. In support, complementary enrichment analyses with FORGE (Methods) showed similar enrichments including in foetal kidney and foetal lung tissues (Z-score=300; Supplementary Table 23; Supplementary Information).

Mendelian Randomization with CVD

Twenty-six new BP loci were also associated with cardiometabolic diseases and risk factors in PhenoScanner[35] (Methods, Figure 3, Supplementary Information and Supplementary Tables 25, 14, 15; Supplementary Information). 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 25; Methods). BP was a predictor of all stroke types analyzed and CAD (Figure 4; the scatter plots showing the causal estimates for each BP trait-outcome pair are provided in Supplementary Figure 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 16). 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, except for LAS (Figure 4; Supplementary Table 16; Methods).

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. We have assembled >1.3 million participants from across >90 studies to have statistical power to detect these effects. We identified 107 new BP loci including 87 rare SNVs involved in BP regulation that highlight potential candidate causal genes both at new and established BP loci (Supplementary Information, Supplementary Tables 13, 23, 24, Supplementary Figure 2). At established loci, rare variants validate previously hypothesized candidate genes and potential new candidate genes. Of the 107 new BP-associated loci 72 had common sentinel variants and 3 had low-frequency sentinel variants. Across the novel loci, there were 160 conditionally independent common or low-frequency variants, and 183 across the known loci that had not been identified previously. The rare SNV-BP associations had larger effects than previously reported common SNV associations, consistent with findings from other complex traits[28,36]. We found a suggestive inverse relationship of DBP with LAS having accounted for the effects of increased SBP, which

could reflect arterial stiffening. An inverse relationship between DBP and stroke above age 50 years has also been reported[37]. SBP was superior for risk of other stroke types, consistent with observational studies[37]. We found genetically determined 3-methylglutarycarnitine(2) was predictive of DBP in both univariable and multivariable MR analyses (Supplementary Table 18). 3-methylglutarylcarnitine belongs to the class of organic compounds known as acyl carnitines involved in long-chain fatty acid metabolism in mitochondria and in leucine metabolism (Supplementary Information).

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 13). 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 in the transcription factor *GATA5* (rs200383755, p.Ser19Trp, predicted deleterious by SIFT) is associated with increased SBP and DBP. *GATA5* causes congenital heart defects multiple types 5, 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 (Supplementary Table 13); *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 by Combined Annotation Dependent Depletion (CADD) to be amongst the top 1% of most deleterious substitutions[39]. The established common variant at *FOXS1* was not associated with BP in the conditional analysis and so was not considered significant, 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 characterised 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 at this locus. Previously, we identified a rare missense BP-associated variant in *RRAS*, a gene also causing Noonan syndrome[13]. Our discoveries of rare missense variants at known BP loci provides additional support for candidate genes at these loci.

We report new low frequency variant associations, one example is the missense variant, rs45573936 (T>C, Ile216Thr) in *SLC29A1*. The minor allele is associated with both decreased SBP and DBP (Table 1, Supplementary Table 5) and the SNV has been shown to affect the function of the encoded protein, equilibrative nucleoside transporter (ENT1)[44]. A study by Best et al.[45] showed 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 foetal versus adult heart muscle tissue. These results suggest that BP-associated SNVs may influence the expression of genes that are critical for foetal 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 foetal heart[48]. The

788 authors hypothesized that the corresponding genes acting during foetal development increase risk of atrial
789 fibrillation[48]. Together these data suggest that early development and/or remodeling of cardiac tissues may
790 be an important driver of BP regulation later in life.
791
792 The BP measures we have investigated here are correlated; amongst the 107 new genetic BP loci, only two
793 are genome-wide significant across all four BP traits (*RP11-284M14.1* and *VTN*; Figure 2). None of the new
794 loci were unique to HTN (Figure 2), perhaps as HTN is derived from SBP and DBP, or perhaps due to
795 reduced statistical power for a binary trait. The results from our study indicate rare BP associated variants
796 contribute to BP variability in the general population, and their identification has provided information on
797 new candidate genes and potential causal pathways. We have primarily focused on the exome array which is
798 limited, future studies using both exome and whole genome sequencing in population cohorts e.g UKBB and
799 TopMed, will lead to identification of further rare variant associations and may advance the identification of
800 causal BP genes across the ~1000 reported BP loci.

Online Methods

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 1 and 2 (and in Supplementary Table 1 and 2 of Surendran *et al.*[13] and Supplementary Table 20 of Liu *et al.*[14] for the previously published studies).

For EAWAS, summary association statistics were requested (for the SNVs with $P<5x10^{-8}$, 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 1 and 2.

Stage 1 of the RV-GWAS used data from 445,360 EUR individuals from UKBB (Supplementary Table 1 and 2, 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.

827 **Phenotypes**

828 SBP, DBP, PP and HTN were analysed. Details of the phenotype measures for the previously
829 published studies can be found in the Supplementary Information of the Surendran *et al.* and Liu *et*
830 *al.* papers (URLs) and further details of the additional studies are provided in Supplementary Table 2
831 and Supplementary Information. Typically, the average of two baseline measurements of SBP and
832 DBP were used. For individuals known to be taking BP-lowering medication, 15 and 10 mm Hg
833 were added to the raw SBP and DBP values, respectively, to obtain medication-adjusted values[49]. PP
834 was defined as SBP minus DBP after medication adjustment. For HTN, individuals were classified
835 as hypertensive cases if they satisfied at least one of the following criteria: (i) SBP ≥ 140 mm Hg, (ii)
836 DBP ≥ 90 mm Hg, or (iii) use of antihypertensive or BP-lowering medication. All other individuals
837 were considered controls. Further information on study specific BP measurements are provided in
838 Supplementary Table 2.

839

840 **Genotyping**

841 The majority of the studies were genotyped using one of the Illumina HumanExome BeadChip
842 arrays (Supplementary Table 2). An Exome chip quality control standard operating procedure (SOP:
843 URLs) developed by A. Mahajan, N.R.R. and N.W.R. at the Wellcome Trust Centre for Human
844 Genetics, University of Oxford was used by some studies for genotype calling and quality control,
845 while the CHARGE implemented an alternative approach[50]. (Supplementary Table 2 and
846 Supplementary Table 3 and 21 respectively of Surendran et al.[13] and Liu et al.[14]). All genotypes were
847 aligned to the plus strand of the human genome reference sequence (build 37) before any analyses
848 and any unresolved mappings were removed. UKBB, MVP and deCODE were genotyped using
849 GWAS arrays (Supplementary Table 2).

850

851 **Study-level analyses**

Each contributing Stage 1 study conducted exome-wide analyses of inverse normal transformed SBP, DBP and PP as well as HTN. The analyses of the transformed traits were performed to minimize sensitivity to deviations from normality in the analysis and discovery of rare variants. The 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. These normalized residuals were used to test trait-SNV associations using RMW[51] version 4.13.3 by all studies except four studies which used SNPTEST v2.5.1 (EPIC-Norfolk, Fenland-GWAS, Fenland-OMICS and EPIC-InterAct-GWAS: Supplementary Table 1; Supplementary Methods), assuming an additive allelic effects model and two-sided tests with a linear or linear mixed regression model. All SNVs that passed quality control were analysed for association with the continuous traits without any further filtering by MAF. For HTN, only SNVs with a minimum minor allele count (MAC) of 10 were analysed.

Quality control of study level data was performed centrally and included plots comparing the inverse of the standard error versus square root of sample size for each study to detect any issues with trait transformations, and checks for concordant MAFs across studies. Five studies (CARDIA, NFBC1986, ALSPAC_Mothers, WHI: African Americans and WHI: Europeans) were excluded from analyses of HTN as they have insufficient numbers of hypertensive cases to provide reliable estimates. We did not observe excessively high inflation in study level data (maximum lambda=1.06, 1.07, 1.14 for SBP, DBP, PP, respectively).

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. Study specific association summaries were meta-analysed 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 5). 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 $P<5x10^{-8}$ were looked up in individuals from the MVP, deCODE and GENOA studies (data request). Two meta-analyses of the 3 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) $P<5x10^{-8}$ 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].

UK Biobank

A RV-GWAS of non-Exome array variants with HTN and inverse normal transformed SBP, DBP and PP was performed in UKBB European participants (Supplementary Methods, Figure 1). We used UKBB European participants data from both the Affymetrix UK Biobank and UK BiLEVE genotyping arrays and the Human Reference Consortium imputed genotypes[23]. Genotype QC was performed using PLINK1.9 and R v3.3 independently at two sites (Supplementary Information). In total, 784,045 directly genotyped and 39,312,035 imputed variants with imputation quality score (INFO)>0.3 (including 175,430 Exome array variants of which 59,824 variants were genotyped and

115,606 variants were imputed) were available for analysis for association with transformed SBP, DBP and PP in up to 445,360 individuals of European ancestry from UKBB. Of these, up to 175,430 variants were analysed in EAWAS (Stage 1), and up to 29,454,346 additional variants – in RV-GWAS (Stage 1) (Supplementary Methods, Figure 1). For HTN, genetic analysis was performed only on Exome array variants in 364,510 unrelated individuals (192,235 hypertensive cases and 172,275 controls) of European ancestry using two-sided tests in SNPTEST v2.5.4-beta3. Analyses were adjusted for baseline age, baseline age^2, gender, BMI, genotyping array and the first eight PCs. Rare SNVs with $P<1x10^{-7}$ outside of known BP-associated regions were taken forward for analyses in EUR individuals from the MVP (data request). Rare SNVs with $P<5x10^{-8}$ (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. 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. And lastly for RV-GWAS, if the variant was available in UKBB whole exome

data (~50K individuals), we ensured that the minor allele frequencies are 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 4Mb 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 ±500Kb window around the known variant was used. The window was extended by a further 50Kb and overlapping regions were merged (Supplementary Table 4).

Conditional analyses

Within the new BP loci we defined a region based on LD (Supplementary Table 4) within which conditional analysis was performed (five variants were not in the 1000G panel and for these we established a +/-500kb 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 European EAWAS meta-analyses (N=810,865) as LD patterns were modelled using individual level genotype data from 57,718 European individuals from the CHD Exome+ consortium. Variants with $P_{joint}<1x10^{-6}$ 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 Methods; 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 5Mb 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 test were performed using the sequence kernel association test (SKAT)[26] as implemented in the rareMETALS package version 7.1 (URLs) (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 UK Biobank, 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 $P<2.5\times10^{-6}$ (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 $P_{conditional}<1\times10^{-4}$ 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 Methods, Supplementary Table 4) 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 $P_{conditional}<1\times10^{-5}$, 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.

Functional annotation

We used extensive bioinformatic approaches to collate functional annotations of variants and genes within the novel and known BP-associated loci. For variants, we used VEP[27] to obtain comprehensive functional characterization of sentinel and conditionally independent variants and their proxies ($r^2\geq0.8$; using the same approach as for locus definitions) including gene location, conservation and amino acid substitution.

PhenoScanner

To identify diseases and other intermediate phenotypes associated with the novel BP variants (Supplementary Tables 5, 6), we performed a lookup of sentinel and conditionally independent variants and their proxies ($r^2 \geq 0.8$) against publicly available GWAS data using PhenoScanner[35]. A list of datasets queried is available on the phenoscanner website. Results were filtered to include association with $P<5x10^{-8}$ for common variants and $P<1x10^{-4}$ for rare variants. Either the sentinel variant or the proxy with the smallest *P*-value for each trait was further investigated.

We also queried PhenoScanner for associations with publicly available eQTL and pQTL.

Co-localisation with cardiometabolic traits

To estimate the probability that BP shared the same causal variant with other CVD risk factors, we conducted a co-localisation analysis. Using GWAS results from CVD risk factors (BMI[57], HDL Cholesterol[58], LDL Cholesterol[58], Triglycerides[58], fasting glucose[59], type 2 diabetes[60] and CAD[61]), we first identified SNV-CVD risk factor associations at each of the novel BP-associated loci. Within each locus, we conducted a Bayesian test for co-localisation using all shared SNVs using the coloc package in R.[62] Assuming that 1 in 10,000 SNVs are likely to be causal for either test trait, we applied the default prior probabilities for a SNV being associated with trait one only (p1), trait two only (p2), and with both traits (p12), with p1 and p2 set to 0.0001 and p12 set to 0.00001.

Mendelian Randomisation 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 heart disease (CHD). All the new and known BP-associated SNVs (including conditionally independent SNVs) listed in Supplementary Tables 5, 6, 8, 9 and 10, 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/TG), smoking, Type 2 diabetes (T2D) and Atrial Fibrillation (AF) (Supplementary Table 16) 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 CHD[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 100s 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; Supplementary Table 16). 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

1050 associated with SBP and DBP to simultaneously estimate the causal effect of SBP and DBP on
1051 CVDs.
1052 All analyses were performed using R version 3.4.2 with R packages 'TwoSampleMR' and
1053 'MendelianRandomization' and "MRPRESSO".
1054
1055 *Metabolite quantitative trait loci and Mendelian Randomization analyses*
1056 Plasma metabolites were measured in up to 8,455 EUR individuals from the INTERVAL study[71,72]
1057 and up to 5,841 EUR individuals from EPIC-Norfolk[73] using the Metabolon HD4 platform. In both
1058 studies, 913 metabolites passed QC and were analysed for association with ~17 million rare and
1059 common genetic variants. Genetic variants were genotyped using the Affymetrix Axiom UK
1060 Biobank array and imputed using the UK10K+1000Genomes or the HRC reference panel. Variants
1061 with INFO>0.3 and MAC>10 were analysed. Phenotypes were log transformed within each study
1062 and standardised residuals from a linear model adjusted for study specific covariates were calculated
1063 prior to the genetic analysis. Study level genetic analysis was performed using linear mixed models
1064 implemented in BOLT-LMM to account for relatedness within each study and the study
1065 level association summaries were meta-analysed using METAL prior to the lookup of novel BP
1066 variants for association with metabolite levels.
1067 The same methodology for MR analyses as implemented for CVDs was also adopted to test the
1068 effects of metabolites on BP. Causal analyses were restricted to the list of 14 metabolites that
1069 overlapped our BP-associations and were known. We used a Bonferroni significance threshold
1070 (P<0.05/14=0.0036), adjusting for the number of metabolites being tested. We also tested for a
1071 reverse causal effect of BP on metabolite levels. The IVs for the BP traits were the same as those
1072 used for MR with CVDs. For the mvMR analysis of metabolites with BP, we included 3-
1073 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.

Kidney cis-eQTL meta-analysis

We performed kidney eQTL analysis using data from 186 individuals in the TRANSLATE Study[34] and 99 from the Cancer Genome Atlas (TCGA)[74]. Full details on sample collection, gene expression, genotyping and analysis are described in the Supplementary Information. Briefly, samples from both studies were processed in the same manner and gene expression was quantified in transcripts per million (TPM) using Kallisto[75]. Following genotyping, all study results were imputed to the Haplotype Reference Consortium Project.

Multiple linear regression was used to test association between gene expression and genotype and the estimated coefficients from both studies were meta-analysed using inverse-variance weighted fixed effects. For each gene, only those SNVs within 1Mb of the transcription start/stop sites (cis) were included in the analysis. Two thousand permutations were used to derive the empirical distribution of the smallest *P*-value for each gene, which then was used to adjust the observed smallest *P*-value for the gene. The correction for testing multiple genes was based on false discovery rate (FDR) applied to permutation-adjusted *P*-values (via Storey's method as implemented in the R package q-value) with a cut-off of 0.05. Furthermore, the thresholds for nominal *P*-values were derived using a global permutation-adjusted *P*-value closest to FDR of 0.05 and the empirical distributions determined using permutations.

The BP SNVs (N=358 at 214 loci, see Supplementary Table 4b) were considered or proxies (r^2>0.8) if the sentinel SNV was not available. For reporting we only considered genes with FDR<0.05 and significant *cis*-eQTLs at $P<5\times10^{-8}$. If the BP-associated SNV and the eQTL were the same or in high LD (r^2>0.8), the BP SNV was reported as an eQTL

Co-localisation of BP associations with eQTLs

Using the phenoscanner lookups to prioritise BP regions with eQTLs in GTEx version 7, we performed joint co-localisation analysis with the HyPrColoc package in R[31]. HyPrColoc approximates the COLOC method developed by Giambartolomei et al.[62] and extends it to allow colocalisation 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 1MB upstream and downstream of the centre of the gene probe), data were aligned to the same human genome build 37 and strand, and a similar prior structure as the colocalisation analysis with cardiometabolic traits was used (p=0.0001 and γ=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 25). 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: 1) LD-pruning of input variants, 2) calculation of the fold enrichment of various regulatory/functional elements and 3) 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 UK Biobank GWAS of BP traits as input to GARFIELD (Supplementary Table 25).

Drug target prioritisation

The list of genes nearby the low-frequency and rare variant associations in both novel and previously identified loci (Supplementary Table 13) were cross-referenced in the list of "druggable" genes from Finnan et al.[30]. Those that were potentially targetable were queried in Open Targets (opentargets.org) and drugbank (URLs) to assess whether there were pre-existing molecules for these genes.

URLS

Look-ups of the BP-SNVs for association with other diseases, traits including gene expression, were performed with phenoscanner, http://www.phenoscanner.medschl.cam.ac.uk. Drug annotations were performed with drugbank (www.drugbank.ca/) and Open Targets (https://www.opentargets.org). Surendran et al. Supplementary Tables with study information for previously published studies (https://media.nature.com/original/nature-assets/ng/journal/v48/n10/extref/ng.3654-S2.xlsx). Liu et al. Supplementary Tables with study information for previously published studies (https://media.nature.com/original/nature-assets/ng/journal/v48/n10/extref/ng.3660-S1.pdf). Colocalisation using Hypr-Coloc (https://github.com/jrs95/hyprcoloc). Regional colocalisation plots (https://github.com/jrs95/gassocplot). Gene-based SKAT (https://genome.sph.umich.edu/wiki/RareMETALS). SOP for Exome array QC: https://ruderd02.u.hpc.mssm.edu/Exome-chip-QC.pdf

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AUTHOR CONTRIBUTIONS

These authors contributed to the drafting of the manuscript: P.Surendran, E.V.F, N.L, I.N, A.C.M, B.M.P, E.B, D.I.C, D.L, P.B.M, J.M.M.H and the following authors were involved in the central analyses: P.Surendran, E.V.F, N.L, I.N, S.Karthikeyan, J.Cook, D.J.L, F.D, C.N-C, P.B.M, J.M.M.H. All authors critically reviewed and approved the final version of the manuscript. The following authors performed bioinformatics analyses: S.Karthikeyan, L.C, B.M, C.Y, A.T.K, J.H.C, B.P.P, I.D.S, C.P.C, J.M.E, A.A, E.B.F, C.N.F, L.A.L, D.S.P, J.R.S, S.Burgess, M.K, J.P, E.Y, M.R.B, M.T, P.B.M. Study Analysts: J.N.H, A.G, V.T, G.Thorleifsson, B.P.P, J.M.E, A.A, P.L.A, L.F.B, J.C.B, V.S.B, J.A.B, E.W.D, F.D, S.F.N, J.D.F, C.F, T.F, H.G, O.G, F.G, D.F.G, X.G, S.E.H, A.S.H, A.H, J.E.H, S.H, S.Kanoni, J.K, M.G.L, R.L, J.Lindström, Y.L, J.Luan, A.M, G.M, N.G.M, H.M, C.M, D.M, M.Müller-Nurasyid, G.P, M.P, A.P, R.Rainer, M.Richard, T.G.R, N.Sepúlveda, X.S, A.V.S, J.A.S, A.S, P.Sulem, S.Thériault, U.T, S.Trompet, T.V.V, D.R.V.E, G.V, S.W, S.M.W, J.Y, R.Y, B.Y, W.Zhang, J.Z, W.Zhao(UPenn), W.Zhao(UMich), E.E, L.L.B, K.C, T.L, I.L, , M.N, N.W.R, M.Reedik, T.S, I.T, H.R.W, H.Z, S.F, B.J.H, M.I.M, T.D.S, A.S.B, H.H, C.Liu, A.K.M, A.P.M, A.C.M, D.I.C, J.M.M.H. Study Principal Investigators (PI) or Co-PIs: N.F, D.O.M, I.B, P.S.B, C.C, J.Connell, A.F.D, J.M.G, N.G, T.H, F.Karpe, H.A.K, K.K, M.Moitry, C.NA.P, O.Pedersen, N.P, A.R, F.R, P.J.Sever, E.Tõnu, C.J.W, P.Almgren, P.Amouyel, F.W.A, A.I.B, M.B, M.L.B, E.P.B, J.E.B, J.C.C, Y.I.C, R.C, D.C, A.C, G.D.S, R.A.d.B, I.J.D, G.D, P.D, E.D.A, P.E, S.B.F, J.F, I.F, M.F, P.W.F, P.F, G.G, T.R.G, L.G, V.G, T.B.H, C.H, B.J.H, K.H, E.I, T.J, M.J, J.W.J, S.L.K, F.Kee, J.S.K, C.K, L.J.L, L.Lind, R.J.F.L, A.a.S.M, L.M, M.I.M, O.M, K.L.M, A.D.M,

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CONFLICTS OF INTEREST

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 a 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 serves 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, MMcC 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 IN become 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-analyses including 870,217 individuals of EUR, South Asians (SAS), East Asians (EAS), African Ancestry (AA), Hispanics (HIS) and Native Americans (NAm; Supplementary Tables 1, 2; Methods). Summary association statistics for SNVs with $P<5x10^{-8}$ in Stage 1 that were outside of previously reported BP loci (Methods, Supplementary Tables 3, 4) were requested in independent studies (up to 448,667 participants; Supplementary Table 2). 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 $P<5x10^{-8}$ in the combined Stage 2 EUR or PA meta-analyses and had concordant directions of effect across studies ($P_{heterogeneity}>1x10^{-4}$; Methods), were considered significant.

(b) Rare Variant GWAS (RV-GWAS) of SBP, DBP and PP

For SNVs outside of the previously reported BP loci (Methods, Supplementary Tables 4, 7) with $P<1x10^{-7}$ in Stage 1, summary association statistics were requested from MVP (up to 225,112 participants; Supplementary Table 2). 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 $P<5x10^{-8}$ in the combined Stage 2 EUR with concordant directions of effect across UKBB and MVP ($P_{heterogeneity}>1x10^{-4}$; Methods), were considered significant. Justification of the significance thresholds used is detailed in the Methods.

*Total number of participants analysed 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) summarise pleiotropic effects, while circles 5 to 8 summarise 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. * denotes loci with rare variant associations. (b) Venn diagram showing the overlap of the 107 new BP loci across the analysed BP traits (c) functional annotation from VEP of all the identified rare variants in known and novel regions (d) 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 for the novel loci are taken from the Stage 2 EUR analyses, while for the known are from the Stage 1 analyses. Results are from the EAWAS where available and the GWAS if the known variants weren't on the Exome array.

Figure 3 Phenome-wide associations of the new BP loci a) 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 (b) and each circle represents different trait category (c). 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. The y-axes in (b) and (c) represent number of distinct BP-associated variants per trait and number of traits per category respectively. The colour coding for (a) and (b) is relative to (c).

Figure 4 Causal association of BP with stroke and Coronary Artery Disease Mendelian randomisation analyses of the effect of blood pressure on stroke and coronary artery disease. (a) from univariable analyses (b) from multivariable analyses (Methods). Analyses were performed using summary association statistics (Methods). The causal estimates are on the odds ratio (OR) scale. Results on the standard deviation scale are provided in Supplementary Table 16. 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 (95% confidence interval)l. N=the number of disease cases

Figure 5 Annotation of BP loci (a) BP associations shared with eQTL from GTEx through multi-trait colocalisation analyses. Expressed gene and the colocalised SNV are provided on the y-axis, BP trait and eQTL tissues are provided on the x-axis. The colour 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 for DBP and bottom represents PP. Height of the bar indicates the fold enrichment in the listed tissues. The colours represent the enrichment *P*-value.

TABLE TITLES

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

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.

Table 3 Newly identified independent blood pressure associated rare SNVs (MAF≤0.01) at known loci UK Biobank only.

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	V/A	missense	PP	0.016	-0.37	2.74×10^{-9}	0.24	1,159,900
11	rs61747728†	1:179,526,214	*NPHS2*	T/C	Q/R	missense	DBP	0.040	0.26	8.74×10^{-13}	0.22	1,160,530
16	rs4149909	1:242,023,898	*EXO1*	G/A	N/S	missense	SBP	0.033	0.36	2.46×10^{-8}	0.09	1,158,190
32	rs3821033†	2:219,507,302	*ZNF142*	T/C	T/A	missense	DBP	0.033	-0.29	1.42×10^{-13}	0.75	1,160,530
	rs16859180†	2:219,553,468	*STK36*	T/C	W/R	missense	DBP	0.049	-0.26	1.11×10^{-16}	0.34	1,160,530
44	**rs145072852**	**3:101,476,645**	***CEP97***	**T/C**	**F/L**	**missense**	**PP**	**0.004**	**1.05**	$\mathbf{1.42\times10^{-13}}$	**0.01**	**1,158,820**
46	**rs139600783**	**3:119,109,769**	***ARHGAP31***	**T/C**	**S/P**	**missense**	**HTN**	**0.008**	**5.85**	$\mathbf{5.05\times10^{-9}}$	**0.19**	**975,381**
50	**rs73181210**	**3:169,831,268**	***PHC3***	**C/T**	**K/E**	**missense**	**DBP**	**0.009**	**-0.66**	$\mathbf{9.14\times10^{-15}}$	**0.04**	**1,159,580**
52	rs11937432†	4: 2,233,709	*HAUS3*	G/A	I/T	missense	DBP	0.046	0.21	9.56×10^{-10}	0.26	1,160,520
58	rs1229984	4:100,239,319	*ADH1B*	T/C	H/R	missense	PP	0.026	-0.75	2.97×10^{-25}	0.54	686,104
63	**rs143057152**	**4:149,075,755**	***NR3C2***	**T/C**	**H/R**	**missense**	**SBP**	**0.003**	**1.75**	$\mathbf{4.14\times10^{-14}}$	**0.22**	**1,128,880**
71	rs61755724	5:132,408,967	*HSPA4*	A/G	T/A	missense	DBP	0.024	0.26	9.75×10^{-9}	0.36	1,160,530
72	rs33956817	5:137,278,682	*FAM13B*	C/T	M/V	missense	SBP	0.044	0.31	1.76×10^{-8}	0.27	1,158,190
77	rs34471628†	5:172,196,752	*DUSP1*	G/A	Y/H	missense	DBP	0.039	-0.23	3×10^{-10}	0.42	1,153,300
85	rs45573936	6: 44,198,362	*SLC29A1*	C/T	I/T	missense	DBP	0.027	-0.38	3.7×10^{-19}	0.59	1,160,530
100	rs144867634	7:111,580,166	*DOCK4*	C/T	M/V	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	M/V	missense	DBP	0.025	0.31	1.4×10^{-10}	0.26	1,160,530
114	rs76767219	8: 81,426,196	*ZBTB10*	A/C	E/A	missense	SBP	0.034	-0.44	4.41×10^{-13}	0.18	1,160,830
119	rs61732533†	8:145,108,151	*OPLAH*	A/G	Y	synonymous	DBP	0.049	-0.21	2.05×10^{-10}	0.86	1,085,170
	rs34674752†	8:145,154,222	*SHARPIN*	A/G	S/P	missense	DBP	0.049	-0.19	5.89×10^{-10}	0.91	1,132,350
146	rs117874826	11: 64,027,666	*PLCB3*	C/A	E/A	missense	SBP	0.014	0.71	4.67×10^{-12}	0.42	1,153,360
	rs145502455	**11: 64,031,030**	***PLCB3***	**A/G**	**I/V**	**missense**	**SBP**	**0.005**	**0.9**	$\mathbf{5.01\times10^{-9}}$	**0.04**	**1,156,310**
154	**rs141325069**	**12: 20,769,270**	***PDE3A***	**A/G**	**Q/R**	**missense**	**SBP**	**0.003**	**1.45**	$\mathbf{6.25\times10^{-11}}$	**0.82**	**1,134,260**
158	**rs77357563**	**12:114,837,349**	***TBX5***	**A/C**	**Y/D**	**missense**	**PP**	**0.005**	**-1.01**	$\mathbf{7.72\times10^{-22}}$	**0.22**	**1,152,080**
159	rs13141	12:121,756,084	*ANAPC5*	A/G	V/A	missense	DBP	0.011	0.52	1.98×10^{-12}	0.63	1,156,950

168	rs17880989†	14: 23,313,633	*MMP14*	A/G	I/M	missense	DBP	0.027	0.32	2.02×10^{-14}	0.95	1,160,530
169	**rs61754158**	**14: 31,774,324**	***HEATR5A***	**T/C**	**R/G**	**missense**	**SBP**	**0.009**	**-0.7**	$\mathbf{6.28 \times 10^{-9}}$	**0.04**	**1,119,230**
170	**rs72681869**	**14: 50,655,357**	***SOS2***	**C/G**	**R/P**	**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	*/S	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	H/R	missense	DBP	0.035	0.24	4.71×10^{-10}	0.04	1,155,020
186	rs62051555	16: 72,830,539	*ZFHX3*	G/C	H/Q	missense	PP	0.048	0.47	1.19×10^{-25}	0.43	797,332
206	rs11699758	20: 60,901,762	*LAMA5*	T/C	I/V	missense	PP	0.034	-0.26	6.68×10^{-11}	0.54	1,154,410
	rs13039398	20: 60,902,402	*LAMA5*	A/G	W/R	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**	**R/G**	**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	5.2×10^{-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	1.6	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**	**S/W**	**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 set of results are provided in Supplementary Tables 5 and 8. 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.

† indicates novel variants identified in this study which are in linkage disequilibrium (LD: r^2>0.6 rare SNVs and r^2>0.1 common SNVs) with a variant which has recently been reported by Evangelou et al. [20] and/or Giri et al. [21] within +/-500Kb 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**	**F/L**	**Missense**	**SBP**	**0.0008**	**0.166**	**7.49E-09**	**758,252**	14
	rs61757359	**1: 153658297**		**A/G**	**S/G**	**Missense**		**0.0034**	**-0.0812**	**6.10E-09**	**794,698**	
	rs35479618 **	1: 153662423		A/G	K/E	Missense		0.017	0.0694	1.19E-28	774,862	
28	**rs1805090**	**1: 230840034**	***AGT*** +	**T/G**	**M/L**	**Missense**	**DBP**	**0.0023**	**0.107**	**6.00E-10**	**759,349**	8
	rs699	1: 230845794		G/A	T/M	Missense	DBP	0.408	0.0225	2.12E-45	806,731	
94	**rs111620813**	**4: 8293193**	***HTRA3*** +	**A/G**	**M/V**	**Missense**	**PP**	**0.011**	**-0.0432**	**1.38E-08**	**798,063**	18
	rs7437940 **	4: 7887500	*AFAP1*	T/C	-	Intron	PP	0.406	-0.0131	1.62E-16	806,708	
102	**rs112519623**	**4: 103184239**	***SLC39A8*** +	**A/G**	**F/L**	**Missense**	**DBP**	**0.016**	**-0.0391**	**3.02E-10**	**803,151**	6
	rs13107325 **	4: 103188709		T/C	T/A	Missense	DBP	0.072	-0.0615	9.69E-88	806,731	
	rs4699052	4: 104137790	*CENPE*	T/C	-	Intergenic	DBP	0.388	-0.0121	7.31E-14	806,731	
105	rs6825911	4: 111381638	***ENPEP***	T/C	-	Intron	DBP	0.205	-0.0215	$1.47x10^{-28}$	801,965	
	rs33966350	**4: 111431444**		**A/G**	***/W**	**Stop/lost**	**DBP**	**0.0128**	**0.0735**	**$2.40x10^{-25}$**	**798,385**	
144	rs4712056 **	6: 53989526	*MLIP*	G/A	V/I	Missense	PP	0.360	0.00912	1.86E-08	806,708	14,16,13
	rs115079907	**6: 55924005**	***COL21A1*** +	**T/C**	**R/G**	Missense	**PP**	**0.0015**	**0.206**	**8.33E-17**	**783,546**	
	rs12209452	6: 55924962		G/A	P/L	Missense	PP	0.049	0.0411	5.49E-26	743,036	
	**rs200999181 ** **	**6: 55935568**		**A/C**	**V/G**	Missense	**PP**	**0.0012**	**0.335**	**4.74E-43**	**764,864**	
	rs35471617	6: 56033094		A/G	M/T	Missense/splice region	PP	0.073	0.0249	1.03E-15	806,708	
	rs2764043	**6: 56035643**		**G/A**	**P/L**	**Missense**	**PP**	**0.0016**	**0.153**	**5.11E-14**	**785,643**	
	rs1925153 **	6: 56102780		T/C	-	Intron	PP	0.448	-0.00955	1.03E-08	786,734	
	rs4294007	6: 57512510	*PRIM2*	T/G	-	Splice acceptor	PP	0.379	0.00957	1.13E-07	632,625	
208	rs507666	9:136149399	*ABO*	A/G	-	Intron	DBP	0.189	-0.0293	7.53E-47	796,103	13,15
			LL09NC01-	A/G	-	Exon (noncoding transcript)	DBP					
	rs3025343	9:136478355	*254D11.1*					0.1109	-0.0126	4.91E-07	806,731	
	rs77273740	9:136501728	*DBH*	T/C	W/R	Missense	DBP	0.0273	-0.0845614	3.85E-11	790,500	
	rs3025380	**9:136501756**	***DBH***	**C/G**	**A/G**	**Missense**	**DBP**	**0.0045**	**-0.103**	**5.37E-18**	**795,263**	
	rs74853476	**9:136501834**	***DBH***	**T/C**	**-**	**Splice donor**	**DBP**	**0.0021**	**0.100**	**3.69E-08**	**775,793**	
223	**rs201422605**	**10: 95993887**	***PLCE1***	**G/A**	**V/M**	**Missense**	**SBP**	**0.0026**	**-0.0837**	**1.41E-07**	**795,009**	7,14
	rs11187837	10: 96035980		C/T	-	Intron	SBP	0.110	-0.0198	4.23E-14	801,969	
	rs17417407	10: 95931087		T/G	L/R	Missense	SBP	0.167	-0.0122	9.97E-09	806,735	
	rs9419788	10: 96013705		G/A	-	Intron	SBP	0.387	0.0137	9.63E-16	806,735	
229	**rs60889456**	**11: 723311**	***EPS8L2*** +	**T/C**	**L/P**	**Missense**	**PP**	**0.017**	**0.0303**	**6.37E-07**	**799,021**	17
	rs7126805 **	11: 828916	*CRACR2B*	G/A	R/Q	Missense	PP	0.271	-0.0134	1.43E-13	752,026	
246*	**rs56061986**	**11: 89182686**	***NOX4*** +	**C/T**	**G/S**	**Missense**	**PP**	**0.0029**	**-0.108**	**2.25E-11**	**798,273**	17 16
	rs139341533	**11: 89182666**		**A/C**	**F/L**	**Missense**	**PP**	**0.0043**	**-0.0947**	**6.82E-14**	**785,947**	

	rs10765211	11: 89228425		A/G	-	Intron	PP	0.342	-0.0176	8.77E-27	806,708	
250	**rs117249984**	**11: 107375422**	***ALKBH8***	**A/C**	**Y/D**	**Missense**	**SBP**	**0.019**	**-0.0304**	**2.90E-07**	**805,695**	16
	rs3758911	11: 107197640	*CWF19L2*	C/T	C/Y	Missense	SBP	0.341	0.0113	1.54E-11	806,735	
304	**rs61738491**	**16: 30958481**	***FBXL19*** +	**A/G**	**Q/R**	**Missense**	**PP**	**0.010**	**-0.0460**	**1.25E-08**	**796,459**	17,16
	rs35675346 **	16: 30936081		A/G	K/E	Missense	PP	0.241	-0.0125	1.06E-11	802,932	
130 *	**rs114280473**	**5: 122714092**	***CEP120*** +	**A/G**	**F/L**	**Missense**	**PP**	**0.0063**	**-0.0584**	**9.98E-08**	**805,632**	13, 12, 14, 15
	rs2303720	5: 122682334		T/C	H/R	Missense	PP	0.029	-0.0419	3.44E-18	806,708	
	rs1644318	5: 122471989	*PRDM6*	C/T	-	Intron	PP	0.387	0.0192	2.43E-32	790,025	
179 *	rs3735080	7: 150217309	*GIMAP7*	T/C	C/R	Missense	DBP	0.237	-0.00924	6.56E-07	806,731	9, 14, 10
	rs3807375	7: 150667210	*KCNH2*	T/C	-	Intron	DBP	0.364	-0.00840	3.94E-07	806,731	
	rs3918234	**7: 150708035**	***NOS3*** +	**T/A**	**Q/L**	**Missense**	**DBP**	**0.0037**	**-0.0727**	**1.33E-07**	**786,541**	
	rs891511 **	7: 150704843		A/G	-	Intron	DBP	0.331	-0.0231	1.56E-40	778,271	
	rs10224002 **	7: 151415041	*PRKAG2*	G/A	-	Intron	DBP	0.286	0.0186	7.41E-27	806,731	
190 *	**rs138582164**	**8: 95264265**	***GEM*** +	**A/G**	***/R**	**Stop lost**	**PP**	**0.0008**	**0.281**	**1.90E-17**	**735,507**	16, 78
195 *	**rs112892337**	**8: 135614553**	***ZFAT*** +	**C/G**	**S/C**	**Missense**	**SBP**	**0.0045**	**-0.0831**	**4.39E-12**	**792,203**	17
	rs12680655	8: 135637337		G/C	-	Intron	SBP	0.398	0.0118	1.81E-13	797,982	
259 *	**rs145878042**	**12: 48143315**	***RAPGEF3*** +	**G/A**	**P/L**	**Missense**	**SBP**	**0.012**	**-0.0453**	**9.28E-10**	**805,791**	16, 13
	rs148755202	**12: 48191247**	***HDAC7***	**T/C**	**H/R**	**Missense**	**SBP**	**0.016**	**0.0310**	**9.07E-07**	**806,735**	
	rs1471997	12: 48723595	*H1FNT*	A/G	Q/R	Missense	SBP	0.216	0.0130	1.15E-11	806,735	
	rs1126930 **	12: 49399132	*PRKAG1*	C/G	S/T	Missense	SBP	0.035	0.0408	1.45E-21	793,216	
	rs52824916 **	12: 49993678	*FAM186B*	T/C	Q/R	Missense	SBP	0.088	-0.0155	1.70E-08	806,735	
	rs7302981 **	12: 50537815	*CERS5*	A/G	C/R	Missense	SBP	0.375	0.0219	1.52E-41	806,735	
312 *	**rs61753655**	**17: 1372839**	***MYO1C*** +	**T/C**	**K/E**	Missense	**SBP**	**0.011**	**0.0653**	**6.48E-18**	**806,735**	17, 16
	rs1885987	17: 2203025	*SMG6*	G/T	T/N	Missense	SBP	0.371	-0.0127	3.94E-15	806,735	
339 *	**rs34093919**	**19: 41117300**	***LTBP4*** +	**A/G**	**N/D**	**Missense/splice region**	**PP**	**0.014**	**-0.0631**	**4.18E-20**	**805,764**	19
	rs814501	19: 41038574	*SPTBN4*	G/A	G/S	Missense	PP	0.482	-0.0115	2.40E-13	806,708	
346	**rs45499294**	**20: 30433126**	***FOXS1*** +	**T/C**	**K/E**	**Missense**	**SBP**	**0.0037**	**-0.0732**	**2.36E-08**	**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 4). 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 10. Bold font highlights variants with MAF<0.02. Locus ID: the known locus identifier used in Supplementary Table 4. 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 analysed. 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 < $2x10^{-6}$, see Supplementary Table 11.

1 **Table 3 Newly identified independent blood pressure 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	4.70E-21	rs2982373, rs5066, rs55892892	0.55	122.5	9,2,79
18	rs756799918	1:153464738	*RN7SL44P*	0.89	T/C	intergenic	SBP	0.00043	0.26	4.30E-07	rs12030242	0.36	27.49	14
28	rs1805090	1:230840034	*AGT*	NA	T/G	missense	SBP	0.0025	0.11	6.80E-08	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	0.127	3.20E-09	rs2493135, rs3889728	0.83	30.97	8
33	rs56152193	2:20925891	*LDAH*	0.76	C/G	intron	PP	0.00061	-0.23	8.10E-07	rs7255	0.360	17.95	17, 16
55	rs759606582	2:178325956	*AGPS*	0.96	G/A	intron	PP	0.00031	0.29	1.90E-07	rs56726187	0.570	7.48	16
72	rs555934473	3:48899332	*SLC25A20*	0.74	T/G	intron	DBP	0.0012	-0.17	2.50E-06	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	3.80E-13	rs3821843, rs7340705, rs11707607	0.58	29.45	18, 16
	rs144980716	3:53776904	*CACNA1D*	0.91	A/G	intron	PP	0.0065	0.073	2.60E-08	rs36031811, rs77347777	0.570	18.42	
85	rs547947160	3:141607335	*ATP1B3*	0.75	G/A	intron	PP	0.00075	0.20	6.00E-06	rs6773662	0.540	7.04	13
86	rs545513277	3:143113550	*SLC9A9*	0.70	A/G	intron	PP	0.00056	-0.24	6.90E-06	rs1470121	0.560	11.97	16
92	rs186525102	3:185539249	*IGF2BP2*	0.85	A/G	intron	SBP	0.0086	-0.061	6.70E-07	rs4687477	0.56	8.08	17
94	rs111620813	4:8293193	*HTRA3*	NA	A/G	missense	PP	0.010	-0.049	2.00E-06	rs28734123	0.530	12.54	18

132	rs181585444	5:129963509	*AC005741.2*	0.83	C/T	intergenic	DBP	0.00032	-0.30	3.80E-06	rs274555	0.55	10.70	14, 13
137	rs546907130	6:8156072	*EEF1E1*	0.90	T/C	intergenic	SBP	0.0017	-0.14	1.90E-07	rs3812163	0.70	8.57	16
141	rs72854120	6:39248533	*KCNK17*	0.91	C/T	intergenic	SBP	0.0073	-0.076	3.10E-09	rs2561396	0.76	10.49	16
141	rs72854118	6:39248092	*KCNK17*	0.91	G/A	intergenic	DBP	0.0072	-0.066	2.70E-07	rs1155349	0.85	11.12	16
164	rs138890991	7:40804309	*SUGCT*	0.94	C/T	intron	PP	0.010	0.055	1.60E-07	rs17171703	0.770	19.08	17
179	rs561912039	7:150682950	*NOS3*	0.74	T/C	intergenic	DBP	0.0017	-0.13	6.40E-06	rs3793341, rs3918226, rs6464165, rs7788497, rs891511	0.34	81.75	9,14,10
183	rs570342886	8:23380012	*SLC25A37*	0.85	C/G	intergenic	DBP	0.00013	-0.48	9.80E-07	rs7842120	0.58	15.74	16
190	rs201196388	8:95265263	*GEM*	NA	T/C	splice donor	PP	0.00054	0.26	2.40E-09	rs2170363	0.340	31.80	16, 78
193	rs532252660	8:120587297	*ENPP2*	0.79	T/C	intron	DBP	0.0025	-0.11	4.10E-07	rs7017173	0.81	26.53	6
193	rs181416549	8:120678125	*ENPP2*	0.84	A/G	intron	PP	0.0026	0.20	5.10E-21	rs35362581, rs80309268	0.950	113.21	6
212	rs138765972	10:20554597	*PLXDC2*	0.94	C/T	intron	DBP	0.0075	-0.067	4.40E-08	rs61841505	0.49	9.06	16
219	rs192036851	10:64085523	*RP11-120C12.3*	0.92	C/T	intergenic	SBP	0.0062	0.062	6.40E-06	rs10995311	0.28	19.55	16, 13
234	rs150090666	11:14865399	*PDE3B*	NA	T/C	stop gained	DBP	0.0010	-0.16	5.20E-07	rs11023147, rs2597194	0.55	12.93	16
242	rs139620213	11:61444612	*DAGLA*	0.89	T/C	upstream gene	PP	0.0019	0.11	5.90E-06	rs2524299	0.480	6.64	15
246	rs540659338	11:89183302	*NOX4*	0.85	C/T	intron	PP	0.0027	-0.14	2.60E-10	rs2289125, rs494144	0.620	58.09	17, 16
260	rs186600986	12:53769106	*SP1*	0.91	A/G	upstream gene	PP	0.0030	-0.094	1.10E-06	rs73099903	0.480	12.91	19
266	rs137937061	12:111001886	*PPTC7*	0.74	A/G	intron	SBP	0.0048	-0.085	1.30E-06	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	1.70E-07	rs4759375	0.720	9.50	13
270	rs541261920	13:30571753	*RP11-629E24.2*	0.79	G/C	intergenic	SBP	0.00048	0.24	9.20E-06	rs7338758	0.54	10.09	16
281	rs149250178	14:100143685	*HHIPL1*	0.75	A/G	3' UTR	DBP	0.00036	-0.29	2.30E-06	rs7151887	0.51	7.93	16

299	rs139491786	16:2086421	*SLC9A3r2*	NA	T/C	missense	DBP	0.0068	-0.12	1.60E-20	rs28590346,rs34165865,rs62036942,rs8061324	0.57	50.80	[16]
304	rs2234710	16:30907835	*BCL7C*	0.79	T/G	upstream gene	SBP	0.0075	-0.081	2.30E-09	-	0.52	6.29	[17, 16]
304*	rs148753960	16:31047822	*STX4*	0.89	T/C	intron	PP	0.0099	-0.067	1.80E-09	rs7500719	0.420	12.21	[17, 16]
317	rs756906294	17:42323081	*SLC4A1*	0.73	T/C	downstream gene	PP	0.0030	0.099	8.30E-06	rs66838809	0.270	18.94	[17]
322	rs16946721	17:61106371	*TANC2*	0.91	G/A	intron	DBP	0.0100	-0.073	1.40E-11	rs1867624,rs4291	0.51	20.91	[17, 16]
333	rs55670943	19:11441374	*RAB3D*	0.87	C/T	intron	SBP	0.0085	-0.10	2.10E-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	6.20E-09	-	0.85	9.86	[16]
362	rs115089782	22:42329632	*CENPM*	0.93	T/C	intergenic	SBP	0.00011	0.53	4.20E-06	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 4) using the BOLTLMM results in UKBB, the full detailed listing of results is provided in Supplementary Table 10. Locus ID: the known locus identifier provided in Supplementary Table 4. 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 BOLTLMM analysis. *P*-value: the single variant *P*-value from the mixed model in the BOLTLMM 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 analysed. 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.

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-analyses including 870,217 individuals of EUR, South Asians (SAS), East Asians (EAS), African Ancestry (AA), Hispanics (HIS) and Native Americans (NAm; Supplementary Tables 1, 2; Methods). Summary association statistics for SNVs with $P<5x10^{-8}$ in Stage 1 that were outside of previously reported BP loci (Methods, Supplementary Tables 3, 4) were requested in independent studies (up to 448,667 participants; Supplementary Table 2). 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 $P<5x10^{-8}$ in the combined Stage 2 EUR or PA meta-analyses and had concordant directions of effect across studies ($P_{heterogeneity}>1x10^{-4}$; Methods), were considered significant.

(b) Rare Variant GWAS (RV-GWAS) of SBP, DBP and PP

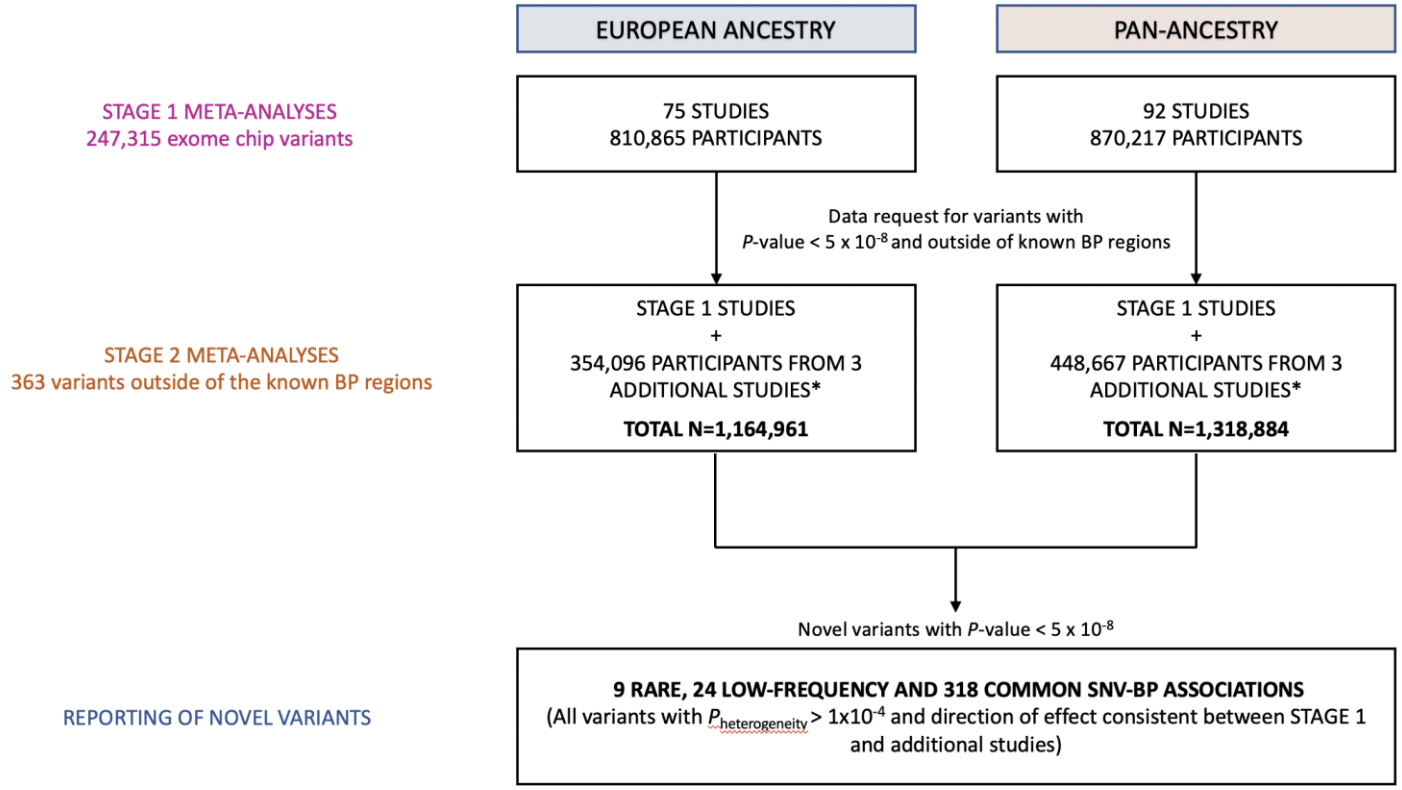
For SNVs outside of the previously reported BP loci (Methods, Supplementary Tables 4, 7) with $P<1x10^{-7}$ in Stage 1, summary association statistics were requested from MVP (up to 225,112 participants; Supplementary Table 2). In Stage 2, we performed meta-analyses of Stage 1 and MVP for SBP, DBP and PP in EUR. SNVs that were associated with a BP trait at $P<5x10^{-8}$ in the combined Stage 2 EUR with concordant directions of effect across UKBB and MVP ($P_{heterogeneity}>1x10^{-4}$; Methods), were considered significant. Justification of the significance thresholds used is detailed in the Methods.

*Total number of participants analysed within each study that provided single variant association summaries following the data request

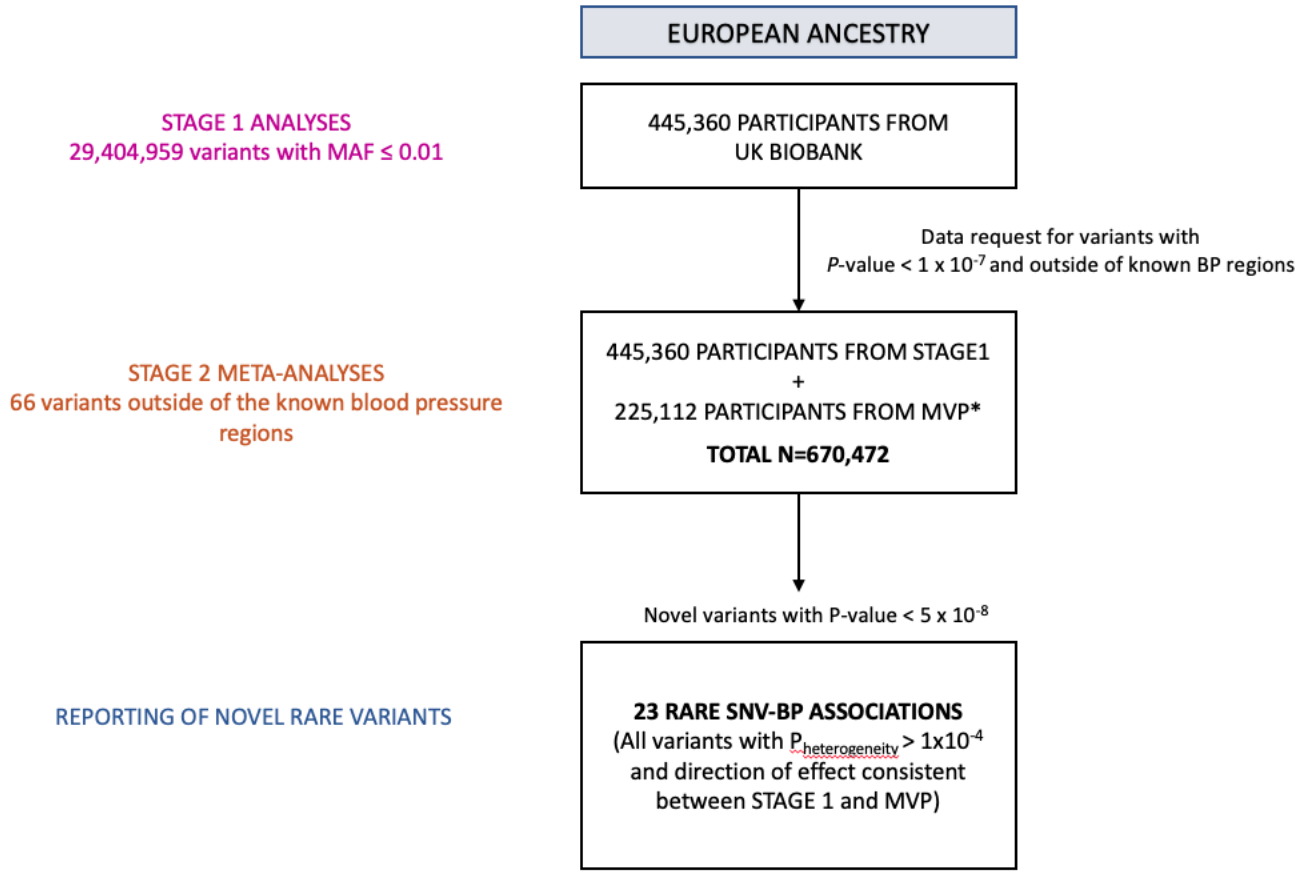
- **EAWAS EUR**: Million Veterans Program (MVP: 225,113), deCODE (127,478) and GENOA (1,505)
- **EAWAS PA**: Million Veterans Program (MVP: 225,113 EUR; 63,490 AA; 22,802 HIS; 2,695 Nam; 4,792 EAS), deCODE (127,478 participants from Iceland) and GENOA (1,505 EUR; 792 AA)

- **RV-GWAS EUR:** Million Veterans Program (MVP: 225,112 EUR)

(a)

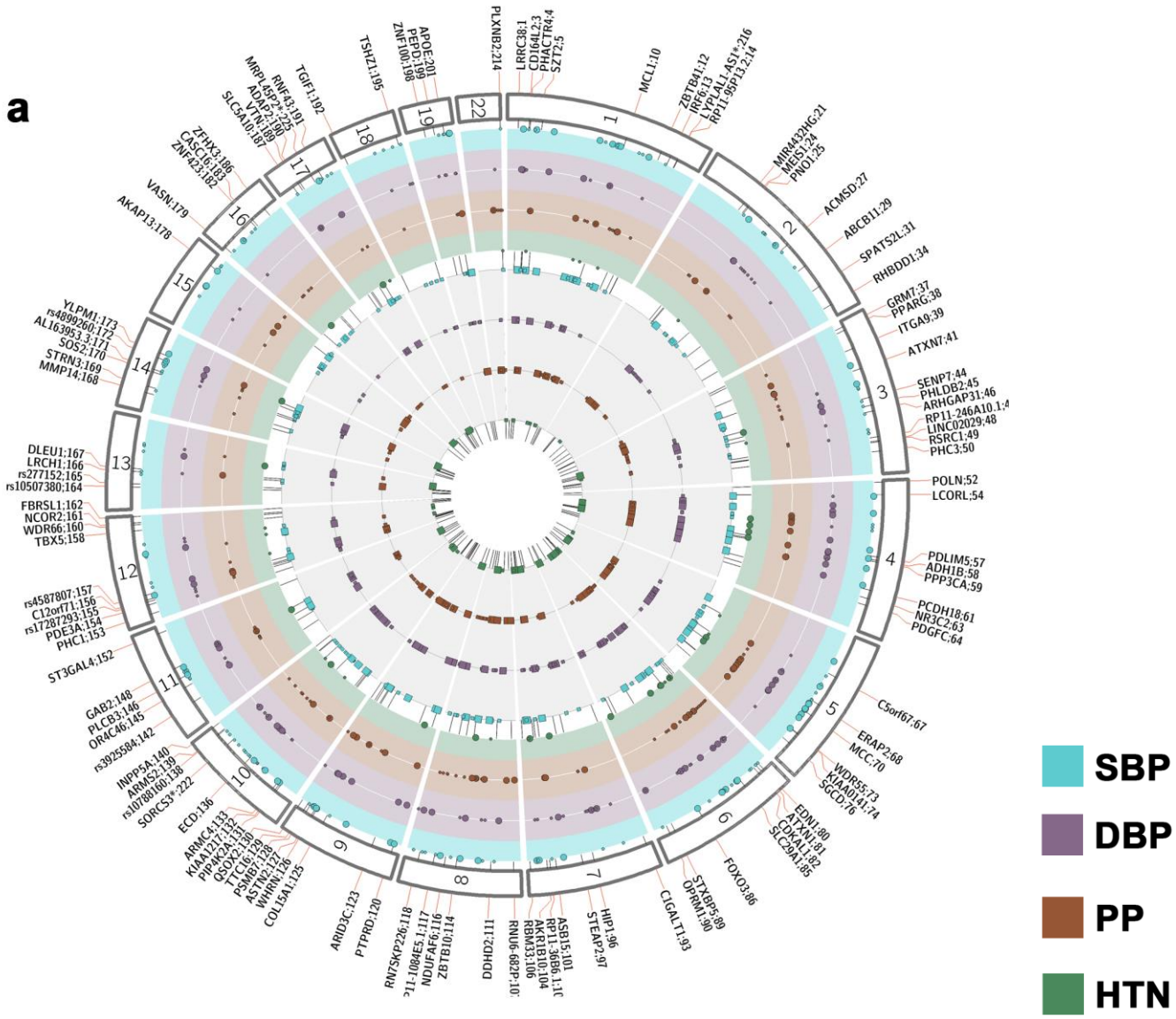

EUROPEAN ANCESTRY
PAN-ANCESTRY
STAGE 1 META-ANALYSES
247,315 exome chip variants
75 STUDIES
810,865 PARTICIPANTS
92 STUDIES
870,217 PARTICIPANTS
Data request for variants with
P-value < 5 x 10-8 and outside of known BP regions
STAGE 2 META-ANALYSES
363 variants outside of the known BP regions
STAGE 1 STUDIES
+
354,096 PARTICIPANTS FROM 3
ADDITIONAL STUDIES*
TOTAL N=1,164,961
STAGE 1 STUDIES
+
448,667 PARTICIPANTS FROM 3
ADDITIONAL STUDIES*
TOTAL N=1,318,884
Novel variants with P-value < 5 x 10-8
REPORTING OF NOVEL VARIANTS
9 RARE, 24 LOW-FREQUENCY AND 318 COMMON SNV-BP ASSOCIATIONS
(All variants with Pheterogeneity > 1x10-4 and direction of effect consistent between STAGE 1
and additional studies)

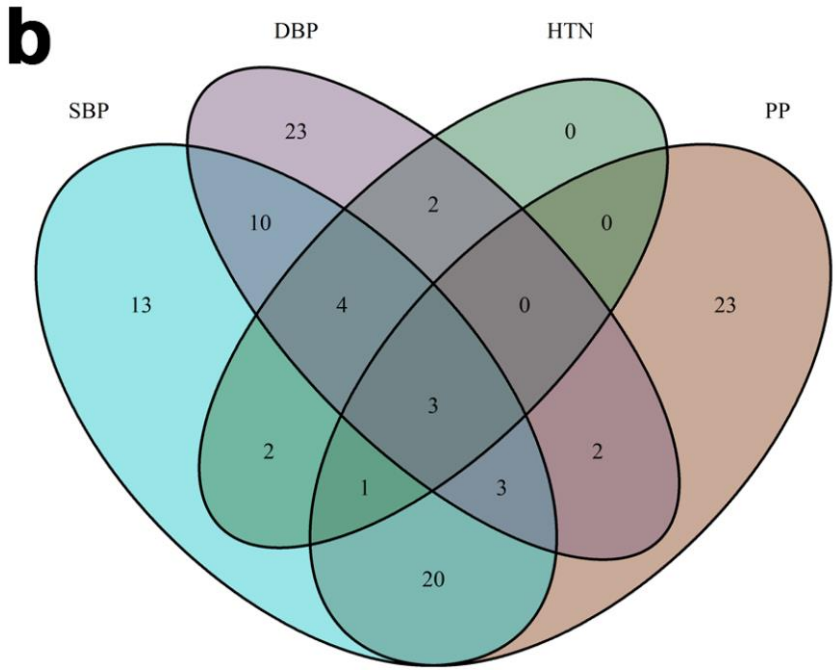
(b)

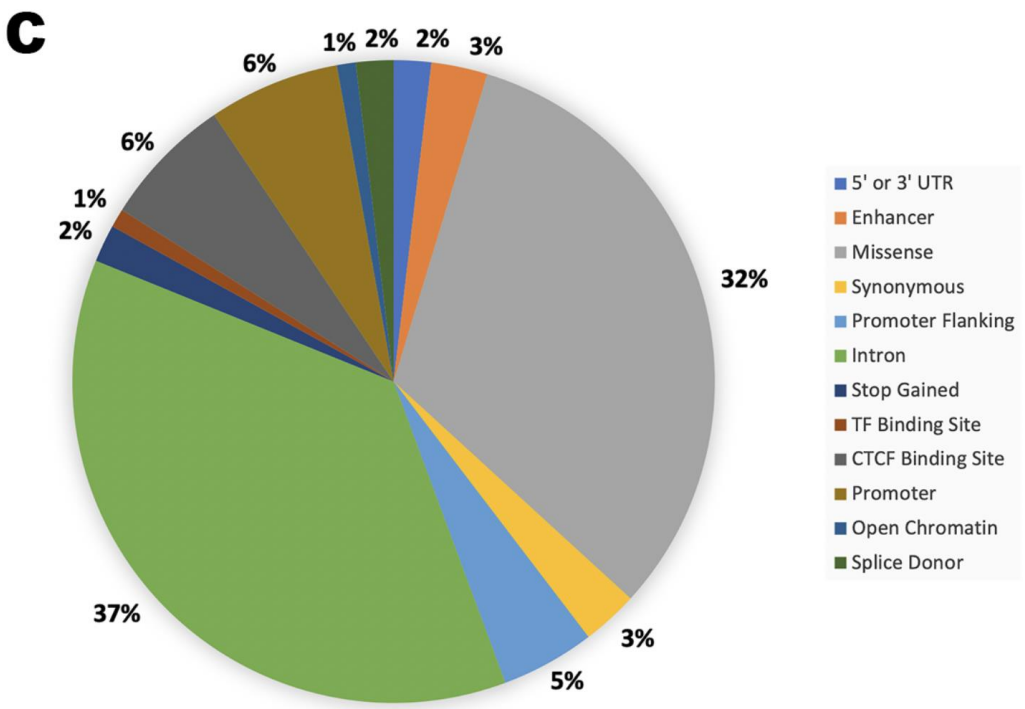

EUROPEAN ANCESTRY
STAGE 1 ANALYSES
29,404,959 variants with MAF ≤ 0.01
445,360 PARTICIPANTS FROM
UK BIOBANK
Data request for variants with
P-value < 1 x 10-7 and outside of known BP regions
STAGE 2 META-ANALYSES
66 variants outside of the known blood pressure regions
445,360 PARTICIPANTS FROM STAGE1
+
225,112 PARTICIPANTS FROM MVP*
TOTAL N=670,472
Novel variants with P-value < 5 x 10-8
REPORTING OF NOVEL RARE VARIANTS
23 RARE SNV-BP ASSOCIATIONS
(All variants with Pheterogeneity > 1x10-4
and direction of effect consistent
between STAGE 1 and MVP)

69

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) summarise pleiotropic effects, while circles 5 to 8 summarise 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. * denotes loci with rare variant associations. (b) Venn diagram showing the overlap of the 107 new BP loci across the analysed BP traits (c) functional annotation from VEP of all the identified rare variants in known and novel regions (d) 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 for the novel loci are taken from the Stage 2 EUR analyses, while for the known are from the Stage 1 analyses. Results are from the EAWAS where available and the GWAS if the known variants weren't on the Exome array.

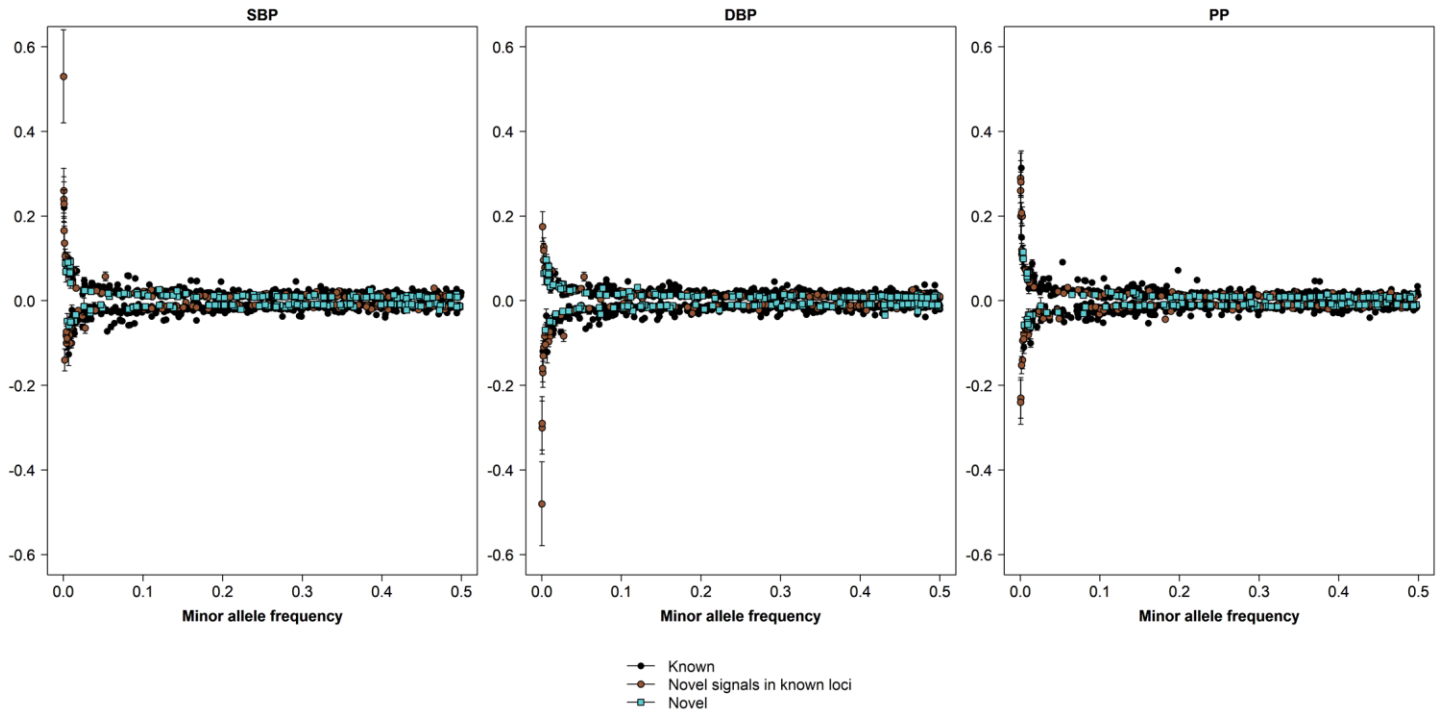

a
SBP
DBP
PP
HTN


b
DBP
HTN
SBP
PP
23
0
2
10
0
13
4
0
23
3
2
2
1
3
20


c
1%
2%
2%
3%
6%
6%
1%
2%
32%
37%
3%
5%
5' or 3' UTR
Enhancer
Missense
Synonymous
Promoter Flanking
Intron
Stop Gained
TF Binding Site
CTCF Binding Site
Promoter
Open Chromatin
Splice Donor

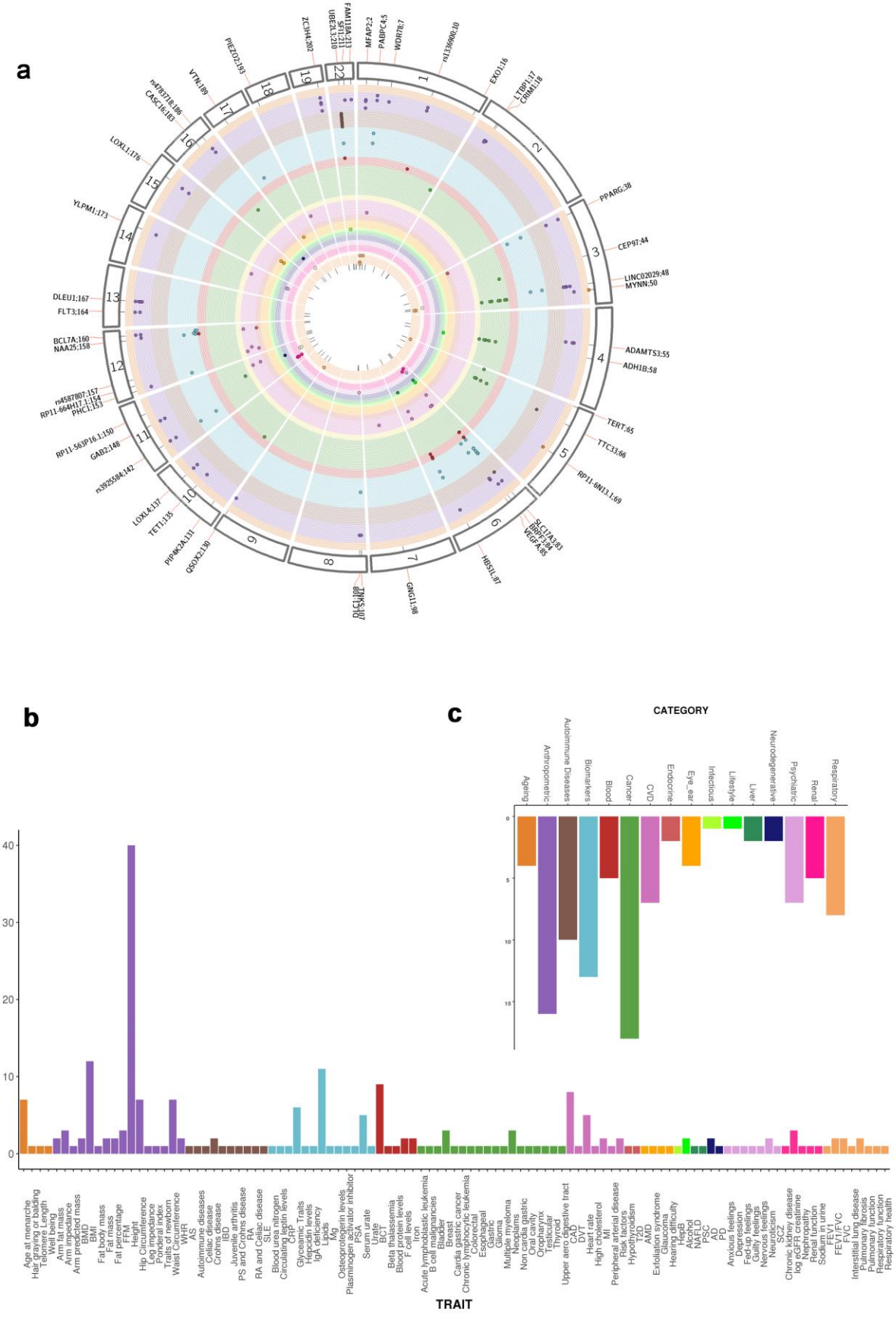
81

d


SBP
DBP
PP
0.6
0.4
0.2
0.0
-0.2
-0.4
-0.6
0.0
0.1
0.2
0.3
0.4
0.5
Minor allele frequency
Known
Novel signals in known loci
Novel

82
83

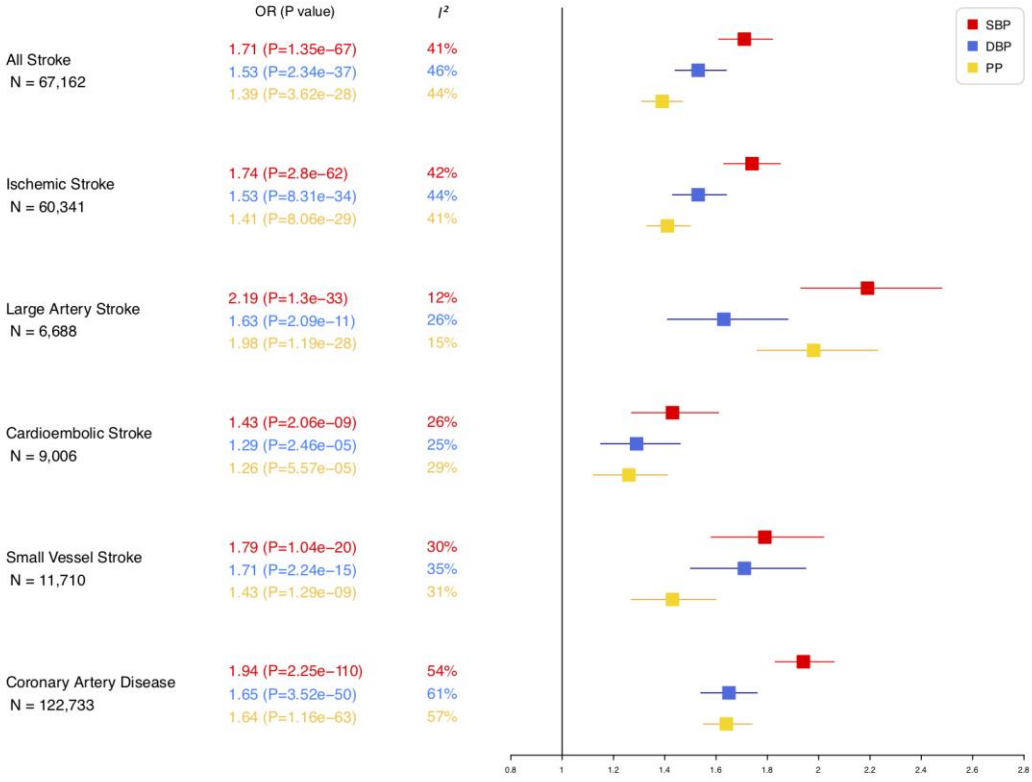
Figure 3 Phenome-wide associations of the new BP loci a) a modified Fuji plot of the genome-wide significant associated SNVs from the Stage 2 EAWAS and Stage 2 rare variant GWAS (novel loci only). Each dot resents a novel locus where a conditionally independent variant or a variant in LD with the conditionally independent variant has been previously associated with one or more traits unrelated to blood pressure (b) and each circle represents different trait category (c). 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. The y-axes in (b) and (c) represent number of distinct BP-associated variants per trait and number of traits per category respectively. The colour coding for (a) and (b) is relative to (c).


a
b
c
CATEGORY
Ageing
Anthropometric
Autoimmune Diseases
Biomarkers
Blood
Cancer
CVD
Endocrine
Eye_ear
Infectious
Lifestyle
Liver
Neurodegenerative
Psychiatric
Renal
Respiratory
TRAIT

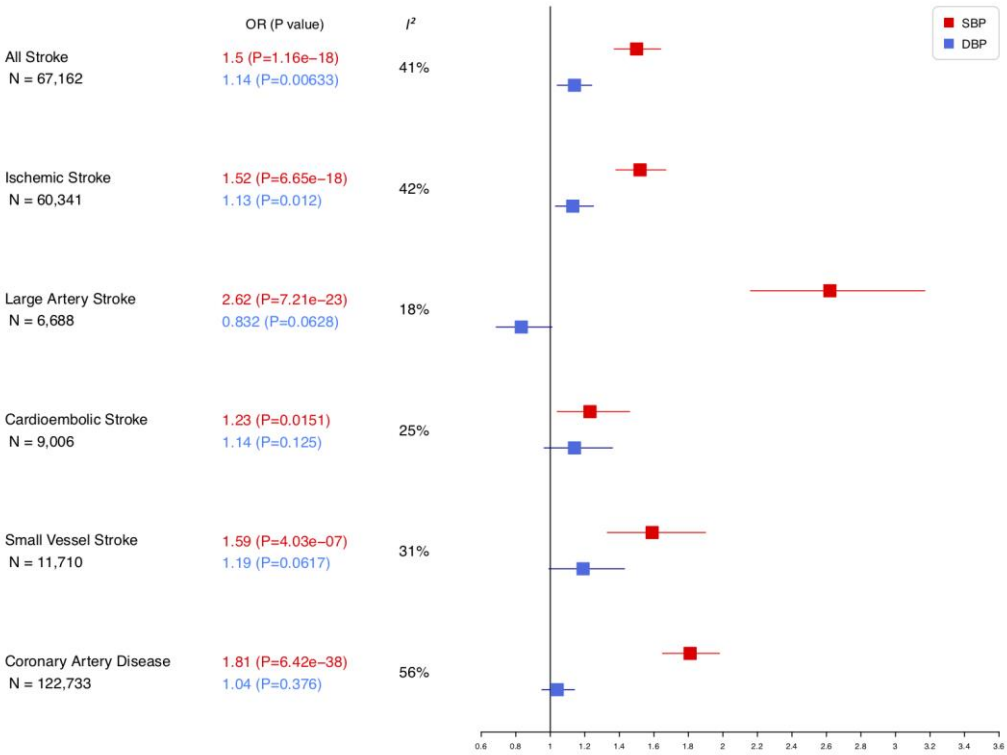
96

Figure 4 Causal association of BP with cardiovascular diseases (CVDs). Mendelian randomisation analyses of the effect of blood pressure on stroke and coronary artery disease. (a) from univariable analyses (b) from multivariable analyses (Methods). Analyses were performed using summary association statistics (Methods). The causal estimates are on the odds ratio (OR) scale. Results on the standard deviation scale are provided in Supplementary Table 16. 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. N=the number of disease cases; OR: Odds ratio (causal estimate P value). I^2: heterogeneity in the Mendelian randomization analysis (inverse-variance weighted method).

(a)



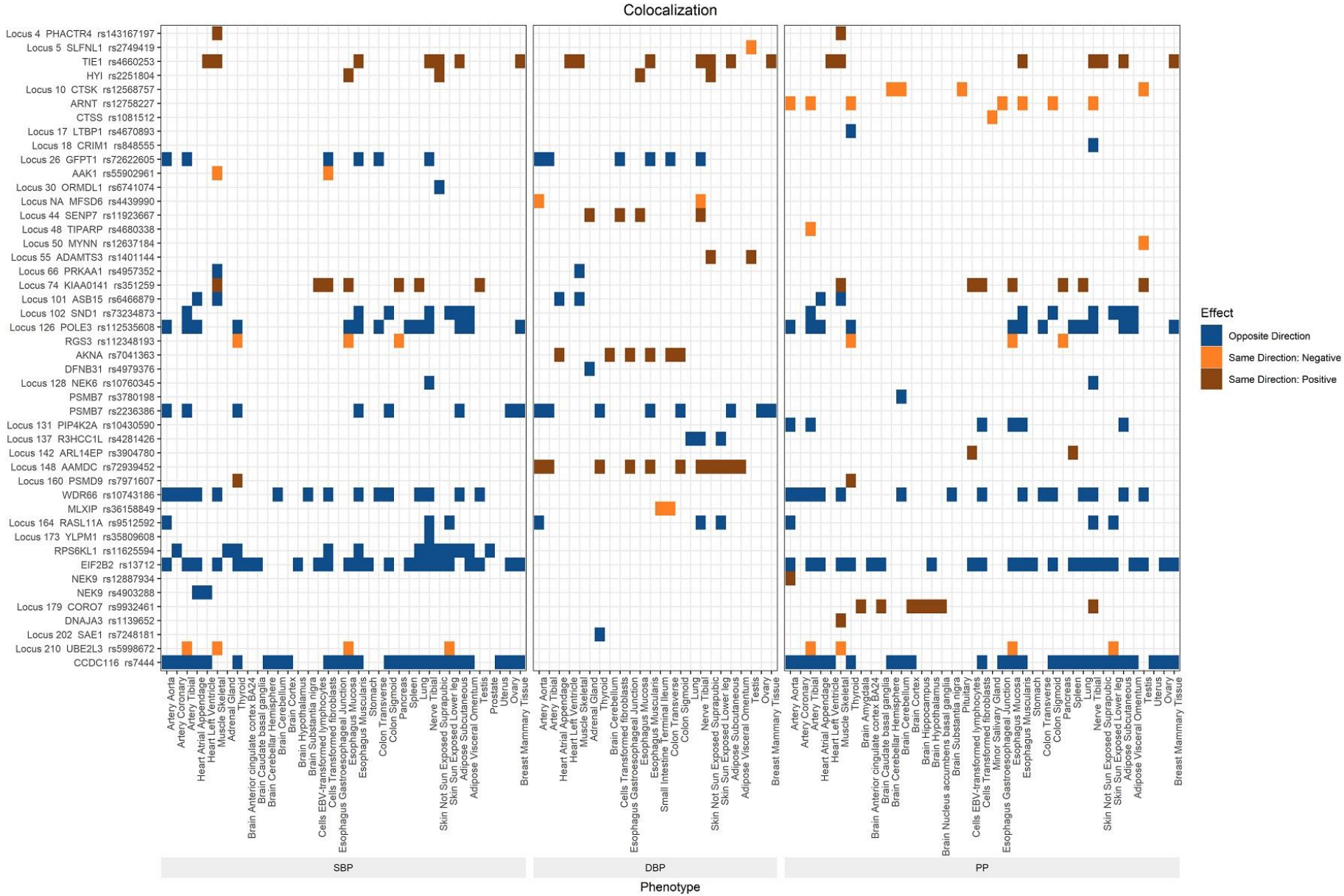
(b)


OR (P value)
I²
All Stroke
N = 67,162
1.5 (P=1.16e−18)
1.14 (P=0.00633)
41%
Ischemic Stroke
N = 60,341
1.52 (P=6.65e−18)
1.13 (P=0.012)
42%
Large Artery Stroke
N = 6,688
2.62 (P=7.21e−23)
0.832 (P=0.0628)
18%
Cardioembolic Stroke
N = 9,006
1.23 (P=0.0151)
1.14 (P=0.125)
25%
Small Vessel Stroke
N = 11,710
1.59 (P=4.03e−07)
1.19 (P=0.0617)
31%
Coronary Artery Disease
N = 122,733
1.81 (P=6.42e−38)
1.04 (P=0.376)
56%
SBP
DBP
0.6
0.8
1
1.2
1.4
1.6
1.8
2
2.2
2.4
2.6
2.8
3
3.2
3.4
3.6

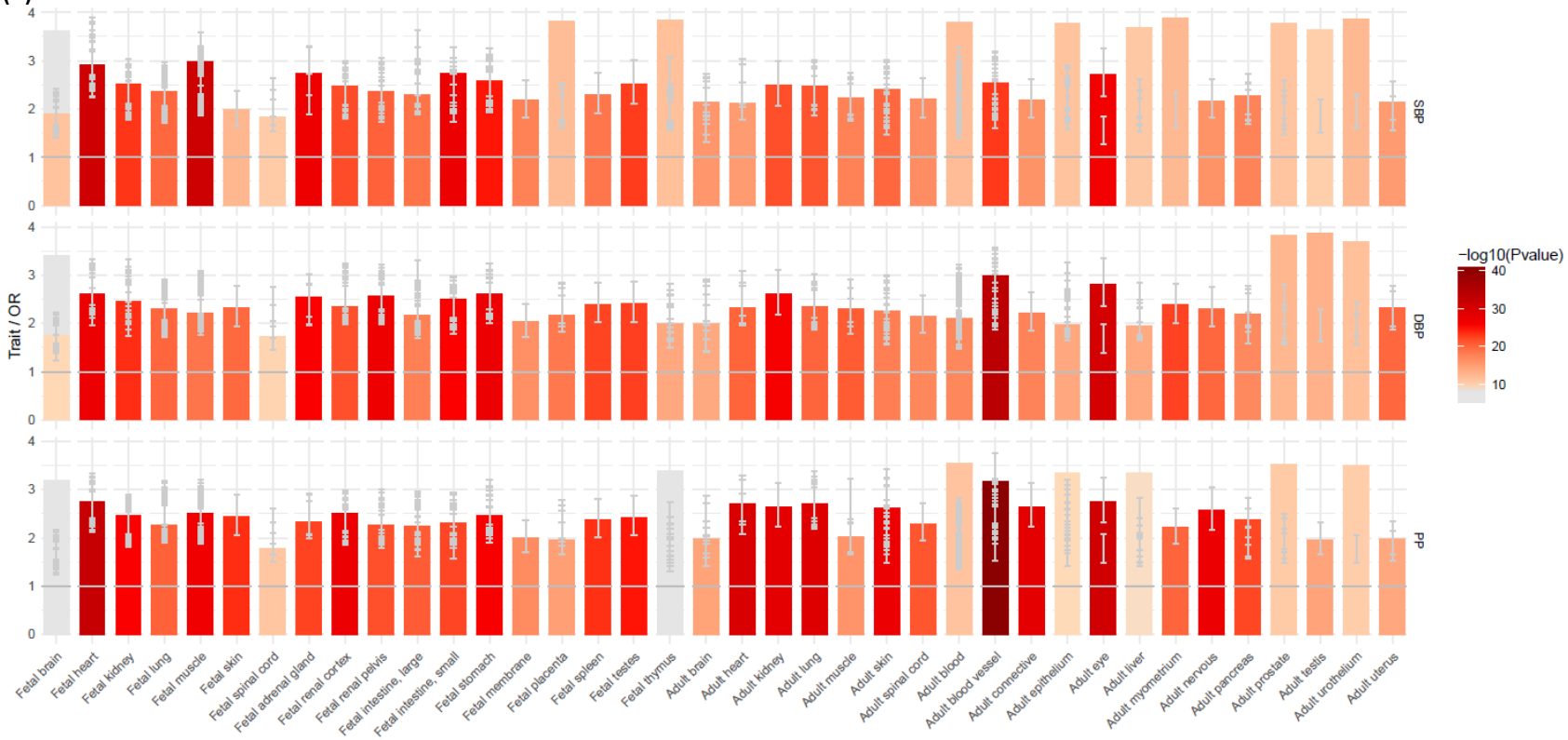
110

Figure 5 Annotation of BP loci (a) BP associations shared with eQTL from GTEx through multi-trait colocalisation analyses. Expressed gene and the colocalised SNV are provided on the y-axis, BP trait and eQTL tissues are provided on the x-axis. The colour 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 for DBP and bottom represents PP. Height of the bar indicates the fold enrichment in the listed tissues. The colours represent the enrichment *P*-value.

(a)


Colocalization
Locus 4 PHACTR4 rs143167197
Locus 5 SLFNL1 rs2749419
TIE1 rs4660253
HYI rs2251804
Locus 10 CTSK rs12568757
ARNT rs12758227
CTSS rs1081512
Locus 17 LTBP1 rs4670893
Locus 18 CRIM1 rs848555
Locus 26 GFPT1 rs72622605
AAK1 rs55902961
Locus 30 ORMDL1 rs6741074
Locus NA MFSD6 rs4439990
Locus 44 SENP7 rs11923667
Locus 48 TIPARP rs4680338
Locus 50 MYNN rs12637184
Locus 55 ADAMTS3 rs1401144
Locus 66 PRKAA1 rs4957352
Locus 74 KIAA0141 rs351259
Locus 101 ASB15 rs6466879
Locus 102 SND1 rs73234873
Locus 126 POLE3 rs112535608
RGS3 rs112348193
AKNA rs7041363
DFNB31 rs4979376
Locus 128 NEK6 rs10760345
PSMB7 rs3780198
PSMB7 rs2236386
Locus 131 PIP4K2A rs10430590
Locus 137 R3HCC1L rs4281426
Locus 142 ARL14EP rs3904780
Locus 148 AAMDC rs72939452
Locus 160 PSMD9 rs7971607
WDR66 rs10743186
MLXIP rs36158849
Locus 164 RASL11A rs9512592
Locus 173 YLPM1 rs35809608
RPS6KL1 rs11625594
EIF2B2 rs13712
NEK9 rs12887934
NEK9 rs4903288
Locus 179 CORO7 rs9932461
DNAJA3 rs1139652
Locus 202 SAE1 rs7248181
Locus 210 UBE2L3 rs5998672
CCDC116 rs7444
Artery Aorta
Artery Coronary
Artery Tibial
Heart Atrial Appendage
Heart Left Ventricle
Muscle Skeletal
Adrenal Gland
Thyroid
Brain Anterior cingulate cortex BA24
Brain Caudate basal ganglia
Brain Cerebellar Hemisphere
Brain Cortex
Brain Hypothalamus
Brain Substantia nigra
Cells EBV-transformed lymphocytes
Cells Transformed fibroblasts
Esophagus Gastroesophageal Junction
Esophagus Mucosa
Esophagus Muscularis
Stomach
Colon Transverse
Colon Sigmoid
Pancreas
Spleen
Lung
Nerve Tibial
Skin Not Sun Exposed Suprapubic
Skin Sun Exposed Lower leg
Adipose Subcutaneous
Adipose Visceral Omentum
Testis
Prostate
Uterus
Ovary
Breast Mammary Tissue
Small Intestine Terminal Ileum
Brain Amygdala
Brain Hippocampus
Brain Nucleus accumbens basal ganglia
Pituitary
Minor Salivary Gland
SBP
DBP
PP
Phenotype
Effect
Opposite Direction
Same Direction: Negative
Same Direction: Positive

(b)


Trait / OR
SBP
DBP
PP
−log10(Pvalue)
40
30
20
10
Fetal brain
Fetal heart
Fetal kidney
Fetal lung
Fetal muscle
Fetal skin
Fetal spinal cord
Fetal adrenal gland
Fetal renal cortex
Fetal renal pelvis
Fetal intestine, large
Fetal intestine, small
Fetal stomach
Fetal membrane
Fetal placenta
Fetal spleen
Fetal testes
Fetal thymus
Adult brain
Adult heart
Adult kidney
Adult lung
Adult muscle
Adult skin
Adult spinal cord
Adult blood
Adult blood vessel
Adult connective
Adult epithelium
Adult eye
Adult liver
Adult myometrium
Adult nervous
Adult pancreas
Adult prostate
Adult testis
Adult urothelium
Adult uterus