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

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show the correlation between published and observed effect sizes. Plots (B), (C) and (D) are trait-specific plots for SBP, DBP and PP, respectively (SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure). Across all plots, the 284 "known" SNPs (black squared) from plot (A) are compared against the 325 novel sentinel SNPs from the 2-stage analysis (red circles), the 210 novel sentinel SNPs from the 1-stage analysis (green triangles), and the 92 SNPs (blue diamonds) replicated for the first time from Hoffman et al[9]. Each SNP is only plotted in one of the trait-specific plots, according to the published primary trait for the known SNPs, or the primary trait for the novel / replicated SNPs. For all SNPs we show the relationship between Minor Allele Frequency (MAF) on the x-axis and the effect size (mmHg) on the y-axis, where results are taken from the UKB+ICBP discovery meta-analysis. All meta-analysis results were computed using inverse variance fixed effects models. The different symbols and colours distinguish the "known" vs "novel-2stage" vs "novel-1stage" vs "replicated-Hoffman" SNPs, and show that in general, the novel SNPs have smaller effect sizes than known SNPs, and that there is no significant difference (P=0.447) between the effect sizes of the 1-stage (N=757,601) and 2-stage (N=1,006,863) novel SNPs. (UKB: UK Biobank; ICBP: International Consortium of Blood Pressure).

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**Supplementary Figure 4: Overview of functional annotation and prioritisation of genome-wide associated variants and genes**. SNPs: single nucleotide polymorphisms; LD: Linkage Disequilibrium; eQTL: expression Quantitative Trait Loci; UCSC: University of California Santa Cruz (UCSC) genome browser; IPA: Ingenuity Pathway Analysis (IPA) software (IPA®,QIAGEN Redwood City,www.qiagen.com/ingenuity); DEPICT: Data-driven Expression Prioritized Integration for Complex Traits; GREAT: Genomic Regions Enrichment of Annotations Tool.

**Supplementary figure 5: DEPICT enrichment analysis.** DEPICT software was used to investigate enrichment of a range of biological properties, in each case we compared known sentinel SNPS (N=357) to all known and novel SNPs with P-value $<1x10^{-12}$ (N=227). The gene set enrichment analysis algorithm is described in Pers et al[66]. Enrichment –log p value is reported for both groups, we also present delta –log p value as a measure of novelty introduced by novel associations reported. Enrichment categories are as follows. a) Enrichment of tissues and cell types. b) GO annotation. c) Protein-protein interaction subnetwork annotation. d) Mammalian phenotype annotation.

**Supplementary Fig 6: Enrichments of eQTLs**. 535 novel blood pressure associated SNPs and the SNPs in LD $r^2$>0.8 were annotated for their effect on gene expression using the GTEx portal. The number of eGenes associated with BP SNPs in a given tissue/ cell type was normalised with the total number of eGenes in that tissue and z-score was calculated using the trimmed mean and standard deviation of the normalised scores. Tissues of the same tissue group were coloured the same.

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**Supplementary Figure 8**: **Ingenuity pathway analysis of BP genes.** For genes mapped to 357 sentinel SNPs at 274 known loci and genes mapped to all 901 loci. Sentinel gene mapping is compared to genes identified by extended LD ($r^2$>0.8). Pathway enrichment is represented as – log p value. A) Canonical pathway enrichment. B) Upstream regulator enrichment. C) Disease and Biofunction enrichment.

**Supplementary Figure 9: Exploring known and novel drug mechanisms in blood pressure.** The figure summarises known and novel target opportunities highlighted by blood pressure genetics. Ingenuity pathway analysis was used to create a network of 6,562 genes showing direct interaction with 145 known blood pressure target genes. This network was compared with all genes that are either directly associated with BP or linked by LD ($r^2$>0.8). Overlap between genetic associated genes and the BP drug interactome demonstrates genetic support for known drug mechanisms. Drugged or druggable genes showing genetic association with BP, but no interaction with the known BP drug interactome, represent potentially new mechanisms in blood pressure drug development and repositioning. Number of known and novel drugged/druggable gene associations are shown in parentheses.

**Supplementary figure 10: Comparison of beta effect sizes between individuals of European (N=757,601), African (N=7,782) and South Asian (N=10,323) ancestry.**

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**Supplementary Figure 11**: **Correlation and distribution of minor allele frequencies (MAF) of BP variants in individuals of European (N=757,601), African (N=7,782) and South Asian (N=10,323) ancestry.** Scatterplot showing the correlation and the distribution of MAF of novel (red) and known (grey) BP variants between a) Europeans and Africans and b) Europeans and South Asians. ρ is the Pearson correlation coefficient.

**Supplementary Figure 12: Ethnicity clustering performed using PCA.** PC1 is plotted against PC2 for all N=486,683 UK Biobank participants post-QC, colour-coded according to the five ethnic clusters created from our K-means PCA clustering, from which only "White" Caucasians are selected for analysis of individuals of European ancestry. Plot (A) shows the clustering for all subjects, whereas plot (B) only shows the subsets of individuals selected for race-stratified analysis, after combining information together from both the PCA clustering and the self-reported ethnicity. PCA: Principal Component Analysis; QC: Quality Control; PCs: Principal Components.

**Supplementary Figure 13: Quantile-Quantile plots.** QQ plots of results for (A) systolic blood pressure (SBP), (B) diastolic blood pressure (DBP), (C) pulse pressure (PP) from GWAS discovery (N=757,601). The black curves are based on all SNPs in the corresponding analysis, with Minor Allele Frequency ≥ 1%. The green curves are results after excluding SNPs within the 274 known loci (±500kb; Linkage Disequilibrium $r^2 \geq 0.1$). The *P*-values have been derived from inverse variance fixed effects meta-analysis.

## Supplementary Methods

### 1. UK Biobank data

The UK Biobank cohort includes ~500,000 volunteers aged 40-69 years of age ascertained through NHS registers[1]. Following informed consent participants completed a standardised questionnaire on life course exposures, medical history and treatments and underwent a standardised portfolio of phenotypic tests including two blood pressure (BP) measurements taken seated after two minutes rest using an appropriate cuff and an Omron HEM-7015IT digital blood pressure monitor. A manual sphygmometer was used if the standard automated device could not be employed. Body mass index (BMI) was calculated as weight (kg) divided by height squared ($m^2$) with weight measured using an electronic weighing scale (Tanita BC-418). The participants undergo longitudinal life course linkage to electronic health data including Hospital Episode Statistics and Office for National Statistics cause of death data.

The UK Biobank and UK BiLEVE genotyping arrays were purpose-designed specifically for the UK Biobank project and share 95% marker content. Variants 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[2]. For current analysis only SNPs imputed from the HRC panel were analysed (N=39,235,157), of which ~7.1 million SNPs with minor allele frequency (MAF) >1% and imputation quality INFO > 0.1 are analysed here for GWAS.

### 2. UKB Quality Control

All SNPs had passed central Quality Control (QC) checks, such as departures from Hardy-Weinberg Equilibrium, batch and plate effects, sex effects, array effects and discordance across control replicates. The SNPs that failed QC were set to missing for all individuals in the corresponding batch within the final genetic data files provided. Likewise, the QC performed centrally for each sample tested for heterozygosity and missing rates. Genotypes of 488,377 UKB participants were released after the QC. Full details of the QC of the genetic data performed centrally by UK Biobank are available[2].

Additionally, we excluded 968 individuals listed as QC outliers for heterozygosity or missingness and 378 individuals with sex discordance resulting to 486,683 individuals in both the post-QC genetic data and the overall phenotype data to consider for analysis, using information and data in the sample QC files provided centrally by UKB.

We restricted our data to a subset of European ancestry individuals for analysis. First, we excluded anyone who self-reported as a non-European ancestry keeping only those with self-reported ethnicity categorised as either White, other, mixed, or missing (NA). Then, using principal components (PC) provided by UK Biobank, we performed a 4-means clustering according to each of PC1 and PC2 separately using the *kmeans* algorithm in R statistical software, corresponding to four ethnic groups (White, Black, Asian, Chinese) and created an intersection of these two clusterings, to create five final clusters (White,

Black, Asian, Chinese, Mixed/Other) (**Supplementary Fig. 12**). Finally, we combined the information from the self-reported (White, other, mixed or NA) and the PCA-ancestry data to get an intersection of a total N=460,468 Europeans.

### 3. Phenotypic data

We performed analyses for systolic (SBP) and diastolic (DBP) BP and for pulse pressure. 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. These phenotypic sample exclusions were applied to all individuals who had passed the above genetic QC. Following both genetic and phenotypic data QC and by excluding pregnant women (n=372) and those individuals who had withdrawn consent (N=36), the sample size for analysis therefore included N=458,577 and N=458,575 European ancestry individuals for SBP and DBP, respectively.

Analysis of the summary descriptive statistics of the UK Biobank sample shows there were small but significant differences when comparing the UK Biobank vs UK BiLEVE participants, for age and BMI, due to large sample sizes. UK BiLEVE participants were slightly older and heavier compared to the UK Biobank participants. Moreover males and females were equally represented in the UK BiLEVE sample whereas more females (54.7%) were included in UK Biobank data (**Supplementary Table 1a).**

### 4. UKB analysis

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[3]. We used genotyped SNPs filtered for MAF > 5%; HWE $P > 1x10^{-6}$; missingness < 0.015, to estimate the parameters of the linear mixed model, for the initial modelling step only. Within the association analysis, we adjusted 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 and different study ascertainment. The association analysis performed by BOLT-LMM (v2.3) corrects for population structure and cryptic relatedness in very large datasets such as UKB. The genome-wide association analysis of all imputed SNPs was restricted to variants with MAF ≥ 1% and INFO > 0.1. We ran all analyses independently in parallel by two analysts across different sites and results were compared for consistency.

## 5. Genomic inflation and confounding

We applied the univariate LD score regression method (LDSR)[4] to test for genomic inflation that is expected for polygenic traits like BP, with large sample sizes, and especially also from analyses of such dense genetic data with so many SNPs in high-LD[5]. LDSR intercepts were 1.217 (standard error (se) 0.018), 1.219 (se:0.020) and 1.185 (se: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**.**

## 6. International Consortium for Blood Pressure (ICBP) GWAS

ICBP GWAS is an international consortium to investigate BP genetics[6-8]. We combined previously reported post-quality control (QC) GWAS data from 54 studies (N=150,134)[8], with newly available GWAS data from a further 23 independent studies (N=148,890) using a fixed effects inverse variance weighted meta-analysis. All study participants were of European descent and were imputed to either the 1000 Genomes Project Phase 1 integrated release version 3 [March 2012] all ancestry reference panel or the Haplotype Reference Consortium (HRC) panel. The final enlarged ICBP GWAS dataset included 77 studies comprising data from 299,024 individuals from the following cohorts: The initial ICBP GWAS included: AGES (n=3215), ARIC (n=9402), ASPS (n=828), B58C (n=6458), BHS (n=4492), CHS (n=3254), Cilento study (n=999), COLAUS (n=5404), COROGENE-CTRL (n=1878), CROATIA-Vis (n=945), CROATIA-Split (n=494), CROATIA-Korcula (n=867), EGCUT (n=6395), EGCUT2 (n=1844), EPIC (n=2100), ERF (n=2617), Fenland (n=1357), FHS (n=8096), FINRISK-ctrl (n=861), FINRISK CASE (n=839), FUSION (n=1045), GRAPHIC (n=1010), H2000-CTRL (n=1078), HealthABC (n=1661), HTO (n=1000), INGI-CARL (n=456), INGI-FVG (n=746), INGI-VB (n=1775), IPM (n=300), KORAS3 (n=1590), KORAS4 (n=3748), LBC1921 (n=376), LBC1936 (n=800), LOLIPOP-EW610 (n=927), MESA (n=2678), MICROS (n=1148), MIGEN (n=1214), NESDA (n=2336), NSPHS (n=1005), NTR (n=1490), PHASE (n=4535), PIVUS (n=945), PROCARDIS (n=1652), SHIP (n=4068), ULSAM (n=1114), WGHS (n=23049), YFS (n=1987), ORCADES (n=1908), RS1 (n=5645), RS2 (n=2152), RS3 (n=3018), TRAILS (n=1262), TRAILS-CC (n=282) and TWINGENE (n=9789). The enhanced dataset includes ASCOT-SC (n=2462), ASCOT-UK (n=3803), BRIGHT (n=1791), Dijon 3C (n=4061), EPIC-CVD (n=8375), GAPP (n=1685), HCS (n=2112), GS:SFHS (n=19429), Lifelines (n=13292), JUPITER (n=8719), PREVEND (n=3619), TWINSUK (n=4973), Fenland-GWAS (n=1358), InterAct-GWAS (n=6675) OMICS-EPIC (n=17850) OMICS-Fenland (n=8526) UKHLS (n=7462) GoDARTS-Illumina and GoDarts-Affymetrix (n=7413), NEO (n=5731), MDC (n=5271), SardiNIA (n=6021), METSIM (n=8262). Full study names, cohort information and general study methods are provided in supplementary tables **(Supplementary Table 1b; Supplementary Tables 20a-c)**.

Definition of phenotype data and GWAS analyses of SBP, DBP and PP were as per our previous ICBP protocol for 54 studies[8], extended to the additional 23 studies for which new data were available. Residuals were calculated for each trait using a normal linear regression of the medication-adjusted[9] trait values (mmHg) on sex, age, age$^2$ and BMI, with optional

inclusion of additional covariates to account for population stratification. Methods to account for relatedness within a study were used where appropriate (**Supplementary Table 20b**). Association testing was carried out by linear regression under an additive genetic model.

Prior to meta-analysis of all 77 ICBP GWAS studies, we undertook central QC checks across all studies. This included checks to ensure allele frequency consistency (across studies and with reference populations), checks of effect size and standard error distributions (i.e. to highlight phenotype issues) and generation of quantile-quantile (QQ) plots and genomic inflation factor lambdas to check for over- or under-inflation of test statistics. Genomic control was applied (if lambda>1) at study-level. Variants with imputation quality <0.3 were excluded prior to meta-analysis. EasyQC was used for the QC process[10]. Finally, data were filtered to SNPs with MAF ≥ 1% and N effective sample size > 60%. Meta-analysis was performed using METAL and inverse variance weighted fixed effects models. Between-study heterogeneity was assessed using the Cochran's Q statistic and we performed additional filtering removing heterogeneous variants with Cochran's Q $p<1x10^{-4}$.

### 7. Meta-analyses of discovery datasets

We performed a fixed-effects inverse variance weighted meta-analysis[11] using METAL[12] 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% present in both the HRC-imputed UKB data and ICBP meta-analysis for all three traits. To verify concordance of the MAF between the two datasets in the discovery stage we checked the consistency of the effect allele frequencies between the two datasets.

### 8. Linkage Disequilibrium calculations

Linkage Disequilibrium (LD) was calculated between all published and novel sentinel SNPs within the full genetic dataset using PLINK2 software[13]. In order to do this, all genetic data with INFO > 0.1, were converted from BGEN format to PLINK binary files in best-guess genotype format, using PLINK2 software with default parameters. For any given SNP for which LD calculations were performed, the LD was estimated for all variants within a 5 mb window downstream and upstream of this reference SNP. All variants in LD with the reference SNP reaching an $r^2 \geq 0.1$ threshold were identified. LD calculations were done within HRC imputed data only and proxies were used for 13 of the 357 published SNPs not contained within the HRC imputed UKB data. These proxies were obtained using previous LD data from the interim UKB 150K release which contained additional 1000G/UK10K imputations. They were selected as the SNP with highest $r^2$, contained within HRC (within 500kb). To ensure that all published loci were captured, we also calculated LD for lower frequency published SNPs using the full UKB BGEN dataset even though our analysis was restricted to MAF ≥ 1%.

### 9. Locus definition

SNPs within +/-500kb of sentinel SNPs were extracted from the PLINK best-guess genotype format files using PLINK2 software. SNPs were filtered for those included in the HRC imputation panel and were combined with the SNPs in LD ($r^2 \geq 0.1$) per sentinel SNP, to obtain the list of all unique SNPs within a locus.

### 10. 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 from primary analyses from previous BP genetic association studies[7,14-19].[20]. 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), according to a threshold of $r^2 \geq 0.1$. 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 reported SNPs ($r^2 \geq 0.1$). This allows us to exclude all SNPs in published BP loci from our discovery meta-analysis, in order to only consider novel findings. Additionally, we are able to extract results from the discovery meta-analysis for all SNPs in LD with the 357 published SNPs, for each of the three BP traits to confirm that the previously reported BP associations show support for association with at least one of the three BP traits within our data too. The HLA region was considered as known and due to complexity, we excluded the whole region completely (chr 6:25-34 mb).
All SNPs within the loci were mapped to genes (GRCh37.75) when the variant localized within 5kb of the start or end of the gene's transcription (bedtools v2.17). Any genes which were annotated from previously reported-LD variants were listed and referred to as previously reported BP genes **(Supplementary Table 5)**.

### 11. Genomic inflation and polygenicity (QC)

We checked Quantile-Quantile plots (**Supplementary Fig. 13**) of the overall meta-analysis with and without exclusion of all SNPs within published loci. After inspection of our QQ-plots, we applied the LD score regression approach[21] to determine whether any inflation was due to polygenicity or underlying population stratification. We calculated the LDSR intercept, after the exclusion of the SNPs at published loci in the discovery meta-analysis of UKB and ICBP. It was 1.090 (0.017), 1.097 (0.017) and 1.064 (0.0146) for SBP, DBP and PP respectively; hence showing very little inflation in the discovery GWAS after the exclusion of published loci.
We also used the LD score regression to estimate the potential overlap between UKB and UK-based cohorts in ICBP by calculating the inflation of the effect estimates due to confounding from overlapping samples. The overlap is minimal as provided by the estimated calculation of the ratio ($intercept_{(LDSR)}$-1)/Mean $\chi^2$-1). Specifically, the ratios were 0.072,

0.073 and 0.062 for SBP, DBP and PP respectively, suggests that ~93-94 of the inflation for BP traits is due to polygenicity rather than population stratification, cryptic relatedness or technical artefacts.

## 12. Selection of variants for follow-up

After exclusion of all SNPs within the 274 published loci, we considered for follow-up any SNPs remaining with $P < 1x10^{-6}$ from the discovery meta-analysis for any of the three BP traits, and 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: with the top-ranked SNP being the sentinel (most significant) SNP of the 1st signal and subsequently removing all SNPs ±500kb within the same locus; then the top-ranked SNP of the remaining list becoming the sentinel SNP of the 2nd signal, etc, until the list is empty. Secondly, we calculated the pairwise LD of all sentinel SNPs, and merged together any SNPs in LD ($r^2 \geq 0.1$) belonging to the same locus. Our final selection of lookup SNPs for follow-up hence contained the sentinel SNP from each association signal, with all selected SNPs being pairwise-independent by LD ($r^2 < 0.1$). To aid replication meta-analyses across different datasets with different genetic coverage, we also selected up to two of the best proxies for each sentinel SNP. The proxies were selected as the two SNPs tagging the same signal in high LD ($r^2 \geq 0.8$) which are also associated with at least one BP trait ($P < 1x10^{-5}$) and at a similar level of significance as the sentinel SNP (<1.5-fold difference in the ratio of the $-\log_{10}$(P-value) results of the sentinel and proxy SNP). Of the 1,062 novel loci containing previously unreported SNPs with MAF ≥ 1%, and $P < 1x10^{-6}$, 1021 lead SNPs were available in both datasets from the replication resources (MVP and EGCUT); for the remaining 41 SNPs we used one of the two best proxies **(Supplementary Table 22)**. Overall, all 1,062 signals considered for lookups were available for replication analysis, either by the sentinel SNP or a good proxy **(Supplementary Table 23)**.

## 13. Replication datasets and meta-analysis for two-stage design

We used two independent external data sets for replication. We considered SNPs with MAF ≥ 1% and performed a reciprocal replication exchange with the Million Veteran's Program (max N = 220,520). We also sought independent replication in the Estonian Genome Center, University of Tartu (EGCUT) Biobank (max N=28,742). This provides a total of N = 249,262 independent samples of European descent available for replication.

The Million Veteran Program (MVP) is a large cohort of fully consented participants who were recruited from the patient populations of approximately 51 Veteran's Administration (VA) medical facilities. Recruitment began in 2011 and is conducted in-person, which is initiated by an invitation letter and completed by answering baseline and lifestyle questionnaires, providing a blood sample, and providing access to medical records, and giving permission for re-contact. Consent to participate is provided after counselling by research staff and mailing of informational materials. All documents and protocols have

been approved by the VA Central Institutional Review Board. Blood samples are collected by phlebotomists and banked at the VA Central Biorepository in Boston, MA. Genotyping was conducted using a customized Affymetrix Axiom Biobank Array chip with additional content added to provide coverage of African and Hispanic haplotypes, as well as markers for common diseases in the VA population. Researchers are provided with de-identified versions of these data, and do not have the ability or authorization to link these details with a participants' identity.

For this analysis, we selected adults (age ≥ 18) and used the earliest median eligible non-Emergency Department outpatient measured SBP in the EHR, and also used the corresponding DBP from this measure. Measures are ineligible if they occur at or after an ICD-9 code from the groups 585, 405, or 428. If pain scores were available, we censored BP measures taken during encounters when a pain score ≥5 was recorded. For measures taken while a patient was on an antihypertensive medication we added 15 mm Hg to SBP and 10 mm Hg to DBP. We adjusted linear regression models analysing SNP associations for age at BP measure, age$^2$, sex, BMI measured within 1 year of BP measure, and 10 principal components of ancestry in analyses. Primary analyses were conducted using SNPTEST by self-reported race/ethnicity for MVP (White non-Hispanic).

Similarly, EGCUT ran a GWAS for unrelated individuals of European descent using the same model in EPACTS for dosage data that were imputed using the EstRef imputation panel[22]. Allele frequencies and strand alignments were tracked for consistency with the two datasets. The two independent datasets were quality controlled to ensure concordant MAF with those of the discovery effort and were synthesized using fixed effect inverse variance weighted meta-analysis.

### 14. Combined meta-analyses for two-stage design

In the combined two-stage meta-analysis we synthesized the results of the discovery meta-analysis (UKB and ICBP GWAS) with the lookup results from the two independent replication studies (replication meta-analysis) using fixed effect inverse variance weighted meta-analysis. For consistency with the SNPs present in the replication data sets, the results for the proxy SNPs were used within the discovery input for the variants that required proxies or alternative SNPs to the sentinel SNPs for the lookups. Genomic control had already been applied in both the UKB and ICBP datasets at study-level. No further GC corrections were applied in METAL for our combined meta-analyses.

### 15. Significance thresholds for two-stage design

All of the following criteria must 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 ($P < 1\times10^{-6}$) 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 ($P < 5\times10^{-8}$) 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 replicated BP trait with the most significant association from the combined meta-analysis of discovery and replication (in the case of many SNPs replicating for more than one BP trait).

We note that the standard genome-wide significance threshold ($P < 5 \times 10^{-8}$) is appropriate for our combined meta-analysis. The UK Biobank-GWAS analysis follows up 7 million SNPs with MAF ≥ 1% and coverage in HRC data. In addition, we require replication support of $P < 0.01$ which is more stringent than a range of thresholds calculated according to False Discovery Rate (FDR) which gives FDR thresholds of $0.01 < P < 0.04$ using the approaches proposed by Benjamini and Hochberg [23]and Benjamini and Yekutieli[24] respectively. As a further protection against false positive findings, we require concordance in direction of effect between the discovery and replication meta-analysis results.

**16. <u>Significance thresholds from one-stage design</u>**

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 must 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 $P < 5\times10^{-9}$ 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[17]

We selected the one-stage *P*-value threshold to be more stringent than a genome-wide significance *P*-value, in order to ensure robust findings and to minimize false positives. The threshold of $P < 5 \times 10^{-9}$ has been proposed as a more conservative statistical significance threshold, e.g. for whole-genome sequencing-base studies[25]. This is even more conservative than the number of independent statistical tests performed in our data that they were calculated by assessing the correlation between nearby test statistics empirically[26].

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

**17. <u>Conditional analysis</u>**

For conditional analysis, we used two different methodological approaches, each using the Genome-wide Complex Traits Analysis (GCTA) software: (i) genome-wide conditional analysis; and (ii) locus-specific conditional analysis.

*(i) Genome-wide conditional analysis*

Conditional analysis was conducted within GCTA software, using the *–cojo* method, which performs iterative conditional and joint analysis simultaneously with stepwise model selection. The summary statistics from the GWAS discovery meta-analysis of UKB and ICBP were used as the input summary data. Three sets of analyses were performed, one for each BP trait, using the trait-specific meta-analysis results. The UKB genetic data was used as the reference genotype-level data, in PLINK format, restricted to MAF ≥ 1%. As the UKB genetic data is stored individually by chromosome, the GCTA analyses were performed separately per chromosome. With the combination of these two input data files, analysis was therefore restricted to the ~7 million HRC-imputed SNPs with MAF ≥ 1% in common to both UKB and ICBP data from the GWAS discovery meta-analysis. Within the UKB genetic data, LD was calculated between all pairwise SNPs. By using the UKB data as our reference genotype data, our analysis is equivalent to a full multiple regression analysis between the actual genotype data and the BP phenotypic traits. Within the GCTA analysis, a p-value cut-off of $5x10^{-8}$ was used as the selection threshold, in order to identify secondary signals at the genome-wide significance level. For the collinearity threshold we used the default cut-off value of 0.9, so that SNPs are not selected if the multiple regression with the current SNPs in the model has $R^2 \geq 0.9$. After combining all the 22 chromosome output files together, each trait-specific analysis results in a distinct set of jointly independent significant signals. Then, for each BP trait, by excluding all SNPs which are in LD ($r^2 \geq 0.1$) with any of the 357 published SNPs (**Supplementary Table 4**) or any of the sentinel SNPs at the 535 novel loci (**Supplementary Tables 2a-c and Supplementary Tables 3a-c**) or 92 newly replicated loci (**Supplementary Table 5**), all remaining SNPs are additional, independent secondary signals associated with the given BP trait. However, after merging together all genome-wide results across all three BP traits, some signals could be duplicated across traits, so pairwise LD was calculated for the list of all unique SNPs. For any sets of SNPs in LD ($r^2 \geq 0.1$), we selected the most significant SNP with the minimum p-value across all BP traits from the GCTA joint model. Hence all final SNPs are pairwise-LD-independent.

*(ii) Locus-specific conditional analysis*

Here we considered each of the 901 BP loci separately.

Within each of the 535 novel loci (**Supplementary Tables 2a-c and Supplementary Tables 3a-c)** and the 92 loci replicated for the first time (**Supplementary Table 5**), we searched for any potential secondary signals, which are independently associated in addition to the sentinel SNP. Conditional analysis was performed on all HRC-imputed SNPs with MAF ≥ 1% within the 1Mb locus region centred ±500kb around the sentinel SNP, conditioning on the sentinel SNP. Analysis was performed for association of the primary validated BP trait of the sentinel SNP.

For known loci (**Supplementary Table 4**) we initially considered all 274 loci containing all 357 published SNPs. However, we excluded the HLA region (chr 6:25-34MB), as the long-range LD within this region could potentially confound the conditional analysis. Furthermore, 28 of the 357 exact SNPs were not present within the UKB HRC-imputed data at MAF ≥ 1%. For 14 of these SNPs we were able to use a good proxy SNP instead ($r^2 \geq 0.8$), but the remaining 14 SNPs were excluded due to lack of signal coverage, which excluded some loci completely if no other published SNP existed within this locus. Of the 329 published SNPs present in the UKB data, only 6 SNPs did not reach Bonferroni significance for any BP trait within the GWAS discovery meta-analysis (although the locus was still confirmed as SNPs in LD with $r^2 \geq 0.1$ within the 1Mb locus region reached nominal significance with $P < 0.01$). These 6 SNPs were therefore excluded, with the entire locus also being excluded from analysis if no other published SNPs were present. Overall this resulted in a total of 259 known loci being analysed. For loci containing only one published SNP, the 1Mb locus region centred ±500kb around the published SNP was used for analysis. For loci containing multiple published SNPs, the interval was wider than 1Mb, with the locus region starting 500kb downstream from the first SNP and ending 500kb upstream from the last SNP. For known loci containing only one published SNP, conditional analysis was performed on all HRC-imputed SNPs with MAF ≥ 1% within the 1Mb region, conditioning on the single published SNP within the locus, testing for association of the primary, most significantly associated BP trait of this published SNP from the GWAS discovery meta-analysis (see **Supplementary Table 4**). For known loci containing more than one published SNP, conditional analysis was performed within the wider locus region, conditioning jointly on all published SNPs within the locus. If any pairs of SNPs at a locus were in high LD ($r^2 \geq 0.9$) beyond the collinearity cut-off, the most significant SNP with the minimum P-value across all

BP traits from the GWAS discovery meta-analysis was selected. If all published SNPs at the locus had the same primary BP trait, GCTA testing was only performed for one trait, but if the primary traits differed across multiple published SNPs within a locus, then GCTA was run for each of the primary associated BP traits. (The post-GCTA filtering removes any duplication of signals across traits afterwards.) Of the 259 known loci analysed, 50 loci conditioned on multiple SNPs, and of these 14 loci were tested for more than one BP trait.

All these locus-specific conditional analyses used the "--cojo-cond" command in GCTA, with the list of sentinel or published SNPs being input as the conditional SNP-list. As for the genome-wide approach, the trait-specific GWAS discovery meta-analysis results were used as the input summary data, and the UKB genetic data was used as the reference PLINK dataset.

The output provides the conditional analysis results of all SNPs within the locus region after conditioning on the sentinel or published SNPs. These results are then filtered to obtain a list of potential secondary SNPs which are both significant and independent according to the following four criteria:

(a) $P < 5x10^{-8}$ from original GWAS discovery primary meta-analysis, so the SNP is significantly associated with BP itself, at genome-wide significance level

(b) $Pc < 5x10^{-8}$ from the conditional analysis, so that the SNP is also significantly associated with BP after conditioning on the sentinel / published SNPs

(c) -log10(p) / -log10(p_cond) < 1.5, i.e. there is less than a 1.5 fold difference between the GWAS P-value and the conditional *P*-value of the SNP, implying that conditioning on the sentinel / published SNPs has had little impact on the association of the potential secondary SNP, and hence it is statistically independent

(d) not in LD with any of the 357 published SNPs or any of the sentinel SNPs at the 535 novel loci or 92 newly replicated loci ($r^2 < 0.1$)

All significant independent SNPs meeting the above criteria, from all loci across all chromosomes are combined together into one list. This is a longer list than from approach (i), as it contains all possible secondary SNPs, rather than only one lead SNP per independent signal, and many of the SNPs corresponding to the same signal will be in LD.

The outputs from the two different approaches are therefore combined together. For robustness, a secondary signal is only claimed if the SNP is obtained from both approaches. By only selecting SNPs from approach (i) if they are also present from the results of approach (ii), we ensure that all secondary signals belong to one of the 901 BP-associated loci confirmed from our primary analysis, either from a validated novel locus, or a published

locus. By only selecting from the many SNPs from approach (ii), those which are in the final GCTA model from approach (i), we reduce the list of SNPs to signals and ensure that these signals are jointly independent. As a final check, we confirmed again, by LD calculation within the UKB genetic data using PLINK, that all the final secondary SNPs are pairwise-LD-independent ($r^2 < 0.1$). In all cases the UKB genetic data used for LD calculation was restricted to individuals of European ancestry only.

The final list of secondary SNPs which we report are therefore:

- significantly associated with BP
- statistically independent in addition to the novel sentinel SNPs and published SNPs from our primary analysis
- independent to the novel sentinel SNPs and published SNPs by LD
- jointly independent with each other statistically
- pairwise-LD-independent from each other
- within 500kb from one of the novel sentinel SNPs or published SNPs, and hence contained within one of the 901 loci from our primary analysis

The curated list of 357 published SNPs (**Supplementary Table 4**) excluded from our discovery GWAS was restricted to published SNPs which had been identified as the sentinel SNP from primary GWAS analyses and validated with independent replication. Other published BP genetics studies have also reported secondary signals from secondary analyses using a variety of different approaches. We calculated pairwise LD between all of our secondary SNPs versus all previously reported. For any of our secondary SNPs overlapping with previous findings ($r^2 \geq 0.1$), the corresponding publication is cited.

### 18. Look ups in non-European ancestries

As a secondary analysis, we look up all known and novel SNPs in non-European ancestry samples of UK Biobank. These analyses are stratified by ancestry, according to two main non-European ancestry ethnicity categories within UKB: Africans and South Asians. As with the identification of European ancestry (described above), participants were selected according to both self-reported ethnicity data and PCA ancestry clustering, e.g. for Africans, those with self-reported ethnicity (Africans, other, mixed or NA) and PCA-ancestry = Africans, giving a total of N=7,782 Africans; similarly for 10,322 South Asians and 2,156 Chinese ancestry. An equivalent GWAS-LMM analysis is performed using BOLT-LMM for this subset of variants within each stratified ancestry. (Note that analysis for 2,156 Chinese is not performed as BOLT-LMM is only recommended for N>5,000)

### 19. Genetic risk scores analyses

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 UK Biobank

data. We first created 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 weighted BP increasing alleles by the trait-specific beta coefficients from the ICBP meta-analysis GWAS that is part of the discovery stage **(Supplementary Table 24)**. For the novel and the 92 previously reported variants that have not been replicated before, beta coefficients of the replication meta-analysis for each BP trait were used as independent, unbiased weights. We then derived 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. We assessed the association of the continuous GRS variable on BP by simple linear regression, and we used logistic regression to examine the association of the GRS with risk of hypertension, with and without adjustment for sex. We then applied 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. We restricted our analysis to unrelated individuals of European ancestry from UKB excluding 1$^{st}$ and 2$^{nd}$ degree relatives. Specifically, we used the centrally provided kinship data from UKB to remove one of each pair of related individuals, related of 1st, and 2$^{nd}$ degree relationship. We used kinship index of 0.08838835 to exclude individuals (n=36,182) who were related to at least one individual in the final database for analysis. This resulted to N=392,092 unrelated individuals.

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 used logistic regression with binary outcome variables for composite incident cardiovascular disease, incident myocardial infarction and incident stroke (using the algorithmic UKB definitions) and GRS as explanatory variable (with and without sex adjustment) **(Supplementary Table 25)**.

As a secondary analysis, and to see whether BP-associated SNPs identified from GWAS predominantly in Europeans area also associated with BP in populations of non-European ancestry, we also performed GRS analyses in non-European ancestry samples of UK Biobank. As with the identification of European ancestry (see section '2. UKB Quality Control'), participants were selected according to both self-reported ethnicity data and PCA ancestry clustering, e.g. for Africans, those with self-reported ethnicity (Africans other, mixed or NA) and PCA-ancestry = Africans, giving a total of N=7,782 participants of African descent; similarly, for 10,322 South Asians. As the sample size for participants of Chinese ancestry was much lower, we focused analyses only on Africans and South Asians. For the GRS analyses using simple linear regression, the samples also had to be restricted to a set of unrelated subjects, by using the centrally provided kinship data from UKB, as described above. This resulted in final sample sizes for analysis of 6,264 unrelated Africans and 7,881 unrelated South Asians.

## 20. Airwave study data

The Airwave Health Monitoring Study (Airwave)[27] was used as an independent cohort for the GRS analyses, the analysis of metabolomics data and calculation of the percentage of the variance explained. The Airwave analyses included 14,004 participants with high quality HRC imputed genetic data. Systolic and diastolic blood pressures were measured as three consecutive readings using a digital blood pressure monitor (Omron HEM 705-CP digital BP monitor). Mean SBP and DBP adjusted for medication (as previously defined) were calculated from available readings and were used as dependent variables in the analyses. We calculated a 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 Airwave study data[27] to assess effect in an independent cohort, thus avoiding any over-fitting or bias by "winner's curse".
To calculate the percent of variance in BP explained by genetic variants in an independent dataset, we generated the residuals from a regression of each trait against age, age$^2$, sex and body mass index in Airwave. We then fit a second linear model for the trait residuals with all the variants in 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.
From the Airwave plasma $^1$H NMR metabolomics we use $^1$H NMR lipidomics data on plasma from a subset of 2,022 participants. For each replicated BP-associated SNP we ran association tests with the lipidomics data using linear regression analyses, adjusted for age and sex. We computed significance thresholds using a Bonferroni correct *P*-value ($4.7 \times 10^{-4}$). We also examined associations between each replicated SNP and a subset of 1,941 participants in Airwave with data from Metabolon platform.

## 21. Cardiovascular outcomes data in UK Biobank

To classify cardiovascular disease (CVD) outcomes we used self-reported baseline information on CVD prevalence available in UKB, and linkage to Hospital Episodes Statistics (HES) and mortality data **(Supplementary Table 25)**. HES provides detailed information for participants admitted to hospital and includes coded data on diagnoses and operations. Coronary artery disease and stroke were classified using International Classification of Disease (ICD) 9 and 10 codes and operation codes. All events occurring before assessment were categorized as pre-existing disease and were excluded from the CVD analysis (n=22,829). Final sample used for CVD analysis, consisted of 392,092 European ancestry individuals. The large UK Biobank cohort with sufficient numbers of cardiovascular events enables the assessment of cardiovascular risk within the same data set, noting that results are still independent, as the variants within the GRS are selected for their association with BP, not for cardiovascular outcomes.

## 22. Functional analyses

We used an integrative bioinformatics approach to collate functional annotation at both the variant and gene level for each SNP within the reported blood pressure loci. SNPs in LD $r^2 \geq 0.8$ with the blood pressure-associated SNPs are considered after extraction using PLINK. 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.

GTEx database: 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 (www.gtexportal.org), 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 lead SNP, suggesting that the eQTL signal co-localises with the sentinel SNP.

Fantom5: We annotated nearest genes, eGenes and Hi-C interactors with HUVEC, HVSMC and HAEC expression from the Fantom5 project (fantom.gsc.riken.jp/5). Genes that had higher then median expression levels in the given cell types were indicated as expressed.

DeepSEA: 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 biding and modification patterns of ~900 cell/factor combinations[28]. A change > 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.

Hi-C analysis: We identified potential target genes of regulatory SNPs using long-range chromatin interaction (Hi-C) data from HUVECs, aorta, adrenal glands, neural progenitor and mesenchymal stem cell, which are tissues and cell types that are considered relevant for regulating blood pressure. 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). We found the most significant promoter interactions for all potential regulatory SNPs (RegulomeDB score$\leq$5)[29] in LD ($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 performed overall enrichment testing across all loci.

DEPICT: Firstly, we used DEPICT[30] (Data-driven Expression Prioritized Integration for Complex Traits) to identify highly expressed tissues and cells within the blood pressure loci. DEPICT uses a large number of microarrays (~78k) to identify cells and tissues where the

genes are highly expressed and uses precomputed GWAS phenotypes to adjust for co-founding sources. Secondly, we used 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 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 based on the algorithm described in Pers et al[30]. We report significant enrichments with a false discovery rate <0.01. The variants tested were the 357 published blood pressure associated SNPs at the time of analysis and a set including all BP (for novel: combined *P*-value $<1 \times 10^{-12}$) variants. The *P*-value threshold was selected in order to include as many as possible variants in the analysis
FORGE: 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[31]. The results of analyses from only the published sentinel SNPs were compared to the results from analyses of SNPs at all loci, including also the novel loci discovered in our study in order to evaluate the overall tissue specific enrichment of blood pressure associated variants.

Functional Analyses: Genes

IPA: At the gene level, we used Ingenuity Pathway Analysis (IPA) software (IPA®,QIAGEN Redwood City,www.qiagen.com/ingenuity) to review genes with prior links to blood pressure, 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 (http://www.informatics.jax.org/batch) to identify BP and cardiovascular relevant mouse knockout phenotypes for all genes linked to all BP variants. We also used IPA to identify genes which 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 (dgidb.genome.wustl.edu).

### 23. Cross-trait lookups

PhenoScanner and GWAS catalog: We query SNPs against PhenoScanner[32] and GWAS catalog[33] to investigate trait pleiotropy, 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 all 535 sentinel novel SNPs, to highlight the novel loci with strongest evidence of association with other traits.
DisGeNET: We further evaluated pleiotropic effects using DisGeNET, a resource that integrates data from expert curated repositories, GWAS catalogues, animal models and the literature[34,35]. 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 in it from published-only, to all BP loci, indicates that pleiotropy is more frequent in the novel BP loci. At the gene level,

overrepresentation enrichment analysis (ORA) with WebGestalt[36] (on the nearest genes to all BP loci) was carried out.

Global Biobank Engine and GeneATLAS: We tested sentinel SNPs at all (n=901) BP 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. Both are search engines for GWAS findings for multiple phenotypes in UK Biobank. We used a Bonferroni corrected significance threshold of $P < 1x10^{-6}$ to deem significance.

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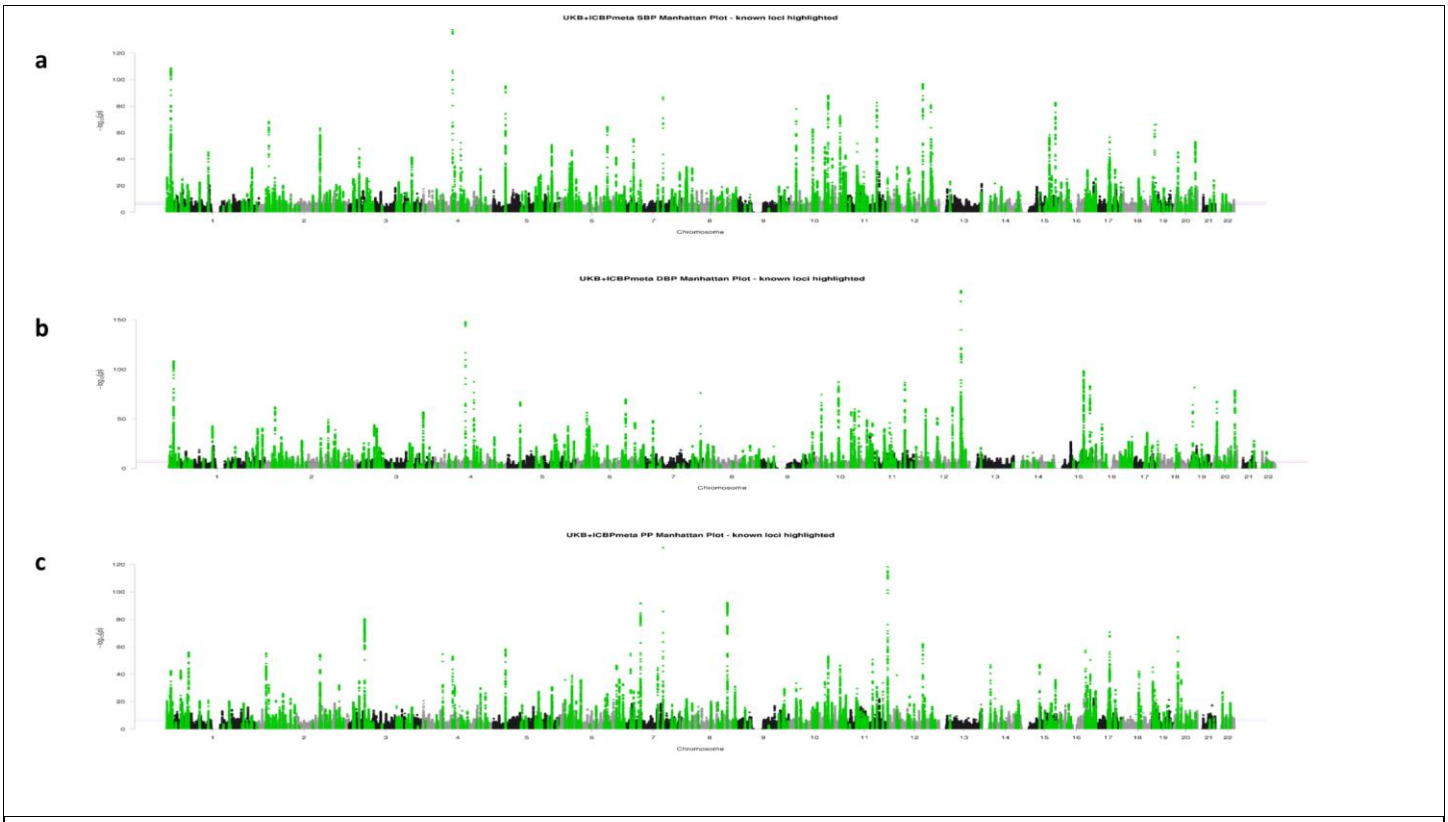
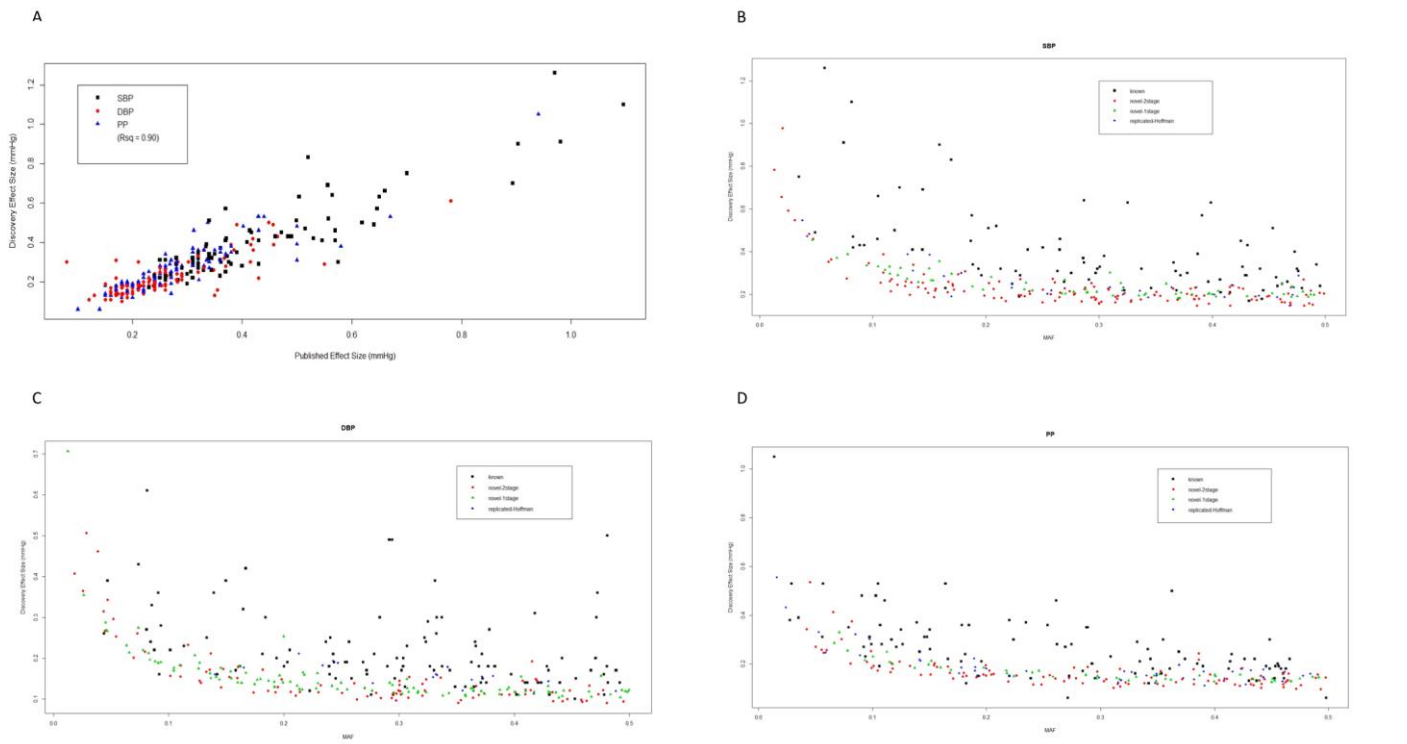



**Supplementary Figure 1**

**GWAS discovery Manhattan plots**.

Manhattan plots (a), (b) and (c) for systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse pressure (PP) respectively. P-value results from the GWAS discovery meta-analysis (N=757,601), were derived using inverse variance fixed effects meta-analysis and they are plotted on a – log10 scale for all SNPs with Minor Allele Frequency (MAF) ≥ 1%. SNPs within the 274 known loci (±500kb; Linkage Disequilibrium $r^2 \geq 0.1$) are highlighted in green.




**Supplementary Figure 2**

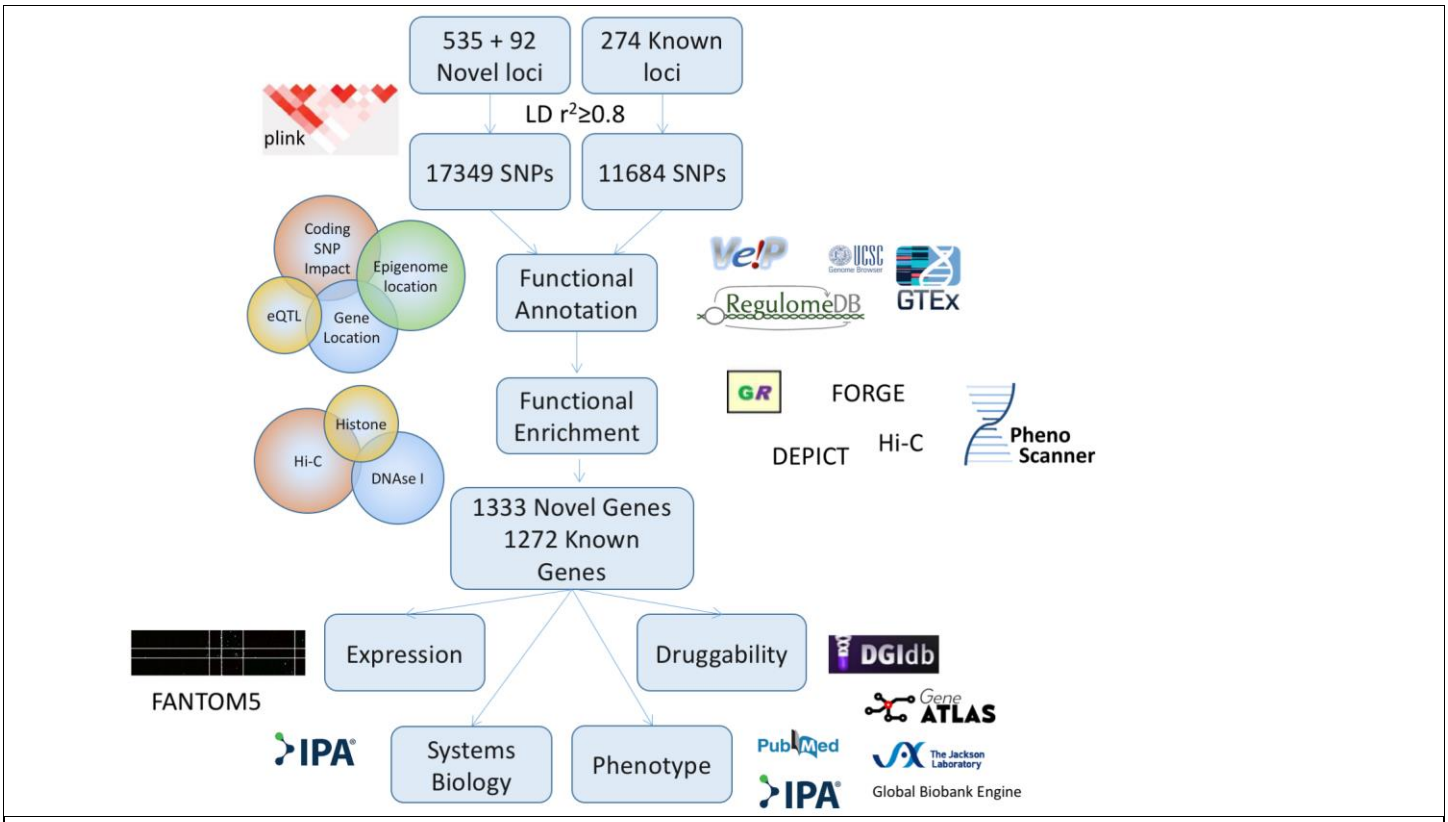
**Effect Sizes of all Blood Pressure associated loci.**

Plot (A) shows strong correlation between the published effect size estimates (x-axis) from literature vs the effect sizes from our discovery meta-analysis (y-axis), for known SNPs, colour-coded according to the published primary trait from the first published report. From the 357 validated SNPs listed in Supplementary Table 4 from the 274 published loci, 327 are available within the MAF ≥ 1% HRC-imputed data. For comparison of effect sizes, we only consider 299 such SNPs which have been identified from main-effect genetic association studies within Europeans (i.e. excluding any SNPs from interaction/stratified/multi-phenotype analysis, or from studies of other ancestries). For reliable comparison of effect sizes, we further restrict to the 284 known SNPs which reach genome-wide significance within the discovery meta-analysis for at least one BP trait. The $r^2$ value is presented to show the correlation between published and observed effect sizes. Plots (B), (C) and (D) are trait-specific plots for SBP, DBP and PP, respectively (SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure). Across all plots, the 284 "known" SNPs (black squared) from plot (A) are compared against the 325 novel sentinel SNPs from the 2-stage analysis (red circles), the 210 novel sentinel SNPs from the 1-stage analysis (green triangles), and the 92 SNPs (blue diamonds) replicated for the first time from Hoffman et al[9]. Each SNP is only plotted in one of the trait-specific plots, according to the published primary trait for the known SNPs, or the primary trait for the novel / replicated SNPs. For all SNPs we show the relationship between Minor Allele Frequency (MAF) on the x-axis and the effect size (mmHg) on the y-axis, where results are taken from the UKB+ICBP discovery meta-analysis. All meta-analysis results were computed using inverse variance fixed effects models. The different symbols and colours distinguish the "known" vs "novel-2stage" vs "novel-1stage" vs "replicated-Hoffman" SNPs, and show that in general, the novel SNPs have smaller effect sizes than known SNPs, and that there is no significant difference (P=0.447) between the effect sizes of the 1-stage (N=757,601) and 2-stage (N=1,006,863) novel SNPs. (UKB: UK Biobank; ICBP: International Consortium of Blood Pressure).


**Supplementary Figure 3**

**Venn diagram of novel loci results.**

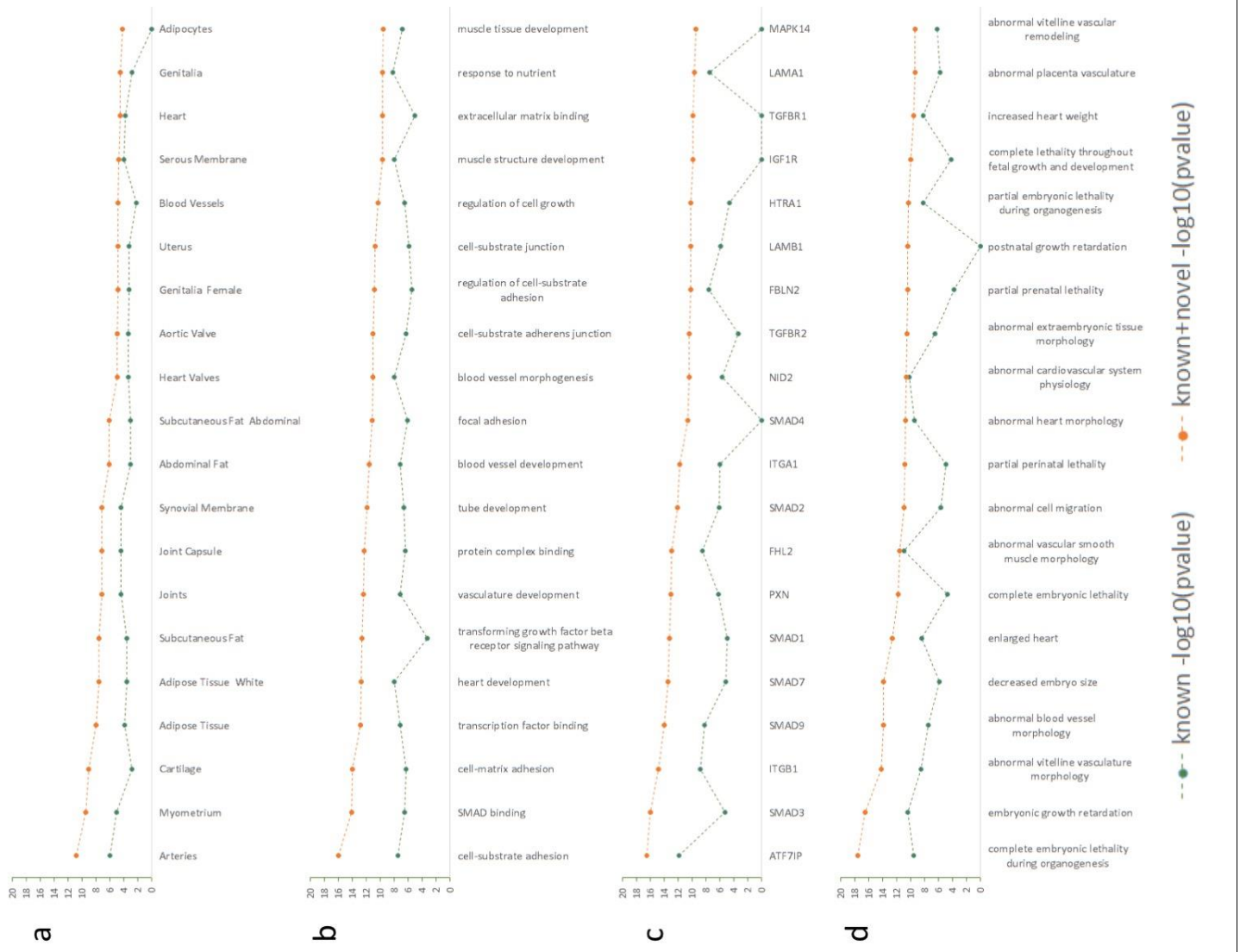
For all 535 novel loci, we show the blood pressure traits associated with each locus. We present the two-stage loci first, followed by the one-stage loci. The locus names provided in alphabetical order correspond to the nearest annotated gene. SNPs: Single nucleotide polymorphisms; SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; UKB: UK Biobank; ICBP: International Consortium of Blood Pressure.




**Supplementary Figure 4**

**Overview of functional annotation and prioritisation of genome-wide associated variants and genes.**

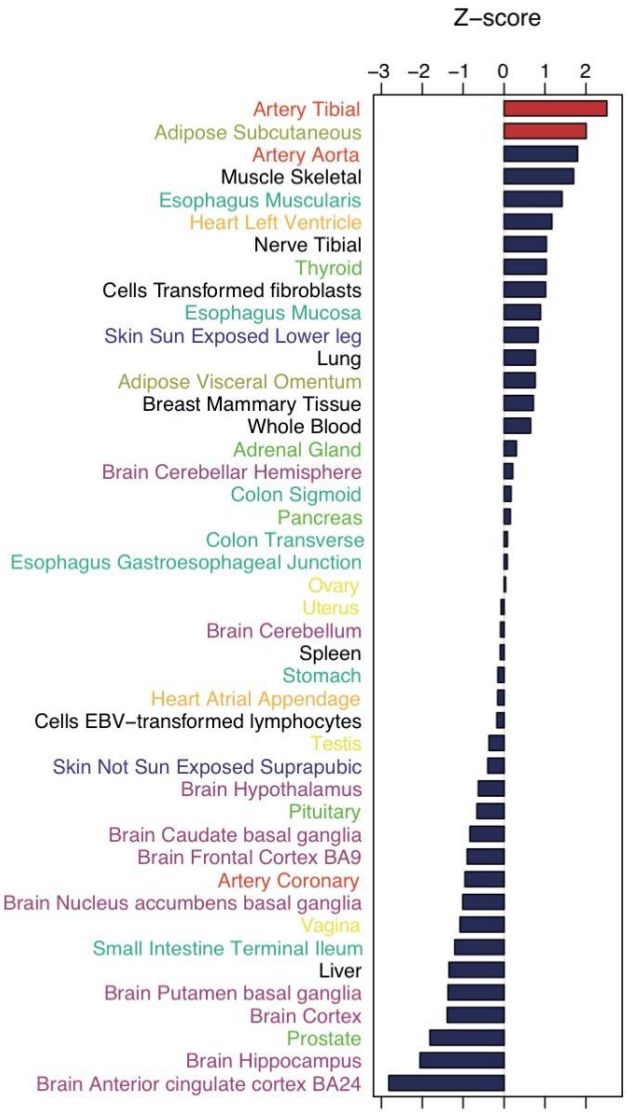
SNPs: single nucleotide polymorphisms; LD: Linkage Disequilibrium; eQTL: expression Quantitative Trait Loci; UCSC: University of California Santa Cruz (UCSC) genome browser; IPA: Ingenuity Pathway Analysis (IPA) software (IPA®,QIAGEN Redwood City,www.qiagen.com/ingenuity); DEPICT: Data-driven Expression Prioritized Integration for Complex Traits; GREAT: Genomic Regions Enrichment of Annotations Tool.




**Supplementary Figure 3**

**DEPICT enrichment analysis.**

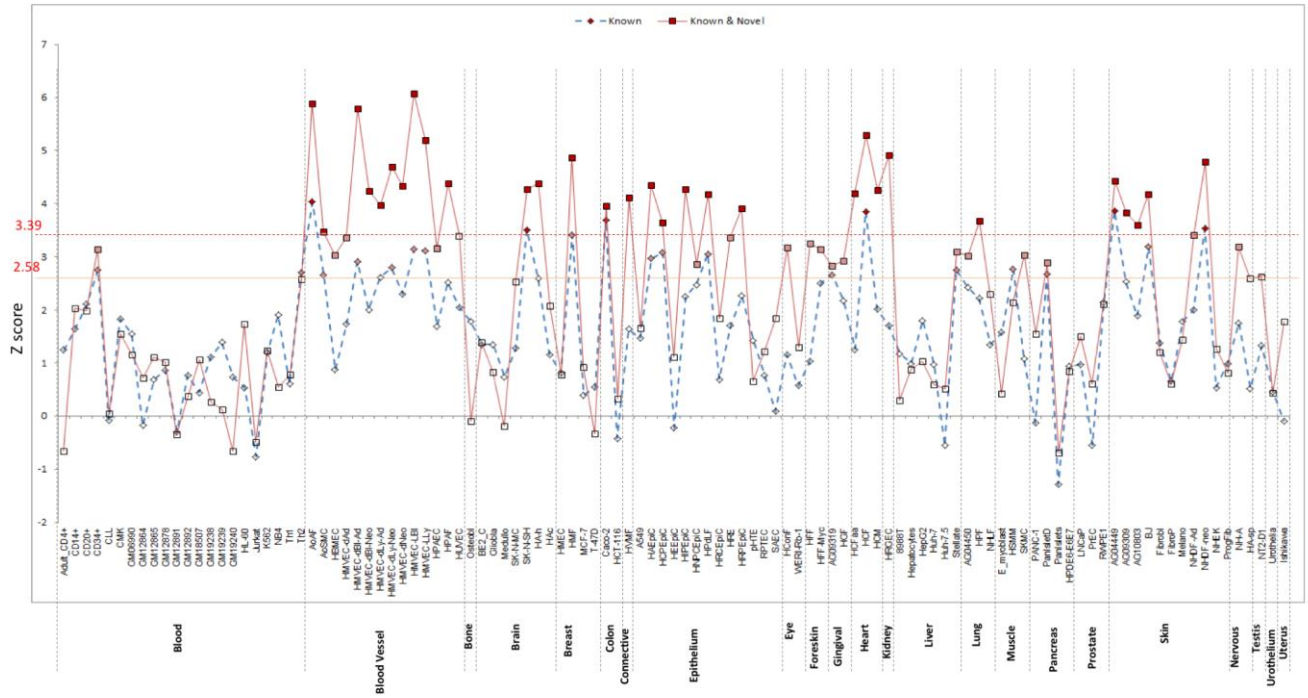
DEPICT software was used to investigate enrichment of a range of biological properties, in each case we compared known sentinel SNPS (N=357) to all known and novel SNPs with P-value $<1x10^{-12}$ (N=227). The gene set enrichment analysis algorithm is described in Pers et al[66]. Enrichment –log p value is reported for both groups, we also present delta –log p value as a measure of novelty introduced by novel associations reported. Enrichment categories are as follows. a) Enrichment of tissues and cell types. b) GO annotation. c) Protein-protein interaction subnetwork annotation. d) Mammalian phenotype annotation.




**Supplementary Figure 6**

**Enrichments of eQTLs.**

535 novel blood pressure associated SNPs and the SNPs in LD $r^2$>0.8 were annotated for their effect on gene expression using the GTEx portal. The number of eGenes associated with BP SNPs in a given tissue/ cell type was normalised with the total number of eGenes in that tissue and z-score was calculated using the trimmed mean and standard deviation of the normalised scores. Tissues of the same tissue group were coloured the same.




**Supplementary Figure 7**

**FORGE Dnase I sensitive region enrichment in known sentinel SNPs, compared to known and novel sentinel SNP associations for blood pressure.**

Sentinel SNPs were investigated for enrichment in ENCODE DNase I regulatory regions using FORGE. The background probability of overlap is determined from the 1000 background set overlap counts and the probability of the observed test result under a binomial distribution is calculated. The *P*-value thresholds of 0.05 and 0.01 are corrected for multiple testing by division by the number of tissue groupings tested, and the corrected threshold is used. Strongest enrichment in known SNPs was seen in vasculature (Human Aortic artery fibroblast (AoAF) and also Human Villous Mesenchymal Fibroblasts (HVMF) found in placenta). Enrichment in all known and novel SNPS was increased across vasculature (AoAF; HMVEC, Human microvascular endothelial cells) and highly vascularised tissues. Tissues in red are significant after correction for false discovery.

a)

| Canonical Pathway | known sentinel genes | known LD genes | All sentinel genes | All LD genes |
|---|---|---|---|---|
| Gap Junction Signaling | 9.1 | 6.8 | 6.5 | 4.7 |
| Cellular Effects of Sildenafil (Viagra) | 8.8 | 7.0 | 7.2 | 3.9 |
| Nitric Oxide Signaling in the CV System | 6.6 | 5.5 | 7.6 | 4.9 |
| G-Protein Coupled Receptor Signaling | 7.0 | 4.4 | 7.6 | 4.2 |
| Protein Kinase A Signaling | 5.4 | 4.5 | 7.2 | 5.4 |
| P2Y Purigenic Receptor Signaling Pathway | 6.8 | 5.4 | 5.8 | 4.2 |
| Relaxin Signaling | 6.1 | 5.3 | 6.7 | 3.7 |
| Dopamine-DARPP32 Feedback in cAMP Sign | 7.6 | 5.7 | 4.5 | 3.3 |
| PPARα/RXRα Activation | 5.4 | 5.1 | 5.6 | 4.7 |
| Role of NFAT in Cardiac Hypertrophy | 5.1 | 3.6 | 7.4 | 4.6 |
| Cardiac β-adrenergic Signaling | 5.8 | 4.6 | 6.2 | 3.6 |
| Sperm Motility | 7.0 | 4.9 | 4.8 | 3.2 |
| Axonal Guidance Signaling | 5.7 | 3.2 | 7.5 | 3.4 |
| CREB Signaling in Neurons | 6.0 | 4.4 | 5.9 | 3.3 |
| Molecular Mechanisms of Cancer | 4.5 | 4.4 | 5.9 | 4.4 |
| Chronic Myeloid Leukemia Signaling | 3.4 | 3.1 | 6.7 | 5.4 |
| PEDF Signaling | 5.7 | 4.4 | 4.8 | 3.3 |
| Corticotropin Releasing Hormone Signaling | 5.7 | 4.1 | 4.9 | 2.2 |
| Synaptic Long Term Potentiation | 5.4 | 3.8 | 4.5 | 3.0 |
| HER-2 Signaling in Breast Cancer | 3.8 | 3.6 | 4.8 | 4.3 |

b)

| Upstream regulators | known sentinel genes | known LD genes | All sentinel genes | All LD genes |
|---|---|---|---|---|
| AGT | 9.13 | 11 | 13 | 11.8 |
| ESR1 | 5.82 | 6.68 | 7.44 | 7 |
| NPR1 | 7.56 | 7.01 | 5.61 | 4.66 |
| nifedipine | 7.41 | 5.85 | 7.2 | 3.55 |
| losartan potassium | 4.15 | 4.34 | 6.54 | 5.38 |
| candesartan | 5.81 | 5.04 | 4.55 | 4.71 |
| KMT2A | 2.31 | 4.46 | 7.17 | 5.73 |
| AGTR1 | 3.88 | 3.55 | 6.05 | 5.41 |
| TGFB1 | 0 | 2.88 | 7.34 | 8.42 |
| SP1 | 5.01 | 4.64 | 5.26 | 3.72 |
| COMMD3-BMI1 | 1.81 | 8.73 | 1.81 | 5.99 |
| darusentan | 4.69 | 3.9 | 5.08 | 4.08 |
| PIAS1 | 3.05 | 3.89 | 4.65 | 6.14 |
| NR3C2 | 5.02 | 3.01 | 6.54 | 2.86 |
| progesterone | 4.52 | 3.67 | 5.51 | 2.9 |
| MAPK7 | 2.45 | 3 | 5.08 | 5.78 |
| PCGF2 | 5.24 | 4.75 | 3.58 | 2.75 |
| VCAN | 4.32 | 4.19 | 4.09 | 3.55 |
| HOXA10 | 1.56 | 5.25 | 3.55 | 5.38 |
| REN | 4.6 | 4.39 | 3.38 | 2.78 |

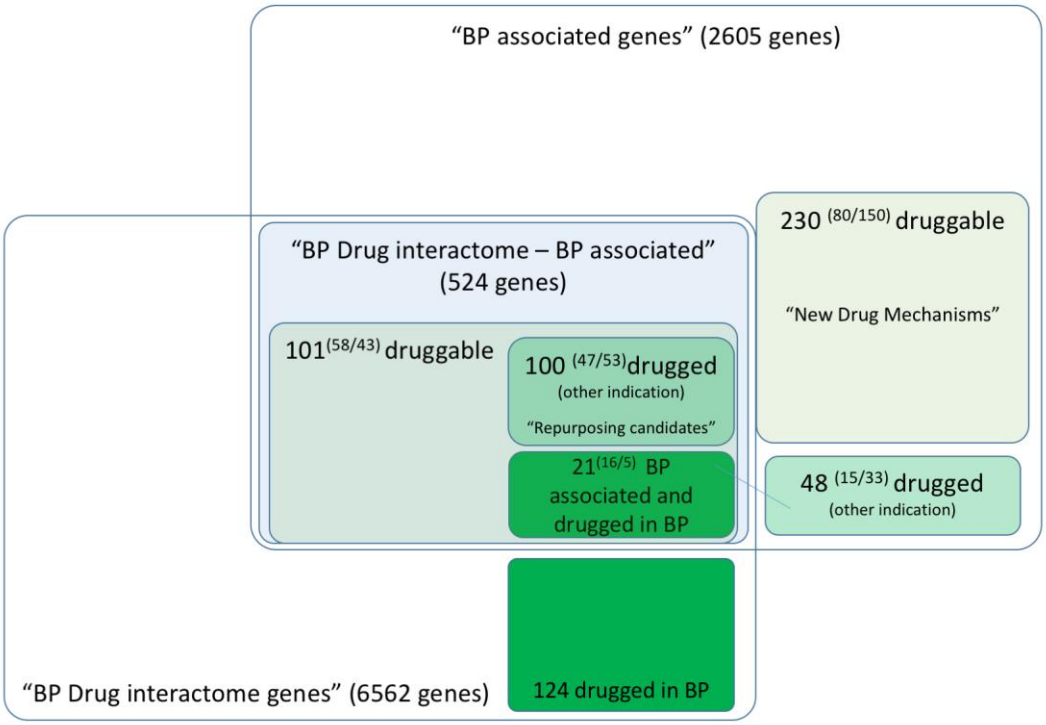
c)

| Diseases and Bio Functions | known sentinel genes | known LD genes | All sentinel genes | All LD genes |
|---|---|---|---|---|
| morphology of cardiovascular system | 14.73 | 13.83 | 20.85 | 17.01 |
| morphology of heart | 15.19 | 12.9 | 20.14 | 14.7 |
| morphology of body cavity | 15.87 | 13.17 | 17.94 | 11.99 |
| organismal death | 11.8 | 10.28 | 20.58 | 13.26 |
| morbidity or mortality | 11.88 | 10.16 | 20.18 | 12.7 |
| morphology of heart ventricle | 12.1 | 11.61 | 16.39 | 12.42 |
| skin lesion | 6.696 | 4.877 | 23 | 16.96 |
| morphology of muscle | 11.71 | 11.66 | 14.11 | 12.66 |
| development of vasculature | 10.35 | 9.228 | 19.05 | 10.96 |
| abnormal morphology of cardiovascular | 10.22 | 9.081 | 14.07 | 10.49 |
| development of body trunk | 8.922 | 8.063 | 16.08 | 10.52 |
| angiogenesis | 8.331 | 6.831 | 17.92 | 10.14 |
| primary hypertension | 11.22 | 9.003 | 12.44 | 10.15 |
| familial cardiovascular disease | 8.063 | 5.735 | 16.96 | 10.31 |
| hypertrophy of heart | 7.684 | 7.93 | 14.02 | 11.43 |
| abnormal morphology of body cavity | 11.55 | 9.621 | 11.94 | 7.423 |
| liver lesion | 4.977 | 4.891 | 16.44 | 14.09 |
| vasculogenesis | 6.576 | 6.361 | 15.89 | 10.8 |
| morphology of cardiac muscle | 9.097 | 8.926 | 11.18 | 10.03 |
| morphology of cardiomyocytes | 8.775 | 8.932 | 11.07 | 9.968 |

**Supplementary Figure 8**

**Ingenuity pathway analysis of BP genes.**

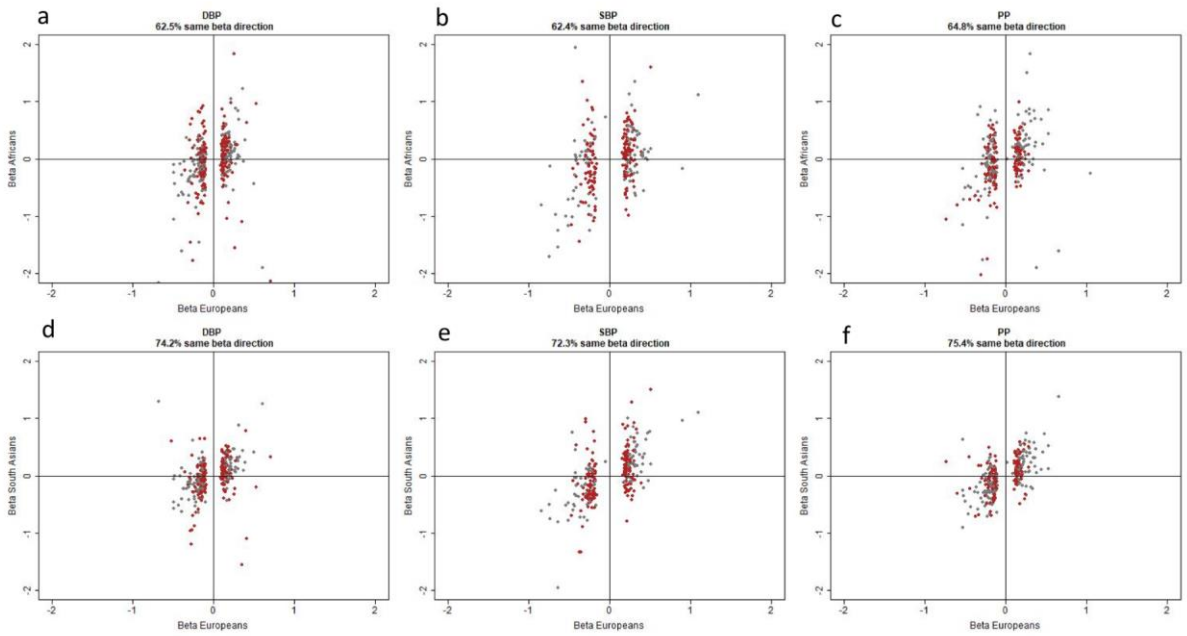
For genes mapped to 357 sentinel SNPs at 274 known loci and genes mapped to all 901 loci. Sentinel gene mapping is compared to genes identified by extended LD ($r^2$>0.8). Pathway enrichment is represented as – log p value. A) Canonical pathway enrichment. B) Upstream regulator enrichment. C) Disease and Biofunction enrichment.




**Supplementary Figure 9**

**Exploring known and novel drug mechanisms in blood pressure.**

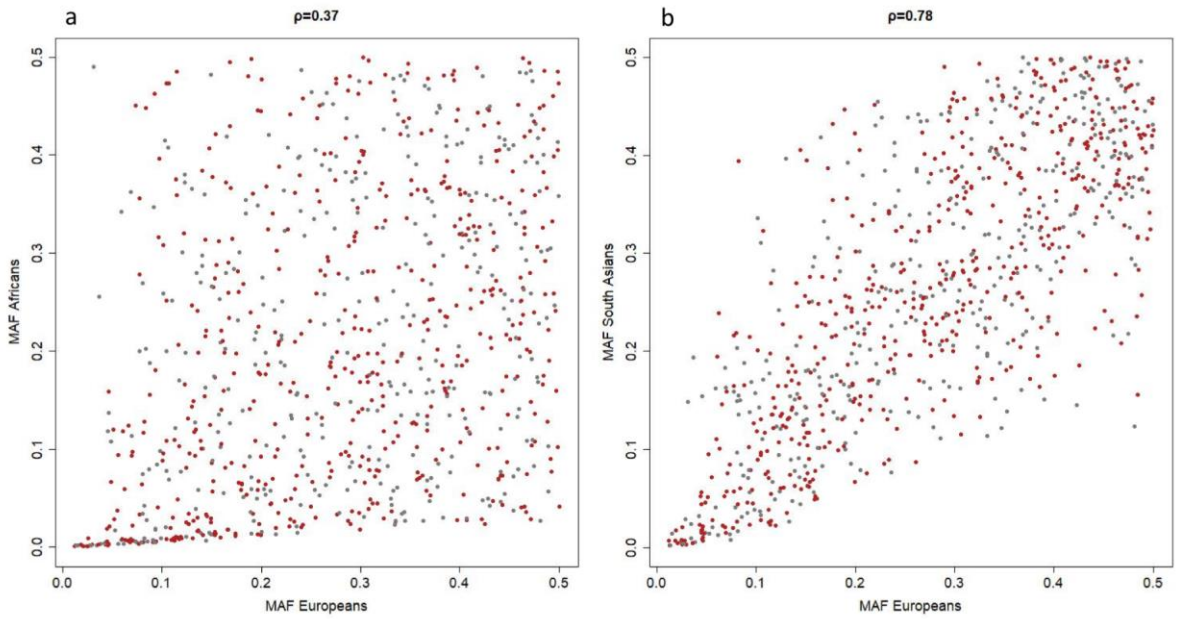
The figure summarises known and novel target opportunities highlighted by blood pressure genetics. Ingenuity pathway analysis was used to create a network of 6,562 genes showing direct interaction with 145 known blood pressure target genes. This network was compared with all genes that are either directly associated with BP or linked by LD ($r^2$>0.8). Overlap between genetic associated genes and the BP drug interactome demonstrates genetic support for known drug mechanisms. Drugged or druggable genes showing genetic association with BP, but no interaction with the known BP drug interactome, represent potentially new mechanisms in blood pressure drug development and repositioning. Number of known and novel drugged/druggable gene associations are shown in parentheses.




**Supplementary Figure 10**

**Comparison of beta effect sizes between individuals of European (N=757,601), African (N=7,782) and South Asian (N=10,323) ancestry.**

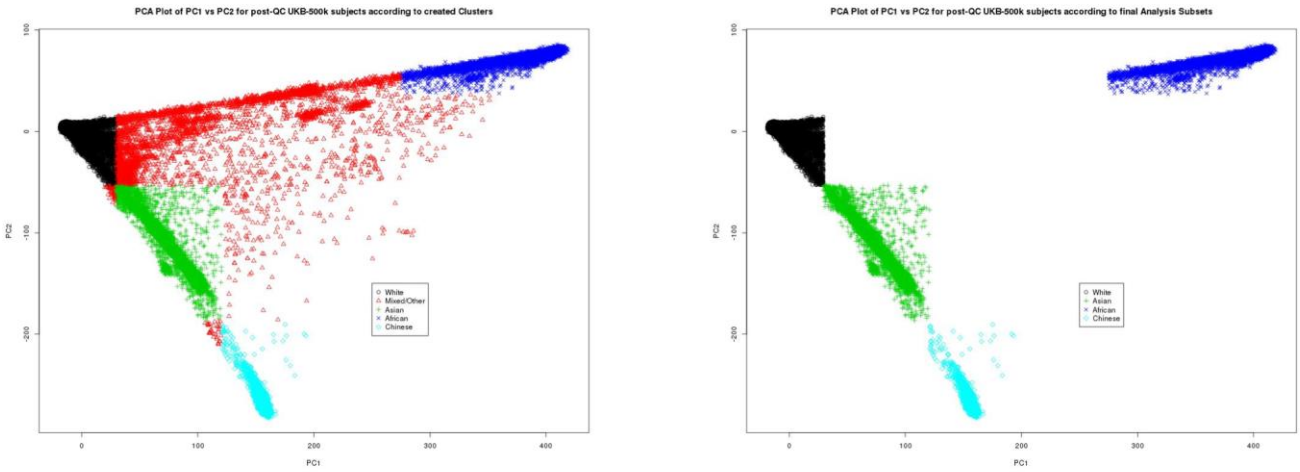
Scatterplots showing the direction of the standardized regression coefficient (beta) of novel (red) and known (grey) BP variants between Europeans and Africans (a,b,c) and South Asians (d,e,f), on the three studied BP phenotypes.




**Supplementary Figure 11**

**Correlation and distribution of minor allele frequencies (MAF) of BP variants in individuals of European (N=757,601), African (N=7,782) and South Asian (N=10,323) ancestry**.

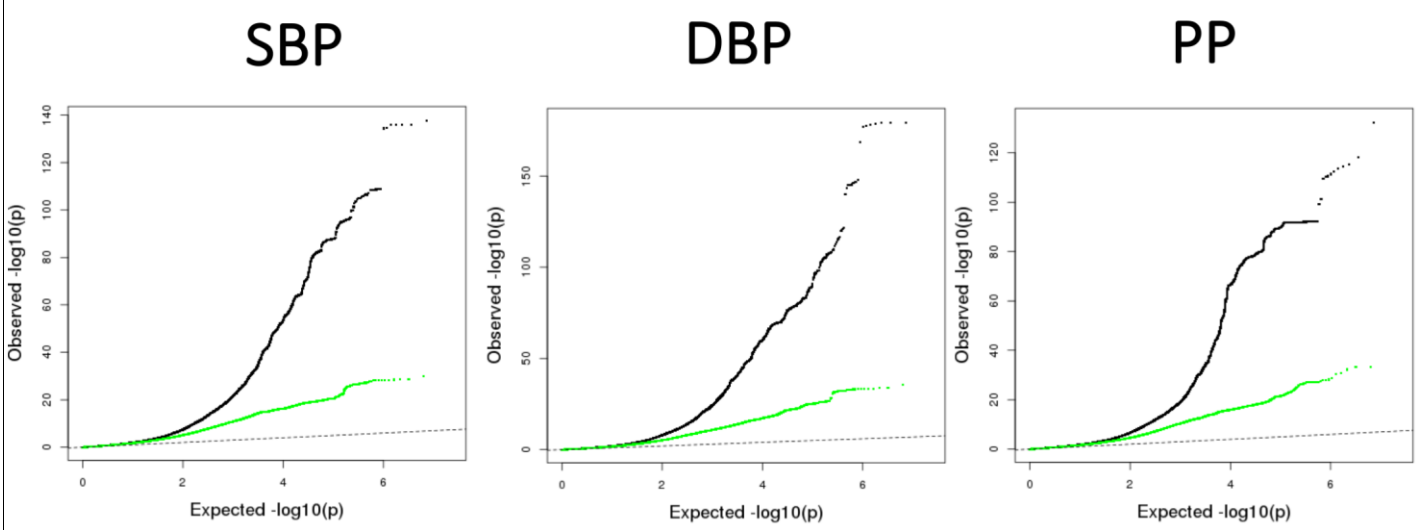
Scatterplot showing the correlation and the distribution of MAF of novel (red) and known (grey) BP variants between a) Europeans and Africans and b) Europeans and South Asians. ρ is the Pearson correlation coefficient.




**Supplementary Figure 12**

**Ethnicity clustering performed using PCA.**

PC1 is plotted against PC2 for all N=486,683 UK Biobank participants post-QC, colour-coded according to the five ethnic clusters created from our K-means PCA clustering, from which only “White” Caucasians are selected for analysis of individuals of European ancestry. Plot (A) shows the clustering for all subjects, whereas plot (B) only shows the subsets of individuals selected for race-stratified analysis, after combining information together from both the PCA clustering and the self-reported ethnicity. PCA: Principal Component Analysis; QC: Quality Control; PCs: Principal Components.




**Supplementary Figure 13**

**Quantile-Quantile plots**.

QQ plots of results for (A) systolic blood pressure (SBP), (B) diastolic blood pressure (DBP), (C) pulse pressure (PP) from GWAS discovery (N=757,601). The black curves are based on all SNPs in the corresponding analysis, with Minor Allele Frequency ≥ 1%. The green curves are results after excluding SNPs within the 274 known loci (±500kb; Linkage Disequilibrium $r^2 \geq 0.1$). The *P*-values have been derived from inverse variance fixed effects meta-analysis.