



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

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

Increased blood pressure (BP) is a major risk factor for cardiovascular disease (CVD) and related disability worldwide¹. Its complications are estimated to account for ~10.7 million premature deaths annually¹. Genome-wide association studies (GWAS) and exome array-wide association studies (EAWAS) have identified over 1,000 BP-associated single-nucleotide variants (SNVs)^{2–19} for this complex, heritable, polygenic trait. The majority of these are common SNVs (minor allele frequency (MAF) > 0.05) with small effects on BP. Most reported associations involve noncoding 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, that is, 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* and *DBH*)^{13,14} and a rare nonsense BP variant in *ENPEP*, encoding an aminopeptidase with a known role in BP regulation¹³. These findings confirmed the utility of rare-variant studies for identifying potential causal genes. These rare-variant associations had larger effects on BP (typically ~1.5 mm Hg per minor allele) than common variants identified by previous studies (typically ~0.5 mm Hg per minor allele), many of which had power to detect common variants with large effects. Here, we combine the studies from our previous two exome array reports with additional studies, including the UK Biobank (UKBB) study, to analyze up to ~1.32 million participants and investigate the role of rare SNVs in BP regulation.

Results

We performed an EAWAS and a rare-variant GWAS (RV-GWAS) of imputed and genotyped SNVs to identify variants associated with BP traits, hypertension (HTN), 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 the RV-GWAS is provided in Fig. 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 the UKBB) for association with BP (stage 1; Fig. 1, Methods and Supplementary Note). There were 362 BP loci known at the time of the analysis (Supplementary Table 1), 240 of which were covered on the exome array. To improve statistical power for discovery for a subset of variants significant in stage 1 at $P < 5 \times 10^{-8}$ outside of the known BP regions (Supplementary Table 1a), we requested summary association statistics from three additional studies (Million Veteran Program (MVP), deCODE and the Genetic Epidemiology Network of Arteriopathy (GENOA)). We then performed meta-analyses of the three data request studies and stage 1 results to discover new variants associated with BP. In total, 343 SNVs (200 genomic regions; Methods) were associated ($P < 5 \times 10^{-8}$) with one or more BP traits in the stage 2 single-variant EAWAS meta-analyses involving up to ~1.168 million individuals of European (EUR) ancestry (Table 1, Fig. 2, Supplementary Table 2 and Supplementary Note). A further seven SNVs (seven genomic regions) were only associated ($P < 5 \times 10^{-8}$) in the pan-ancestry (PA) meta-analyses of ~1.32 million individuals (Supplementary Table 2). All 350 SNV–BP associations were new at the time of analysis (204 loci), 220 have subsequently been reported^{20,21} and 130 SNVs (99 loci) remain new, including 9 rare and 13 low-frequency SNVs (Fig. 2, Supplementary Table 2 and Supplementary Fig. 1).

All nine new rare BP-associated SNVs identified in the EAWAS were conditionally independent of common variant associations within the respective regions (Supplementary Table 3) using the multi-SNP-based conditional and joint association analysis (genome-wide complex trait analysis (GCTA) v1.91.4)²² with the stage 1 EUR EAWAS results (Methods and Supplementary Table 4). In addition to the rare variants, there were 147 additional distinct ($P < 1 \times 10^{-6}$) common SNV–BP associations (46% were missense variants) and 18 distinct low-frequency SNVs (89% were missense). Approximately 59% of the distinct BP-associated SNVs were coding or in strong LD ($r^2 > 0.8$) with coding SNVs. In total, 42 of the 99 new loci had two or more distinct BP-associated SNVs in the conditional analyses. Of the 50 loci that were previously identified

using the UKBB^{16,17} and were on the exome array, 43 replicated at $P < 0.001$ (Bonferroni correction for 50 known variants) in samples independent of the original discovery (Supplementary Table 5).

Blood pressure associations from EUR RV-GWAS. We tested a further 29,454,346 (29,404,959 imputed and 49,387 genotyped) rare SNVs for association with BP in 445,360 UKBB participants²³ using BOLT-LMM²⁴ (Fig. 1 and Methods). The SNVs analyzed as part of the EAWAS were not included in the RV-GWAS. Similar to EAWAS, within RV-GWAS we performed single discovery meta-analyses to identify rare SNVs associated with BP. In stage 1 (UKBB), 84 rare SNVs outside of the known BP loci (at the time of our analyses) were associated with one or more BP traits at $P < 1 \times 10^{-7}$ (Supplementary Table 6). Additional data were requested from MVP for the 84 BP-associated SNVs in up to 225,112 EUR individuals from the MVP, and 66 were available. Meta-analyses of stage 1 (UKBB) and MVP results were performed for new rare-variant discovery. We identified 23 unique rare SNVs associated with one or more BP traits ($P < 5 \times 10^{-8}$) with consistent direction of effects in a meta-analysis of the UKBB and MVP (minimum P value for heterogeneity (P_{het}) = 0.02; Table 1, Fig. 2, Supplementary Table 7 and Supplementary Fig. 1). Two of the SNVs, rs55833332 (p.Arg35Gly) in *NEK7* and rs200383755 (p.Ser19Trp) in *GATA5*, were missense. Eleven rare SNVs were genome-wide significant in the UKBB alone but were not available in MVP and await further support in independent studies (Supplementary Table 7).

Rare and low-frequency variant associations at established BP loci. It is difficult to prioritize candidate genes at common variant loci for functional follow-up. We believe that analysis of rare (MAF < 0.01) and very-low-frequency (MAF \leq 0.02) coding variants in known loci may provide further support for or identify a candidate causal gene at a locus. Twelve of the 240 BP-associated regions had one or more conditionally independent rare-variant associations ($P < 10^{-6}$ in the GCTA joint model of the EUR stage 1 EAWAS; Methods, Table 2 and Supplementary Table 3). A further nine loci had one or more conditionally independent BP-associated SNVs with MAF \leq 0.02 (Table 2 and Supplementary Table 8). In total, 183 SNVs (rare and common) across 110 known loci were not identified previously.

We performed fine-mapping using FINEMAP²⁵ for 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 8), and 251 loci had multiple common variant associations. We also replicated rare-variant associations that we reported previously^{13,14} at *RBM47*, *COL21A1*, *RRAS* and *DBH* ($P < 5 \times 10^{-5}$) in the UKBB

(independent of previous studies). Overall, from both FINEMAP and GCTA, we identified 40 loci with one or more rare SNV associations, independent of previously reported common variant associations (Table 3, Fig. 2, Supplementary Table 8 and Supplementary Note).

We note that, of 256 known variants identified without UKBB participants (Supplementary Table 1a), 229 replicated at $P < 1.95 \times 10^{-4}$ (Bonferroni adjusted for 256 variants) in the UKBB.

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 the sequence kernel association test (SKAT)²⁶, including SNVs with MAF \leq 0.01 that were predicted by VEP²⁷ 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* and *SCARF2*) and two in the RV-GWAS (*FRY* and *CENPJ*) were associated with BP ($P < 2.5 \times 10^{-6}$; Bonferroni adjusted for $\sim 20,000$ genes) and were outside known and new BP loci (Supplementary Tables 1 and 9). To ensure these associations were not attributable to a single (sub-genome-wide significant) rare variant, we also performed SKAT tests conditioning on the variant with the smallest P value in the gene (Methods and Supplementary Table 9). *FRY* had the smallest conditional P value ($P = 0.0004$), but did not pass our pre-determined conditional significance threshold (conditional SKAT $P \leq 0.0001$; Methods), suggesting that all gene associations were due to single (sub-genome-wide significant) rare variants and not due to the aggregation of multiple rare variants.

Among the known loci, five genes (*NPR1*, *DBH*, *COL21A1*, *NOX4* and *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 Note and Supplementary Table 9) confirming the findings in the single-variant conditional analyses above (Supplementary Table 8).

We also performed gene-based tests using a MAF threshold of ≤ 0.05 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 Note and Supplementary Table 9).

Rare-variant BP associations. In total, across the EAWAS and the RV-GWAS, there were 32 new BP-associated rare variants spanning 18 new loci (Table 1 and Fig. 2). Of these 32 variants, 5 (representing 5 loci) were genome-wide significant for HTN, 22 (10 loci) for SBP, 14 (6 loci) for DBP and 15 (10 loci) for PP (Supplementary Tables 1–3, 6 and 7). Ten of the new rare variants were missense. Within

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

previously reported loci, there were 55 independent rare-variant associations (40 loci) from either the EAWAS or RV-GWAS, representing a total of 87 independent rare-variant BP associations. We identified 45 BP-associated genes, 8 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 (for example, enhancers), highlighting a genetic influence

on BP levels through gene expression (Fig. 2). The rare variants contributed to BP variance explained (Supplementary Note).

Power calculations are provided in the Supplementary Note and show that our study had 80% power to detect an effect of 0.039 standard deviations (s.d.) for a MAF = 0.01 (Extended Data Fig. 1). As anticipated, given statistical power, some rare variants displayed larger effects on BP regulation than common variants (Fig. 2 and

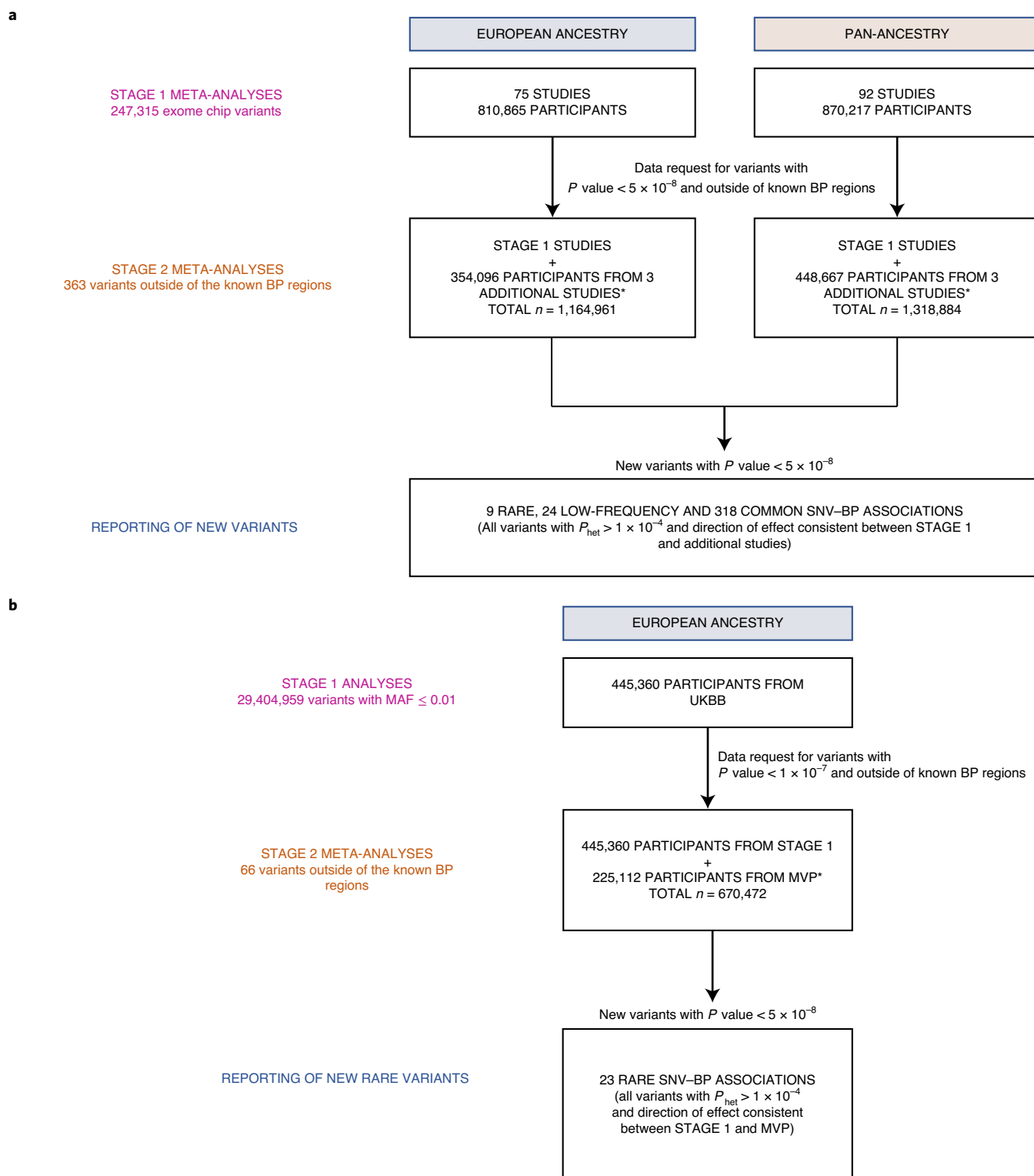


Table 1 | Rare and low-frequency SNV-BP associations in EUR participants from EAWAS and RV-GWAS that mapped to new BP loci

Locus ID	rsID	Chr: pos	Gene	EA/OA	Amino acids	Consequence	Trait	EAF	β	<i>P</i>	<i>P</i> _{het}	<i>n</i>
EAWAS												
10	rs11580946	1: 150551327	<i>MCL1</i>	A/G	p.Val227Ala	Missense	PP	0.016	-0.37	2.74×10^{-9}	0.24	1,159,900
11	rs61747728 ^a	1: 179526214	<i>NPHS2</i>	T/C	p.Gln229Arg	Missense	DBP	0.040	0.26	8.74×10^{-13}	0.22	1,160,530
16	rs4149909	1: 242023898	<i>EXO1</i>	G/A	p.Ser279Asn	Missense	SBP	0.033	0.36	2.46×10^{-8}	0.09	1,158,190
32	rs3821033 ^a	2: 219507302	<i>ZNF142</i>	T/C	p.Thr1313Ala	Missense	DBP	0.033	-0.29	1.42×10^{-13}	0.75	1,160,530
	rs16859180 ^a	2: 219553468	<i>STK36</i>	T/C	p.Trp477Arg	Missense	DBP	0.049	-0.26	1.11×10^{-16}	0.34	1,160,530
44	rs145072852	3: 101476645	<i>CEP97</i>	T/C	p.Phe399Leu	Missense	PP	0.004	1.05	1.42×10^{-13}	0.01	1,158,820
46	rs139600783	3: 119109769	<i>ARHGAP31</i>	T/C	p.Ser274Pro	Missense	HTN	0.008	5.85	5.05×10^{-9}	0.19	975,381
50	rs73181210	3: 169831268	<i>PHC3</i>	C/T	p.Glu692Lys	Missense	DBP	0.009	-0.66	9.14×10^{-15}	0.04	1,159,580
52	rs11937432 ^a	4: 2233709	<i>HAUS3</i>	G/A	p.Thr586Ile	Missense	DBP	0.046	0.21	9.56×10^{-10}	0.26	1,160,520
58	rs1229984	4: 100239319	<i>ADH1B</i>	T/C	p.His48Arg	Missense	PP	0.026	-0.75	2.97×10^{-25}	0.54	686,104
63	rs143057152	4: 149075755	<i>NR3C2</i>	T/C	p.His771Arg	Missense	SBP	0.003	1.75	4.14×10^{-14}	0.22	1,128,880
71	rs61755724	5: 132408967	<i>HSPA4</i>	A/G	p.Thr159Ala	Missense	DBP	0.024	0.26	9.75×10^{-9}	0.36	1,160,530
72	rs33956817	5: 137278682	<i>FAM13B</i>	C/T	p.Met802Val	Missense	SBP	0.044	0.31	1.76×10^{-8}	0.27	1,158,190
77	rs34471628 ^a	5: 172196752	<i>DUSP1</i>	G/A	p.His187Tyr	Missense	DBP	0.039	-0.23	3.00×10^{-10}	0.42	1,153,300
85	rs45573936	6: 44198362	<i>SLC29A1</i>	C/T	p.Ile295Thr	Missense	DBP	0.027	-0.38	3.70×10^{-19}	0.59	1,160,530
100	rs144867634	7: 111580166	<i>DOCK4</i>	C/T	p.Val326Met	Missense/ splice region	DBP	0.025	-0.26	2.62×10^{-8}	0.04	1,160,530
109	rs56335308 ^a	8: 17419461	<i>SLC7A2</i>	A/G	p.Met545Val	Missense	DBP	0.025	0.31	1.40×10^{-10}	0.26	1,160,530
114	rs76767219	8: 81426196	<i>ZBTB10</i>	A/C	p.Glu346Ala	Missense	SBP	0.034	-0.44	4.41×10^{-13}	0.18	1,160,830
119	rs61732533 ^a	8: 145108151	<i>OPLAH</i>	A/G	-	Synonymous	DBP	0.049	-0.21	2.05×10^{-10}	0.86	1,085,170
	rs34674752 ^a	8: 145154222	<i>SHARPIN</i>	A/G	p.Ser294Pro	Missense	DBP	0.049	-0.19	5.89×10^{-10}	0.91	1,132,350
146	rs117874826	11: 64027666	<i>PLCB3</i>	C/A	p.Ala564Glu	Missense	SBP	0.014	0.71	4.67×10^{-12}	0.42	1,153,360
	rs145502455	11: 64031030	<i>PLCB3</i>	A/G	p.Ile806Val	Missense	SBP	0.005	0.90	5.01×10^{-9}	0.04	1,156,310
154	rs141325069	12: 20769270	<i>PDE3A</i>	A/G	p.Gln459Arg	Missense	SBP	0.003	1.45	6.25×10^{-11}	0.82	1,134,260
158	rs77357563	12: 114837349	<i>TBX5</i>	A/C	p.Tyr111Asp	Missense	PP	0.005	-1.01	7.72×10^{-22}	0.22	1,152,080
159	rs13141	12: 121756084	<i>ANAPC5</i>	A/G	p.Val630Ala	Missense	DBP	0.011	0.52	1.98×10^{-12}	0.63	1,156,950
168	rs17880989 ^a	14: 23313633	<i>MMP14</i>	A/G	p.Ile355Met	Missense	DBP	0.027	0.32	2.02×10^{-14}	0.95	1,160,530
169	rs61754158	14: 31774324	<i>HEATR5A</i>	T/C	p.Arg1670Gly	Missense	SBP	0.009	-0.70	6.28×10^{-9}	0.04	1,119,230
170	rs72681869	14: 50655357	<i>SOS2</i>	C/G	p.Arg191Pro	Missense	SBP	0.010	-1.22	2.25×10^{-22}	0.25	1,144,040
177	rs150843673	15: 81624929	<i>TMC3</i>	T/G	p.Ser1045Ter	Stop/lost	DBP	0.021	0.36	1.43×10^{-12}	0.14	1,154,000
181	rs61739285	16: 27480797	<i>GTF3C1</i>	T/C	p.His1630Arg	Missense	DBP	0.035	0.24	4.71×10^{-10}	0.04	1,155,020
186	rs62051555	16: 72830539	<i>ZFH3</i>	G/C	p.His2014Gln	Missense	PP	0.048	0.47	1.19×10^{-25}	0.43	797,332
206	rs11699758	20: 60901762	<i>LAMA5</i>	T/C	p.Ile1757Val	Missense	PP	0.034	-0.26	6.68×10^{-11}	0.54	1,154,410
	rs13039398	20: 60902402	<i>LAMA5</i>	A/G	p.Trp1667Arg	Missense	PP	0.033	-0.26	1.89×10^{-10}	0.44	1,133,830
RV-GWAS												
215	rs55833332	1: 198222215	<i>NEK7</i>	G/C	p.Arg35Gly	Missense	PP	0.008	0.62	4.58×10^{-8}	0.08	670,129
	rs143554274	1: 198455391	<i>ATP6V1G3</i>	T/C	-	Intergenic	PP	0.008	0.71	1.26×10^{-9}	0.14	670,128
216	rs12135454	1: 219310461	<i>LYPLAL1-AS1</i>	T/C	-	Intron	PP	0.010	-0.62	1.61×10^{-8}	0.22	665,523
	rs12128471	1: 219534485	<i>RP11-392017.1</i>	A/G	-	Intergenic	PP	0.010	-0.68	2.99×10^{-9}	0.19	670,130
217	rs114026228	4: 99567918	<i>TSPAN5</i>	C/T	-	Intron	PP	0.008	-0.65	5.20×10^{-9}	0.03	670,128
	rs145441283	4: 99751794	<i>EIF4E</i>	G/A	-	Intergenic	PP	0.010	-0.71	2.01×10^{-11}	0.08	670,128
219	rs187207161	6: 122339304	<i>HMGB3P18</i>	C/T	-	Intergenic	PP	0.009	-0.63	2.16×10^{-10}	0.02	670,130
221	rs149165710	8: 121002676	<i>DEPTOR</i>	A/G	-	Intron	PP	0.003	1.32	2.78×10^{-12}	0.03	665,523
222	rs184289122	10: 106191229	<i>CFAP58</i>	G/A	-	Intron	SBP	0.008	1.31	1.66×10^{-13}	0.53	670,472
	rs7076147	10: 106250394	<i>RP11-12704.3</i>	G/A	-	Intergenic	SBP	0.010	1.11	1.71×10^{-14}	0.75	670,472
	rs75337836	10: 106272188	<i>RP11-12704.3</i>	T/G	-	Intergenic	SBP	0.010	1.12	2.67×10^{-15}	0.54	670,472
	rs142760284	10: 106272601	<i>RP11-12704.3</i>	A/C	-	Intergenic	SBP	0.009	1.22	2.19×10^{-15}	0.92	670,472
	rs576629818	10: 106291923	<i>RP11-12704.3</i>	T/C	-	Intergenic	SBP	0.009	1.24	1.02×10^{-15}	0.71	670,472
	rs556058784	10: 106322283	<i>RP11-12704.2</i>	G/A	-	Intergenic	SBP	0.009	1.26	4.54×10^{-16}	0.57	665,861
	rs535313355 ^a	10: 106399140	<i>SORCS3</i>	C/T	-	Upstream gene	SBP	0.009	1.36	1.04×10^{-17}	0.22	670,472
	rs181200083 ^a	10: 106520975	<i>SORCS3</i>	C/A	-	Intron	SBP	0.009	1.60	1.08×10^{-21}	0.58	665,861
	rs540369678 ^a	10: 106805351	<i>SORCS3</i>	T/A	-	Intron	SBP	0.010	1.18	2.29×10^{-14}	0.16	670,472

Continued

Table 1 | Rare and low-frequency SNV-BP associations in EUR participants from EAWAS and RV-GWAS that mapped to new BP loci (continued)

Locus ID	rsID	Chr: pos	Gene	EA/OA	Amino acids	Consequence	Trait	EAf	β	<i>P</i>	<i>P</i> _{het}	<i>n</i>
	rs117627418	10: 107370555	<i>RP11-45P22.2</i>	T/C	-	Intergenic	SBP	0.009	1.11	1.98×10^{-11}	0.1	665,861
224	rs138656258	14: 31541910	<i>AP4S1</i>	G/T	-	Intron	SBP	0.007	-0.93	1.15×10^{-8}	0.13	665,861
228	rs6061911	20: 60508289	<i>CDH4</i>	C/T	-	Intron	SBP	0.010	-0.85	4.67×10^{-8}	0.09	665,861
	rs114580352	20: 60529963	<i>TAF4</i>	A/G	-	Intron	SBP	0.009	-0.84	1.99×10^{-8}	0.04	665,860
	rs11907239	20: 60531853	<i>TAF4</i>	A/G	-	Intron	SBP	0.009	-0.82	4.99×10^{-8}	0.05	670,472
	rs200383755	20: 61050522	GATA5	C/G	p.Trp19Ser	Missense	DBP	0.006	1.00	1.01×10^{-13}	0.49	670,172

Newly identified rare and low-frequency SNV inverse-normal transformed BP associations are reported from stage 2 of the EAWAS and GWAS. The reported associations are for the trait with the smallest *P* value in the stage 1 meta-analysis; full results are provided in Supplementary Tables 2 and 7. SNVs are ordered by trait, chromosome and position. Locus ID, the known locus identifier used in Supplementary Table 1; rsID, dbSNP rsID; Chr: pos, Chromosome: NCBI build 37 position; Gene, gene containing the SNV or the nearest gene; EA/OA, effect allele (also the minor allele) and other allele; Amino acids, reference and variant amino acids from VEP; Consequence, consequence of the SNV to the transcript as annotated by variant effector predictor (VEP); Trait, BP trait for which association is reported; EAf, effect allele frequency based on stage 1; β , effect estimate (mm Hg) 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 BP trait from the stage 2 meta-analyses; *n*, sample size. Bold font indicates rare missense variants. *New variants identified in this study that are in LD ($r^2 > 0.6$ for rare SNVs and $r^2 > 0.1$ for common SNVs) with a variant that has been reported by Evangelou et al.²⁰ and/or Giri et al.²¹ within ± 500 kb of the new variant.

Supplementary Tables 3, 7 and 8); mean effects of rare SNVs for SBP and DBP were ~ 7.5 times larger than common variants (mean effect ~ 0.12 s.d./minor allele for rare SNVs, ~ 0.035 s.d./minor allele for low-frequency and ~ 0.016 s.d./minor allele for common SNVs) and for PP were 8.5 times larger for rare variants compared to common variants (mean effect ~ 0.135 s.d./minor allele for rare SNVs, ~ 0.04 s.d./minor allele for low-frequency and ~ 0.016 s.d./minor allele for common SNVs). Our study was exceptionally well powered to detect common variants (MAF > 0.05) with similarly large effects but found none, consistent with earlier BP GWAS and genetic studies of some other common complex traits^{28–30}.

Overlap of rare BP associations with monogenic BP genes.

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

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

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

implicated by rare SNVs at known loci were enriched in ‘tissue remodeling’ and ‘artery aorta’ (GO). Genes implicated by rare SNVs at new BP loci were enriched in rare circulatory system diseases (including HTN 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 new and known loci were potentially druggable as suggested by the ‘druggable genome’ (ref.³¹; Supplementary Note and Supplementary Tables 4 and 14). Six genes (four with rare variants) are already drug targets for CVD conditions, while 15 others are in development or used for other conditions. As an example, the renin-angiotensin-aldosterone system (RAAS) is one of the principal homeostatic mechanisms for BP control, and aldosterone is the main mineralocorticoid (secreted by adrenal glands) and binds receptors, including *NR3C2*, resulting in sodium retention by the kidney and increased potassium excretion. Spironolactone is an aldosterone antagonist widely used in heart failure and as a potassium-sparing antihypertensive medication that targets *NR3C2* (Open Targets: <https://www.opentargets.org/>).

Overlap of new BP associations with metabolites. To identify new 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 $\sim 14,000$ individuals (Methods and Supplementary Table 4). Nine BP-associated variants were associated with 25 metabolites ($P < 5 \times 10^{-8}$) involved in carbohydrate, lipid, cofactor and vitamin, nucleotide (cysteine) and amino acid metabolism (Supplementary Table 15), while 11 metabolites were unknown.

We performed MR analyses to assess the influence of the 14 known metabolites (Supplementary Table 15) on BP. Lower levels of 3-methylglutaryl carnitine(2) (acyl carnitines involved in long-chain fatty acid metabolism in mitochondria and in leucine metabolism) were significantly associated with increased DBP ($P < 0.003 = 0.05/14$ metabolites; Supplementary Table 16). There was no suggestion of reverse causation, that is, BP did not affect 3-methylglutaryl carnitine(2) ($P > 0.04$; Supplementary Table 16). We further tested whether the association with 3-methylglutaryl carnitine(2) was due to pleiotropic effects of other metabolites in a multivariable MR (mvMR) framework but found it was still causally associated with DBP (Supplementary Note and Supplementary Table 16).

New BP-associated SNVs are gene eQTLs across tissues. Sentinel variants from 66 new BP loci were associated ($P < 5 \times 10^{-8}$) with gene

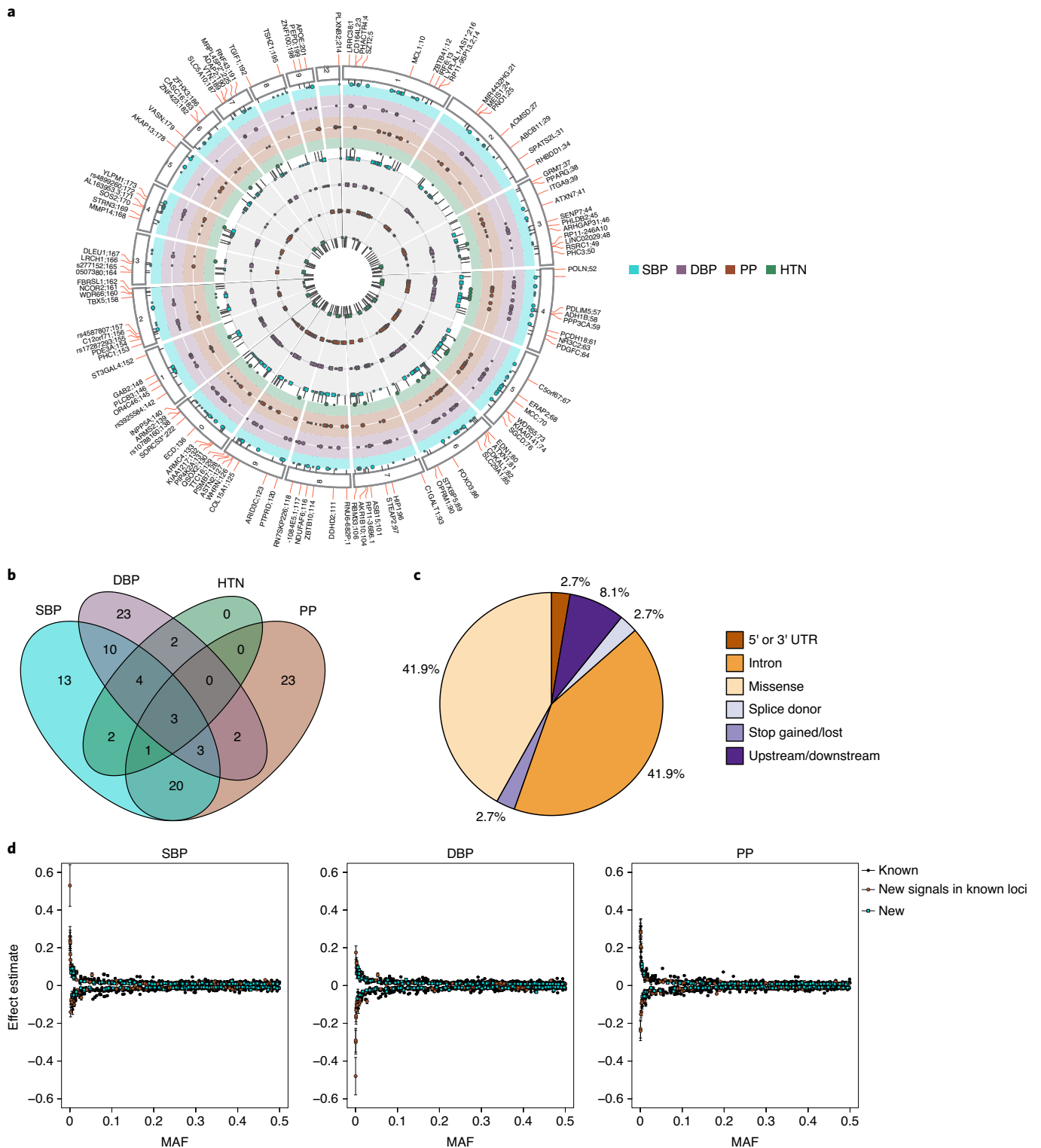


Fig. 2 | New BP associations. **a**, Fuji plot of the genome-wide significant BP-associated SNVs from stage 2 EAWAS and stage 2 RV-GWAS. The first four circles (from inside to outside) and the last circle (locus annotation) summarize pleiotropic effects, while circles 5 to 8 summarize the genome-wide significant associations. Every dot or square represents a BP-associated locus; large dots represent new BP-associated loci, while small dots represent loci containing new variants identified in this study, which are in LD 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. Asterisks denote loci with rare-variant associations. **b**, Venn diagram showing the overlap of the 106 new BP loci across the analyzed BP traits. **c**, Functional annotation from VEP of all the identified rare variants in known and new regions. **d**, Plots of MAF against effect estimates on the transformed scale for the BP-associated SNVs. Blue squares are new BP-associated SNVs, black dots represent SNVs at known loci and red dots are newly identified distinct BP-associated SNVs at known loci. Effect estimates and standard errors for the new loci are taken from the stage 2 EUR analyses (up to 1,164,961 participants), while those for the known loci are from stage 1 analyses (up to 810,865 participants). Results are from the EAWAS where available and from the GWAS (up to 670,472 participants) if the known variants were not on the exome array. Data from Supplementary Tables 1, 3, 7, 8, and 25 were used.

Table 2 | Conditionally independent rare and very-low-frequency SNV associations from exome array at known loci in stage 1 EUR studies

Locus ID	rsID	Chr: pos	Gene	EA/OA	Amino acids	Consequence	Trait	EAF	β_{joint}	P_{joint}	<i>n</i>	Ref.
18	rs116245325	1: 153665650	<i>NPR1</i>^a	T/C	p.Phe1034Leu	Missense	SBP	0.001	0.1660	7.49×10^{-9}	758,252	14
	rs61757359	1: 153658297		A/G	p.Ser541Gly	Missense		0.003	-0.0812	6.10×10^{-9}	794,698	
	rs35479618 ^b	1: 153662423		A/G	p.Lys967Glu	Missense		0.017	0.0694	1.19×10^{-28}	774,862	
28	rs1805090	1: 230840034	<i>AGT</i>^a	T/G	p.Met392Leu	Missense	DBP	0.002	0.1070	6.00×10^{-10}	759,349	8
	rs699	1: 230845794		G/A	p.Thr268Met	Missense	DBP	0.408	0.0225	2.12×10^{-45}	806,731	
94	rs111620813	4: 8293193	<i>HTRA3</i>^a	A/G	p.Met269Val	Missense	PP	0.011	-0.0432	1.38×10^{-8}	798,063	18
	rs7437940 ^b	4: 7887500	<i>AFAP1</i>	T/C	-	Intron	PP	0.406	-0.0131	1.62×10^{-16}	806,708	
102	rs112519623	4: 103184239	<i>SLC39A8</i>^a	A/G	p.Phe449Leu	Missense	DBP	0.016	-0.0391	3.02×10^{-10}	803,151	6
	rs13107325 ^b	4: 103188709		T/C	p.Thr391Ala	Missense	DBP	0.072	-0.0615	9.69×10^{-88}	806,731	
	rs4699052	4: 104137790	<i>CENPE</i>	T/C	-	Intergenic	DBP	0.388	-0.0121	7.31×10^{-14}	806,731	
105	rs6825911	4: 111381638	<i>ENPEP</i>	T/C	-	Intron	DBP	0.205	-0.0215	1.47×10^{-28}	801,965	
	rs33966350	4: 111431444		A/G	p.Ter413Trp	Stop/lost	DBP	0.013	0.0735	2.40×10^{-25}	798,385	
144	rs4712056 ^b	6: 53989526	<i>MLIP</i>	G/A	p.Val159Ile	Missense	PP	0.360	0.0091	1.86×10^{-8}	806,708	13,14,16
	rs115079907	6: 55924005	<i>COL21A1</i>^a	T/C	p.Arg882Gly	Missense	PP	0.003	0.2060	8.33×10^{-17}	783,546	
	rs12209452	6: 55924962		G/A	p.Pro821Leu	Missense	PP	0.049	0.0411	5.49×10^{-26}	743,036	
	rs200999181^b	6: 55935568		A/C	p.Val665Gly	Missense	PP	0.001	0.3350	4.74×10^{-43}	764,864	
	rs35471617	6: 56033094		A/G	p.Met343Thr	Missense/ splice region	PP	0.073	0.0249	1.03×10^{-15}	806,708	
	rs2764043	6: 56035643		G/A	p.Pro277Leu	Missense	PP	0.002	0.1530	5.11×10^{-14}	785,643	
	rs1925153 ^b	6: 56102780		T/C	-	Intron	PP	0.448	-0.0096	1.03×10^{-8}	786,734	
rs4294007	6: 57512510	<i>PRIM2</i>	T/G	-	Splice acceptor	PP	0.379	0.0096	1.13×10^{-7}	632,625		
208	rs507666	9:136149399	<i>ABO</i>	A/G	-	Intron	DBP	0.189	-0.0293	7.53×10^{-47}	796,103	13,15
	rs3025343	9:136478355	<i>LL09NC01-254D11.1</i>	A/G	-	Exon (noncoding transcript)	DBP	0.112	-0.0126	4.91×10^{-7}	806,731	
	rs77273740	9:136501728	<i>DBH</i>	T/C	p.Trp65Arg	Missense	DBP	0.027	-0.0846	3.85×10^{-11}	790,500	
	rs3025380	9: 136501756	<i>DBH</i>	C/G	p.Ala74Gly	Missense	DBP	0.005	-0.1030	5.37×10^{-18}	795,263	
rs74853476	9: 136501834	<i>DBH</i>	T/C	-	Splice donor	DBP	0.002	0.1000	3.69×10^{-8}	775,793		
223	rs201422605	10: 95993887	<i>PLCE1</i>	G/A	p.Val678Met	Missense	SBP	0.003	-0.0837	1.41×10^{-7}	795,009	7,14
	rs11187837	10: 96035980		C/T	-	Intron	SBP	0.110	-0.0198	4.23×10^{-14}	801,969	
	rs17417407	10: 95931087		T/G	p.Leu548Arg	Missense	SBP	0.167	-0.0122	9.97×10^{-9}	806,735	
	rs9419788	10: 96013705		G/A	-	Intron	SBP	0.387	0.0137	9.63×10^{-16}	806,735	
229	rs60889456	11: 723311	<i>EPS8L2</i>^a	T/C	p.Leu471Pro	Missense	PP	0.017	0.0303	6.37×10^{-7}	799,021	17
	rs7126805 ^b	11: 828916	<i>CRACR2B</i>	G/A	p.Gln77Arg	Missense	PP	0.271	-0.0134	1.43×10^{-13}	752,026	
246 ^c	rs56061986	11: 89182686	<i>NOX4</i>^a	C/T	p.Gly67Ser	Missense	PP	0.003	-0.1080	2.25×10^{-11}	798,273	16,17
	rs139341533	11: 89182666		A/C	p.Phe97Leu	Missense	PP	0.004	-0.0947	6.82×10^{-14}	785,947	
	rs10765211	11: 89228425		A/G	-	Intron	PP	0.342	-0.0176	8.77×10^{-27}	806,708	
250	rs117249984	11: 07375422	<i>ALKBH8</i>	A/C	p.Tyr653Asp	Missense	SBP	0.019	-0.0304	2.90×10^{-7}	805,695	16
	rs3758911	11: 07197640	<i>CWF19L2</i>	C/T	p.Cys894Tyr	Missense	SBP	0.341	0.0113	1.54×10^{-11}	806,735	
304	rs61738491	16: 30958481	<i>FBXL19</i>^a	A/G	p.Gln652Arg	Missense	PP	0.010	-0.0460	1.25×10^{-8}	796,459	16,17
	rs35675346 ^b	16: 30936081		A/G	p.Lys10Glu	Missense	PP	0.241	-0.0125	1.06×10^{-11}	802,932	
130 ^c	rs114280473	5: 122714092	<i>CEP120</i>^a	A/G	p.Phe712Leu	Missense	PP	0.006	-0.0584	9.98×10^{-8}	805,632	12-15
	rs2303720	5: 122682334		T/C	p.His947Arg	Missense	PP	0.029	-0.0419	3.44×10^{-18}	806,708	
	rs1644318	5: 122471989	<i>PRDM6</i>	C/T	-	Intron	PP	0.387	0.0192	2.43×10^{-32}	790,025	
179 ^c	rs3735080	7: 150217309	<i>GIMAP7</i>	T/C	p.Cys83Arg	Missense	DBP	0.237	-0.0092	6.56×10^{-7}	806,731	9,10,14
	rs3807375	7: 150667210	<i>KCNH2</i>	T/C	-	Intron	DBP	0.364	-0.0084	3.94×10^{-7}	806,731	
	rs3918234	7: 150708035	<i>NOS3</i>^a	T/A	p.Leu982Gln	Missense	DBP	0.004	-0.0727	1.33×10^{-7}	786,541	
	rs891511 ^b	7: 150704843		A/G	-	Intron	DBP	0.331	-0.0231	1.56×10^{-40}	778,271	
rs10224002 ^b	7: 151415041	<i>PRKAG2</i>	G/A	-	Intron	DBP	0.286	0.0186	7.41×10^{-27}	806,731		
190 ^c	rs138582164	8: 95264265	<i>GEM</i>^a	A/G	p.Ter199Arg	Stop lost	PP	0.001	0.2810	1.90×10^{-17}	735,507	16,49
195 ^c	rs112892337	8: 135614553	<i>ZFAT</i>^a	C/G	p.Cys470Ser	Missense	SBP	0.005	-0.0831	4.39×10^{-12}	792,203	17
	rs12680655	8: 135637337		G/C	-	Intron	SBP	0.398	0.0118	1.81×10^{-13}	797,982	

Continued

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

Locus ID	rsID	Chr: pos	Gene	EA/OA	Amino acids	Consequence	Trait	EAF	β_{joint}	P_{joint}	n	Ref.
259 ^c	rs145878042	12: 48143315	RAPGEF3^a	G/A	p.Pro258Leu	Missense	SBP	0.012	-0.0453	9.28×10^{-10}	805,791	13,16
	rs148755202	12: 48191247	HDAC7	T/C	p.His166Arg	Missense	SBP	0.016	0.0310	9.07×10^{-7}	806,735	
	rs1471997	12: 48723595	HIFNT	A/G	p.Gln174Arg	Missense	SBP	0.216	0.0130	1.15×10^{-11}	806,735	
	rs1126930 ^b	12: 49399132	PRKAG1	C/G	p.Ser98Thr	Missense	SBP	0.035	0.0408	1.45×10^{-21}	793,216	
	rs52824916 ^b	12: 49993678	FAM186B	T/C	p.Gln582Arg	Missense	SBP	0.088	-0.0155	1.70×10^{-8}	806,735	
	rs7302981 ^b	12: 50537815	CERSS	A/G	p.Cys75Arg	Missense	SBP	0.375	0.0219	1.52×10^{-41}	806,735	
312 ^c	rs61753655	17: 1372839	MYO1C^a	T/C	p.Lys866Glu	Missense	SBP	0.011	0.0653	6.48×10^{-18}	806,735	16,17
	rs1885987	17: 2203025	SMG6	G/T	p.Thr341Asn	Missense	SBP	0.371	-0.0127	3.94×10^{-15}	806,735	
339 ^c	rs34093919	19: 41117300	LTBP4^a	A/G	p.Asn715Asp	Missense/ splice region	PP	0.014	-0.0631	4.18×10^{-20}	805,764	19
	rs814501	19: 41038574	SPTBN4	G/A	p.Gly1331Ser	Missense	PP	0.482	-0.0115	2.40×10^{-13}	806,708	
346	rs45499294	20: 30433126	FOXSI^a	T/C	p.Lys74Glu	Missense	SBP	0.004	-0.0732	2.36×10^{-8}	801,284	16

GCTA was used to perform conditional analyses of the meta-analysis results from the exome array study from the stage 1 meta-analysis of EUR studies in known BP regions (Supplementary Table 1). All SNVs had $P_{\text{het}} < 0.0001$. 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: rare, very low frequency (MAF < 0.02; highlighted in bold), low frequency and common. A detailed listing of results is provided in Supplementary Table 8; 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; Ref., reference of the first reports of association in the listed region. ^aIndicates that the listed gene had an unconditional SKAT P value < 2×10^{-6} (Supplementary Table 9). ^bIndicates that the listed variant is the known variant or its proxy ($r^2 > 0.8$ in 1000 Genomes EUR). ^cIndicates that one or more of the previously reported variants in the locus were not on exome array.

expression (or had $r^2 > 0.8$ in 1000 Genomes EUR with eQTLs) in publicly available databases (Methods and Supplementary Tables 4 and 11). We performed colocalization for 49 of the 66 BP loci (169 genes) with significant eQTLs available in GTEx v7, jointly across all 48 tissues and the BP traits using HyPrColoc³² (Methods) to verify that the eQTL and BP-SNV associations were due to the same SNVs and not due to LD or spurious pleiotropy³³. The BP associations and eQTLs colocalized at 17 BP loci with a single variant (PPa > 0.6), that is, the expression and BP associations were due to the same underlying causal SNV (Fig. 3 and Supplementary Table 17). A further ten loci had PPa > 0.6 for colocalization of BP associations and eQTLs for multiple nearby genes (Fig. 3). Colocalization analyses were also performed for the 35 eQTLs in whole blood from the Framingham Heart Study, and five additional loci were consistent with a shared SNV between BP and gene expression (Supplementary Table 17).

Given the central role of the kidney in BP regulation, we investigated if BP-associated SNVs from the EAWAS were kidney eQTLs using TRANScriptome of renal human Tissue study and The Cancer Genome Atlas study ($n = 285$; Methods^{34,35}; Supplementary Note). We observed significant eQTL associations ($P < 5 \times 10^{-8}$) at three newly identified BP loci (*MFAP2*, *NFU1* and *AAMDC*, which were also identified in GTEx) and six at previously published loci (*ERAP1*, *ERAP2*, *KIAA0141*, *NUDT13*, *RP11-582E3.6* and *ZNF100*; Supplementary Table 18).

New BP-associated SNVs are pQTLs. Eighteen BP loci had sentinel variants (or were in LD with BP SNVs, $r^2 > 0.8$ in 1000 Genomes EUR) that were also protein QTLs (pQTLs) in plasma. Across the 18 loci, BP SNVs were pQTLs for 318 proteins (Supplementary Table 19). Low-frequency SNVs in *MCL1* and *LAMA5* were *cis*-pQTL for *MCL1* and *LAMA5*, respectively. The BP-associated SNV rs4660253 is a *cis*-pQTL and *cis*-eQTL for *TIE1* across eight tissues in GTEx, including the heart (Fig. 3 and Supplementary Table 17). The DBP-associated SNV rs7776054 is in strong LD with rs9373124, which is a *trans*-pQTL for erythropoietin, a hormone mainly synthesized by the kidneys, which has links to hypertension.

Pathway and enrichment analyses. The overrepresentation of rare and common BP SNVs in DNase I-hypersensitive sites (DHS), which mark open chromatin, was tested using GARFIELD (Methods and Supplementary Table 4). The most significant

enrichment in DHS hotspots for SBP-associated SNVs was in fetal heart tissues, with an ~threefold enrichment compared to ~twofold in adult heart (Fig. 3 and Supplementary Note). This difference in enrichment was also reflected in fetal muscle compared to adult muscle for SBP-associated SNVs. The most significant enrichment for DBP- and PP-associated SNVs (~threefold) was in blood vessels (Fig. 3 and Supplementary Note). There was also enrichment across SBP, DBP and PP in fetal and adult kidney and fetal adrenal gland tissue. In support, complementary enrichment analyses with FORGE (Methods) showed similar enrichments, including in fetal kidney and fetal lung tissues (z -score = 300; Supplementary Table 13 and Supplementary Note).

Mendelian randomization with cardiovascular disease. Twenty-six new BP loci were also associated with cardiometabolic diseases and risk factors in PhenoScanner³⁶ (<http://www.phenoscanner.medschl.cam.ac.uk/>; Methods, Fig. 4, Supplementary Note and Supplementary Tables 4, 20 and 21). Given that BP is a key risk factor for CVD, we performed MR analyses to assess the causal relationship of BP with any stroke (AS), ischemic stroke (IS), large artery stroke (LAS), cardioembolic stroke (CE), small vessel stroke (SVS) and coronary artery disease (CAD) using all the distinct BP-associated SNVs from our study (both known and new; Supplementary Table 4 and Methods). BP was a predictor of all stroke types and CAD (Fig. 5 and Supplementary Fig. 2). Notably, SBP had the strongest effect on all CVD phenotypes, with the most profound effect on LAS, increasing risk by more than twofold per s.d. (Supplementary Table 22). BP had weakest effect on CE, which may reflect the greater role of atrial fibrillation versus BP in CE risk. Multivariable MR analyses, including both SBP and DBP, showed that the effect of DBP attenuated to zero once SBP was accounted for (consistent with observational studies³⁷), except for LAS (Fig. 5, Supplementary Table 22 and Methods), where SBP and DBP had a suggestive inverse relationship, perhaps reflecting arterial stiffening. An inverse relationship between DBP and stroke above age 50 years has also been reported³⁷.

Discussion

Unlike most previous BP studies that focused primarily on common variant associations, we performed an extensive analysis of rare variants, both individually and in aggregate within a gene. Many of

Table 3 | Newly identified independent BP-associated rare SNVs at known loci in the UKBB only

Locus ID	rsID	Chr. pos	Gene	Info	EA/OA	Consequence	Trait	Unconditional SNV analysis			FINEMAP output			Ref.
								EAF	β	P value	Common SNVs in top configuration	PPa of n SNVs	$\log_{10}(\text{BF})$	
5	rs41300100	1:11908146	NPPA	0.82	G/C	5' UTR	SBP	0.010	-0.10	4.70×10^{-21}	rs2982373, rs5066, rs55892892	0.55	122.50	2,9,50
18	rs756799918	1:153464738	RN7SL44P	0.89	T/C	Intergenic	SBP	0.0004	0.26	4.30×10^{-7}	rs12030242	0.36	27.49	14
28	rs1805090	1:230840034	AGT	NA	T/G	Missense	SBP	0.0025	0.11	6.80×10^{-8}	rs3889728, rs2493135	0.79	26.23	8
28	rs539645495	1:230860071	RP11-99J16_A.2	0.97	G/A	Intron, noncoding transcript	DBP	0.0024	0.13	3.20×10^{-9}	rs2493135, rs3889728	0.83	30.97	8
33	rs56152193	2:20925891	LDAH	0.76	C/G	Intron	PP	0.0006	-0.23	8.10×10^{-7}	rs7255	0.36	17.95	16,17
55	rs759606582	2:178325956	AGPS	0.96	G/A	Intron	PP	0.0003	0.29	1.90×10^{-7}	rs56726187	0.57	7.48	16
72	rs555934473	3:48899332	SLC25A20	0.74	T/G	Intron	DBP	0.0012	-0.17	2.50×10^{-6}	rs36022378, rs6442105, rs6787229	0.25	35.71	6,11,16,17
73	rs76920163	3:53857055	CHDH	0.96	G/T	Intron	SBP	0.0059	0.10	3.80×10^{-13}	rs3821843, rs7340705, rs11707607	0.58	29.45	16,18
	rs144980716	3:53776904	CACNA1D	0.91	A/G	Intron	PP	0.0065	0.07	2.60×10^{-8}	rs36031811, rs77347777	0.57	18.42	
85	rs547947160	3:141607335	ATP1B3	0.75	G/A	Intron	PP	0.0008	0.20	6.00×10^{-6}	rs6773662	0.54	7.040	13
86	rs545513277	3:143113550	SLC9A9	0.70	A/G	Intron	PP	0.0006	-0.24	6.90×10^{-6}	rs1470121	0.56	11.97	16
92	rs186525102	3:185539249	IGF2BP2	0.85	A/G	Intron	SBP	0.0086	-0.06	6.70×10^{-7}	rs4687477	0.56	8.08	17
94	rs111620813	4:8293193	HTRA3	NA	A/G	Missense	PP	0.0100	-0.05	2.00×10^{-6}	rs28734123	0.53	12.54	18
132	rs181585444	5:129963509	ACO05741.2	0.83	C/T	Intergenic	DBP	0.0003	-0.30	3.80×10^{-6}	rs274555	0.55	10.70	13,14
137	rs546907130	6:8156072	EEF1E1	0.90	T/C	Intergenic	SBP	0.0017	-0.14	1.90×10^{-7}	rs3812163	0.70	8.57	16
141	rs72854120	6:39248533	KCNK17	0.91	C/T	Intergenic	SBP	0.0073	-0.08	3.10×10^{-9}	rs2561396	0.76	10.49	16
141	rs72854118	6:39248092	KCNK17	0.91	G/A	Intergenic	DBP	0.0072	-0.07	2.70×10^{-7}	rs1155349	0.85	11.12	16
164	rs138890991	7:40804309	SUGCT	0.94	C/T	Intron	PP	0.0100	0.06	1.60×10^{-7}	rs17171703	0.77	19.08	17
179	rs561912039	7:150682950	NOS3	0.74	T/C	Intergenic	DBP	0.0017	-0.13	6.40×10^{-6}	rs3793341, rs3918226, rs6464165, rs7788497, rs891511	0.34	81.75	9,10,14
183	rs570342886	8:23380012	SLC25A37	0.85	C/G	Intergenic	DBP	0.0001	-0.48	9.80×10^{-7}	rs7842120	0.58	15.74	16
190	rs201196388	8:95265263	GEM	NA	T/C	Splice donor	PP	0.0005	0.26	2.40×10^{-9}	rs2170363	0.34	31.80	16,49
193	rs532252660	8:120587297	ENPP2	0.79	T/C	Intron	DBP	0.0025	-0.11	4.10×10^{-7}	rs7017173	0.81	26.53	6
193	rs181416549	8:120678125	ENPP2	0.84	A/G	Intron	PP	0.0026	0.20	5.10×10^{-21}	rs35362581, rs80309268	0.95	113.21	6
212	rs138765972	10:20554597	PLXDC2	0.94	C/T	Intron	DBP	0.0075	-0.07	4.40×10^{-8}	rs61841505	0.49	9.06	16
219	rs192036851	10:64085523	RP11-120C12.3	0.92	C/T	Intergenic	SBP	0.0062	0.06	6.40×10^{-6}	rs10995311	0.28	19.55	13,16
234	rs150090666	11:14865399	PDE3B	NA	T/C	Stop gained	DBP	0.0010	-0.16	5.20×10^{-7}	rs11023147, rs2597194	0.55	12.93	16
242	rs139620213	11:61444612	DAGLA	0.89	T/C	Upstream gene	PP	0.0019	0.11	5.90×10^{-6}	rs2524299	0.48	6.64	15
246	rs540659338	11:89183302	NOX4	0.85	C/T	Intron	PP	0.0027	-0.14	2.60×10^{-10}	rs2289125, rs494144	0.62	58.09	16,17
260	rs186600986	12:53769106	SP1	0.91	A/G	Upstream gene	PP	0.0030	-0.09	1.10×10^{-6}	rs73099903	0.48	12.91	19
266	rs137937061	12:111001886	PPTC7	0.74	A/G	Intron	SBP	0.0048	-0.09	1.30×10^{-6}	rs9739637, rs35160901, rs10849937, rs3184504	0.34	55.74	4,5,16
268	rs190870203	12:123997554	RILPL1	0.85	T/G	Intron	PP	0.0020	0.12	1.70×10^{-7}	rs4759375	0.72	9.50	13
270	rs541261920	13:30571753	RP11-629E24.2	0.79	G/C	Intergenic	SBP	0.0005	0.24	9.20×10^{-6}	rs7338758	0.54	10.09	16
281	rs149250178	14:100143685	HHIPL1	0.75	A/G	3' UTR	DBP	0.0004	-0.29	2.30×10^{-6}	rs7151887	0.51	7.93	16
299	rs139491786	16:2086421	SLC9A3r2	NA	T/C	Missense	DBP	0.0068	-0.12	1.60×10^{-20}	rs28590346, rs34165865, rs62036942, rs8061324	0.57	50.80	16

Continued

Table 3 | Newly identified independent BP-associated rare SNVs at known loci in the UKBB only (continued)

Locus ID	rsID	Chr: pos	Gene	Info	EA/OA	Consequence	Trait	Unconditional SNV analysis			FINEMAP output			Ref.
								EA	β	P value	Common SNVs in top configuration	PPa of n SNVs	$\log_{10}(\text{BF})$	
304	rs2234710	16: 30907835	<i>BCL7C</i>	0.79	T/G	Upstream gene	SBP	0.0075	-0.08	2.30×10^{-9}	-	0.52	6.29	16,17
304*	rs148753960	16: 31047822	<i>STX4</i>	0.89	T/C	Intron	PP	0.0099	-0.07	1.80×10^{-9}	rs7500719	0.42	12.21	16,17
317	rs756906294	17: 42323081	<i>SLC4A1</i>	0.73	T/C	Downstream gene	PP	0.0030	0.01	8.30×10^{-6}	rs66838809	0.27	18.94	17
322	rs16946721	17: 61106371	<i>TANC2</i>	0.91	G/A	Intron	DBP	0.0100	-0.07	1.40×10^{-11}	rs1867624, rs4291	0.51	20.91	16,17
333	rs55670943	19: 11441374	<i>RAB3D</i>	0.87	C/T	Intron	SBP	0.0085	-0.10	2.10×10^{-17}	rs12976810, rs4804157, rs160838, rs167479	0.78	85.45	13-15
346*	rs149972827	20: 30413439	<i>MYLK2</i>	0.98	A/G	Intron	SBP	0.0036	-0.10	6.20×10^{-9}	-	0.85	9.86	16
362	rs115089782	22: 42329632	<i>CENPM</i>	0.93	T/C	Intergenic	SBP	0.0001	0.53	4.20×10^{-6}	rs1399919	0.44	14.12	13,17

FINEMAP²⁵ was used to identify the most likely causal variants within the known loci (Supplementary Table 1) using the BOLT-LMM results in the UKBB (Supplementary Table 8). Info, imputation information score; NA, SNV was genotyped and not imputed; β , single-variant effect estimate for the rare variant in the BOLT-LMM analysis; P value, the single-variant P value from the mixed model in the BOLT-LMM analysis; PPa of n SNVs, the posterior probability of association of the number of causal variants; $\log_{10}(\text{BF})$, \log_{10} Bayes factor for the top configuration. rs540659338 identified in UKBB in *NOX4* has $r^2=1$ in 1000 Genomes 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.

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 HTN, hypotension or impaired cardiac function/development (Supplementary Table 12). For example, rs139600783 (p.Pro274Ser) was associated with increased DBP and is located in the *ARHGAP31* gene that causes Adams–Oliver syndrome, which can be accompanied by pulmonary HTN and heart defects. A further three (of the six) genes that cause Adams–Oliver syndrome are located in BP-associated loci (*DLL4* (ref. 16), *DOCK6* (refs. 13,15) and *NOTCH1*, a new BP locus). The missense variant rs200383755 (p.Ser19Trp, predicted deleterious by SIFT), located in the *GATA5* gene, encodes a transcription factor and is associated with increased SBP and DBP. *GATA5* mutations cause congenital heart defects, including bicuspid aortic valve and atrial fibrillation, while a *Gata5*-null mouse model had increased SBP and DBP at 90 days³⁸.

Within the known loci, we detected new rare-variant associations at several candidate genes, for example, the rare missense SNV rs1805090 (MAF=0.0023) in the angiotensinogen (*AGT*) gene was associated with increased BP independently of the known common variant association. *AGT* is known to have an important role in BP regulation, and the variant is predicted to be among the top 1% of most deleterious substitutions³⁹. The established common variant at *FOXSI* was not associated with BP in the conditional analysis, but new rare variants in *FOXSI* (rs45499294, p.Glu74Lys; MAF=0.0037) and *MYLK2* (rs149972827; MAF=0.0036; Supplementary Note) 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 macrophages⁴⁰, and a negative regulator of vascular endothelial growth factor (VEGF)-mediated vascular permeability, a key process in ischemic disease and cancer⁴¹. *PLCβ3* deficiency is associated with decreased atherogenesis, increased macrophage apoptosis in atherosclerotic lesions and increased sensitivity to apoptotic induction in vitro⁴⁰. Variants in *SOS2* have previously been linked to kidney development/function⁴² and also cause Noonan syndromes 1 and 9, which are rare inherited conditions characterized by craniofacial dysmorphic features and congenital heart defects, including hypertrophic cardiomyopathy⁴³. Here we report the rare variant rs72681869 (p.Arg191Pro) in *SOS2* as associated with SBP, DBP,

PP and HTN, highlighting *SOS2* as a candidate gene. Previously, we identified a rare missense BP-associated variant in *RRAS*, a gene causing Noonan syndrome¹³. Our discoveries of rare missense variants at known BP loci provide additional support for candidate genes at these loci.

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

We found greater enrichment of SBP-associated SNVs in DHS hotspots in fetal versus adult heart muscle tissue. These results suggest that BP-associated SNVs may influence the expression of genes that are critical for fetal development of the heart. This is consistent with our finding that some BP-associated genes also cause congenital heart defects (see above). Furthermore, de novo mutations in genes with high expression in the developing heart, as well as in genes that encode chromatin marks that regulate key developmental genes, have previously been shown to be enriched in congenital heart disease patients^{46,47}. A recent study of atrial fibrillation genetics, for which BP is a risk factor, described enrichment in DHS in fetal heart⁴⁸. The authors hypothesized that the corresponding genes acting during fetal development increase the risk of atrial fibrillation⁴⁸. Together, these data suggest that early development and/or remodeling of cardiac tissues may be an important driver of BP regulation later in life.

The BP measures we have investigated here are correlated; among the 106 new genetic BP loci, only two are genome-wide significant across all four BP traits (*RP11-284M14.1* and *VTN*; Fig. 2). None of the new loci were unique to HTN (Fig. 2), perhaps as HTN is derived from SBP and DBP, or due to reduced statistical power for a binary trait. The results from our study indicate rare BP-associated variants contribute to BP variability in the general population, and their identification has provided information on new candidate genes and potential causal pathways. We have primarily focused

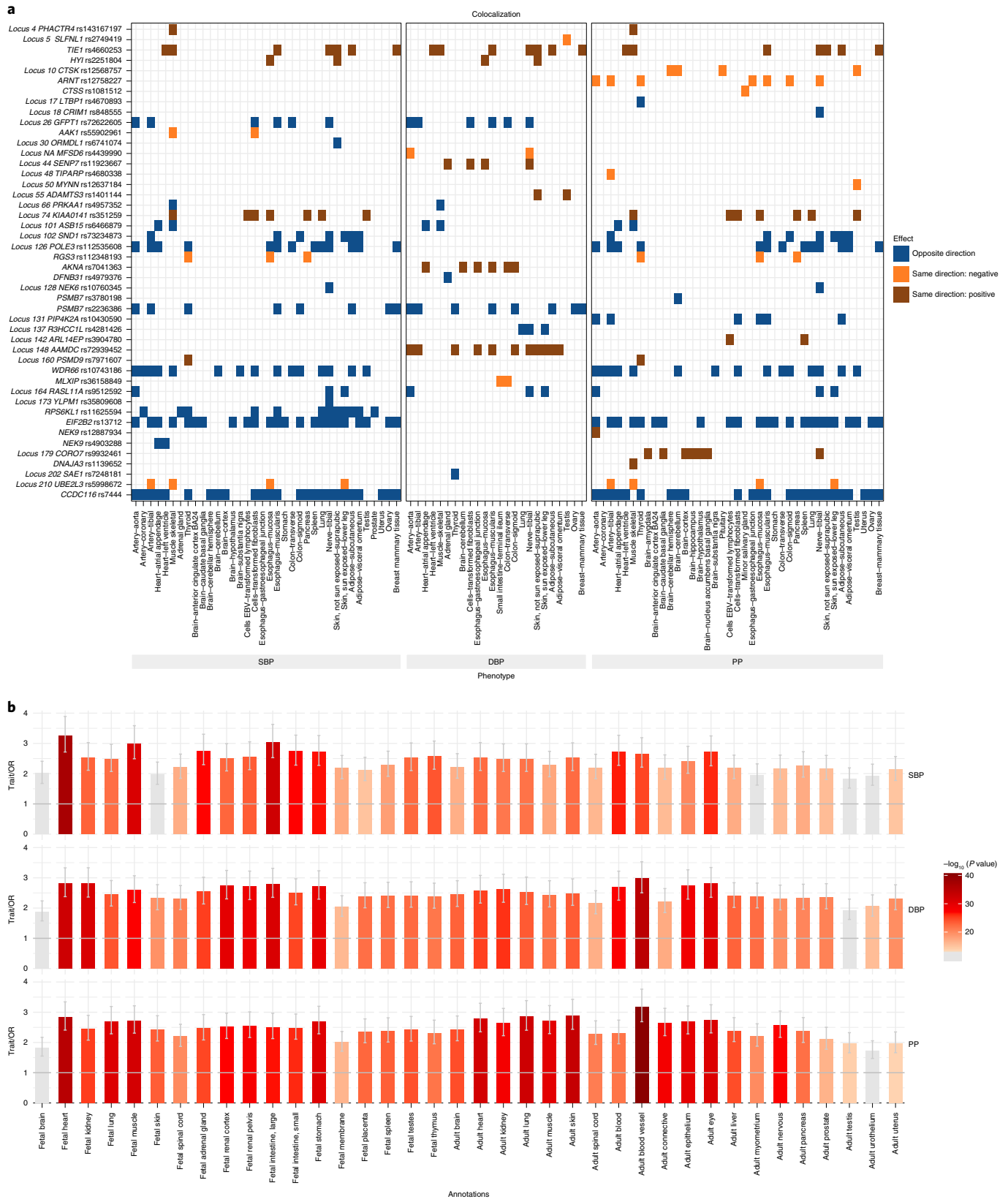
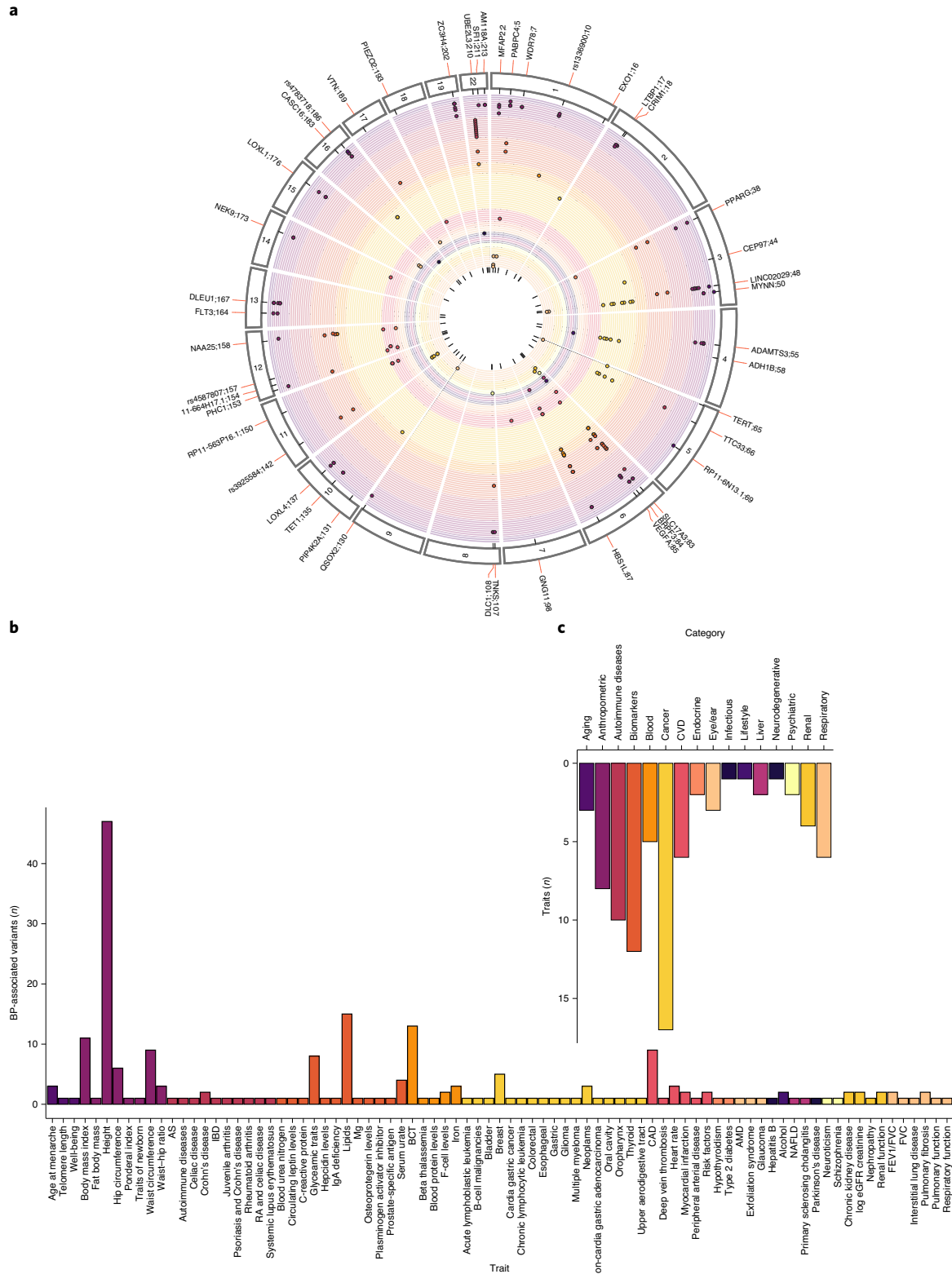


Fig. 3 | Annotation of BP loci. a, BP associations shared with eQTLs from GTEx through multi-trait colocalization analyses. Expressed gene and the colocalized SNVs are provided on the y axis. BP trait and eQTL tissues are provided on the x axis. The color indicates whether the candidate SNV increases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



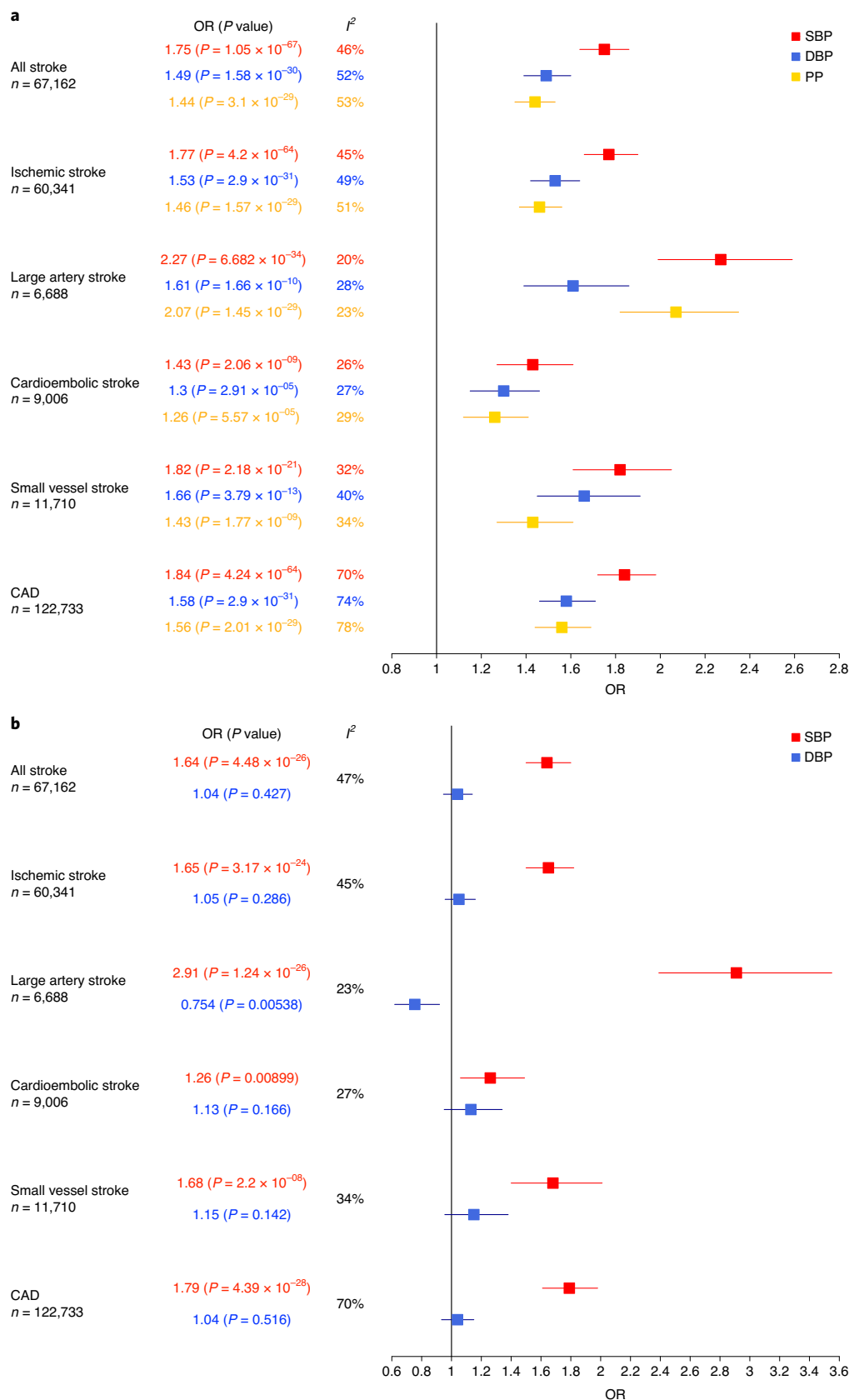


Fig. 5 | Causal association of BP with stroke and CAD. a, b, MR analyses of the effect of BP on stroke and CAD. **a**, Univariable analyses. **b**, Multivariable analyses performed using summary association statistics (Methods). The squares are the causal estimates on the OR scale, and whiskers represent the 95% confidence intervals for these ORs. Results on the s.d. scale are provided in Supplementary Table 22. The genetic variants for the estimation of the causal effects in this plot are sets of SNVs after removing the confounding SNVs and invalid instrumental variants. *P* values were determined from the inverse-variance-weighted two-sample MR method. Statistical heterogeneity was assessed using the *I*² statistic. *n*, number of participants in each disease group.

on the exome array, which is limited. Future studies using both exome and whole-genome sequencing in population cohorts (for example, UKBB and TOPMed) will lead to identification of further rare-variant associations and may advance the identification of causal BP genes across the ~1,000 reported BP loci.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at <https://doi.org/10.1038/s41588-020-00713-x>.

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Methods

Participants. The cohorts contributing to stage 1 of the EAWAS comprised 92 studies from four consortia (CHARGE, CHD Exome+, GoT2D:T2DGenes, ExomeBP) and the UKBB, totaling 870,217 individuals of EUR ($n = 810,865$), AA ($n = 21,077$), SAS ($n = 33,689$) and HIS ($n = 4,586$) ancestries. Study-specific characteristics, sample quality control (QC) and descriptive statistics for the new studies are provided in Supplementary Tables 23 and 24 and in Supplementary Tables 1 and 2 of work by Surendran et al.¹³ and Supplementary Table 20 of work by Liu et al.¹⁴.

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

Stage 1 of the RV-GWAS used data from 445,360 EUR individuals from the UKBB (Supplementary Tables 23 and 24 and Supplementary Note), 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 linked DNA extracted from discarded blood collected during routine clinical testing to de-identified medical records.

Phenotypes. SBP, DBP, PP and HTN were analyzed. Details of the phenotype measures for the previously published studies can be found in the Supplementary Information of the works by Surendran et al.¹³ and Liu et al.¹⁴, and further details of the additional studies are provided in Supplementary Table 24 and Supplementary Note. Typically, the average of two baseline measurements of SBP and DBP were used. For individuals known to be taking BP-lowering medication, 15 mm Hg and 10 mm Hg were added to the raw SBP and DBP values, respectively, to obtain medication-adjusted values⁵¹. PP was defined as SBP minus DBP after medication adjustment. For HTN, individuals were classified as hypertensive cases if they satisfied at least one of the following criteria: (1) SBP ≥ 140 mm Hg, (2) DBP ≥ 90 mm Hg or (3) use of antihypertensive or BP-lowering medication. All other individuals were considered controls. Further information on study-specific BP measurements is provided in Supplementary Table 24. Residuals from the null model obtained after regressing the medication-adjusted trait on the covariates (age, age², sex, body mass index and principal components (PCs) to adjust for population stratification, in addition to any study-specific covariates) within a linear regression model were ranked and inverse normalized (Supplementary Note).

Genotyping. The majority of the studies were genotyped using one of the Illumina HumanExome BeadChip arrays (Supplementary Table 24). An exome chip QC standard operating procedure⁵² developed by A.M., N.R.R. and N.W.R. at the Wellcome Trust Centre for Human Genetics at the University of Oxford was used by some studies for genotype calling and QC, while the CHARGE implemented an alternative approach⁵³ (Supplementary Table 24 and Supplementary Tables 3 and 21, respectively, of Surendran et al.¹³ and Liu et al.¹⁴). All genotypes were aligned to the plus strand of the human genome reference sequence (build 37) before any analyses and any unresolved mappings were removed. UKBB, MVP and deCODE were genotyped using GWAS arrays (Supplementary Table 24).

Exome array meta-analyses. Study-specific analyses were performed to test for the association of 247,315 SNVs with SBP, DBP, PP and HTN in 810,865 EUR individuals (75 studies) and additionally in 59,352 individuals of non-European ancestry comprising individuals of SAS (5 studies), AA (10 studies) and HIS (2 studies) ancestries (Supplementary Note). Study-specific association summaries were meta-analyzed in stage 1 using inverse-variance-weighted fixed-effect meta-analyses implemented in METAL⁵⁴. Fixed-effect and random-effects meta-analyses showed concordant results (Supplementary Table 2). For the binary trait (HTN), we performed sample-size-weighted meta-analysis.

Minimal inflation in the association test statistic (λ) was observed ($\lambda = 1.18$ for SBP, 1.20 for DBP, 1.18 for PP and 1.18 for HTN in the EUR meta-analyses; and $\lambda = 1.19$ 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 centers, and results were found to be concordant across the centers.

Following stage 1, SNVs outside of known BP-associated regions with $P < 5 \times 10^{-8}$ were looked up in individuals from the MVP, deCODE and GENOA studies (data request). Two meta-analyses of the three additional studies for each trait were performed by two independent analysts, one involving EUR individuals (354,096) only and one involving PA individuals (448,667). Likewise, two stage 2 meta-analyses for each trait were performed by two independent analysts, one involving EUR participants (1,167,961) and one PA (1,318,884). SNVs with (a conservative) $P < 5 \times 10^{-8}$ in the stage 2 meta-analysis with consistent directions of effect in stage 1 and data request studies,

with no evidence of heterogeneity ($P > 0.0001$), were considered potentially new⁵⁵.

RV-GWAS. Rare SNVs with $P < 5 \times 10^{-8}$ (a widely accepted significance threshold^{56,57}) in the inverse-variance-weighted meta-analysis of the UKBB and MVP with consistent directions of effect in stage 1 and MVP, and no evidence of heterogeneity ($P > 0.0001$), were considered potentially new.

Quality control. As part of the sample QC, plots comparing the inverse of the standard error as a function of the square root of the study sample size for all studies were manually reviewed for each trait, and phenotype-specific study outliers were excluded. In addition, inflation of the test statistic was manually reviewed for each study and for each phenotype, and confirmed as minimal or no inflation before stage 1 meta-analyses. For EAWAS and RV-GWAS, we performed our own QC for genotyped variants as we were specifically interested in rare variants and knew that these were most vulnerable to clustering errors. Full details of the UKBB QC approaches are provided in the Supplementary Note. To ensure that the reported variants were not influenced by technical artifacts nor 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 artifacts and removed poorly clustered variants. Lastly, for RV-GWAS, if the variant was available in UKBB whole-exome data (~50,000 individuals), we ensured that the MAFs were consistent with the imputed MAF despite restricting the reporting to only variants with a good imputation quality 'INFO' score of > 0.8 .

Definition of known loci. For each known variant, pairwise LD was calculated between the known variant and all variants within the 4-Mb region in the 1000 Genomes phase 3 data restricted to EUR samples. 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; for these variants, a ± 500 -kb window around the known variant was used. The window was extended by a further 50 kb, and overlapping regions were merged (Supplementary Table 1).

Conditional analyses. Within the new BP loci, we defined a region based on LD (Supplementary Table 1) within which conditional analysis was performed (five variants were not in the 1000 Genomes panel, and for these we established a ± 500 -kb window definition). Conditional and joint association analysis as implemented in GCTA (v1.91.4)²³ was performed using the EAWAS results to identify independent genetic variants associated with BP traits within newly identified and known regions available in the exome array. We restricted this analysis to the summary data from stage 1 EUR EAWAS meta-analyses ($n = 810,865$) as LD patterns were modeled using individual level genotype data from 57,718 EUR individuals from the CHD Exome+ consortium. Variants with $P_{\text{joint}} < 1 \times 10^{-6}$ were considered conditionally independent.

We used the UKBB GWAS results and FINEMAP²⁵ v1.1 to fine-map the known BP-associated regions to identify rare variants that are associated with BP independently of the known common variants (Supplementary Note; due to lack of statistical power, we did not use UKBB GWAS data alone to perform conditional analyses within the new EAWAS loci). For each known region, we calculated pairwise Pearson correlations for all SNVs within a 5-Mb window of the known SNVs using LDstore v1.1. Z-scores calculated in the UKBB single-variant association analyses were provided as input to FINEMAP along with the correlation matrix for the region. We selected the configuration with the largest Bayes factor and largest posterior probability as the most likely causal SNVs. We considered causal SNVs to be significant if the configuration cleared a threshold of $\log_{10}(\text{BF}) > 5$ 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 the UKBB between the selected variants. For loci that included rare variants identified by FINEMAP, we validated the selected configuration using a linear regression model in R.

Gene-based tests. Gene-based tests were performed using SKAT²⁶ as implemented in the rareMETALS package v7.1 (<https://genome.sph.umich.edu/wiki/RareMETALS>), which allows for the variants to have different directions and magnitudes of effect, to test whether rare variants in aggregate within a gene are associated with BP traits. For the EAWAS, two gene-based meta-analyses were performed for inverse-normal transformed DBP, SBP and PP, one involving EUR and a second involving PA individuals, 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 the UKBB, we considered summary association results from 364,510 unrelated individuals only. We annotated all SNVs on the exome array using

VEP²⁷. A total of 15,884 (EUR) and 15,997 (PA) genes with two or more variants with $MAF \leq 0.01$ annotated as high or moderate impact according to VEP were tested. The significance threshold was set at $P < 2.5 \times 10^{-6}$ (Bonferroni adjusted for ~20,000 genes).

A series of conditional gene-based tests were performed for each significant gene. To verify the gene association was due to more than one variant (and not due to a single sub-genome-wide significance threshold variant), gene tests were conditioned on the variant with the smallest P value in the gene (top variant). Genes with $P_{\text{conditional}} < 1 \times 10^{-4}$ were considered significant, which is in line with locus-specific conditional analyses used in other studies⁵⁸. To ensure that gene associations located in known or newly identified BP regions (Supplementary Note and Supplementary Table 1) were not attributable to common BP-associated variants, analyses were conditioned on the conditionally independent known/new common variants identified using GCTA within the known or new regions, respectively, for the EAWAS (or identified using FINEMAP for the GWAS). Genes mapping to either known or new loci with $P_{\text{conditional}} < 1 \times 10^{-5}$ were considered significant. The P value to identify gene-based association not driven by a single variant was set in advance of performing gene-based tests and was estimated on the basis of the potential number of genes that could be associated with BP.

Mendelian randomization with cardiovascular disease. We used two-sample MR to test for causal associations between BP traits and AS, any IS, LAS, CE, SVS and CAD. All new and known BP-associated SNVs (including conditionally independent SNVs) listed in Supplementary Tables 2, 3, 5, 7 and 8 were used as instrumental variables (IVs). In addition to trait-specific analyses, we performed an analysis of 'generic' BP, in which we used the SNVs associated with any of the traits. Where variants were associated with multiple BP traits, we extracted the association statistics for the trait with the smallest P value (or the largest posterior probability for the known loci). To exclude potentially invalid (pleiotropic) genetic instruments, we used PhenoScanner²⁶ to identify SNVs associated with CVD risk factors, cholesterol (LDL, HDL and triglycerides), smoking, type 2 diabetes and atrial fibrillation (Supplementary Table 22) and removed these from the list of IVs. We extracted estimates for the associations of the selected instruments with each of the stroke subtypes from the MEGASTROKE PA GWAS results (67,162 cases and 454,450 controls)⁵⁹ and from a recent GWAS for CAD⁶⁰. 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 model because we had hundreds of IVs for BP⁶¹. 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 holds⁶². While MR-Egger has been shown to be conservative⁶³, it has the useful property that the MR-Egger-intercept can give an indication of (unbalanced) pleiotropy, which allowed us to test for pleiotropy among the IVs. We used MR-PRESSO to detect outlier IVs⁶⁴. To assess instrument strength, we computed the F statistic⁶⁴ for the association of genetic variants with SBP, DBP and PP (Supplementary Note and Supplementary Table 22). We also assessed heterogeneity using the Q statistic. Although these methods may have different statistical power, the rationale is that, if these methods give a similar conclusion regarding the association of BP and CVD, then we are more confident in inferring that the positive results are unlikely to be driven by violation of the MR assumptions⁶⁵.

Moreover, we used mvMR to estimate the effect of multiple variables on the outcome^{61,66}. This is useful when two or more correlated risk factors are of interest (for example, SBP and DBP) and may help to understand whether both risk factors exert a causal effect on the outcome, or whether one exerts a leading effect on the outcome. Thus, we used multiple genetic variants associated with SBP and DBP to simultaneously estimate the causal effect of SBP and DBP on CVD.

All analyses were performed using R v3.4.2 with R packages 'TwoSampleMR' and 'MendelianRandomization' and 'MRPRESSO'.

Metabolite quantitative trait loci and Mendelian randomization analyses.

Plasma metabolites were measured in up to 8,455 EUR individuals from the INTERVAL study^{67,68} and up to 5,841 EUR individuals from EPIC-Norfolk⁶⁹ using the Metabolon HD4 platform. In both studies, 913 metabolites passed QC and were analyzed for association with ~17 million rare and common genetic variants. Genetic variants were genotyped using the Affymetrix Axiom UKBB array and imputed using the UK10K + 1000Genomes or the HRC reference panel. Variants with an INFO score > 0.3 and minor allele count > 10 were analyzed. Phenotypes were log transformed within each study, and standardized residuals from a linear model adjusted for study-specific covariates were calculated before the genetic analysis. Study-level genetic analysis was performed using linear mixed models implemented in BOLT-LMM to account for relatedness within each study, and the study-level association summaries were meta-analyzed using METAL before the lookup of new BP variants for association with metabolite levels.

The same methodology for MR analyses as implemented for CVD was also adopted to test the effects of metabolites on BP. Causal analyses were restricted to the list of 14 metabolites that overlapped our BP associations and were known. We used a Bonferroni significance threshold ($P < 0.05/14 = 0.0036$), adjusting for the number of metabolites being tested. We also tested for a reverse causal effect

of BP on metabolite levels. The IVs for the BP traits were the same as those used for MR with CVD. For the mvMR analysis of metabolites with BP, we included 3-methylglutaryl carnitine(2) and the three metabolites that shared at least one IV with 3-methylglutaryl carnitine(2) in the mvMR model. A union set of genetic IVs for all the metabolites were used in the mvMR model to simultaneously estimate the effect size of each metabolite on DBP.

Colocalization of BP associations with eQTLs. Details of kidney-specific eQTLs are provided in the Supplementary Note. Using the PhenoScanner lookups to prioritize BP regions with eQTLs in GTEx v7, we performed joint colocalization analysis with the HyPrColoc package in R³² (<https://github.com/jrs95/hyprcoloc>; regional colocalization plots: <https://github.com/jrs95/gassocplot>). HyPrColoc approximates the COLOC method developed by Giambartolomei et al.⁷⁰ and extends it to allow colocalization analyses to be performed jointly across many traits simultaneously and pinpoint candidate shared SNVs. Analyses were restricted to SNVs present in all the datasets used (for GTEx data, this was 1 Mb upstream and downstream of the center of the gene probe), data were aligned to the same human genome build 37 and strand, and a similar prior structure as the colocalization analysis with cardiometabolic traits was used ($P = 0.0001$ and $\gamma = 0.99$).

Gene-set enrichment analyses. In total, 4,993 GO biological process, 952 GO molecular function, 678 GO cellular component, 53 GTEx, 301 KEGG, 9,537 MGI and 2,645 Orphanet gene sets were used for enrichment analyses (Supplementary Note).

We restricted these analyses to the rare BP-associated SNVs (Supplementary Table 4). For each set of gene sets, the significance of the enrichment of the genetically identified BP genes was assessed as the Fisher's exact test for the overabundance 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 knockout 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^{71,72}. 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 while accounting for MAF, the distance to the nearest transcription start site and the number of LD proxies of the GWAS variants. We used the SNVs from the full UKBB GWAS of BP traits as input to GARFIELD (Supplementary Table 4).

Reporting Summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

Summary association results for all the traits are available to download from <https://app.box.com/s/1ev9iaktips70k8t4cm8j347if0ef2u> and from CHARGE dbGaP Summary (<https://www.ncbi.nlm.nih.gov/gap/>) under accession number phs000930.

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Author contributions

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Competing interests

The following authors affiliated with deCODE genetics/Amgen are employed by the company: V.T., G. Thorleifsson, A.H., P. Sulem, G. Thorgeirsson, H. H., D.F.G., U.T. and K.S. B.P. serves on the steering committee of the Yale Open Data Access Project funded by Johnson & Johnson. J.D. reports grants, personal fees and nonfinancial support from Merck Sharp & Dohme; grants, personal fees and nonfinancial support from Novartis; grants from Pfizer; and grants from AstraZeneca outside the submitted work. J.D. sits on the International Cardiovascular and Metabolic Advisory Board for Novartis (since 2010); the Steering Committee of UK Biobank (since 2011); the MRC International Advisory Group (ING) member, London (since 2013); the MRC High Throughput Science ‘Omics Panel Member, London (since 2013); the Scientific Advisory Committee for Sanofi (since 2013); the International Cardiovascular and Metabolism Research and Development Portfolio Committee for Novartis; and the AstraZeneca Genomics Advisory Board (2018). A.B. reports grants outside of this work from AstraZeneca, Biogen, Merck, Novartis and Pfizer and personal fees from Novartis. V.S. has participated in a conference trip sponsored by Novo Nordisk and received an honorarium for participating in an advisor board meeting, outside the present study. V.S. also has ongoing research collaboration with Bayer, outside the present study. The spouse of C.J.W. works at Regeneron. N.S. is partially supported by Fundação para a Ciência e Tecnologia, Portugal (grant ref. UID/MAT/00006/2013 and UID/MAT/00006/2019). M.E.J. has received research grants from AMGEN, Sanofi Aventis, AstraZeneca and Boehringer Ingelheim. M.E.J. holds shares in Novo Nordisk. J.T. has received honoraria from AstraZeneca, Eli Lilly and Merck, and research funding from Bayer, Boehringer Ingelheim and Merck, and is a stock owner of Orion Pharma. D.O.M.-K. is a part-time clinical research consultant for Metabolon. M.I.M. has served on advisory panels for Pfizer, Novo Nordisk, Zoe Global, has received honoraria from Merck, Pfizer, Novo Nordisk and Eli Lilly and

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Additional information

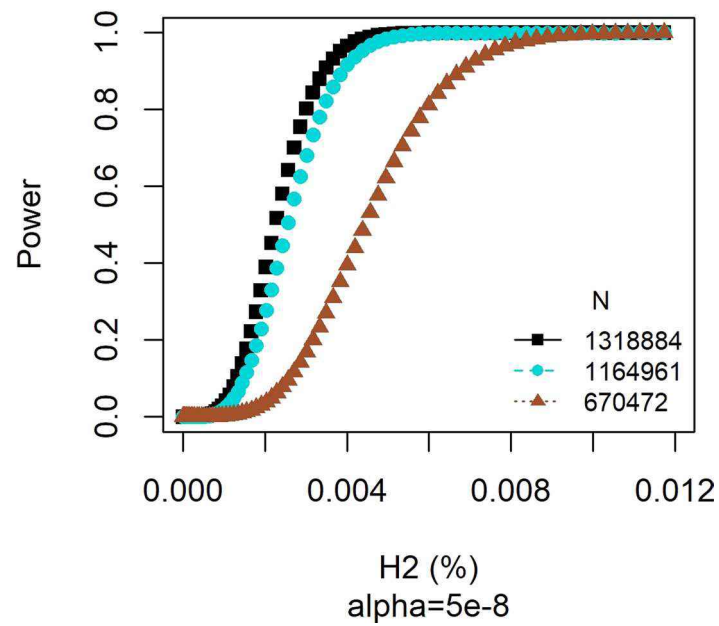
Extended data is available for this paper at <https://doi.org/10.1038/s41588-020-00713-x>.

Supplementary information is available for this paper at <https://doi.org/10.1038/s41588-020-00713-x>.

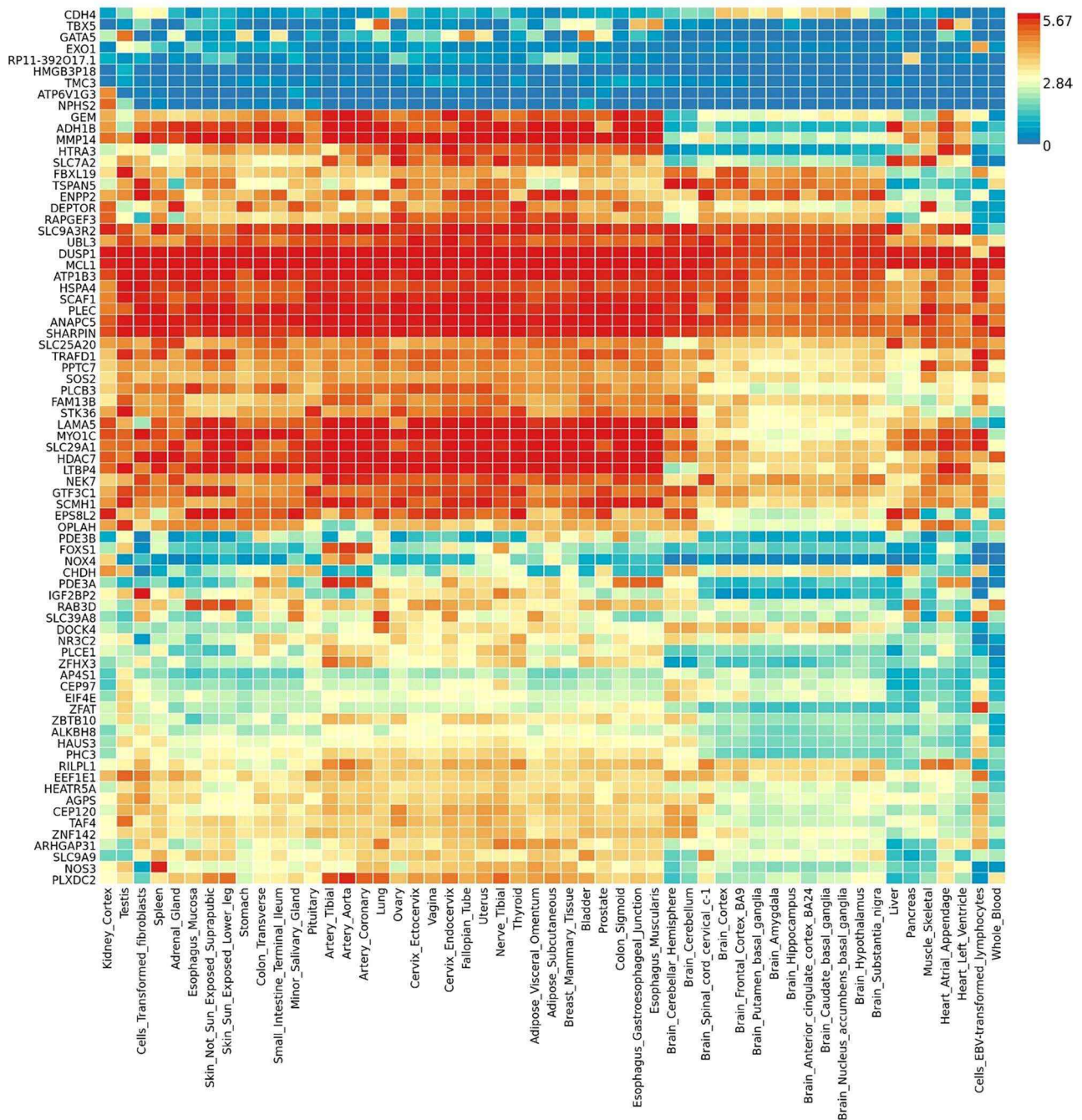
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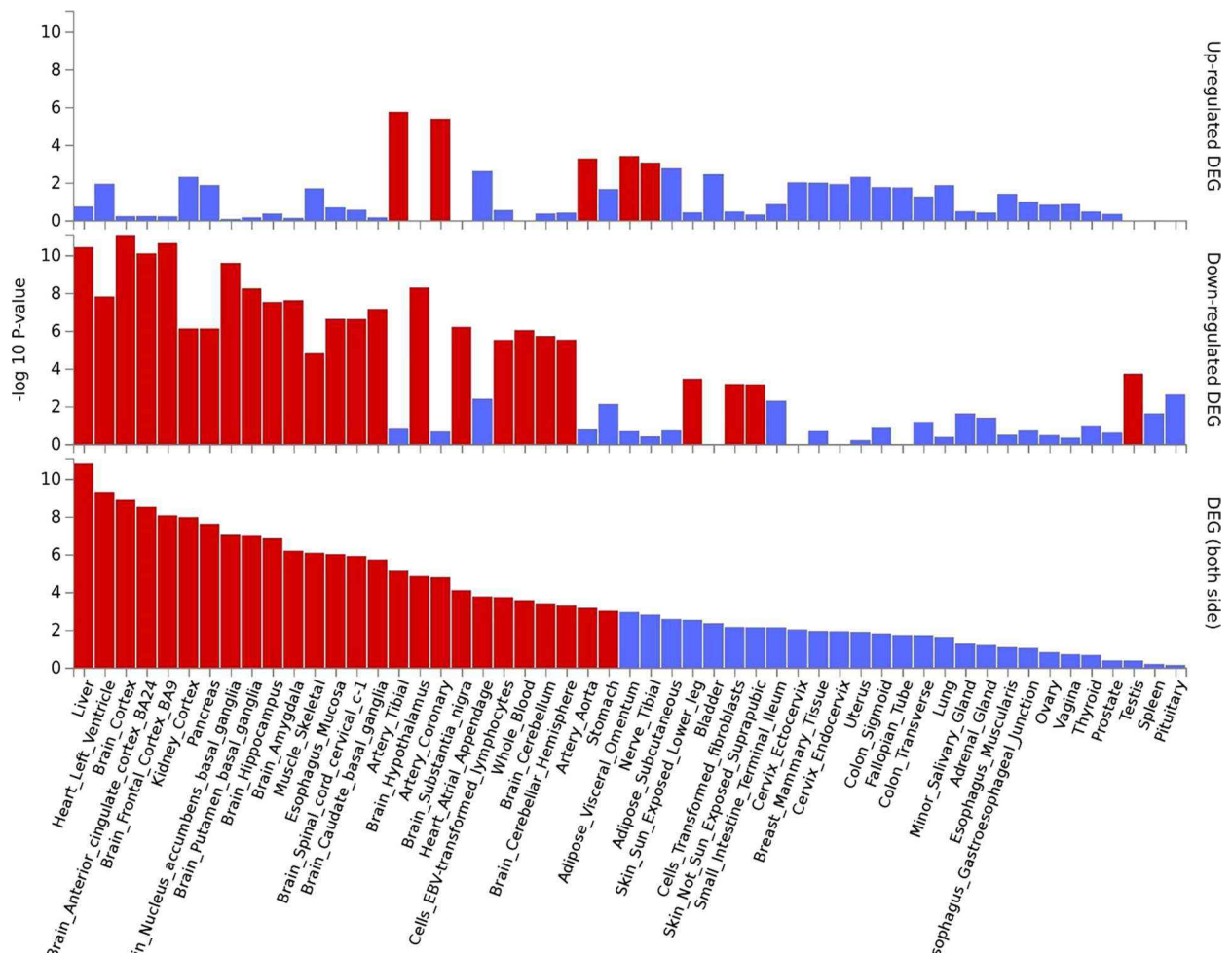
Power Estimation



Extended Data Fig. 1 | Power estimation for stage 2 meta-analyses. Power calculations were performed assuming that, for any given variant, there were 1,318,884 individuals for EAWAS PA analyses, 1,164,961 participants for EAWAS EA analyses, and 670,472 participants for RV-GWAS analyses. Calculations were performed in R (https://genome.sph.umich.edu/wiki/Power_Calculations:_Quantitative_Traits).



Extended Data Fig. 2 | Expression of genes implicated by the rare SNVs in GTEx v7 tissues. We used FUMA GWAS to perform these analyses. We included genes closest to the identified rare variants from the EAWAS and the RV-GWAS.



Extended Data Fig. 3 | Tissue enrichment of rare variant gene expression levels in GTEx v7. We used FUMA GWAS to perform these analyses. We included genes closest to the identified rare variants from the EAWAS and the RV-GWAS.

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- A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
- For null hypothesis testing, the test statistic (e.g. F , t , r) with confidence intervals, effect sizes, degrees of freedom and P value noted
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Software and code

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Data collection

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

Data analysis

Genotype QC: PLINK 1.9 and R v3.3
Study-level analysis of exome array variants: RMW version 4.13.3, SNPTTEST v2.5.1
RV-GWAS and analysis of exome array variants in Europeans from UKBB: BOLT-LMM v2.3
Genetic analysis of exome array variants for Hypertension (HTN): SNPTTEST v2.5.4-beta3
Meta-analysis of study level association summaries: METAL (version released on 2011-03-25)
LD calculations to define known and novel loci: PLINK 1.9
Fine mapping of known blood pressure (BP) loci in UKBB: FINEMAP v1.1
Pairwise Pearson correlation within known BP loci in UKBB: LDstore v1.1.
Validation of selected configuration for FINEMAP: linear regression model in R v3.3.
Conditional analysis within novel and known loci: GCTA v1.91.4
Gene based tests: SKAT implemented in rareMETALS package version 7.1

Annotation of genetic variants: Variant Effect Predictor (VEP) tool version 99
 Look for association of BP variants with diseases and intermediate phenotypes: Phenoscanner V2
 Colocalisation of BP variants with cardiovascular disease risk factors: coloc package in R version 4.0-0
 Regional colocalisation plots: gassocplot package in R version 1.0
 Mendelian Randomisation with cardiovascular diseases: R version 3.4.2 with R packages 'TwoSampleMR' version 0.4.22, 'MendelianRandomization' version 0.4.1, and "MRPRESSO" version 1.0
 Colocalisation of BP associations with eQTLs: HyPrColoc package in R version 1.0
 Functional enrichment using BP associated variants: GARFIELD v2
 Gene-set enrichment: GO (download from <http://geneontology.org/> on December 9, 2018, using the files go-basic.obo and goa_human.gaf), GTEx (download from <https://gtexportal.org> on December 9, 2018, using the file GTEx_Analysis_2016-01-15_v7_RNASeQCv1.1.8_gene_median_tpm.gct.gz), KEGG (downloaded from <ftp.pathways.jp> on December 9, 2018 using the files hsa.list and map_title.tab), MGI (downloaded from <http://www.informatics.jax.org> downloads/reports on December 9, 2018, using the files MPheno_OBO.ontology.obo, HMD_HumanPhenotype.rpt and MGI_PhenogenoMP.rpt) and Orphanet (downloaded from <http://www.orphandata.org/data/ORDO/> on December 9, 2018, using the files ordo.owl).
 Gene-set enrichment gene references: Homo_sapiens.gene_info file obtained from ftp://ftp.ncbi.nih.gov/gene/DATA/GENE_INFO/Mammalia
 Drug target prioritization: DrugBank version 5.1.2, Open Targets Version 1
 Kidney gene expression quantification: Kallisto v0.45.0
 Kidney gene expression: genotype imputation: minimac3

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Single variant association summaries from the European (EUR) and Pan-ancestry (PA) meta-analyses are available at the link below:

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Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	To analyze rare variants associated with blood pressure variation, we collected data from individual studies with genetic association summaries available for systolic blood pressure, diastolic blood pressure, pulse pressure and hypertension. Our aim was to maximize the sample size to gain power for rare variant detection and hence no prior criteria on sample size was set. Obtained sample size of up to 1.3 mln. participants was considered sufficient, since it was the largest sample size available. Detailed power estimations are presented in Extended Data Fig. 1.
Data exclusions	Quality control of study level summary data was performed centrally prior to the meta-analyses 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 minor allele frequencies across studies. Any outlying studies (n=5, HTN) were excluded from downstream analyses. All exclusion criteria were pre-established.
Replication	No replication was attempted since no replication dataset comparable in magnitude to discovery dataset was available; we did ensure there was no heterogeneity in the data and that the direction of effect was consistent between the stages.
Randomization	N/A
Blinding	N/A

Reporting for specific materials, systems and methods

Materials & experimental systems

Methods

- n/a | Involved in the study
- Antibodies
- Eukaryotic cell lines
- Palaeontology
- Animals and other organisms
- Human research participants
- Clinical data

- n/a | Involved in the study
- ChIP-seq
- Flow cytometry
- MRI-based neuroimaging

Human research participants

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Population characteristics

Exome array wide association study (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, age2, 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 RMW2 version 4.13.3 by all studies except four studies which used SNPTTEST 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.

UK Biobank specific analyses

The UK Biobank (UKBB) is a large prospective study of 502,642 participants aged 40–69 years when recruited between 2006–2010 at 22 assessment centres across the United Kingdom^{73,74}. The study has collected and continues to collect a large amount of phenotypic measurements including systolic and diastolic blood pressure (BP).

Processing, quality control and analyses of the data provided by UK Biobank, were performed at two sites independently and were confirmed to be concordant at each step of the process.

Blood pressure measurement

BP was measured twice in a seated position after two minutes rest with a one minute rest before the second measurement [UK Biobank. UKB : Resource 100225 - Blood-pressure measurement procedures using ACE - Version 1.0. Available at: <http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=100225>. Accessed October 2, 2017]. An appropriate cuff and an Omron 705IT digital BP monitor, was used to measure BP in the majority of participants (UK Biobank data fields: SBP: f.4080.0.0 and f.4080.0.1; DBP: f.4079.0.0 and f.4079.0.1). If the largest cuff size was too small for the participant, or the electronic BP monitor failed, a sphygmomanometer with an inflatable cuff was used in conjunction with a stethoscope to perform a manual measurement (UK Biobank data fields: SBP: f.93.0.0 and f.93.0.1; DBP: f.93.0.0 and f.93.0.1). Of the 502,642 UKBB participants, 488,366 had both BP measurements and genotype data available, we therefore restricted phenotype quality control (QC) to these individuals. At baseline there were 446,611 participants with two automated BP measurements; 14,133 participants with one automated and one manual measurement and 26,615 with both manual measurements. The 1,007 samples with only one blood pressure measurement at baseline were excluded. Comparison of the BP distributions obtained using automated and manual approaches were concordant and reassured us both approaches were accurate. Individuals missing SBP or DBP at baseline assessment were removed (n=1,834). The mean of both measurements at baseline for a given participant was calculated to create an overall measure for SBP, DBP and PP. Phenotype QC was performed in R version v3.3.

Blood pressure measurement quality control Participants were excluded from analysis if

1. the difference between the first and second blood pressure measurement > 99.9th percentile (n=857);
2. covariates were missing: Age (n=0), gender (n=0), BMI (n=3105) using respectively UK Biobank data fields: f.21003.0.0, f.31.0.0 and f.21001.0.0;
3. they were pregnant at time of blood pressure measurement (n=131) UK Biobank data field: f.3140.0.0;
4. BMI >99.9th or <0.01 percentile (n=970).

In total 483,515 participants remained following quality control.

Adjustment of BP measurement for treatment effect For all UKBB participants that were on anti-hypertensive medication at time of blood pressure measurement (n=48,800) we added 15mmHg to the mean observed SBP, 10mmHg to the mean observed DBP and 5mmHg to the mean observed PP.

Definition of hypertension UKBB participants were defined as having hypertension when at least one of the following criteria was met:

1. Mean observed SBP \geq 140 mmHg
2. Mean observed DBP \geq 90 mmHg
3. History of hypertension: which was defined using the “non-cancer illnesses and associated first diagnosis timestamp” collected through the verbal interview (UK Biobank data field: f.20002.0.0) at baseline assessment for each UKBB participant. That is, where the following codes: “1065 hypertension”, “1072 essential hypertension” are present in data field f.20002.0.0. No ICD

codes were used to define hypertension.

4. Use of anti-hypertensive medication: at a baseline survey, we used responses to the “Medication for cholesterol, blood pressure or diabetes” question for males and responses to the “Medication for cholesterol, blood pressure, diabetes, or take exogenous hormones” question for females, both collected through the touchscreen questionnaire and providing information on regular medication use (UK Biobank data fields: f.6177.0.0 and f.6153.0.0, respectively). If a participant selected “2 Blood pressure medication” we defined this participant as having a current status of taking anti-hypertensive medication (27,931 females, 22,630 males).

255,794 individuals were defined as hypertensive and 227,721 were non-hypertensive.

Recruitment

The UK Biobank (UKBB) is a large prospective study of 502,642 participants aged 40–69 years when recruited between 2006–2010 at 22 assessment centres across the United Kingdom^{73,74}. The study has collected and continues to collect a large amount of phenotypic measurements including systolic and diastolic blood pressure (BP).

Ethics oversight

All participants provided written informed consent and the studies were approved by their local research ethics committees and/or institutional review boards (study references are available in Supplementary Table 1, and in Supplementary Table 2 of Surendran et al. 2016 and Supplementary Methods and Notes of Liu et al. 2016 for the previously published studies). The BioVU biorepository, performed DNA extraction on discarded blood collected during routine clinical testing, and linked to de-identified medical records. This research was conducted using the UK Biobank Resource under Application Numbers 20480 and 15293.

Note that full information on the approval of the study protocol must also be provided in the manuscript.