Genetic analysis of over 1 million people identifies 535 new loci associated with blood pressure traits

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Genetic analysis of over one million people identifies 535 novel loci for blood pressure.

Short title: Blood pressure GWAS in one million people

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Abstract

High blood pressure is a highly heritable and modifiable risk factor for cardiovascular disease. We report the largest genetic association study of blood pressure traits (systolic, diastolic, pulse pressure) to date in over one million people of European ancestry. We identify 535 novel blood pressure loci that not only offer new biological insights into blood pressure regulation but also reveal shared genetic architecture between blood pressure and lifestyle exposures. Our findings identify new biological pathways for blood pressure regulation with potential for improved cardiovascular disease prevention in the future.

High blood pressure (BP) is a leading heritable risk factor for stroke and coronary artery disease and was responsible for an estimated 7.8 million deaths and 148 million disability life years lost worldwide in 2015 alone[1]. Studies indicate that an individual's blood pressure (BP) level is determined by complex interactions between life course exposures and their genetic background[2-4]. Previous genetic association studies have included genome-wide meta-analyses, customised cardiovascular candidate gene centric analyses and evaluation of exome variation. These have identified and validated variants at 274 loci, with modest effects on population BP that in aggregate explain only ~3% of the trait variance[5-12].

Here, we report genome-wide discovery analyses of BP traits (systolic - SBP, diastolic - DBP and pulse pressure -PP) in people of European ancestry drawn from UK Biobank (UKB)[13] and the International Consortium of Blood Pressure-Genome Wide Association Studies (ICBP)[11,12]. We adopted a combination of a one and two-stage study design to test common and low-frequency single nucleotide polymorphisms (SNPs) with minor allele frequency (MAF) $\geq$ 1% in association with BP traits (**Fig. 1**). We studied over 1 million people of European descent across both discovery and replication, including replication data from the US Million Veterans Program (MVP)[14] and the Estonian Genome Centre, University of Tartu (EGCUT) Biobank[15].

Briefly, UKB is a prospective cohort study of ~500,000 individuals recruited at ages 40-69 years who have been richly phenotyped including BP measurements[14]. Participants were genotyped using a customized array with imputation from the Haplotype Reference Consortium (HRC) panel, yielding ~7 million SNPs (imputation quality score (INFO) $\geq$ 0.1 and MAF $\geq$ 1%)[16]. After quality control (QC) and exclusions (Online Methods) we performed genome-wide association studies (GWAS) of BP traits using data from 458,577 UKB participants of European descent under an additive genetic model[17] (**Supplementary Table 1a**). Following LD-score regression[18], genomic control was applied to the UKB data prior to meta-analysis (Online methods).

In addition, we performed GWAS analyses for BP traits in the newly extended ICBP GWAS data comprising 77 independent studies including up to 299,024 participants of European ancestry genotyped with various arrays, and imputed to either the 1,000 Genomes Reference Panel or the HRC platforms (**Supplementary Table 1b**). After QC we applied genomic control at the individual study level and obtained summary effect sizes for ~7 million SNPs with INFO $\geq$ 0.3 and Cochran's Q statistic[19] (test of heterogeneity) filtered at $P \geq 1 \times 10^{-4}$ (Online Methods).

We then combined the UKB and ICBP GWAS results using inverse-variance weighted fixed effects meta-analysis (Online Methods), giving a total discovery sample of 757,601 individuals[20].

In our two-stage design we attempted replication of 1,062 SNPs at $P < 1 \times 10^{-6}$ from discovery with concordant effect direction between UKB and ICBP, using the sentinel SNP (i.e. SNP with smallest *P*-value at the locus) after excluding the HLA region (chr 6:25-34MB) and all SNPs in Linkage Disequilibrium (LD) ($r^2 \geq 0.1$) or $\pm$500 Kb from any previously validated BP-associated SNPs at the 274 published loci. We used MVP (up to 220,520 people of European descent) and EGCUT (up to 28,742 Europeans) for independent external

replication[14,15] (**Supplementary Table 1c**). Our replication criteria for the two-stage design were genome-wide significance ($P < 5 \times 10^{-8}$) in the combined meta-analysis, with $P < 0.01$ in the replication data and concordant direction of effect between discovery and replication.

Given the larger size of the two discovery datasets (UKB and ICBP) compared with replication resources, we additionally undertook a one-stage design with internal replication, to minimize the risk of missing true positive associations from our two-stage analysis. To ensure the robustness of this approach, and to avoid false positive findings, we used $P < 5 \times 10^{-9}$ as the *P*-value threshold from the discovery meta-analysis, i.e. an order of magnitude more stringent than genome-wide significance[21]. We also required an internal replication *P*-value of < 0.01 in each of the UKB and ICBP GWAS analyses and with concordant direction of effect, to ensure support from both data sources.

We then explored the putative function of the BP associated signals using a range of *in silico* resources, including expression quantitative trait loci (eQTLs), tissue and DNase I site enrichment, long range chromatin interactions (Hi-C), pathway analysis and 'druggability'. We investigated metabolomic signatures associated with our novel sentinel SNPs, evaluated the overlap with lifestyle exposures that influence BP, and examined the co-occurrence of BP-associated loci with other complex traits and diseases. We also carried out conditional analyses using genome-wide complex trait analysis (GCTA)[22]. Finally, we developed a genetic risk score and performed analysis to model the impact that all BP-associated variants have on BP level, risk of hypertension (HTN), other cardiovascular diseases and on BP in non-European ancestries.

RESULTS

We present a total of 535 novel loci (**Fig.2, Supplementary Fig. 1**): 325 loci claimed from the two-stage design (**Supplementary Tables 2a-c**) and an additional 210 claimed from our one-stage design with internal replication (**Supplementary Tables 3a-c**). Of the 325 two-stage variants, 204 would also have met the one-stage criteria, while 121 were uniquely identified from our two-stage design (**Fig. 3a**). Thus using this dual approach, we were able to identify large numbers of additional loci that would not have been detected by either the one- or two-stage designs alone, as well as finding considerable overlap (**Fig. 3a**). For SBP, the distributions of effect sizes of the one-stage loci (median = 0.219 mmHg per allele; Inter-Quartile Range (IQR) = 0.202-0.278) and two-stage loci (median = 0.224; IQR = 0.195-0.267) are similar within the discovery data ($P = 0.447$) (**Supplementary Fig. 2**). Of the 210 loci found only in the one-stage analysis of UKB and ICBP, 186 are also genome-wide significant ($P < 5 \times 10^{-8}$) in the combined meta-analysis of all four discovery and replication resources, with all variants, except one, having concordant direction of effect between discovery and replication (**Supplementary Tables 3a-c**). Of the remaining 24 SNPs which are not genome-wide significant overall in the combined meta-analysis, 10 still have concordant direction of effect.

We confirm previous findings with support in our data for all 274 published BP loci (**Supplementary Fig. 1 & 2** and **Supplementary Table 4**) and >95% of the previously reported SNPs covered within our data are genome-wide significant. Only 6 available SNPs

did not reach Bonferroni-significance, likely because they were originally identified from non-European ancestries (e.g. rs6749447, rs10474346, rs11564022), or from a gene-age interaction analysis (rs16833934). In addition, we confirmed a further 92 loci that had previously been reported but not replicated (**Supplementary Table 5**)[9]. Overall, with 274 previously reported loci confirmed, 92 loci replicated for the first time, and 535 novel loci identified here, there are 901 BP-associated loci in total.

Discovery of novel genetic loci for blood pressure

Of the 535 independent novel loci, 363 SNPs were associated with only one trait; 160 with two traits and 12 with all three BP traits (**Fig. 3b**), reflecting the inter-correlations between BP traits despite their different physiology.

From the conditional analyses using GCTA we additionally identified 163 independent secondary signals with MAF ≥ 1%, which are associated with BP at genome-wide significance level **(Supplementary Table 6)**. Of these 163 secondary signals, 19 SNPs are in LD ($r^2 \geq 0.1$) with previously reported secondary signals, resulting in a total of 144 new secondary signals identified here. Hence in total there are now over 1,000 independent BP signals reported.

The estimated SNP-wide heritability (h^2) of BP traits in our data was 0.213, 0.212 and 0.194 for SBP, DBP and PP respectively, and there is a gain in the percentage of BP variance explained. For example, for SBP, the percentage variance explained increased from 2.8 % for the 274 previously published loci to 5.7% for all sentinel and secondary SNPs identified at all 901 loci **(Supplementary Table 7)**.

Functional analyses

Our functional analyses approach is summarised in **Supplementary Figure 3**. First, for each of the 901 loci we annotated all SNPs (based on LD $r^2 \geq 0.8$) to the nearest gene within 5kb of a SNP. There were 1644 genes in the novel loci and 962 genes in the known loci. Then we investigated these loci for tissue enrichment, DNase hypersensitivity site enrichment and pathway analyses**.** At 66 of the 535 novel loci we identified 97 non-synonymous SNPs, including 8 predicted to be damaging (**Supplementary Table 8**).

We used chromatin interaction Hi-C data from endothelial cells (HUVEC)[23], neural progenitor cells (NPC), mesenchymal stem cells (HVMSC) and tissue from the aorta (HAEC) and adrenal gland[24] to identify distal associated genes. There were 498 novel loci that contained a potential regulatory SNP and in 484 of these we identified long-range interactions in at least one of the tissues or cell types. We found several potential long-range target genes that do not overlap with the sentinel SNPs in the LD block. For example, the *TGFB2* gene forms a 1.2Mb long regulatory loop with the SNPs in the *SLC30A10* locus, and the *TGFBR1* promoter forms a 100kb loop with the *COL15A1* locus **(Supplementary Table 8)**.

Our eQTL analysis identified 60 novel loci with eQTLs in arterial tissue and 20 in adrenal tissue **(Supplementary Table 9);** this is a substantial increase over those identified in our previously published GWAS on ~140K UKB individuals[10]. An example is SNP rs31120122 which defines an aortic eQTL that affects expression of the *MED8* gene within the *SZT2*

locus. In combination with Hi-C interaction data in MSC this finding supports a role for *MED8* in BP regulation, possibly mediated through repression of smooth muscle cell differentiation. Hi-C interactions provide supportive evidence for involvement of a further 36 arterial eGenes (genes whose expression is affected by the eQTLs) that were distal to their eQTLs (e.g *PPHLN1, ERAP2, FLRT2, ACVR2A*, *POU4F1*).

We investigated which transcription factors and chromatin marks are involved in regulatory interactions using the functional predictions from DeepSEA. We found 198 SNPs in 121 novel loci with predicted effects on transcription factor binding or on chromatin marks in tissues relevant for BP biology, such as vascular tissue, smooth muscle and the kidney **(Supplementary Table 8)**.

We used our genome-wide data at a false discovery rate (FDR) < 1% to robustly assess the tissue enrichment of BP loci using DEPICT and identified enrichment across 50 tissues and cells (**Supplementary Fig 4**; **Supplementary Table 10a**). Enrichment was greatest for the cardiovascular system especially blood vessels ($P = 1.5 \times 10^{-11}$) and the heart ($P = 2.7 \times 10^{-5}$). Enrichment was high in adrenal tissue ($P = 3.7 \times 10^{-4}$) and, for the first time, we observed high enrichment in adipose tissues ($P = 9.8 \times 10^{-9}$) corroborated by eQTL enrichment analysis ($P < 0.05$) **(Supplementary Fig. 4; Supplementary Table 10a)**. Evaluation of enriched mouse knockout phenotype terms also points to the importance of vascular morphology ($P = 6 \times 10^{-15}$) and development ($P = 2.1 \times 10^{-18}$) in BP. Due to the addition of our novel BP loci, we identified new findings from both the gene ontology and protein-protein interaction subnetwork enrichments, which highlight the TGFβ ($P = 2.3 \times 10^{-13}$) and related SMAD pathways ($P = 7 \times 10^{-15}$) (**Supplementary Table 10b, Supplementary Fig. 5b-d**).

We used FORGE[25] to investigate the regulatory regions for cell type specificity from DNase I hypersensitivity sites, which showed strongest enrichment ($P < 0.001$) in the vasculature and highly vascularised tissues, as reported in previous BP genetic studies[10] **(Supplementary Fig. 6).**

Potential therapeutic targets

Ingenuity pathway analysis and upstream regulator assessment showed enrichment of canonical pathways implicated in cardiovascular disease including pathways targeted by antihypertensive drugs (e.g. nitric oxide signalling) and also suggested some potential new targets, such as relaxin signalling. Notably, upstream regulator analysis identified several known mediators of BP including therapeutic targets such as angiotensinogen, calcium channels, progesterone, natriuretic peptide receptor, angiotensin converting enzyme, angiotensin receptors and endothelin receptors **(Supplementary Fig. 7)**.

We developed a cumulative tally of functional evidence at each variant to assist in variant/gene prioritisation at each locus.

We present a summary of the vascular expressed genes contained within the 535 novel loci, including a review of their potential druggability **(Supplementary Fig. 8)**. The overlap between genes associated with BP and those associated with antihypertensive drug targets, further demonstrates new genetic support for known drug mechanisms. For example, we

report five novel BP associations with the targets of five antihypertensive drug classes **(Supplementary Table 11).** These include the *PKD2L1, SLC12A2, CACNA1C, CACNB4 and CA7* loci, which are targeted by potassium-sparing diuretics (amiloride), loop diuretics (bumetanide and furosemide), dihydropyridine, calcium channel blockers, non-dihydropyridines and thiazide-like diuretics (chlortalidone) respectively. Notably in all but the last case, functional variants in these genes are the best candidates in each locus.

Concordance of BP variants and lifestyle exposures

UK Biobank has collected extensive lifestyle related data, some of which are associated with BP epidemiologically and in trials. These include macronutrients, water, tea, caffeine and alcohol intake, anthropomorphic traits, physical activity and inactivity, smoking and urinary sodium, potassium and creatinine excretion[14]. We investigated whether sentinel SNPs at the 901 BP loci were associated with lifestyle traits in UKB in either the Stanford Global Biobank Engine (N = 327,302) or Gene ATLAS (N = 408,455), with corrected $P < 1 \times 10^{-6}$. For example, we found that a BP SNP rs34783010 in *GIPR* is associated with daily fruit intake ($P = 1.03 \times 10^{-7}$), urinary sodium and creatinine concentration ($P = 1.5 \times 10^{-13}$ and 1.2×10^{-9} respectively), body mass index (BMI, $P = 3.3 \times 10^{-41}$), weight ($P = 7.3 \times 10^{-35}$) and waist circumference ($P = 7.7 \times 10^{-30}$); rs6495122, near *CPLX3* and *ULK3*, and rs1378942 in *CSK* are associated with water ($P = 1.3 \times 10^{-22}$ and 2.6×10^{-20} respectively), caffeine ($P = 1.3 \times 10^{-46}$ and 2.2×10^{-43}) and tea intake ($P = 7.6 \times 10^{-38}$ and 8.1×10^{-33}), as well as urinary creatinine concentrations ($P = 5.6 \times 10^{-8}$ and $P = 3.2 \times 10^{-8}$ respectively). In addition, the BP SNP rs13107325 in *SLC39A8*, is a novel locus for frequency of drinking alcohol ($P = 3.5 \times 10^{-15}$) and time spent watching TV ($P = 2.3 \times 10^{-11}$) as well as being associated with BMI ($P = 1.6 \times 10^{-33}$), weight ($P = 8.8 \times 10^{-16)}$ and waist circumference ($P = 4.7 \times 10^{-11}$) **(Supplementary Table 12).** We used unsupervised hierarchical clustering for the 36 BP loci that showed at least one association with the lifestyle related traits in UKB at $P < 1 \times 10^{-6}$ (**Fig. 4).** The heatmap summarises the locus specific associations across the range of traits and highlights heterogeneous effects with anthropometric traits across the range of loci examined. For example, it shows a cluster of associations between BP raising alleles and increased adult height and weight and another cluster of genes that show associations between BP raising alleles and decreased adult height and weight. We note that some observed cross-trait associations are in counter-directions to what may be expected epidemiologically.

Association lookups with other traits and diseases

We further evaluated cross-trait and disease associations using GWAS catalog[26], PhenoScanner[27] and DIsGeNET, which integrates data from expert curated repositories, GWAS catalogues, animal models and the literature[28,29]. The GWAS catalog and PhenoScanner search of published GWAS showed that 77 of our 535 novel loci (using sentinel SNPs or proxies; $r^2 \geq 0.8$) are also significantly associated with other traits and diseases (**Fig. 5, Supplementary Table 13**). We identified *APOE* as a highly cross-related BP locus showing associations with lipid levels, cardiovascular related outcomes and Alzheimer's disease, a finding that highlights a common link between cardiovascular risk and

cognitive decline (**Fig. 5**). Several other loci overlap with anthropometric traits, including BMI, birth weight and height (**Fig 5)**. DisGeNET terms related to lipid measurements, cardiovascular outcomes and obesity overlap with BP loci **(Fig. 6)**.

We used ^{1}H NMR lipidomics data on plasma (N=2,022) and data from the Metabolon platform (N=1,941) for subsets of participants of the Airwave Health Monitoring Study[30] for lookups of our sentinel SNPs. We also used PhenoScanner to test each SNP against published significant ($P < 5 \times 10^{-8}$) genome vs metabolome-wide associations in plasma and urine (Online Methods). Ten BP SNPs show association with lipid particle metabolites and a further 31 SNPs (8 also on PhenoScanner) show association with metabolites on the Metabolon platform, highlighting lipid pathways, amino acids (glycine, serine, glutamine), tri-carboxylic acid cycle intermediates (succinylcarnitine) and drug metabolites (**Supplementary Tables 14 and 15**). These findings suggest a close metabolic coupling of BP regulation with lipid, and for the first time, with energy metabolism.

Genetic risk of increased blood pressure, hypertension and cardiovascular disease

We created a genetic risk score (GRS) for BP levels weighted according to the effect estimates from ICBP (for known loci) and the MVP+EGCUT replication (for novel loci) across all 901 loci (Online Methods). The combination of these BP variants was associated with a 10.39 mmHg higher, sex-adjusted mean SBP in UK Biobank for the comparison between the upper and lower quintiles of the GRS distribution (95% CI: 10.19 to 10.58 mm Hg, $P < 1 \times 10^{-300}$) and with 12.85 mmHg difference in SBP (95% CI: 12.57 to 13.13, $P < 1 \times 10^{-300}$) comparing the upper and lower deciles (**Fig. 7a, Supplementary Table 16**). In addition, we observed over two-fold sex-adjusted higher risk of hypertension (OR 2.66; 95% CI: 2.60 to 2.72; $P < 1 \times 10^{-300}$) between the upper and lower quintiles of the GRS in UK Biobank (**Fig. 7**). Sensitivity analyses in the independent Airwave cohort gave similar results (**Supplementary Table 17**).

From record linkage to Hospital Episode Statistics and mortality follow-up in UKB we show that the GRS is associated with increased, sex-adjusted risk of incident stroke, myocardial infarction and all incident cardiovascular outcomes, comparing the upper and lower deciles of the GRS distribution, with odds ratios of 1.47 (95% CI: 1.35 to 1.59, $P = 1.12 \times 10^{-20}$), 1.50 (95% CI: 1.28 to 1.76, $P = 7.99 \times 10^{-7}$) and 1.52 (95% CI: 1.26 to 1.82, $P = 7.4 \times 10^{-6}$) respectively (**Fig. 7b, Supplementary Table 16**).

Extending analyses to other ancestries

We examined associations with BP of both individual SNPs and the GRS among unrelated individuals of African and of South Asian ancestries in UKB, for the 901 known and novel loci. In comparison with the results for European ancestry, 62.4%, 62.5% and 64.8% of the variants among people of African (N=7,782), and 74.2%, 72.3% and 75% of South Asian (N=10,323) ancestry have concordant direction of effect for SBP, DBP and PP respectively **(Supplementary Table 18; Supplementary Fig. 9)**. Pearson correlation coefficients with effect estimates in Europeans were r^2= 0.37 and 0.78 for African and South Asian ancestries respectively **(Supplementary Fig. 10)**. We then applied the GRS derived from European ancestry findings to unrelated individuals of African (N=6,970) and South Asian (N=8,827)

ancestries. BP variants in combination were associated with 6.1 mmHg (95% CI: 4.50 to 7.65; $P = 4.9 \times 10^{-14}$) and 7.4 mmHg (95% CI: 6.00 to 8.69; $P = 1.7 \times 10^{-26}$) higher, sex-adjusted mean systolic pressure among individuals of African and South Asian ancestries, respectively, for the comparison between the upper and lower quintiles of the GRS distribution **(Supplementary Tables 19a and 19b)**.

DISCUSSION

Our study of over 1 million people offers an important step forward in understanding the genetic architecture of BP. We have identified over 1,000 independent signals at 901 loci for BP traits, and with 535 novel loci we have more than tripled the number of BP loci and doubled the percentage variance explained for BP. By now explaining 27% of the estimated heritability for BP, we make major inroads into the missing heritability influencing BP level in the population[31]. These findings illustrate the power of a large-scale standardised approach to data collection, biobanking, genotyping, quality control and imputation, such as was achieved in UKB. The novel loci open the vista of entirely new biology and highlight gene regions in systems not previously implicated in BP regulation. This is particularly timely as the global prevalence of people with SBP over 110-115 mm Hg, above which cardiovascular risk increases in a continuous graded manner, now exceeds 3.5 billion and those within the treatment range exceed 1 billion[32,33].

Our functional analysis highlights the role of the vasculature and associated pathways in the genetics underpinning BP traits. We show a role for several loci in the transforming growth factor beta (TGFβ) pathway including SMAD family genes and the *TGFβ* gene locus itself. This pathway affects sodium handling in the kidney, ventricular remodelling and recently plasma levels of TGFβ have been correlated with hypertension **(Fig. 8)**[34,35]. The activin A receptor type 1C (*ACVR1C*) gene mediates the effects of the TGFβ family of signalling molecules. Another BP locus contains the Bone Morphogenetic Protein 2 (*BMP2*) gene in the TGFβ pathway, which prevents growth suppression in pulmonary arterial smooth muscle cells and is associated with pulmonary hypertension[36]. We identified another BP locus including the Kruppel-like family 14 (*KLF14*) gene of transcription factors which are induced by low levels of TGFβ receptor II gene expression. This gene has also been associated with type 2 diabetes, hypercholesterolaemia and atherosclerosis[37].

Our analysis shows enrichment of BP genes in the adrenal tissue. The adrenal gland has a key role in BP regulation, with autonomous aldosterone production by the adrenal glands thought to be responsible for 5-10% of all hypertension, rising to ~20% amongst people with resistant hypertension[38]. Some of our novel loci are linked functionally to aldosterone secretion[39,40]. For example, the *CTNNB1* locus encodes β-catenin, the central molecule in the canonical Wnt signalling system, required for normal adrenocortical development[41,42]. Somatic adrenal mutations of this gene that prevent serine/threonine phosphorylation lead to hypertension through the generation of aldosterone-producing adenomas[43,44].

Our novel loci also include genes involved in vascular remodelling, such as vascular endothelial growth factor A (*VEGFA*), the gene product of which induces proliferation, migration of vascular endothelial cells and stimulates angiogenesis. Disruption of this gene in mice resulted in abnormal embryonic blood vessel formation, while allelic variants of this

gene have been associated with microvascular complications of diabetes, atherosclerosis and the antihypertensive response to enalapril[45]. We previously reported a fibroblast growth factor (*FGF5*) gene locus in association with BP. Here, we additionally identify a new BP locus encoding FGF9, which has been linked to enhanced angiogenesis and vascular smooth muscle cell differentiation by regulating *VEGFA* expression.

Several of our novel loci contain lipid related genes which supports the observed strong associations across multiple cardio-metabolic traits. For example, the apolipoprotein E gene (*APOE*) encodes the major apoprotein of the chylomicron. Recently, APOE serum levels have been correlated with systolic BP in population-based studies and in murine knockout models; disruption of this gene led to atherosclerosis and hypertension[46,47]. A second novel BP locus contains the low-density lipoprotein receptor-related protein 4 (*LRP4)* gene which may be a target for APOE and is strongly expressed in the heart in mice and humans. In addition, we identified a novel locus including the apolipoprotein L domain containing 1 gene (*APOLD1*) that is highly expressed in the endothelium of developing tissues (particularly heart) during angiogenesis.

Many of our novel BP loci encode proteins which may modulate vascular tone or signalling. For example, the locus containing urotensin-2 receptor (*UTS2R*) gene encodes a class A rhodopsin family G-protein coupled-receptor that upon activation by the neuropeptide urotensin II, produces profound vasoconstriction. One of the novel loci for SBP contains the relaxin gene which encodes a G-protein coupled receptor with roles in vasorelaxation and cardiac function, and which signals by phosphatidylinositol 3-kinase (PI3K)[48,49], an enzyme which inhibits vascular smooth muscle cell proliferation and neo-intimal formation[50]. We identify the *PI3K* gene here as a novel BP locus. We also identify the novel *RAMP2* locus which encodes an adrenomedullin receptor[51]; we previously identified the adrenomedullin (*ADM*) gene as a BP locus[12]. Adrenomedullin is known to exert differential effects on BP in the brain (vasopressor) and the vasculature (vasodilator). In addition, a locus containing Rho guanine nucleotide exchange factor 25 (*ARHGEF25*) gene generates a factor which interacts with Rho GTPases involved in contraction of vascular smooth muscle and regulation of responses to angiotensin II[52].

We evaluated the 901 BP loci for extant or potentially druggable targets. We note that loci encoding *MARK3*, *PDGFC*, *TRHR*, *ADORA1, GABRA2*, *VEGFA* and *PDE3A* are within systems that have existing drugs not currently linked to a known antihypertensive mechanism and may offer repurposing opportunities e.g. detection of *SLC5A1* as the strongest repurposing candidate in a new BP locus which is targeted by the type 2 diabetes drug canagliflozin. This is important as between 8-12% of patients with hypertension exhibit resistance or intolerance to current therapies and repositioning of a therapy with a known safety profile may reduce development costs.

Our findings with larger sample size, strengthen our previously reported genetic risk score analysis indicating that all BP elevating alleles combined could increase systolic BP by 10 mm Hg or more across quintiles or deciles of the population distribution, giving substantially increased risk of cardiovascular events (stroke and coronary disease)[10]. We previously

suggested that genotyping BP elevating variants in the young may lead to targeted lifestyle intervention in early life that might attenuate the BP rise at older ages[10].

We identified several BP-associated loci which are also associated with lifestyle traits, suggesting a possible shared genetic architecture between BP and lifestyle exposures known from randomised clinical trials and observational data to be associated with BP[53]. We adjusted our BP GWAS analyses for BMI, which should have reduced possible confounding effects, though we acknowledge the potential for collider bias between a lifestyle factor and BP[54]. Nonetheless, our findings of possible genetic overlap between loci associated with BP and lifestyle exposures could support renewed focus on altering specific lifestyle measures known to affect BP[55].

Despite smaller sample sizes in the single-variant analyses of non-European ancestry samples, we observed high concordance of the effects of BP variants in people of African (> 62%) and South Asian (> 72%) ancestry for all BP traits. Furthermore, the GRS analyses show that, in combination, BP variants identified in European analyses are also associated with BP in non-European ancestries, though size of the effect was 30-40% smaller. Nonetheless, new knowledge on the genetic architecture of BP in Europeans also extends, at least in part, to populations of other ancestries.

Our discovery of 535 novel loci from a combination of a two-stage GWAS with independent replication and one-stage GWAS design with internal replication illustrates the value of this approach to minimize the effects of stochastic variation and heterogeneity. The one-stage approach was included in order to report signals that had independent and concordant support ($P < 0.01$) from both UKB and ICBP (thus minimizing the impact of winners' curse on our reported findings). Indeed, all but two of the 210 SNPs discovered in the one-stage analysis reach $P < 5 \times 10^{-6}$ in either UKB or ICBP (the two exceptions have $P = 7.8 \times 10^{-6}$ in UKB, $P = 1.4 \times 10^{-5}$ in ICBP; and $P = 1.2 \times 10^{-5}$ in UKB, $P = 5.3 \times 10^{-6}$ in ICBP). To further minimize the risk of reporting false positive loci within our one-stage design, we set a stringent overall discovery meta-analysis *P*-value threshold of $P < 5 \times 10^{-9}$, an order of magnitude smaller than a genome-wide significance *P*-value, in line with thresholds recommended for whole genome sequencing[22]. We also found high concordance in the direction of effects between discovery data in the one-stage approach and the replication resources, with similar distributions of effect sizes for the one-stage vs two-stage discovery data. We note that 24 of the one-stage SNPs which reached $P < 5 \times 10^{-9}$ in discovery failed to reach genome-wide significance ($P < 5 \times 10^{-8}$) in the combined meta-analysis of discovery and replication resources and hence may still require further validation in future studies if larger replication resources became available.

The new discoveries reported here more than triple the number of loci for BP to a total of 901 and represent a substantial advance in understanding the genetic architecture of BP. By identifying so many novel genes across the genome, these findings could partly support an omnigenic model for complex traits where genome-wide association of multiple interconnected pathways is observed. However, as our strong tissue enrichment shows particular relevance to the biology of BP and cardiovascular disease[56], the genetic architecture of BP still shows trait-specificity, which could argue against an omnigenic

model. Our confirmation of the impact of these variants on BP level and cardiovascular events, coupled with identification of shared risk variants for BP and adverse lifestyle could contribute to an early life precision medicine strategy for cardiovascular disease prevention.

URLs

FORGE: http://browser.1000genomes.org/Homo_sapiens/UserData/Forge?db=core
Fantom5 data: http://fantom.gsc.riken.jp/5/
ENCODE DNase I data: (wgEncodeAwgDnaseMasterSites; accessed using Table browser)
ENCODE cell type data: http://genome.ucsc.edu/ENCODE/cellTypes.html.
GTEx: www.gtexportal.org
DeepSEA: http://deepsea.princeton.edu/
WebGetstalt: http://www.webgestalt.org
IPA: www.qiagen.com/ingenuity
Mouse Genome Informatics (MGI): http://www.informatics.jax.org/batch
Drug Gene Interaction database: www.dgidb.org
PhenoScanner: http://www.phenoscanner.medschl.cam.ac.uk (Phenoscanner integrates results from the GWAS catalogue: https://www.ebi.ac.uk/gwas/ and GRASP: https://grasp.nhlbi.nih.gov/)
DisGeNEt: http://www.disgenet.org
GeneATLAS: http//geneatlas.roslin.ed.ac.uk
Global Biobank Engine: https://biobankengine.stanford.edu

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All authors critically reviewed and approved the final version of the manuscript

Figure 1. Study design schematic for discovery and validation of loci. ICBP; International Consortium for Blood Pressure; N, sample size; QC, quality control; PCA, principal-component analysis; GWAS, Genome-wide Association Study; 1000G 1000 Genomes; HRC, Haplotype Reference Panel; BP: blood pressure; SNPs, single nucleotide polymorphisms; BMI, body mass index; LMM; linear mixed model; UKB, UK Biobank, MAF, minor allele frequency; HLA, Human Leukocyte Antigen; MVP, Million Veterans Program; EGCUT; Estonian Genome Center, University of Tartu; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure.

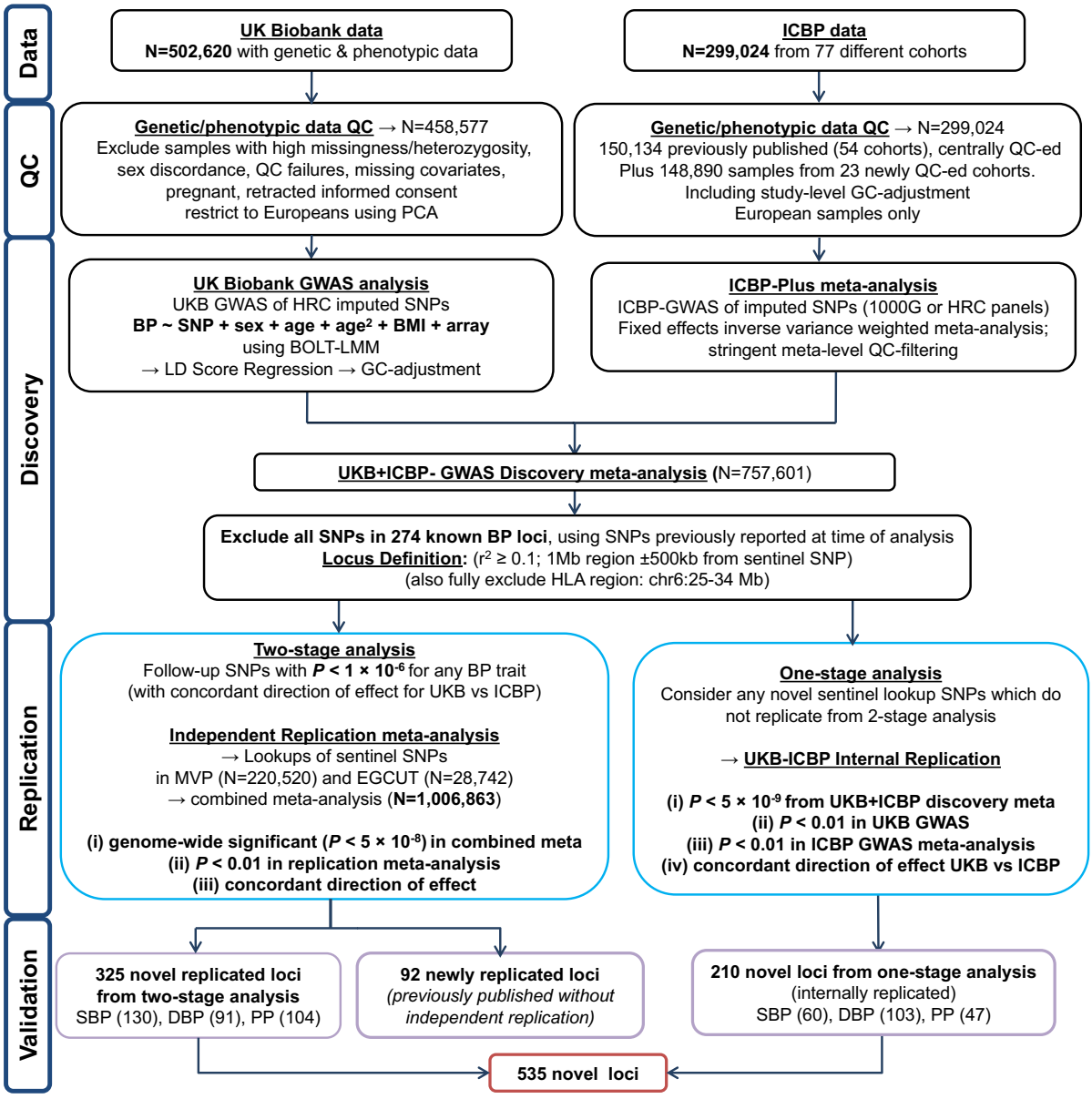


Figure 2. Manhattan plot showing the minimum *P*-value for the association across all blood pressure traits in the discovery stage excluding known and previously reported variants.
Manhattan plot of the discovery genome-wide association meta-analysis in 757,601 individuals excluding variants in 274 known loci. The minimum *P*-value across SBP, DBP and PP is presented. The y axis shows the $-\log_{10} P$ values and the x axis shows their chromosomal positions. Horizontal red and blue line represents the thresholds of $P = 5 \times 10^{-8}$ for genome-wide significance and $P = 1 \times 10^{-6}$ for selecting SNPs for replication, respectively. SNPs in blue are in LD ($r^2 > 0.8$) with the 325 novel variants independently replicated from the 2-stage design whereas SNPs in red are in LD ($r^2 > 0.8$) with 210 SNPs identified through the 1-stage design with internal replication. Any loci in black or grey that exceed the significance thresholds were significant in the discovery meta-analysis, but did not meet the criteria of replication in the one- or two-stage designs.

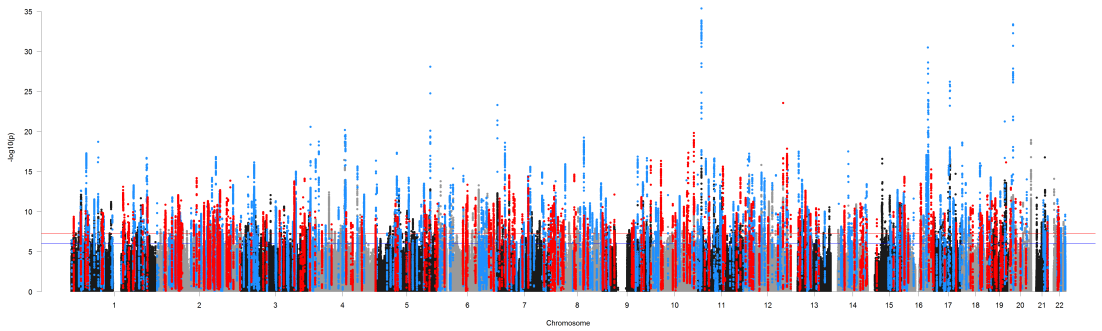


Figure 3: Venn Diagrams of Novel Loci Results (a) "Comparison of 1-stage and 2-stage design analysis criteria": For all 535 novel loci, we compare the results according to the association criteria used for the one-stage and the two-stage design. Two-hundred and ten loci exclusively met the one-stage analysis criteria (P <5x10^{-9} in the discovery meta-analysis, P < 0.01 in UKB, P < 0.01 in ICBP and concordant direction of effect between UKB and ICBP). Of the 325 novel replicated loci from the 2-stage analysis (genome-wide significance in the combined meta-analysis, P < 0.01 in the replication meta-analysis and concordant direction of effect), 204 loci would also have met the one-stage criteria, whereas 121 were only identified by the two-stage analysis. **(b) "Overlap of Associations across Blood Pressure Traits"**. For all 535 novel loci, we show the blood pressure traits associated with each locus. We present the two-stage loci first, followed by the one-stage loci. The locus names provided in alphabetical order correspond to the nearest annotated gene. SNPs: Single nucleotide polymorphisms; SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; UKB: UK Biobank; ICBP: International Consortium of Blood Pressure

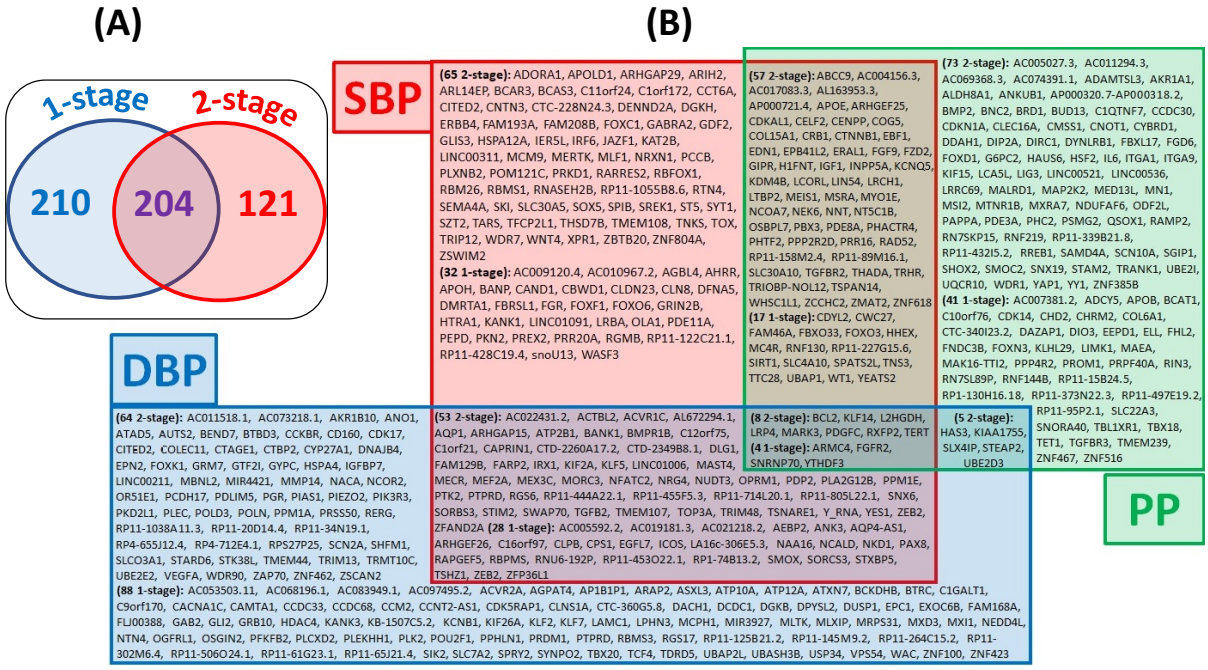


Figure 4. Association of blood pressure loci with lifestyle traits. Plot shows hierarchical clustering of BP loci based on associations with lifestyle-related factors. For the sentinel SNP at each BP locus (x axis), we calculated the -$\log_{10}(P)$*sign(β) (aligned to BP-raising allele) as retrieved from the Gene Atlas catalogue (http://geneatlas.roslin.ed.ac.uk). BP loci and traits were clustered according to the Euclidean distance amongst -$\log_{10}(P)$*sign(β). Red squares indicate direct associations with the trait of interest and blue squares inverse associations. Only SNPs with at least one association at $P < 10^{-6}$ with at least one of the traits examined are annotated in the heat-map. All 901 loci are considered, both known and novel: novel loci are printed in bold font. SNPs: Single Nucleotide Polymorphisms; BP: Blood Pressure.

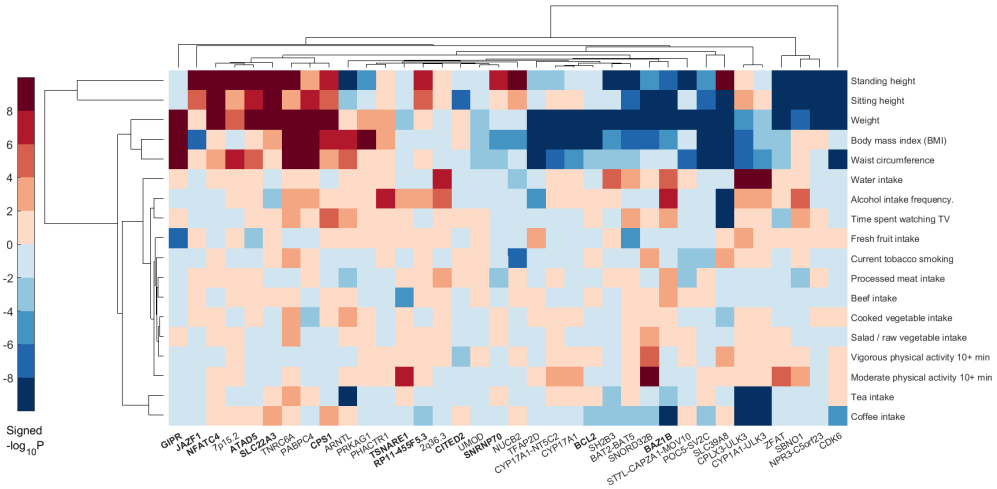
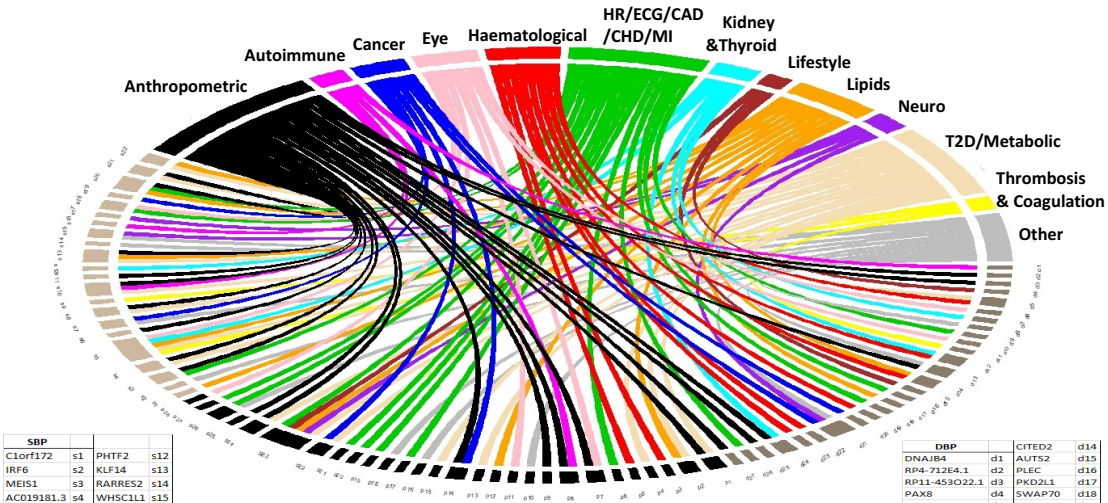


Figure 5. Association of blood pressure loci with other traits. Plot shows results from associations with other traits which were extracted from the GWAS catalog and PhenoScanner databases for the 535 novel sentinel SNPs including proxies in Linkage Disequilibrium ($r^2 \geq 0.8$) with genome-wide significant associations. SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; PP: Pulse Pressure; HR: Heart Rate; ECG: Electrocardiographic traits; CAD: Coronary Artery Disease CHD; Coronary Heart Disease MI; Myocardial Infraction; T2D: Type II Diabetes.



SBP			
C1orf172	s1	PHTF2	s12
IRF6	s2	KLF14	s13
MEIS1	s3	RARRES2	s14
AC019181.3	s4	WHSC1L1	s15
CPS1	s5	Y_RNA	s16
LCORL	s6	TSNARE1	s17
TERT	s7	HTRA1	s18
CDKAL1	s8	PPM1E	s19
STXBP5	s9	MC4R	s20
JAZF1	s10	BCL2	s21
POM121C	s11	PEPD	s22

PP									
SLC30A10	p1	FNDC3B	p7	NDUFAF6	p13	RP11-497E19.2	p19	BMP2	p25
APOB	p2	RN7SL89P	p8	COL15A1	p14	CNOT1	p20	KIAA1755	p26
AC007381.2	p3	FBXL17	p9	MTNR1B	p15	LIG3	p21	AP000320.7,AP000318.2	p27
G6PC2	p4	EBF1	p10	YAP1	p16	ELL	p22	TRIOBP,NOL12	p28
ZNF385B	p5	RREB1	p11	BCAT1	p17	APOE	p23		

DBP			
DNAJB4	d1	AUTS2	d15
RP4-712E4.1	d2	PLEC	d16
RP11-453O22.1	d3	PKD2L1	d17
PAX8	d4	SWAP70	d18
CCNT2-AS1	d5	FAM168A	d19
ZEB2	d6	POLD3	d20
ACVR2A	d7	GAB2	d21
HDAC4	d8	CACNA1C	d22
RP11-145M9.2	d9	NACA	d23
DUSP1	d10	MLXIP	d24
MXD3	d11	NCOR2	d25
VEGFA	d12	CTAGE1	d26
BCKDHB	d13	CDK5RAP1	d27
CITED2	d14		

Figure 6. **Association of blood pressure loci with other traits**. Plots (a) and (b) show overlap between variants associated to (a) traits and (b) diseases in the manually-curated version of the DisGeNET database, and all variants in LD r^2>0.8 with the known (red bars) SNPs from the 274 published loci, and all (green bars) BP variants from all 901 loci. Numbers on top of the bars denote the number of SNPs included in DisGeNET for the specific trait or disease. Traits/diseases with an overlap of at least 5 variants in LD with all markers are shown. The Y axis shows the percentage of variants associated with the diseases that is covered by the overlap. For the sake of clarity, the DisGeNET terms for blood pressure and hypertension are not displayed, whereas the following diseases have been combined: coronary artery disease (CAD), coronary heart disease (CHD) and myocardial infarction (MI); prostate and breast carcinoma; Crohn's and inflammatory bowel diseases.

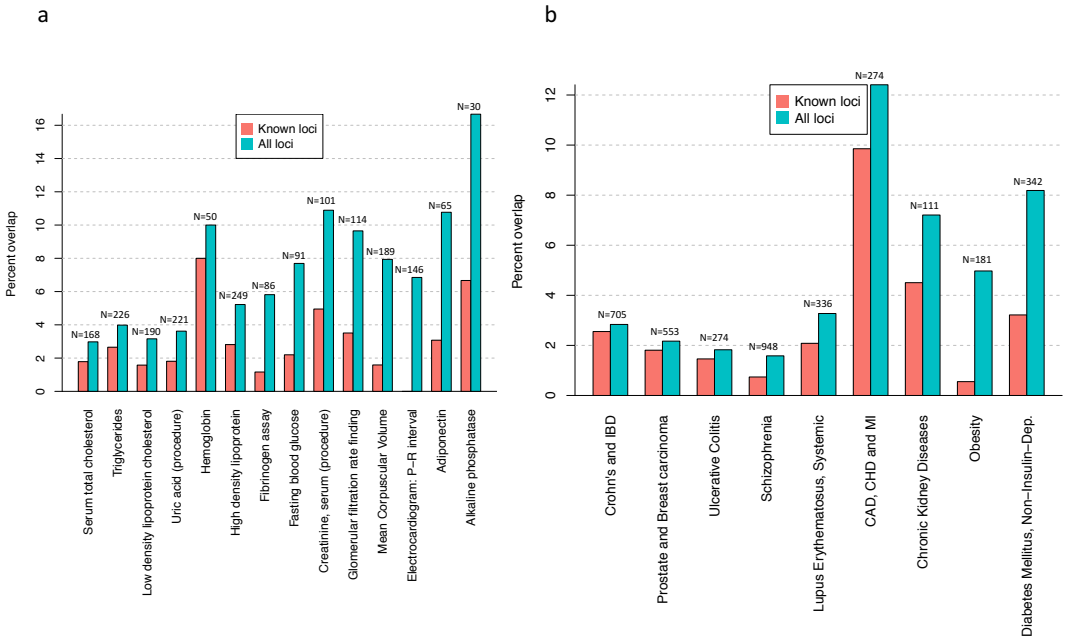


Figure 7. **Relationship of deciles of the genetic risk score (GRS) based on all 901 loci with blood pressure, risk of hypertension and cardiovascular disease in UK Biobank**. The plots show sex-adjusted (**a**) mean systolic blood pressure (SBP) and odds ratios of hypertension (HTN) and (**b**) odds ratios of incident cardiovascular disease (CVD), myocardial infarction (MI) and stroke, comparing each of the upper nine GRS deciles with the lowest decile; dotted lines represent the upper 95% confidence intervals.

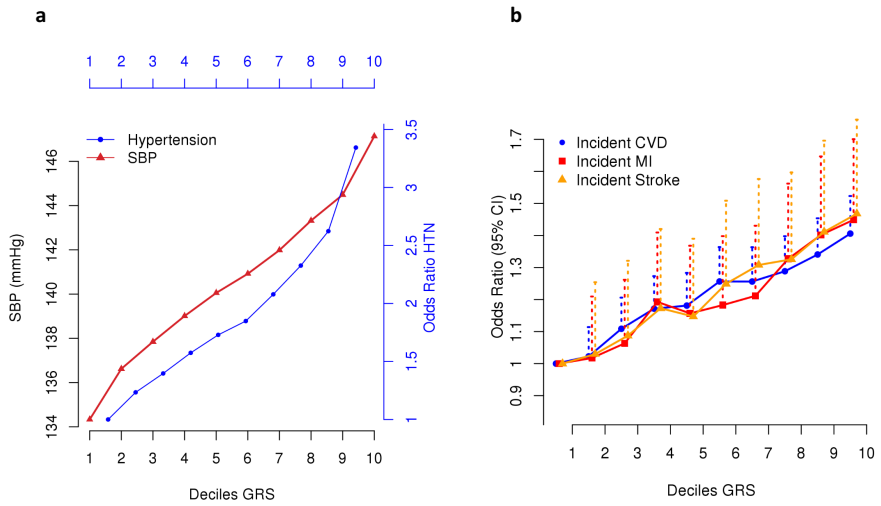
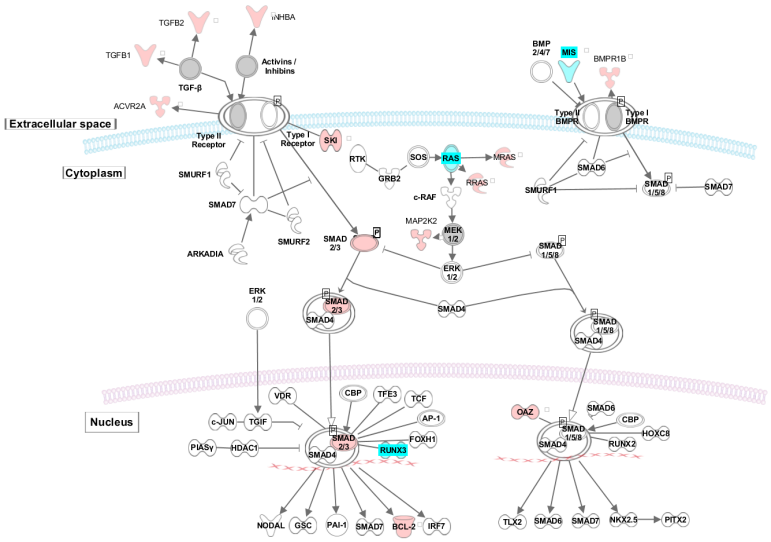


Figure 8: Known and novel BP associations in the TGFβ signalling pathway. Genes with known associations with BP are indicated in cyan. Genes with novel associations with BP reported in this study are indicated in red. TGFβ pathway was derived from an ingenuity canonical pathway. BP: Blood Pressure.



ONLINE METHODS

UK Biobank (UKB) data

We performed a Genome Wide Association Study (GWAS) analysis in 458,577 UKB participants[13] (**Supplementary Methods**). These consist of 408,951 individuals from UKB genotyped at 825,927 variants with a custom Affymetrix UK Biobank Axiom Array chip and 49,626 individuals genotyped at 807,411 variants with a custom Affymetrix UK BiLEVE Axiom Array chip from the UK BiLEVE study[57], which is a subset of UKB. SNPs were imputed centrally by UKB using a reference panel that merged the UK10K and 1000 Genomes Phase 3 panel as well as the Haplotype Reference Consortium (HRC) panel[58]. For current analysis only SNPs imputed from the HRC panel were considered.

UKB phenotypic data

Following Quality Control (QC) **(Supplementary Methods)**, we restricted our data to a subset of post-QC individuals of European ancestry combining information from self-reported and genetic data **(Supplementary Methods)** resulting in a maximum of N=458,577 individuals **(Fig. 1, Supplementary Fig. 11)**.

Three BP traits were analysed: systolic (SBP), diastolic (DBP) and pulse pressure (PP) (difference between SBP and DBP). We calculated the mean SBP and DBP values from two automated (N=418,755) or two manual (N=25,888) BP measurements. For individuals with

one manual and one automated BP measurement (N=13,521), we used the mean of these two values. For individuals with only one available BP measurement (N=413), we used this single value. After calculating BP values, we adjusted for medication use by adding 15 and 10 mmHg to SBP and DBP, respectively, for individuals reported to be taking BP-lowering medication (94,289 individuals)[59]. Descriptive summary statistics are shown in **Supplementary Table 1a.**

UKB analysis models

For the UKB GWAS we performed linear mixed model (LMM) association testing under an additive genetic model of the three (untransformed) continuous, medication-adjusted BP traits (SBP, DBP, PP) for all measured and imputed genetic variants in dosage format using the BOLT-LMM (v2.3) software[17]. We also calculated the estimated SNP-wide heritability (h^2) in our data. We used genotyped SNPs filtered for MAF > 5%; HWE $P > 1 \times 10^{-6}$; missingness < 0.015, to estimate the parameters of the linear mixed model, for the initial modelling step only. Within the association analysis, we adjust for the following covariates: sex, age, age^2, BMI and a binary indicator variable for UKB vs UK BiLEVE to account for the different genotyping chips. The association analysis performed by BOLT-LMM (v2.3) corrects for population structure and cryptic relatedness in very large datasets[17]. The genome-wide association analysis of all HRC-imputed SNPs was restricted to variants with MAF ≥ 1% and INFO > 0.1.

Genomic inflation and confounding

We applied the univariate LD score regression method (LDSR)[18] to test for genomic inflation (expected for polygenic traits like BP, with large sample sizes, and especially also from analyses of such dense genetic data with many SNPs in high LD)[60]. LDSR intercepts (and standard errors) were 1.217 (0.018), 1.219 (0.020) and 1.185 (0.017) for SBP, DBP and PP respectively, and were used to adjust the UKB GWAS results for genomic inflation, prior to the meta-analysis**.**

International Consortium for Blood Pressure (ICBP) GWAS

ICBP GWAS is an international consortium to investigate BP genetics[6]. We combined previously reported post-QC GWAS data from 54 studies (N=150,134)[11,12,61], with newly available GWAS data from a further 23 independent studies (N=148,890) using a fixed effects inverse variance weighted meta-analysis. The 23 studies providing new data were: ASCOT-SC, ASCOT-UK, BRIGHT, Dijon 3C, EPIC-CVD, GAPP, HCS, GS:SFHS, Lifelines, JUPITER, PREVEND, TWINSUK, GWAS-Fenland, InterAct-GWAS, OMICS-EPIC, OMICS-Fenland, UKHLS, GoDARTS-Illumina and GoDarts-Affymetrix, NEO, MDC, SardiNIA, METSIM.

All study participants were of European ancestry and were imputed to either the 1000 Genomes Project Phase 1 integrated release v.3 [March 2012] all ancestry reference panel[62] or the Haplotype Reference Consortium (HRC) panel[16]. The final enlarged ICBP GWAS dataset included 77 cohorts (N=299,024 individuals).

Definition of phenotype data and GWAS analyses of SBP, DBP and PP were as per previous ICBP protocol for 54 studies[11], extended to the additional 23 studies for which new data were available. Full study names, cohort information and general study methods are included in **Supplementary Table 1b** and in **Supplementary Tables 20a-c**. Genomic control was applied at study-level. The LDSR intercepts (standard error) for the ICBP GWAS meta-analysis were 1.089 (0.012), 1.086 (0.012) and 1.066 (0.011) for SBP, DBP and PP, respectively.

Meta-analyses of discovery datasets

We performed a fixed-effects inverse variance weighted meta-analysis using METAL[20,63] to obtain summary results from the combined UKB and ICBP GWAS, for up to N=757,601 participants and ~7.1 M SNPs with MAF ≥ 1% for variants present in both the HRC-imputed UKB data and ICBP meta-analysis for all three traits. The LDSR intercepts (standard error), in the discovery meta-analysis of UKB and ICBP were 1.156 (0.020), 1.160 (0.021) and 1.113 (0.018) for SBP, DBP and PP respectively. The LDSR intercept (standard error), after the exclusion of all published BP variants (see below) in the discovery meta-analysis of UKB and ICBP was 1.090 (0.018), 1.097 (0.017) and 1.064 (0.015) for SBP, DBP and PP respectively, hence showing little inflation in the discovery GWAS after the exclusion of published loci **(Supplementary Fig. 12).** No further correction was applied to the discovery meta-analysis of UKB and ICBP GWAS.

Previously reported variants

We compiled from the peer-reviewed literature all 357 SNPs previously reported to be associated with BP at the time that our analysis was completed, that have been identified and validated as the sentinel SNP in primary analyses from previous BP genetic association studies. These 357 published SNPs correspond to 274 distinct loci, according to locus definition of: (i) SNPs within ±500kb distance of each other; (ii) SNPs in Linkage Disequilibrium (LD), using a threshold of $r^2 \geq 0.1$, calculated with PLINK (v2.0). We then augment this list to all SNPs present within our data, which are contained within these 274 published BP loci, i.e. all SNPs which are located ±500kb from each of the 357 published SNPs and/or in LD with any of the 357 previously validated SNPs ($r^2 \geq 0.1$).

Identification of novel signals: Two-stage and one-stage study designs

To identify novel signals of association with BP, two complementary study designs (which we term here “two-stage design” and “one-stage design”) were implemented in order to maximize the available data and minimize reporting of false positive associations.

Two-stage design: Overview:

All of the following criteria had to be satisfied for a signal to be reported as a novel signal of association with BP using our two-stage design:

(i) the sentinel SNP shows significance ($P < 1 \times 10^{-6}$) in the discovery meta-analysis of UKB and ICBP, with concordant direction of effect between UKB and ICBP;

(ii) the sentinel SNP is genome-wide significant ($P < 5 \times 10^{-8}$) in the combined meta-analysis of discovery and replication (MVP and EGCUT) (replication, described below);

(iii) the sentinel SNP shows support ($P < 0.01$) in the replication meta-analysis of MVP and EGCUT alone **(Supplementary Methods)**;

(iv) the sentinel SNP has concordant direction of effect between the discovery and the replication meta-analyses;

(v) the sentinel SNP must not be located within any of the 274 previously reported loci described above.

The primary replicated trait was then defined as the BP trait with the most significant association from the combined meta-analysis of discovery and replication (in the case where a SNP was replicated for more than one BP trait.)

Two-stage design: Selection of variants from the discovery meta-analysis

We considered for follow-up SNPs in loci non-overlapping with previously reported loci according to both an LD threshold at r^2 of 0.1 and a 1Mb interval region, as calculated by PLINK[64]. We obtained a list of such SNPs with $P < 1 \times 10^{-6}$ for any of the three BP traits, which also had concordant direction of effect between UKB vs ICBP. By ranking the SNPs by significance in order of minimum P-value across all BP traits, we performed an iterative algorithm to determine the number of novel signals **(Supplementary Methods),** and identify the sentinel SNP (most significant) per locus.

Two-stage design: Replication analysis

We used two independent external data sets for replication **(Supplementary Methods)**. We considered SNPs with MAF ≥ 1% for an independent replication in MVP (max N = 220,520)[14] and in EGCUT Biobank (N=28,742)[15]. This provides a total of N = 249,262 independent samples of European descent available for replication. Additional information on the analyses of the two replication datasets is provided in **Supplementary Methods** and in **Supplementary Table 1c**.

The two datasets were then combined using fixed effects inverse variance weighted meta-analysis and summary results for all traits were obtained for the replication meta-analysis dataset.

Two-stage design: Combined meta-analysis of discovery and replication meta-analyses

The meta-analyses were performed within METAL software[63] using fixed effects inverse variance weighted meta-analysis **(Supplementary Methods)**. The combined meta-analysis of both the discovery data (N = 757,601) and replication meta-analysis (max N = 249,262) provided a maximum sample size of N = 1,006,863.

One-stage design: Overview

Variants that were looked-up but did not replicate according to the two-stage criteria were considered in a one-stage design. All of the following criteria had to be satisfied for a signal to be reported as a novel signal of association with BP using our one-stage criteria:

i) the sentinel SNP has $P < 5 \times 10^{-9}$ in the discovery (UKB+ICBP) meta-analysis;
ii) the sentinel SNP shows support ($P < 0.01$) in the UKB GWAS alone;
iii) the sentinel SNP shows support ($P < 0.01$) in the ICBP GWAS alone;
iv) the sentinel SNP has concordant direction of effect between UKB and ICBP datasets;
v) The sentinel SNP must not be located within any of the 274 previously reported loci described above or the recently reported non-replicated loci from Hoffman et al.[9] **(Supplementary Table 21)**.

We selected the one-stage *P*-value threshold to be an order of magnitude more stringent than a genome-wide significance *P*-value, so as to ensure robust results and to minimize false positive findings. The threshold of $P < 5 \times 10^{-9}$ has been proposed as a more conservative statistical significance threshold, e.g. for whole-genome sequencing-based studies[21] and it was more stringent than the suggested p-value (1×10^{-8}) we obtained from our own calculations for the number of independent SNPs tested in the data.

Selection of variants from the meta-analysis of UKB and ICBP was performed as described above for the two-stage design.

Conditional Analysis

We also performed conditional analyses using the GWAS discovery meta-analysis data, in order to identify any independent secondary signals in addition to the sentinel SNPs at the 901 loci. We used two different methodological approaches, each using the Genome-wide Complex Traits Analysis (GCTA) software[22]: (i) full "genome-wide conditional analysis" with joint multivariate analysis and stepwise model selection across all three BP traits; and (ii) "locus-specific conditional analysis" for the primary BP trait conditioning on the sentinel SNPs within each locus (**Supplementary Methods**). For robustness, secondary signals are only reported if obtained from both approaches. All secondary signals were selected at genome-wide significance level, with MAF ≥ 1% and confirmed to be pairwise-LD-independent ($r^2 < 0.1$), as well as not being in LD with any of the published or sentinel SNPs at any of the 901 BP-associated loci ($r^2 < 0.1$). In all cases the UKB data was used as the reference genetic data for LD calculation, restricted to individuals of European ancestry only.

Functional analyses: Variants

We used an integrative bioinformatics approach to collate functional annotation at both the variant level (for each sentinel SNP within all BP loci) and the gene level (using SNPs in LD $r^2 \geq 0.8$ with the sentinel SNPs). At the variant level, we use Variant Effect Predictor (VEP) to obtain comprehensive characterization of variants, including consequence (e.g. downstream

or non-coding transcript exon), information on nearest genomic features and, where applicable, amino acid substitution functional impact, based on SIFT and PolyPhen. The biomaRt R package is used to further annotate the nearest genes.

We evaluate all SNPs in LD ($r^2 \geq 0.8$) with our novel sentinel SNPs for evidence of mediation of expression quantitative trait loci (eQTL) in all 44 tissues using the Genotype-Tissue Expression (GTEx) database, to highlight specific tissue types which show eQTLs for a larger than expected proportion of novel loci. We further seek to identify novel loci with the strongest evidence of eQTL associations in arterial tissue, in particular. A locus is annotated with a given eGene only if the most significant eQTL SNP for the given eGene is in high LD ($r^2 \geq 0.8$) with the sentinel SNP, suggesting that the eQTL signal co-localises with the sentinel SNP.

We annotated nearest genes, eGenes (genes whose expression is affected by eQTLs) and Hi-C interactors with HUVEC, HVMSC and HAEC expression from the Fantom5 project. Genes that had higher then median expression levels in the given cell types were indicated as expressed.

To identify SNPs in the novel loci that have a non-coding functional effect (influence binding of transcription factors or RNA polymerase, or influence DNase hypersensitivity sites or histone modifications), we used DeepSEA, a deep learning algorithm, that learnt the binding and modification patterns of ~900 cell/factor combinations[65]. A change of >0.1 in the binding score predicted by DeepSEA for the reference and alternative alleles respectively has been shown to have high true positive rate ~80-95% and low false positive rate ~5-10%, therefore we used this cut-off to find alleles with non-coding functional effect.

We identify potential target genes of regulatory SNPs using long-range chromatin interaction (Hi-C) data from HUVECs[23], aorta, adrenal glands, neural progenitor and mesenchymal stem cell, which are tissues and cell types that are considered relevant for regulating BP[24]. Hi-C data are corrected for genomic biases and distance using the Hi-C Pro and Fit-Hi-C pipelines according to Schmitt et al. (40kb resolution – correction applied to interactions with 50kb-5Mb span)[24]. We find the most significant promoter interactions for all potential regulatory SNPs (RegulomeDB score ≤ 5) in LD ($r^2 \geq 0.8$) with our novel sentinel SNPs and published SNPs, and choose the interactors with the SNPs of highest regulatory potential to annotate the loci.

We then perform overall enrichment testing across all loci. Firstly, we use DEPICT[66] (Data-driven Expression Prioritized Integration for Complex Traits) to identify tissues and cells which are highly expressed at genes within the BP loci. DEPICT uses a large number of microarrays (~78K) to identify cells and tissues where the genes are highly expressed and uses pre-computed GWAS phenotypes to adjust for cofounding sources. Secondly, we use DEPICT to test for enrichment in gene sets associated with biological annotations (manually curated and molecular pathways, phenotype data from mouse KO studies). Using the co-expression data DEPICT calculates a probability for each gene to belong to a given gene set

and uses this to weight the enrichment of the genes present in the tested loci. DEPICT provides a *P*-value of enrichment and false discovery rates adjusted *P*-values for each tissue/cells or gene set tested. We report significant enrichments with a false discovery rate <0.01. The variants tested were i) the 357 published BP associated SNPs at the time of analysis and ii) a set including all (published and novel) variants (with novel SNPs filtered by highest significance, $P < 1 \times 10^{-12}$).

Furthermore, to investigate cell type specific enrichment within DNase I sites, we used FORGE, which tests for enrichment of SNPs within DNase I sites in 123 cell types from the Epigenomics Roadmap Project and ENCODE[25] **(Supplementary Methods)**. Two analyses were compared (i) using published SNPs only; (ii) using sentinel SNPs at all 901 loci, in order to evaluate the overall tissue specific enrichment of BP associated variants.

Functional analyses: Genes

At the gene level, we use Ingenuity Pathway Analysis (IPA) software (IPA®, QIAGEN Redwood City) to review genes with prior links to BP, based on annotation with the "Disorder of Blood Pressure", "Endothelial Development" and "Vascular Disease" Medline Subject Heading (MESH) terms. We used the Mouse Genome Informatics (MGI) tool to identify BP and cardiovascular relevant mouse knockout phenotypes for all genes linked to BP in our study. We also used IPA to identify genes that interact with known targets of anti-hypertensive drugs. Genes were also evaluated for evidence of small molecule druggability or known drugs based on queries of the Drug Gene Interaction database.

Lookups in non-European ancestries

As a secondary analysis, we look up all known and novel BP-associated SNPs in African (7,782) and South Asian (10,322) ancestry samples of UKB. An equivalent GWAS-LMM analysis was performed using BOLT-LMM for each BP trait within each ancestry **(Supplementary Methods).**

Effects on other traits and diseases

We query SNPs against GWAS catalog[26] and PhenoScanner[27], including genetics and metabolomics databases, to investigate cross-trait effects, extracting all association results with genome-wide significance at $P < 5 \times 10^{-8}$ for all SNPs in high LD ($r^2 \geq 0.8$) with the 535 sentinel novel SNPs, to highlight the loci with strongest evidence of association with other traits. We further evaluated these effects using DisGeNET, a resource that integrates data from expert curated repositories, GWAS catalogues, animal models and the literature[28,29]. Specifically, at the SNP level, overlaps with DisGeNET terms were computed, with roughly the same number of markers in the published and novel BP loci. Thus, given the expected saturation of the overlaps, a more than double increase indicates that strong associations are more frequent for the novel BP loci. At the gene level, overrepresentation enrichment analysis (ORA) with WebGestalt[67] on the nearest genes to all BP loci was carried out. Moreover, we tested sentinel SNPs at all published and novel (N=901) loci for association

with lifestyle related data including food, water and alcohol intake, anthropomorphic traits and urinary sodium, potassium and creatinine excretion using the recently developed Stanford Global Biobank Engine and the Gene ATLAS[68]. Both are search engines for GWAS findings for multiple phenotypes in UK Biobank. We used a Bonferroni corrected significance threshold of $P < 1 \times 10^{-6}$ to deem significance.

Genetic risk scores and percentage of variance explained

We calculated a genetic risk score (GRS) to provide an estimate of the combined effect of the BP raising variants on BP and risk of hypertension, and applied this to the UKB data. We first create two trait-specific weighted GRSs (i.e. SBP, DBP), for all pairwise-independent, LD-filtered ($r^2 < 0.1$) previously reported variants and 535 novel sentinel variants combined**.** For the previously reported variants, we weight BP increasing alleles by the trait-specific beta coefficients from the new ICBP meta-analysis GWAS that is part of the discovery stage (to minimize winner's curse bias compared to using UKB where the majority of discovery of published SNPs has been derived). For the novel variants, beta coefficients of the replication meta-analysis for each BP trait are used as independent, unbiased weights. We then derive a single BP GRS as the average of the GRS for SBP and DBP, and standardize it to have mean zero and standard deviation of one. GRS were calculated for 487,409 individuals. For statistical analysis of GRS, we focused on unrelated individuals only. The UKB database included 502,638 individuals. We removed pregnant women (n=372) and withdrawn individuals (n=19). We merged GRS and phenotype data (n_{merged}=487,048) and excluded individuals with first or second degree related individuals. The final database for analysis included 423,713 unrelated individuals of European ancestry of whom 392,092 individuals were free of cardiovascular events at baseline.

We assess the association of the continuous GRS variable on BP by simple linear regression, and use logistic regression to examine the association of the GRS with risk of hypertension, with and without adjustment for sex. We then use linear and logistic regression to compare BP levels and risk of hypertension, respectively, for individuals in the top vs bottom quintiles of the GRS distribution. Similar analyses were performed for the top vs bottom deciles of the GRS distribution. All analyses were restricted to the 392,092 unrelated individuals of European ancestry from UKB. As a sensitivity analysis to assess for evidence of bias in the UKB results, we also carried out similar analyses in Airwave, an independent cohort of N=14,004 unrelated participants of European descent[30] **(Supplementary Methods).**

We also assessed the association of the GRS with cardiovascular disease in unrelated participants in UKB data, based on self-reported medical history, and linkage to hospitalization and mortality data. We use logistic regression with binary outcome variables for composite incident cardiovascular disease **(Supplementary Methods)**, incident myocardial infarction and incident stroke (using the algorithmic UKB definitions) and GRS as explanatory variable (with and without sex adjustment).

We also calculated the association of this GRS with BP in unrelated individuals of African (N=6,970) and South Asian (N=8,827) ancestry from the UKB using the approach described above, to see whether BP-associated SNPs identified from GWAS predominantly in Europeans are also associated with BP in populations of non-European ancestry.

We calculated the percentage of variance in BP explained by genetic variants using the independent Airwave cohort (N=14,004). We generated the residuals from a regression of each trait against age, age^2, sex and BMI. We then fit a second linear model for the trait residuals with the GRS plus the top 10 principal components, and estimated the percentage variance of the dependent (BP) variable explained by the GRS. We considered three different levels of the GRS: (i) all pairwise-independent, LD-filtered ($r^2 < 0.1$) published SNPs within the known loci; (ii) all known SNPs and sentinel SNPs at novel loci; (iii) all independent signals at all 901 known and novel loci including the 163 secondary SNPs.

Data availability statement

The genetic and phenotypic UKB data are available upon application to the UK Biobank (https://www.ukbiobank.ac.uk). All replication data generated during this study are included in the published article. For example, association results of look-up variants from our replication analyses and the subsequent combined meta-analyses are contained within the Supplementary Tables provided.

Ethics Statement

The UKB study has approval from the North West Multi-Centre Research Ethics Committee. Any participants from UKB who withdrew consent have been removed from our analysis. Each cohort within the ICBP meta-analysis as well as our independent replication cohorts of MVP and EGCUT had ethical approval locally. More information on the participating cohorts is available in **Supplementary Methods**.

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