

Novel Blood Pressure Locus and Gene Discovery Using Genome-Wide Association Study and Expression Data Sets From Blood and the Kidney

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Abstract—Elevated blood pressure is a major risk factor for cardiovascular disease and has a substantial genetic contribution. Genetic variation influencing blood pressure has the potential to identify new pharmacological targets for the treatment of hypertension. To discover additional novel blood pressure loci, we used 1000 Genomes Project–based imputation in 150 134 European ancestry individuals and sought significant evidence for independent replication in a further 228 245 individuals. We report 6 new signals of association in or near *HSPB7*, *TNXXB*, *LRP12*, *LOC283335*, *SEPT9*, and *AKT2*, and provide new replication evidence for a further 2 signals in *EBF2* and *NFKBIA*. Combining large whole-blood gene expression resources totaling 12 607 individuals, we investigated all novel and previously reported signals and identified 48 genes with evidence for involvement in blood pressure regulation that are significant in multiple resources. Three novel kidney-specific signals were also detected. These robustly implicated genes may provide new leads for therapeutic innovation. (*Hypertension*. 2017;70:00-00. DOI: 10.1161/HYPERTENSIONAHA.117.09438.) • **Online Data Supplement**

Key Words: blood pressure ■ cardiovascular risk ■ complex traits ■ eSNP ■ GWAS ■ hypertension

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Genetic support for a drug target increases the likelihood of success in drug development,¹ and there is clear unmet need for novel therapeutic strategies to treat individuals with hypertension.² Several large studies have described blood pressure (BP) variant identification by genome-wide and targeted association approaches.^{3–19} Clinically, the most predictive BP traits for cardiovascular risk are systolic BP (SBP) and diastolic BP (DBP), reflecting roughly the peak and trough of the BP curve, and pulse pressure, the difference between SBP and DBP,²⁰ reflecting arterial stiffness. Using these 3 traits, we undertook a meta-analysis of 150 134 individuals from 54 genome-wide association studies (GWAS) of European ancestry with imputation based on the 1000 Genomes Project Phase 1. To minimize reporting of false-positive associations, we sought stringent evidence for significant independent replication in a further 228 245 individuals. We further followed up novel and previously reported association signals in multiple large gene expression databases and the largest kidney tissue gene expression resource currently available. Finally, we searched for enrichment of associated genes in biological pathways and gene sets and identified whether any of the genes were known drug targets or had tool molecules.

Materials and Methods

Studies Stage 1

Results from 54 independent European-ancestry studies, totaling 150 134 individuals, were included in the stage 1 meta-analysis: 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=23 049), 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). Full study names and general study information is given in Table S1 in the [online-only Data Supplement](#).

Study-Level Genotyping and Association Testing

Three quantitative BP traits were analyzed: SBP, DBP, and pulse pressure (difference between SBP and DBP). Within each study, individuals known to be taking antihypertensive medication had 15 mmHg added to their raw SBP value and 10 mmHg added to their raw DBP values.²¹ A summary of BP phenotypes in each study is given in Table S2. Association testing was undertaken according to a central analysis plan that specified the use of sex, age, age², and body mass index as covariates and optional inclusion of additional covariates to account for population stratification (Table S3). Trait residuals were calculated for each trait using a normal linear regression of the medication-adjusted trait values (mmHg) onto all covariates. The genotyping array, preimputation quality control filters, imputation software, and association testing software used by each study are listed in Table S4. Each participating study imputed genotypes based on the 1000 Genomes Project Phase 1 integrated release version 3 (March 2012) all ancestry reference panel.²² Imputed genotype

dosages were used to take into account uncertainty in the imputation. Association testing was performed using linear regression of the trait residuals onto genotype dosages under an additive genetic model. Methods to account for relatedness within a study were used where appropriate (Table S3). Results for all variants (single nucleotide polymorphisms [SNPs] and insertion/deletion polymorphisms [INDELS]) were then returned to the central analysis group for further quality control checks and meta-analysis.

Stage 1 Meta-Analysis

Central quality control checks were undertaken across all results sets. This included checks to ensure allele frequency consistency (across studies and with reference populations), checks of effect size and standard error distributions (ie, to highlight phenotype issues), and generation of quantile–quantile plots and genomic inflation factor lambdas to check for over- or underinflation 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. Inverse variance-weighted meta-analysis was undertaken. After meta-analysis, variants with a weighted minor allele frequency of <1% or N effective (product of study sample size and imputation quality summed across contributing studies) <60% were then excluded and meta-analysis genomic control lambda calculated and used to adjust the meta-analysis results.

Selection of Regions for Follow-Up

For each trait, regions of association were selected by ranking variants by *P* value, recording the variant with the lowest *P* value as a sentinel variant and then excluding all variants ± 500 kb from the sentinel and reranking the remaining variants. This was undertaken iteratively until all sentinel variants representing 1 Mb regions containing associations with $P < 10^{-6}$ had been identified. To identify additional signals represented by secondary sentinel variants within 500 kb of each of the sentinel variants, GCTA (the Genome-wide Complex Trait Analysis software)²³ was used to run conditional analyses (conditioned on the first sentinel variant) on each of the 1 Mb regions using GWAS summary statistics and linkage disequilibrium (LD) information from ARIC. This was done both for putatively novel regions and for regions that had previously been reported. A χ^2 test of heterogeneity of effect sizes across the 54 studies was run for each sentinel variant, and those with $P < 0.05$ for heterogeneity were excluded from further follow-up. Variants with $P < 10^{-6}$ after conditioning on the sentinel SNP (novel or known) in the region and for which any attenuation of the $-\log_{10} P$ value was <1.5 fold were also taken forward for replication.

Studies Stage 2

Data from 14 independent studies, totaling 87 360 individuals, and the first release of UK Biobank, totaling 140 886 individuals, were combined to replicate the findings from stage 1 (ie, totaling 228 245 individuals). Stage 2 study details, including full study names, are given in Table S6 and included 3C-Dijon (n=4061), Airwave (n=14 023), ASCOT-SC (n=2462), ASCOT-UK (n=3803), BRIGHT (n=1791), GAPP (n=1685), GoDARTs (n=7413), GS:SFHS (n=9749), HCS (n=2112), JUPITER (n=8718), LifeLines (n=13 376), NEO (n=5731), TwinsUK (n=4973), UK Biobank-CMC (n=140 886), and UKHLS (n=7462). Analysis was undertaken using the same methods as described for stage 1 studies. UK Biobank-CMC used a newer imputation reference panel than the other studies, and where a requested variant was not available, a proxy was used (next most significant *P* value with LD $r^2 > 0.6$ with original top variant). Results from all stage 2 studies were meta-analyzed using inverse variance-weighted meta-analysis. Two of the variants, rs1048238 and chr1:243458005:INDEL, were not available in the largest study in stage 2 (UK Biobank-CMC), and so proxy variants were selected (based on *P* value and LD).

Stage 1+Stage 2 Meta-Analysis

After meta-analysis of stage 1 and stage 2 results, signals with a $P > 5 \times 10^{-8}$ were excluded. Of the signals with a final $P < 5 \times 10^{-8}$,

support for independent replication within the stage 2 studies only was sought. Any signals that had $P < 5 \times 10^{-8}$ and evidence for independent replication in stage 2 alone indicated by $P < 8.2 \times 10^{-4}$ (Bonferroni correction for 61 tests) were reported as novel signals of association with BP. Any signals that were subsequently reported by other BP GWAS that were accepted for publication during the time this analysis was ongoing, or signals for which independence from another known signal could not be established, were removed from our list of novel signals at this stage (Table S5).

Genotype and Gene Expression

We searched for signals of association of genotype with gene expression for the 22 signals (including 8 novel) described in this study (Table S7) and all signals reported prior to our study (Table S10)^{3-16,18,24} in 3 whole-blood data sets, 1 kidney data set, and the GTEx (Genotype-Tissue Expression) multiple tissue data resource, which included whole blood.²⁵ We selected cis signals of association, which were significant after controlling for 5% false discovery rate. The 3 whole-blood expression quantitative trait loci (eQTL) data sets were the National Heart, Lung, and Blood Institute SABRe (Systems Approach to Biomarker Research in Cardiovascular Disease) initiative whole-blood eQTL resource (microarray, $n=5257$), NESDA-NTR (microarray, $n=4896$), BIOS (RNAseq, $n=2116$). The whole-blood data from GTEx was based on data from 338 samples. The kidney data set comprised 236 donor kidney samples from 134 donors.²⁶ Full details of each data set can be found in the [online-only Data Supplement](#). The source transcriptomic renal data as described²⁶ have been deposited in the GeneExpression Omnibus (NCBI) and are accessible online through GEO Series accession number GSE43974.

LD Lookup

The 1000 Genomes Project phase 3 release of variant calls was used (February 20, 2015) using 503 subjects of European ancestry.²² r^2 between the sentinel SNPs and all other biallelic SNPs within the corresponding 2 Mb area were calculated using the Tabix and PLINK software package (v1.07).^{27,28} Annotation was performed using the ANNOVAR software package.²⁹

Gene-Based Pathway Analysis

All genes identified in 3 or 4 of the whole-blood eQTL resources above (Table 2) and genes containing a nonsynonymous variant with $r^2 > 0.5$ with the sentinel variant (Table S14) were tested for enrichment of biological pathways and gene ontology (GO) terms using ConsensusPathDB³⁰ using a false discovery rate $< 5\%$ cutoff. Enriched pathways and GO terms containing genes only implicated by a single BP-associated variant were not reported.

Network Analysis

To construct a functional association network, we combined 2 prioritized candidate gene sets into a single query gene set as (1) genes mapping to the nonsynonymous SNPs in high LD ($r^2 > 0.5$) with the corresponding sentinel BP-associated SNP and (2) genes with eQTL evidence from 3 or 4 of the blood eQTL resources. Three sentinel SNPs (rs185819, rs926552, and rs805303) mapping to the HLA (human leukocyte antigen) region on chromosome 6 were excluded from downstream analyses. The single query gene set was then used as input for the functional network analysis.³¹ We used the Cytoscape³² software platform extended by the GeneMANIA³³ plugin (Data Version: August 12, 2014).³⁴ All the genes in the composite network, either from the query or the resulting gene sets, were then used for functional enrichment analysis against GO terms³⁵ to identify the most relevant GO terms using the same plugin.³⁴

DNase1 Hypersensitivity Overlap Enrichment Across Tissue and Cell Types

The functional element overlap analysis of the results of GWAS experiments (Forge tool v1.1)³⁶ was used to test for enrichment of overlap of BP SNPs in tissues and cell lines from the Roadmap and

ENCODE (Encyclopedia of DNA Elements) projects. All 164 SNPs were entered and 143 were included in the analysis. SNPs from 9 commonly used GWAS arrays were used to select background sets of SNPs for comparison, and 10 000 background repetitions were run. A Z score threshold of ≥ 3.39 (estimated false-positive rate of 0.5%) was used to declare significance.

Drug–Gene Interactions

Genes used for pathway and GO enrichment analyses were further investigated for potential druggable or drugged targets using DGIdb (drug gene interaction database).³⁷ Known drug–gene interactions were interrogated across 15 source databases in DGIdb and include all types of interactions. The analysis performed for druggability prediction included all 9 databases exclusively inspecting expert curated data only. We also evaluate genes for known tool compounds using ChEMBL (www.ebi.ac.uk/chembl/; version 22.1).

Results

The stage 1 discovery meta-analysis included 150 134 individuals (Tables S1 through S4 and Figures S1 and S2) and 7 994 604 variants with minor allele frequency $> 1\%$ and an effective sample size of at least 60% of the total. We used the widely used 2-stage design³⁸ and identified 61 signals in the discovery analysis that were candidates for novel BP signals ($P < 10^{-6}$ for any trait; Table S5). To ensure robustness of signals, we examined BP associations in an additional 228 245 individuals from 15 independent studies for replication, including 140 886 individuals from UK Biobank¹⁹ (Table S6). We used the most significant (sentinel) SNP and trait for each locus in replication (61 tests). Twenty-two putatively novel association signals were initially confirmed, showing significant evidence of replication in the independent stage-2 studies ($P < 8.2 \times 10^{-4}$, Bonferroni correction for 61 tests) and genome-wide significance ($P < 5 \times 10^{-8}$) in a meta-analysis across all 378 376 individuals (Table 1 and Table S7). Of these, 14 were subsequently published in 2 other studies^{17,19} which presented genome-wide significant associations with evidence of replication. A further 2 were highlighted as putative novel signals in one of those studies¹⁷ but had not been confirmed by replication. In our study, we report the 6 remaining novel signals, and the 2 previously unconfirmed signals (in *EBF2* and in *NFKBIA*), as novel signals. The 8 novel signals included 7 signals at 7 independent loci (Figure S3) and 1 novel independent signal near a previously reported hit near *TNXB* (Table S8 and Figure S4). The novel signals show both significant evidence of replication in the independent stage-2 studies ($P < 8.2 \times 10^{-4}$, Bonferroni correction for 61 tests) and genome-wide significance ($P < 5 \times 10^{-8}$) in a meta-analysis across all 378 376 individuals. The sentinel variants at all 8 signals were common (minor allele frequency $> 5\%$), and the novel secondary signal at *TNXB* was in high linkage disequilibrium ($r^2 > 0.8$) with a nonsynonymous SNP. With the exception of rs9710247, which was only significant for association with DBP, all signals were significantly associated ($P < 0.006$, Bonferroni corrected for 8 tests) with all 3 traits (Table 1 and Table S9).

We next sought to identify which genes might have expression levels that were associated with genotypes of the BP-associated variants reported in this study and others. Strong evidence of an association with expression of a specific gene may provide clues as to which gene(s) might be functionally relevant to that signal. We took the 139 BP association signals

Table 1. Novel Genome-Wide Significant Signals of Association

Variant ID (Noncoded/Coded Allele), Chr:Position, Nearest Gene(s) (Type*)	CAF	Results for Most Significant Trait									Stage 1+Stage 2 Meta-Analysis <i>P</i> Values for All Traits		
		Stage 1			Stage 2			Stage 1+Stage 2			SBP	DBP	PP
		Beta (SE)	<i>P</i> Value	Neff	Beta (SE)	<i>P</i> Value	Neff	Beta (SE)	<i>P</i> Value	Neff			
SBP													
rs1048238 (C/T), 1:16341649, <i>HSPB7</i> (3'UTR)	0.571	0.366 (0.074)	8.09E-07	140299	NA	NA	NA	NA	NA	NA	NA	NA	NA
rs848309 (proxy) (T/C), 1:16308447	0.567	0.347 (0.072)	1.70E-06	146755	0.347 (0.071)	9.10E-07	140462	0.347 (0.051)	7.07E-12‡	287217	7.07E-12‡	1.07E-10‡	5.48E-06
rs185819 (T/C),† 6:32,050,067, <i>TNXB</i> (ns)	0.513	0.534 (0.073)	1.93E- 13‡	142397	0.277 (0.053)	1.49E-07	221748	0.365 (0.043)	1.04E-17‡	364144	1.04E-17‡	2.24E-11‡	8.50E-15‡
rs6557876 (C/T), 8:25,900,675, <i>EBF2</i>	0.252	-0.411 (0.084)	8.50E-07	143653	-0.350 (0.060)	5.66E-09‡	225803	-0.371 (0.049)	2.85E-14‡	369457	2.85E-14‡	2.50E-10‡	1.51E-08‡
rs35783704 (G/A), 8:105,966,258, <i>LRP12/ZFPM2</i>	0.109	-0.609 (0.121)	4.96E-07	133924	-0.310 (0.089)	4.78E-04	215528	-0.414 (0.072)	7.08E-09‡	349452	7.08E-09‡	1.60E-06	2.92E-07
rs73099903 (C/T), 12:53,440,779, <i>LOC283335</i>	0.074	0.768 (0.143)	8.05E-08	136064	0.396 (0.098)	5.32E-05	207253	0.515 (0.081)	1.95E-10‡	343318	1.95E-10‡	4.53E-06	5.46E-08
rs8904 (G/A), 14:35,871,217, <i>NFKBIA</i> (3'UTR)	0.375	0.377 (0.076)	6.76E-07	140424	0.278 (0.054)	2.31E-07	224771	0.311 (0.044)	1.31E-12‡	365195	1.31E-12‡	1.13E-04	3.44E-12‡
rs57927100 (C/G), 17:75,317,300, <i>SEPT9</i>	0.258	-0.489 (0.086)	1.10E- 08‡	136624	-0.220 (0.061)	3.12E-04	210563	-0.310 (0.050)	4.04E-10‡	347188	4.04E-10‡	1.16E-10‡	1.81E-05
DBP													
rs9710247 (A/G), 19:40,760,449, <i>AKT2</i>	0.447	0.252 (0.051)	8.11E-07	109695	0.129 (0.032)	5.76E-05	198332	0.164 (0.027)	1.61E-09‡	308028	3.82E-02	1.61E-09‡	5.03E-01

Results from stage 1 and stage 2, and the meta-analysis of stage 1 and stage 2, for all novel genome-wide significant signals of association. *P* values of association for all 3 traits from a meta-analysis of stages 1 and 2 are also presented. Results from proxy SNPs are indicated by (proxy); rs848309 was a proxy SNP for rs1048238, and rs10926988 was a proxy SNP for chr1:243458005:INDEL. CAF indicates coded allele frequency; DBP, diastolic blood pressure; Neff, effective sample size; ns, nonsynonymous; PP, pulse pressure; s, synonymous; SBP, systolic blood pressure; and UTR, untranslated region.

*For intragenic variants, the nearest genes are listed; all other variants are intronic unless indicated otherwise.

†Novel signal at previously reported locus.

‡Genome-wide significant *P* values ($P < 5 \times 10^{-8}$).

reported prior to these studies^{17,19} and 22 novel signals of association identified and confirmed in this study and 2 contemporaneous studies^{3-19,24} (Table S10) and searched for evidence of association with gene expression in whole blood (4 studies, total $n=12\,607$; supporting information in the [online-only Data Supplement](#)) and in kidney tissue ($n=134$, the largest kidney eQTL resource currently available). Although of unclear direct relevance to BP, whole blood was studied because of the availability of large data sets enabling a powerful assessment of expression patterns that are likely present across multiple cell and tissue types. Similarly, circulating blood cells have been used for ion transport experiments in the past, and altered ion transport levels in erythrocytes were linked to hypertension.³⁹ Kidney was chosen because of the many renal pathways that regulate BP and outstanding questions about the relevance of kidney pathways to the genetic component of BP regulation in the general population.^{3,15} eQTL signals were filtered by false discovery rate ($<5\%$), and we examined *cis* (within 1 Mb) associations only (supporting information in the [online-only Data Supplement](#)).

The 4 blood eQTL data sets were NESDA-NTR,^{40,41} SABRe,¹⁵ the BIOS resource,⁴² and GTEx²⁵ (supporting information in the [online-only Data Supplement](#)). The BIOS resource ($n=2116$) has not previously been used in the analysis of BP associations, and findings from NESDA-NTR and SABRe have been reported for a subset of the previously published signals.^{16,18} For a total of 369 genes, gene expression was associated with the BP SNP in ≥ 1 of the 4 blood data sets at experiment-wide significance (Table S11). This included 14 genes for 6 of the 8 novel signals. For 110 genes, we found eQTL evidence in 2 out of 4 data sets (Figure), including 4 genes for 2 of the novel signals: *EIF4B* and *TNS2* for rs73099903 and *MAP3K10* and *PLD3* for rs9710247. SNP rs73099903 was in strong LD ($r^2 > 0.9$), with the SNP most strongly associated with *TNS2* expression in the BIOS resource. *TNS2* encodes a tensin focal adhesion molecule and may have a role in renal function.⁴³

For 48 genes, we found evidence in 3 out of the 4 resources (Table 2), suggesting robustness of the SNP–gene expression

Table 2. BP-Associated SNPs Associated With Expression of the Same Gene Across 4 or 3 Independent Whole-Blood eQTL Resources and the Kidney Resource

Sentinel SNP	Chr	Position	Gene	Blood Data Sets	Top eQTL	Signal in Other Tissue(s) in GTEx	Signal in Kidney	eQTL Signal Previously Reported
Signal in 4 whole-blood eQTL resources								
rs17367504	1	11862778	<i>CLCN6</i>	YYYY		Y		Y
rs2169137	1	204497913	<i>MDM4</i>	YYYY	Y	Y		Y
rs10926988	1	243483279	<i>SDCCAG8</i>	YYYY		Y		
rs319690	3	47927484	<i>MAP4</i>	YYYY	Y	Y		Y
rs12521868	5	131784393	<i>SLC22A5</i>	YYYY		Y		
rs900145	11	13293905	<i>ARNTL</i>	YYYY		Y		Y
rs1060105	12	123806219	<i>CDK2AP1</i>	YYYY	Y	Y	Y	
rs1378942	15	75077367	<i>SCAMP2</i>	YYYY				
rs1126464	16	89704365	<i>CHMP1A</i>	YYYY		Y		Y
rs1126464	16	89704365	<i>FANCA</i>	YYYY				Y
rs12946454	17	43208121	<i>DCAKD</i>	YYYY		Y	Y	Y
Signal in 3 (out of 4) whole-blood eQTL resources								
rs17367504	1	11862778	<i>MTHFR</i>	YYN		Y		Y
rs871524	1	38411445	<i>FHL3</i>	NYYY		Y		
rs871524	1	38411445	<i>SF3A3</i>	NYYY		Y		
rs4660293	1	40028180	<i>PABPC4</i>	YYN	Y	Y		Y
rs6749447	2	169041386	<i>STK39</i>	YYN	Y			
rs347591	3	11290122	<i>ATG7</i>	YYN		Y		
rs319690	3	47927484	<i>ZNF589</i>	YYNY		Y		
rs12521868	5	131784393	<i>SLC22A4</i>	YYN		Y		
rs1563788	6	43308363	<i>CRIP3</i>	YYN	Y			Y
rs10943605	6	79655477	<i>PHIP</i>	YYN	Y	Y		Y
rs4728142	7	128573967	<i>IRF5</i>	NYYY		Y	Y	Y
rs4728142	7	128573967	<i>TNPO3</i>	YYN			Y	
rs2898290	8	11433909	<i>BLK</i>	YYN		Y		
rs2898290	8	11433909	<i>FAM167A</i>	NYYY		Y		
rs2898290	8	11433909	<i>FDFT1</i>	YYN		Y		
rs2071518	8	120435812	<i>NOV</i>	YYN		Y		
rs76452347	9	35906471	<i>TPM2</i>	YYN				
rs10760117	9	123586737	<i>MEGF9</i>	YYN		Y		Y
rs4494250	10	96563757	<i>HELLS</i>	YYN				Y
rs11191548	10	104846178	<i>NT5C2</i>	YYN	Y			
rs661348	11	1905292	<i>TNNT3</i>	NYYY		Y		
rs2649044	11	9763969	<i>SBF2</i>	YYN				
rs2649044	11	9763969	<i>SWAP70</i>	YYN	Y	Y		?
rs7129220	11	10350538	<i>ADM</i>	YYN				Y
rs7103648	11	47461783	<i>MYBPC3</i>	YYN				
rs3741378	11	65408937	<i>CTSW</i>	YYN				
rs7302981	12	50537815	<i>LIMA1</i>	YYN				Y
rs7302981	12	50537815	<i>ATF1</i>	YYNY		Y		

(Continued)

Table 2. Continued

Sentinel SNP	Chr	Position	Gene	Blood Data Sets	Top eQTL	Signal in Other Tissue(s) in GTEx	Signal in Kidney	eQTL Signal Previously Reported
rs1036477	15	48914926	<i>FBN1</i>	YNY				
rs1378942	15	75077367	<i>CSK</i>	YYN	Y	Y		Y
rs1378942	15	75077367	<i>MPI</i>	NYY		Y		
rs1378942	15	75077367	<i>ULK3</i>	YNY		Y		Y
rs12946454	17	43208121	<i>NMT1</i>	YYN				Y
rs2304130	19	19789528	<i>GATAD2A</i>	YYN				
rs867186	20	33764554	<i>EIF6</i>	NYY		Y		
rs6095241	20	47308798	<i>PREX1</i>	YYN				
rs9306160	21	45107562	<i>RRP1B</i>	YNY	Y	Y		

Signals of association of SNP genotype and gene expression in other nonblood tissues in GTEx and in kidney are also indicated. Blood data set order: (1) SABRe, (2) NESDA-NTR, (3) BIOS, and (4) GTEx (whole-blood). Top eQTL: top GWAS SNP is top eQTL SNP (or in high LD, $r^2 > 0.9$, with top eQTL SNP) in at least 1 data set. eQTL signal previously reported: Genes for which eQTL signals have been previously reported for that sentinel SNP.^{15,16,18} For full list, see Table S12 in the [online-only Data Supplement](#). eQTL indicates expression quantitative trait loci; GWAS, genome-wide association studies; GTEx, genotype-tissue expression; and LD, linkage disequilibrium; and SABRe, Systems Approach to Biomarker Research in Cardiovascular Disease.

correlation signal and highlighting those genes as potential candidates in genetic BP regulation. Of the 48 genes, 28 have not previously been described in eQTL analyses using BP-associated SNPs, and all were correlated with previously reported BP association signals.

In the kidney data set (TransplantLines),²⁶ there was association of gene expression and genotype for 9 SNPs and 13 genes (Table 2 and Figure; Table S12). Nine of the SNP–gene expression associations were also observed in the whole-blood eQTL data sets, suggesting that those signals may not be unique to the kidney. We report 3 signals that were unique to the kidney and not previously reported (*C4orf34*, *HIP2*, and *ASIC1*) and confirm a previously reported kidney eQTL signal for an antisense RNA for *PSMD5*.¹⁵ The same SNP was also an eQTL for *PSMD5* itself in both blood and kidney. *ASIC1* encodes the acid sensing ion channel subunit 1, which may interact (and be coexpressed) with ENaC subunits, which mediate transepithelial Na transport in the distal nephron of the kidney.⁴⁴ The comparatively small number of signals using kidney tissue (Table 2 and Figure) compared with whole blood could be because of the small sample size. Complete GTEx results are given in Table S13.

For genes implicated by eQTL information from whole blood, we tested for enrichment of biological pathways and GOs. We noted enrichment of the 48 genes implicated by 3 or 4 blood eQTL resources (Table 2) and a further 54 genes containing a nonsynonymous variant with $r^2 > 0.5$ with the top SNP (Table S14) in pathways and ontology terms related to actin and striated muscle (Tables S15 and S16). Network analysis using the same genes highlighted further GO terms relating to muscle function, particularly cardiac muscle (Table S17). We tested the overlap of 161 non-HLA BP-associated variants with DNase hypersensitivity sites identified in the Roadmap and ENCODE cell lines and identified an overall enrichment in multiple cell and tissue types, including heart, kidney, and smooth muscle (Figure S5).

We next investigated these genes for potential suitability as drug targets (druggability), known tool compounds, and

clinically approved drugs using DGIdb³⁷ (Table S18). Twelve genes had known drugs, including 4 genes with known antihypertensive drugs. We noted that drugs modulating all but 1 of the 12 drugged targets had a reported influence on BP, either as a primary antihypertensive indication or as a reported side effect of raised BP. Twenty additional genes were predicted druggable, among these 7 genes have known small molecule tool modulators, based on a query of the ChEMBL database (www.ebi.ac.uk/chembl/db/; version 22.1).

Discussion

Enhanced discovery of BP loci increases the potential targets for therapeutic advances. After major advances in the number of BP loci known over the last years and months, we report 8 novel signals that implicate 5 regions of the genome not previously connected to BP regulation.

Six of the 8 novel signals we report had not previously been reported. Two signals (in *EBF2* and *NFKBIA*) have been suggested previously but without evidence for replication.¹⁷ For these 2 signals, we present, for the first time, stringent evidence of replication, confirming their relevance to BP genetics.

The path from signal to genes is the essential next step toward realizing the therapeutic potential of a genetic locus and understanding the mechanisms of BP regulation. We have used several large eQTL resources as a first step to realize this objective. As expected, we observed that even across eQTL studies of the same tissue, there is limited overlap in experiment-wide significant signals, suggesting either biological variability (differences in the characteristics of the samples or in the methods for extraction and processing of mRNA in each of the studies), technology-specific differences in coverage of genes (use of RNAseq data for the BIOS blood data set and microarray-based expression levels for the kidney and other blood data sets), or the possibility of false-positive results despite stringent within-experiment significance thresholds. We were unable to distinguish these scenarios using the data available to us, but by selecting genes that were significant in at least 3



Figure. Overlap of expression quantitative trait loci (eQTL) evidence from 4 whole-blood and 1 kidney resource. The figure indicates overlap of evidence for eQTLs from 4 whole-blood studies (SABRe, NESDA-NTR, BIOS, and GTEx) and from 1 kidney resource (TransplantLines). Every colored line indicates that this gene was analysis-wide significant in a given resource. Only genes identified by at least 2 resources are shown. The genes are sorted by genomic position on the y axis.

resources, and therefore robust to these differences, we identified 48 genes as candidates for further study. These results are limited by the availability of large eQTL resources for whole blood only, which precludes well-powered comparisons across tissue types, particularly, as the origin of BP control is unlikely to be located in the blood. Enrichment and pathway analyses

using these genes, and genes containing a correlated functional variant, highlight the potential relevance of muscular tissue and pathways, compatible with a vascular and cardiac origin of BP genetics, extending previous evidence.¹⁵ We identify several drugged targets in the pathways identified, including 4 existing hypertension targets. Other drugs identified are not suitable candidates for repositioning to hypertension because most were reported in adverse events to raise BP; however, the targets would be valid for investigation using a reverse mechanism, for example, agonism in place of inhibition. We also identified 7 genes with small molecule tool modulators (mainly inhibitory or binding). These molecules and targets might be suitable candidates for further investigation to build a target validation case to support clinical investigation in hypertension.

Among the genes implicated in our eQTL, analyses were several for which there is already some evidence that they are relevant to BP regulation. The intronic SNP rs10926988 was independently associated with expression of *SDCCAG8* in all 4 whole-blood resources. Rare mutations in *SDCCAG8* cause Bardet-Biedl syndrome, which features hypertension. Expression levels of *MYBPC3* were correlated with rs7103648¹⁵ in the 3 largest blood eQTL resources (ie, SABRe, NESDA-NTR, and BIOS). *MYBPC3* encodes the cardiac isoform of myosin-binding protein C, which is expressed in heart muscle, and mutations in *MYBPC3* are known to cause familial hypertrophic cardiomyopathy.⁴⁵

This study has several limitations. Given the nature of statistical power for genome-wide association analyses, the sample size is limited, even though this is one of the largest efforts in BP GWAS undertaken to date. The study would clearly have benefited from the availability of larger eQTL resources on multiple tissues in sample sizes even larger than those available today. Our analyses were limited to *cis* signals, and future analyses, with larger sample sizes, might also consider *trans* signals.

Perspectives

Our study reports robust novel BP association signals and reports new candidate BP genes, contributing to the transition from variants to genes to explain BP variation. These genes now require further functional validation to establish their potential as drug targets. Our study additionally highlights the challenges of combining and interpreting data from multiple eQTL studies and emphasizes the need for harmonization of data and development of new eQTL resources for multiple tissue types.

In summary, our study reports novel BP association signals and reports new candidate BP genes, contributing to the transition from variants to genes to explain BP variation.

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Author Contributions

Secondary Analyses

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MESA: Study phenotyping, J.I. Rotter; Genotyping or analysis, W. Palmas, X. Guo, J.I. Rotter, J. Yao; Study PI, W. Palmas.

B58C: Study phenotyping, D.P. Strachan; Genotyping or analysis, D.P. Strachan; Study PI, D.P. Strachan.

COLAUS: Study phenotyping, P. Vollenweider; Genotyping or analysis, M. Bochud and Z. Kutalik; Study PI, P. Vollenweider.

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KORA S4: Genotyping or analysis, J.S. Ried; Study PI, A. Peters.

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INGI-FVG: Genotyping or analysis, D. Vuckovic, M. Brumat, and M. Cocca; Study PI, P. Gasparini.

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MIGEN: Study phenotyping, R. Elosua, J. Marrugat, S. Kathiresan, and D. Siscovick; Genotyping or analysis, R. Elosua, S. Kathiresan, and D. Siscovick; Study PI, S. Kathiresan.

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LBC1936: Study phenotyping, I.J. Deary and A.J. Gow; Genotyping or analysis, L.M. Lopez, G. Davies, and A.J. Gow; Study PI, I.J. Deary.

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FUSION: Genotyping or analysis, A.U. Jackson; Study PI, J. Tuomilehto, M. Boehnke, and F. Collins.

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Disclosures

We declare competing financial interests (see corresponding section in the [online-only Data Supplement](#)).

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Novelty and Significance

What Is New?

- The root origin of hypertension and, hence, blood pressure (BP) variability in the population remains unclear.
- This study adds data to explain the genetic basis of BP variability and identifies genes likely active in BP-regulating pathways.

What Is Relevant?

- The results are of relevance for scientists, clinicians, and pharmacologists interested in hypertension.

- The BP loci and the BP genes identified constitute new leads for the understanding of BP pathogenesis and possibly therapeutic innovation.

Summary

Using 1000 Genomes Project–based imputation in 150 134 European ancestry and independent replication in a further 228 245 individuals, we contribute 8 replicated BP loci to the collection of loci currently known. Using these and previous data, 48 BP genes are identified for priority follow-up.

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Online supplement

Novel blood pressure locus and gene discovery using GWAS and expression datasets from blood and the kidney

Running title: Novel blood pressure locus and gene discovery

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Studies contributing to discovery (Stage 1) of signals of association with systolic (SBP) and diastolic blood pressure (DBP), and Pulse Pressure (PP)

All studies contributing genome-wide association results for SBP, DBP and PP to the discovery meta-analysis undertook genome-wide imputation to the 1000 Genomes Project reference panel. Study details are given in **Supplementary Table 1 (S1)** (including study design, ethnicity and key references), **Supplementary Table 2 (S2)** (overall descriptive statistics of SBP, DBP, PP, hypertension, age, sex and BMI, and blood pressure measurement details), **Supplementary Table 3 (S3)** (quality control, association testing method and adjustments for ancestry and relatedness) and **Supplementary Table 4 (S4)** (genotyping and imputation details).

Studies contributing association results for variants selected for replication/follow-up (Stage 2)

Details of all studies contributing data for the 61 variants followed-up to stage 2 are given in **Supplementary Table 5 (S5)**.

Studies contributing eQTL data

SABRe

The expression quantitative trait locus (eQTL) analysis was performed in 5,257 whole blood samples of Framingham Heart Study (FHS) Offspring and Generation 3 cohort participants having both genotypic and expression datasets. The genotypic data came from Affymetrix 500K and 50K MIPS platforms, imputed to the 1000-Genomes “Cosmopolitan” panel. Only 8,510,936 variants having minimum allele frequency (MAF) ≥ 0.01 and imputation $R^2 \geq 0.3$ were chosen. The expression data came from Affymetrix Human Exon Array ST v1.0, processed using robust multi-chip average (RMA) algorithm under Affymetrix Power Tools (APT), yielding a total of 17,873 transcripts in log base 2 values. The association was performed on the expression values as the dependent variable, additive genetic dosage as an independent variable, adjusted for sex, age, imputed blood cell fractions, 20 factors of Bayesian confounding factors (PEER¹), and familial correlations. The full details of eQTL analysis can be found in Joehanes, et al. Integrated Genome-wide Analysis of Expression Quantitative Trait Loci Identifies Putative Disease-Related Genes and Pathways.

The linkage disequilibrium (LD) database for the FHS was computed from 8,481 genotypic samples from individuals of FHS cohorts (Original, Offspring, and Generation 3), using the squared Pearson correlation of the imputed additive genotypic dosage, as defined by Hill and Robertson 1968². All pairwise LDs of at least 0.1 were stored in the database and were used in this analysis.

NESDA/NTR

Subjects for eQTL analysis: The two parent projects that supplied data for the eQTL analysis are large-scale longitudinal studies: the Netherlands Study of Depression and Anxiety (NESDA)³ and the Netherlands Twin Registry (NTR)⁴. NESDA and NTR studies were approved by the Central Ethics Committee on Research Involving Human Subjects of the VU University Medical Center, Amsterdam (institutional review board [IRB] number IRB-2991 under Federal wide Assurance 3703; IRB/institute codes: NESDA 03-183 and NTR 03-180). All participants provided written informed consent. The sample used for eQTL analysis consisted of 4,896 subjects with European ancestry (1,880 unrelated subjects from NESDA, 559 MZ twin pairs, 102 siblings of MZ twins (one per MZ twin pair), 594 DZ

twin pairs, 111 siblings of DZ twins (one per DZ twin pair), 51 parent-sibling trios and 344 unrelated subjects from NTR). The age of the participants ranged from 17 to 88 years (mean=38, $SD=13$); 65% of the sample was female.

Blood sampling, RNA extraction, and RNA expression measurement: Study protocols and biological sample collection methods were harmonized between NTR and NESDA. RNA processing and measurements have been described in detail previously^{5,6}. Venous blood samples were drawn in the morning after an overnight fast. Heparinized whole blood samples were transferred within 20 minutes of sampling into PAXgene Blood RNA tubes (Qiagen, Valencia, California, USA) and stored at -20°C . Gene expression assays were conducted at the Rutgers University Cell and DNA Repository. Samples were hybridized to Affymetrix U219 arrays (Affymetrix, Santa Clara, CA) containing 530,467 probes summarized in 49,293 probe sets. Array hybridization, washing, staining, and scanning were carried out in an Affymetrix GeneTitan System per the manufacturer's protocol. Gene expression data were required to pass standard Affymetrix QC metrics (Affymetrix expression console) before further analysis. We excluded from further analysis probes that did not map uniquely to the hg19 (Genome Reference Consortium Human Build 37) reference genome sequence, as well as probes targeting a messenger RNA (mRNA) molecule resulting from transcription of a DNA sequence containing a single nucleotide polymorphism (based on the dbSNP137 common database). After this filtering step, data for analysis remained for 423,201 probes, which could be summarized into 44,241 probe sets targeting 18,238 genes. Normalized probe set expression values were obtained using Robust Multi-array Average (RMA) normalization as implemented in the Affymetrix Power Tools software (APT, version 1.12.0, Affymetrix). Data for samples that displayed a low average Pearson correlation with the probe set expression values of other samples, and samples with incorrect sex-chromosome expression were removed, leaving 4,896 subjects for analysis.

Gene expression normalization: Inverse quantile normal transformation was applied for each expression probe set to obtain normal distributions. The transformed probeset data were then residualized by multiple linear regression with respect to the covariates sex, age, body mass index (kg/m^2), blood hemoglobin level, smoking status, several technical covariates (plate, well, hour of blood sampling, lab, days between blood sampling and RNA extraction and average correlation with other samples) and the scores on three principal components (PCs) as estimated from the imputed SNP genotype data⁷ using the EIGENSOFT package. The residuals resulting from the linear regression analysis of the probe set intensity values onto the covariates listed above were subjected to a principal component analysis, with the aim to further filter out environmental variation from the data⁸. For each principal component a genome-wide association study was performed, and the first 50 principal components without genome-wide significant SNP associations were removed from the residualized probeset data before eQTL analysis.

DNA extraction and SNP genotyping and imputation: DNA was extracted from peripheral blood or buccal swabs as has described previously⁹. SNP genotype pre-imputation quality control, haplotype phasing and 1000 Genomes imputation were performed as described previously¹⁰. Imputed SNP genotypes were coded into reference allele dosage format, and filtered at $\text{MAF}>0.01$ and $\text{HW } P>1\text{E}-04$ resulting in 8,158,830 remaining SNPs for eQTL analysis.

eQTL analysis and FDR based on permutations accounting for relatedness: eQTL effects were detected with a linear model approach using MatrixeQTL¹¹ with expression level as dependent variable and SNP genotype values as independent variable. To account for relatedness of the NTR subjects, permutations were performed where in each permutation the relatedness was preserved (i.e, in each permutation the genotypes of the MZ twin pairs were assigned the expression of a random MZ twin pair, the genotypes of the DZ twin pairs were assigned the expression of a random DZ twin pair, the genotypes of the MZ twin pairs with sibling were assigned the expression of a random MZ twin pair with sibling, the genotypes of the parent-sibling trios were assigned the expression of a random parent-sibling trios and the genotypes of the unrelated subjects were

assigned the expression of a random subject from the group of unrelated subjects). For each permutation the complete *cis* or *trans* eQTL analysis was repeated, and after each permutation the *P*-value threshold for rejecting at $FDR < 0.05$ was computed. This can be done in 2 ways: 1) divide the total number of significant eQTLs in the permuted data by the total number of significant eQTLs in the unpermuted data (=false positives/true positives) or 2) divide the total number of probesets with a significant eQTL in the permuted data by the total number of probesets with a significant eQTLs in the unpermuted data. We used the the second method which is more conservative and was proposed by⁸ to account for large LD blocks with strong eQTL effects that inflate the FDR when using the first method. Similar as what was observed previously⁸ only 10 permutations were needed to have the *P*-value threshold corresponding to $FDR < 5\%$ converging. Of note, the eQTL *P*-values reported in this manuscript are based on the complete sample with related subject and thus are too liberal: however the FDR takes into account the family structure and should be used to draw conclusions. The reported betas from the linear models can be correctly estimated from samples containing related subjects.

eQTL effects were defined as *cis* when probe set–SNP pairs were at distance $< 1\text{M}$ base pairs (Mb), and as *trans* when the SNP and the probe set were separated by more than 1 Mb on the genome according to hg19. For each probe set that displayed a statistically significant association with at least one SNP in the *cis* region, we identified the most significantly associated SNP (top eQTL). Conditional eQTL analysis was carried out by first residualizing probeset expression using the corresponding top eQTL and then repeating the eQTL analysis using the residualized data.

For this analysis, of the 164 SNPs requested, 12 were not available in the NESDA/NTR dataset leaving 152 for further analysis.

BIOS

eQTL analyses performed by the BIOS consortium have been described previously¹². The method described in these papers are summarized below. Genotype data were harmonized towards the Genome of the Netherlands (GoNL)¹³ using Genotype Harmonizer and subsequently imputed per cohort using Impute2 using the GoNL reference panel (v5). We removed SNPs with an imputation info-score below 0.5, a HWE *P*-value smaller than 10^{-4} , a call rate below 95% or a minor allele frequency smaller than 0.05. Total RNA from whole blood was deprived of globin using Ambions GLOBINclear kit and subsequently processed for sequencing using Illumina's Truseq version 2 library preparation kit. Paired-end sequencing of 2x50bp was performed using Illumina's Hiseq2000, pooling samples at 10 per lane, and aiming for $>15\text{M}$ read pairs per sample. Finally, read sets per sample were generated using CASAVA, retaining only reads passing Illumina's Chastity Filter for further processing. The quality of the raw reads was checked using FastQC. The adaptors identified by FastQC (v0.10.1) were clipped using cutadapt (v1.1) applying default settings (min overlap 3, min length). Sickle (v1.200) (<https://github.com/najoshi/sickle>) used to trim low quality ends of the reads (min length 25, min quality 20). Read alignment was performed using STAR 2.3.0e. To avoid reference mapping bias all GoNL SNPs with $MAF > 0.01$ in the reference genome were masked. Read pairs with at most 8 mismatches, mapping to at most 5 positions were used. Mapping statistics from the BAM files were acquired through Samtools flagstat (v0.1.19-44428cd). The 5' and 3' coverage bias, duplication rate and insert sizes were assessed using Picard tools (v1.86). We estimated expression on the gene, exon, exon ratio and polyA ratio levels using Ensembl v.71 annotation (which corresponds to Gencode v.16). Overlapping exons (on either of the two strands) were merged into meta-exons and expression was quantified for the whole meta-exon. For that, custom scripts were developed which uses coverage per base from coverageBed and intersectBed from the Bedtools suite (v2.17.0) and R (v2.15.1). This resulted in base counts per exon or meta-exon. Expression data was first normalized using Trimmed Mean of M-values (TMM). Then expression values were log₂ transformed, probe and sample means were centred to zero. To correct for batch effects, principal component analysis (PCA) was run on the sample correlation matrix and the first 25

PCs were removed. We saw that removing these PCs resulted in highest number of eQTLs detected. To ascertain that none of these 25 PCs are under genetic control, we ran separate QTL mapping on each principal component and ensured that there were no SNPs associated with them. After QC, data was available from 2,116 samples. Data was available for 123 of the 164 blood pressure associated SNPs. For each of the 123 SNPs, local (*cis*, genes < 1 MB from the SNP) effects were identified by computing Spearman rank correlations between SNPs and local gene expression. FDR was computed based on permutations¹². For each of the significant associations, the genes were selected, the strongest eQTLs were identified for these genes sites, and LD between these strongest eQTLs and the corresponding SNP identified in the GWAS were computed. LD was computed using the European 1000G reference set.

TransplantLines eQTL data (kidney)

We performed an expression quantitative trait locus (eQTL) analysis in order to identify regulatory variants associated with the ICBP SNPs, using a gene-expression database from kidney biopsy specimens. The TransplantLines eQTL cohort used for the kidney analysis is part of a donor cohort for which gene expression results have been described previously¹⁴. The dataset includes kidneys from living donors, donated after brain death and donated after cardiac death (non-heart-beating). Time of biopsy (that is, before transplantation (T1), before reperfusion (T2) and after reperfusion (T3)) was recorded as well. For some donors multiple biopsies from different time points were taken. In addition, for some donors biopsies from both kidneys were available.

Samples were genotyped on the Illumina CytoSNP 12 v2 array and imputed using the 1000Genomes Phase 1 ALL reference panel¹⁵ using Impute2¹⁶. Expression and genotype data were available for 236 kidney biopsies of 134 donors. Of the 164 SNPs identified by the ICBP consortium, two were not present in our dataset (chr 6: rs200999181; chr 9: rs9710247) and three were removed because of their proximity to the HLA region, leaving 159 SNPs available for eQTL analysis. In this study we only tested *cis* effects meaning that the probe was at a distance < 1Mb from the SNP on the genome according to GRCh37/hg19. Mixed model analyses were carried out in R¹⁷ to account for multiple samples from a donor (package lme3 version 1.1.12¹⁸). SNP, sex, age, donor type, time of biopsy, and the first three principal components from the genotype data were included in the model as fixed effects; and sample ID was included as a random effect. Residuals of gene expression values after adjusting for the first 50 expression principal components to filter out environmental variation⁸ were used as dependent variable. Probes with a false discovery rate <5% were considered statistically significant.

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Supplementary Table legends

Supplementary Table 1 (Table S1): Study design summary information for each of the studies contributing to Stage 1.

Details include study acronym, full study name, epidemiological study design, and total study sample size, information about ascertainment, ethnicity and origin and references (as PubMed ID [PMID]).

Supplementary Table 2 (Table S2): Summaries of blood pressure phenotypes and covariates for all studies contributing to Stage 1.

Mean, median, standard deviation (SD), minimum (min) and maximum (max) values for the blood pressure phenotypes being analysed (SBP, DBP and PP) and covariates (age, Body Mass Index [BMI]) in all stage 1 studies separately. Individuals were assigned as hypertension cases if they had SBP ≥ 140 , or DBP ≥ 90 , or used antihypertensive or blood pressure lowering medication. Method of blood pressure measurement is included.

Supplementary Table 3 (Table S3): Summaries of methods used to adjust for population stratification and kinship for all studies contributing to Stage 1.

PCA: Principal Components Analysis, PC: Principal Component. IBS: Identity By State.

Supplementary Table 4 (Table S4): Summary of genotyping and imputation strategy for all studies contributing to Stage 1.

HWE; Hardy-Weinberg Equilibrium P value threshold used for exclusion. MAF; Minor Allele Frequency.

Supplementary Table 5 (Table S5): Results for all 61 variants followed up in stage 2

Stage 2 results are shown separately for UK Biobank_CMC and all other replication studies separately and meta-analysed. The final column (Conclusion) includes an explanation as to why each signal was either classed as a novel signal or otherwise. Top_trait: trait for which the variant was found to be most strongly associated in Stage 1 and for which it was followed up in Stage 2. Se: standard error. gc: Genomic control correction applied. Neff: N effective (sum of the products of imputation quality and sample size for each contributing study). Results for rs1048238 and chr1:243458005:l were not available from UK Biobank_CMC and so proxy SNPs rs848309 and rs10926988 were selected as they had the next most significant P value, were in LD ($r^2 > 0.6$) with the original sentinel variants and were measured in UK Biobank_CMC.

Supplementary Table 6 (Table S6): Stage 2 study details.

Details include study acronym, full study name, epidemiological study design, and total study sample size, information about ascertainment, ethnicity and origin and references (as PubMed ID [PMID]). Mean, median, standard deviation (SD), minimum (min) and maximum (max) values for the blood pressure phenotypes being analysed (SBP, DBP and PP) and covariates (age, Body Mass Index [BMI]) in all stage 1 studies separately. Individuals were assigned as hypertension cases if they had SBP ≥ 140 , or DBP ≥ 90 , or used antihypertensive or blood pressure lowering medication. Method of blood pressure measurement is included. PCA: Principal Components Analysis, PC: Principal Component. IBS: Identity By State. HWE; Hardy-Weinberg Equilibrium P value threshold used for exclusion. MAF; Minor Allele Frequency. *For UK Biobank_CMC, an additional 52 individuals were included in the HTN analysis as they used antihypertensive or blood pressure lowering medication (but did not have full data for SBP, DBP or PP and so were not included in the SBP, DBP and PP analyses).

Supplementary Table 7 (Table S7): a) Stage 1 and Stage 2 results separately and combined for all 22 novel signals of association with blood pressure b) Stage 1 and Stage 2 results separately and combined for a further 14 signals of association with blood pressure that were initially confirmed as putatively novel signals in this study but were subsequently reported in Hoffman et al 2016 and Warren et al 2017.

Results are shown separately for Stage 1, for the UK Biobank_CMC component of Stage 2 and for the other replication studies component of Stage 2 (see **Supplementary Figure 1** for list of other replication studies). Results are ordered by chromosome and position. Se: standard error. gc: Genomic control correction applied. Neff: N effective (sum of the products of imputation quality and sample size for each contributing study). Top_trait: trait for which the variant was found to be most strongly associated in Stage 1 and for which it was followed up in Stage 2.

Supplementary Table 8 (Table S8): Evidence for independence of secondary signals at previously reported loci

Summaries of conditional analyses establishing independence of novel secondary signals at previously reported loci. For each novel variant, association testing was repeated conditioning on the previously reported SNP. The conditional P value and the fold change in $-\log_{10}$ P value following conditioning are reported here. Linkage Disequilibrium (LD) r^2 and D' are from 1000 Genomes Project Phase 1. Se: standard error. gc: Genomic control correction applied. Neff: N effective (sum of the products of imputation quality and sample size for each contributing study).

Supplementary Table 9 (Table S9): Stage 1 association results for all 8 signals for all 3 blood pressure traits (SBP, DBP and PP)

Results from Stage 1 and from a meta-analysis of Stage 1 and Stage 2 are shown for all 3 blood pressure traits for all 8 signals. Genome-wide significant ($P < 5 \times 10^{-8}$) signals are highlighted in green and results are ordered by chromosome and position. Se: standard error. gc: Genomic control correction applied. Neff: N effective (sum of the products of imputation quality and sample size for each contributing study).

Supplementary Table 10 (Table S10): Look-up of results in stage 1 for previously reported genome-wide significant signals of association with quantitative blood pressure traits.

Association results for SBP, DBP and PP from Stage 1 are shown for all previously reported signals of association. P values which are significant after Bonferroni adjustment for 141 tests are shown in green. Se: standard error. gc: Genomic control correction applied. Neff: N effective (sum of the products of imputation quality and sample size for each contributing study).¹⁹⁻³⁴

Supplementary Table 11 (Table S11): Genes with levels of expression associated with novel or previously reported signals of association with blood pressure.

Each row represents a correlation of SNP genotype and gene expression. The 4 whole-blood data sets (BIOS, SABRe, NESDA/NTR, GTEx whole blood) are presented first in columns 6 to 9 followed by the all-tissue results from GTEx and from kidney. The number of blood data sets for which an eQTL signal was significant (FDR<5%) is indicated in column 5.

Supplementary Table 12 (Table S12): Kidney eQTL results

Variants in the TransplantLines eQTL analysis (see Supplementary Note) with a FDR < 0.05. FDR: False Discovery Rate.

Supplementary Table 13 (Table S13): Complete GTEx results.

The complete lookup results for each ICBP sentinel SNP are presented. If a proxy SNP was used for the GTEx lookup, it is indicated in this table.

Supplementary Table 14 (Table S14): LD lookup of sentinel SNPs in 1000G.

Variants with $r^2 > 0.5$ with novel and previously reported BP associated variants. LD: linkage disequilibrium, AF_EUR: Allele Frequency in 1000 Genomes Project EUR samples. Annotation also includes GWAScatalog results.

Supplementary Table 15 (Table S15): Gene-based pathway enrichment analysis of blood pressure genes

Summary of overrepresented known biological pathways for the 49 genes with evidence from 3 or 4 blood eQTL resources. FDR: False Discovery Rate.

Supplementary Table 16 (Table S16): Gene-based Gene Ontology enrichment analysis of blood pressure genes

Summary of overrepresented Gene Ontology (GO) for the 49 genes with evidence from 3 or 4 blood eQTL resources. FDR: False Discovery Rate. GO term categories (m= molecular function, b= biological process, c= cellular component) and levels (1 to 5, with highest level GO terms assigned to level 1) are indicated.

Supplementary Table 17 (Table S17): Network analysis

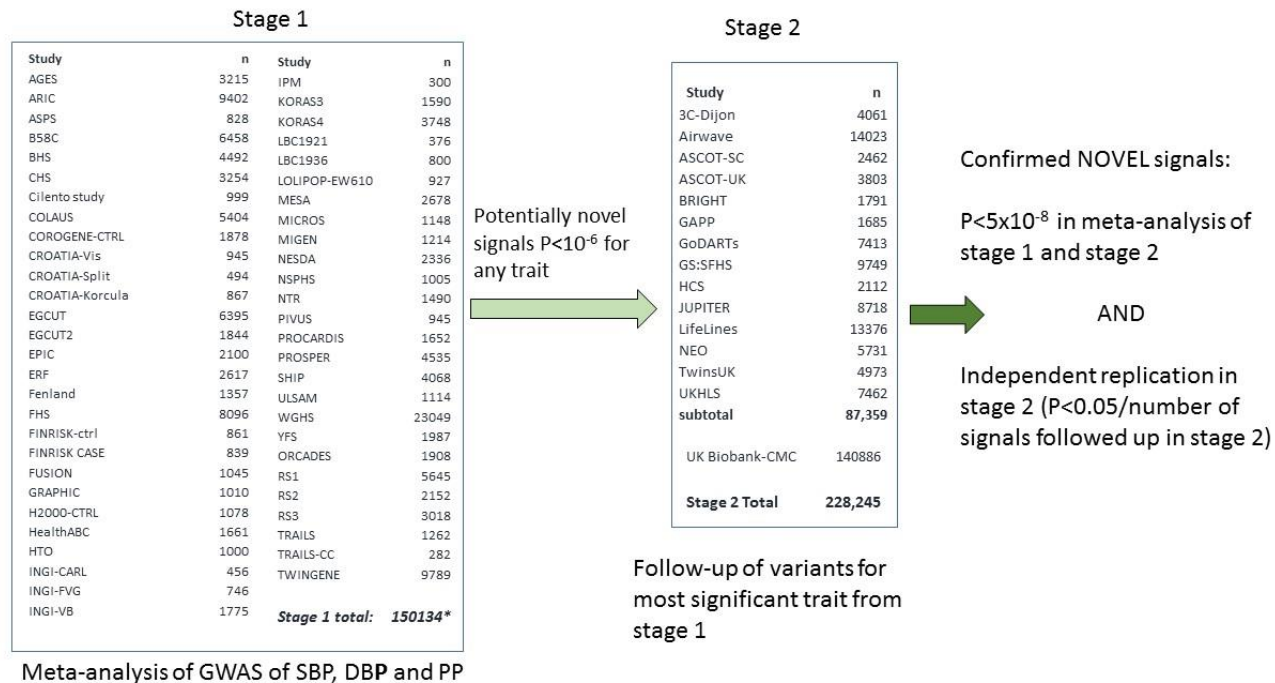
Results of GO term enrichment analysis following functional network construction. FDR: False Discovery Rate. An FDR cutoff of <0.01 was used.

Supplementary Table 18 (Table S18): Drug Target Analysis

Known drug-gene interactions and genes druggability prediction, investigating only expert curated data for the 48 genes with evidence from 3 or 4 blood eQTL resources and the non-synonymous SNPs in high LD ($r^2 > 0.50$) with the sentinel BP associated SNPs (**Supplementary Table 13 (S13)**).

Supplementary Figures

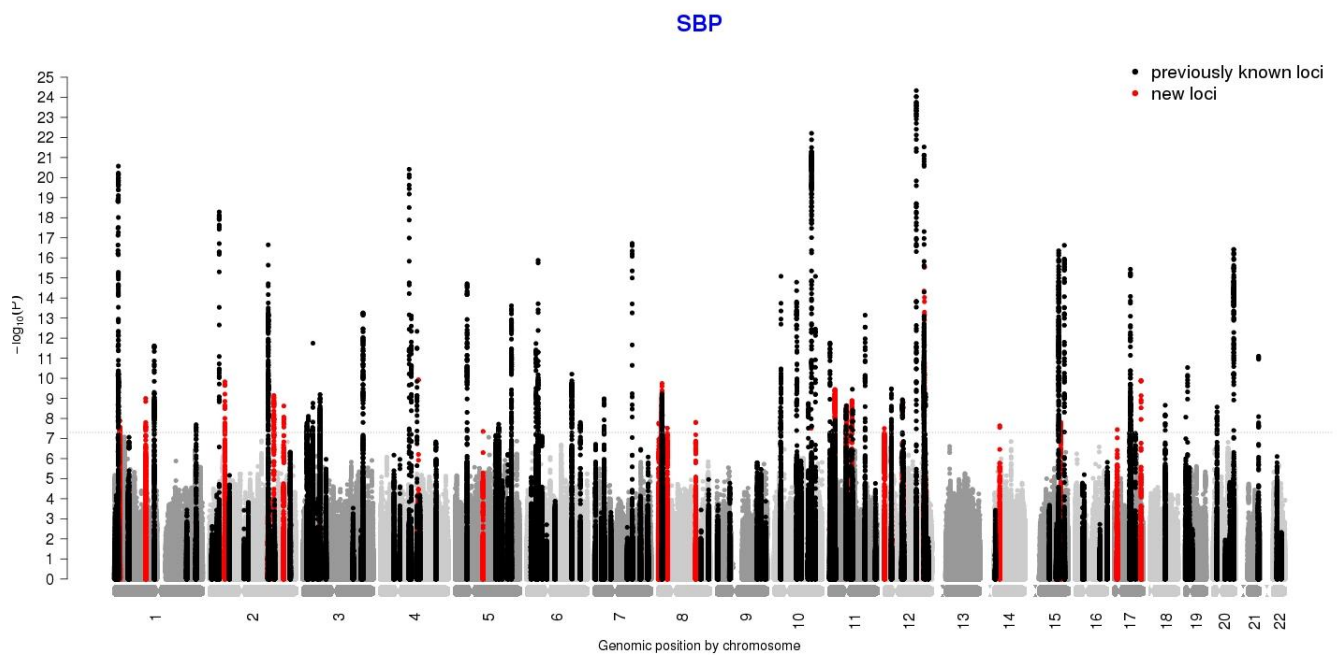
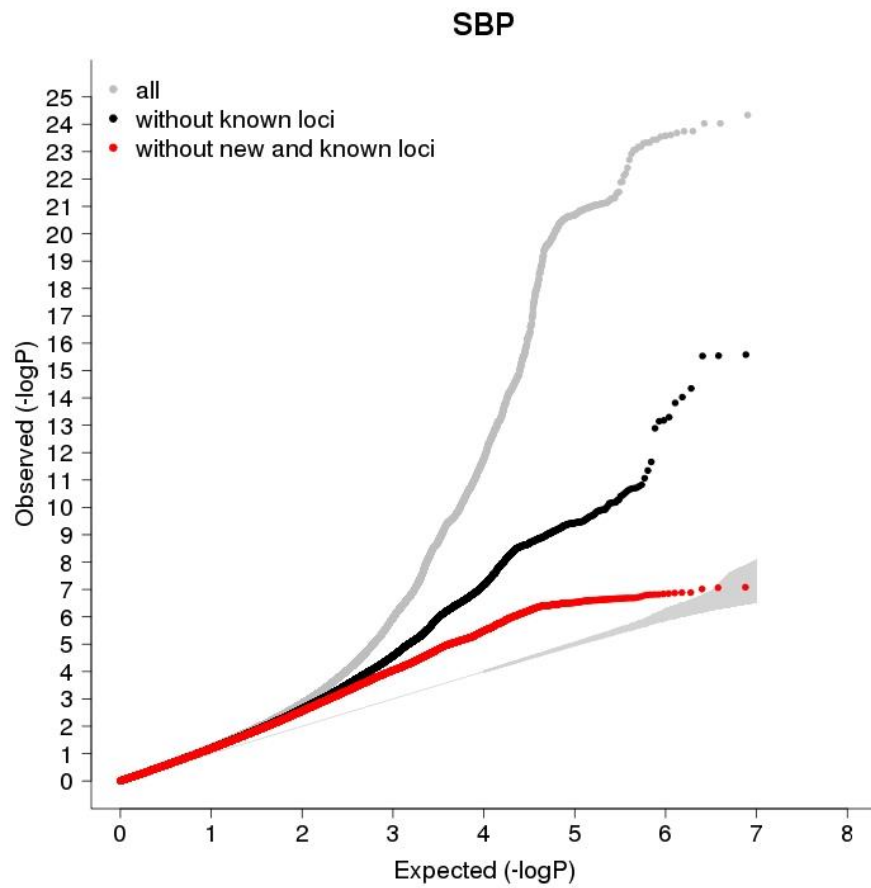
Supplementary Figure 1 (Figure S1): Study design.



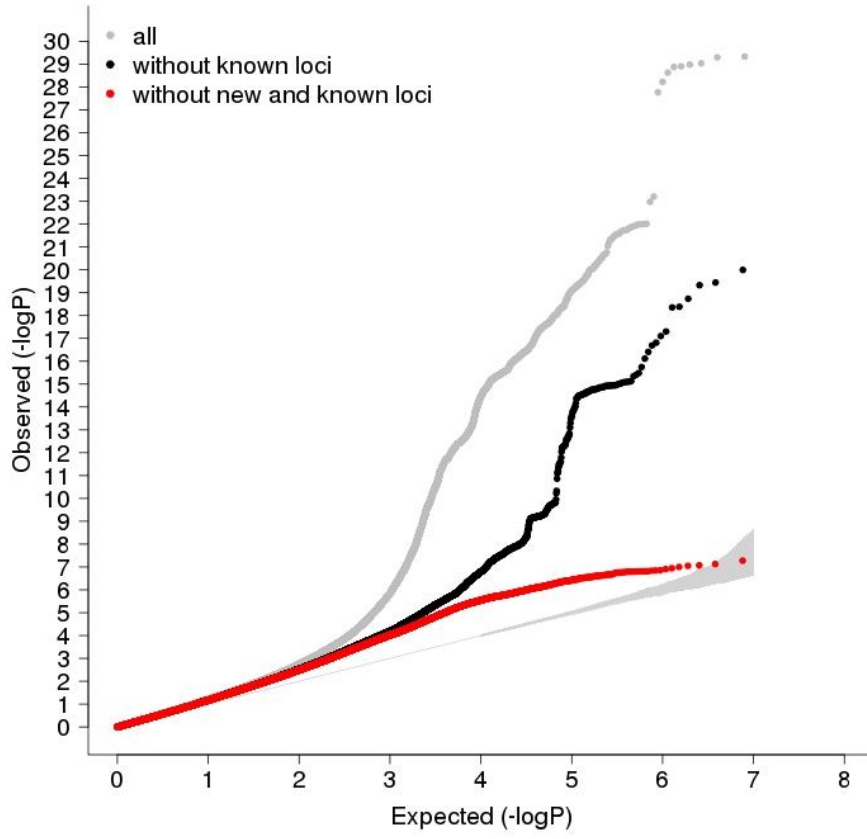
*Max N for any SNP was 150,100

Overview of study design showing studies contributing to stage 1 (discovery) and studies contributing to stage 2 (replication/follow-up). Full study names are given in **Supplementary Table 1 (S1)** (Stage 1) and **Supplementary Table 6 (S6)** (Stage 2).

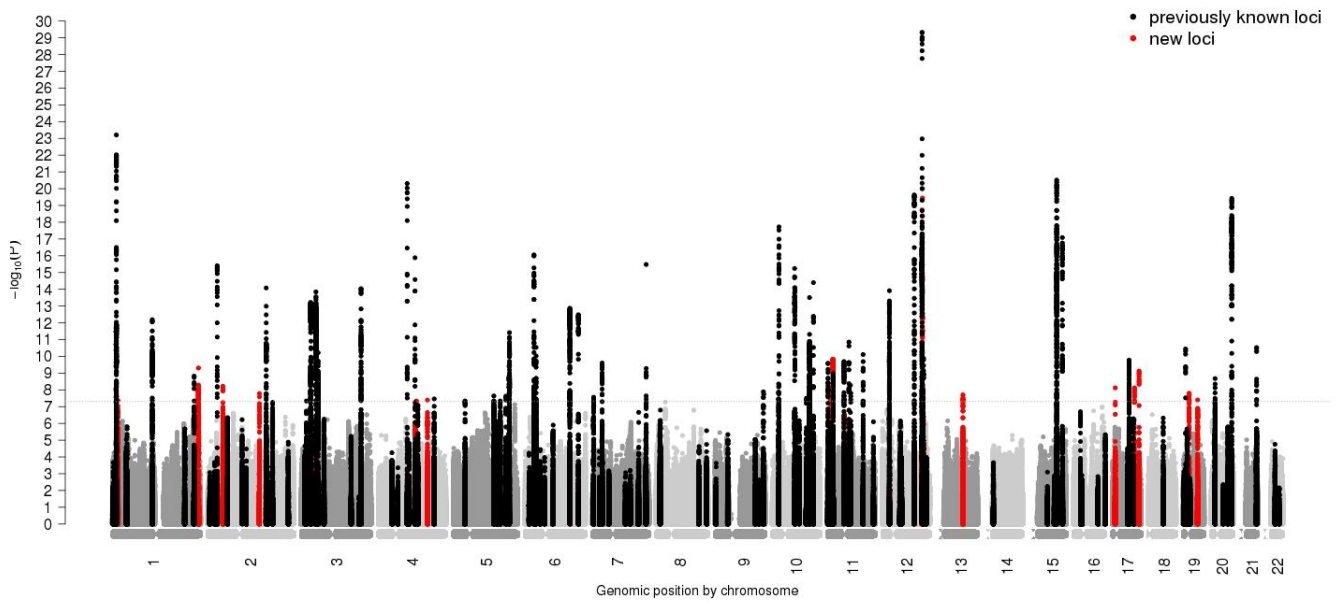
Supplementary Figure 2 (Figure S2): Manhattan and QQ plots

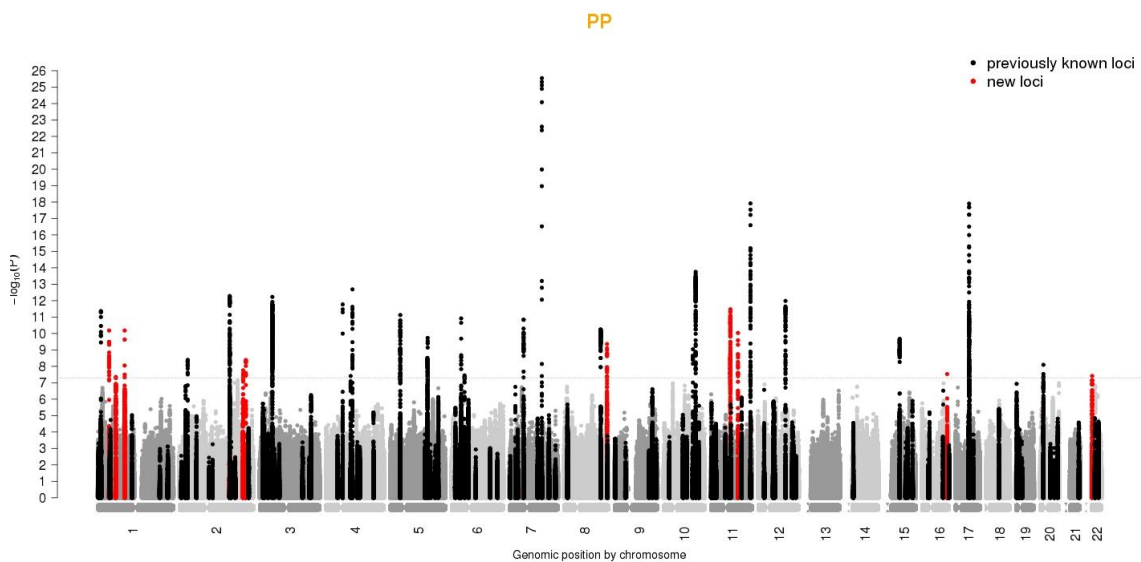
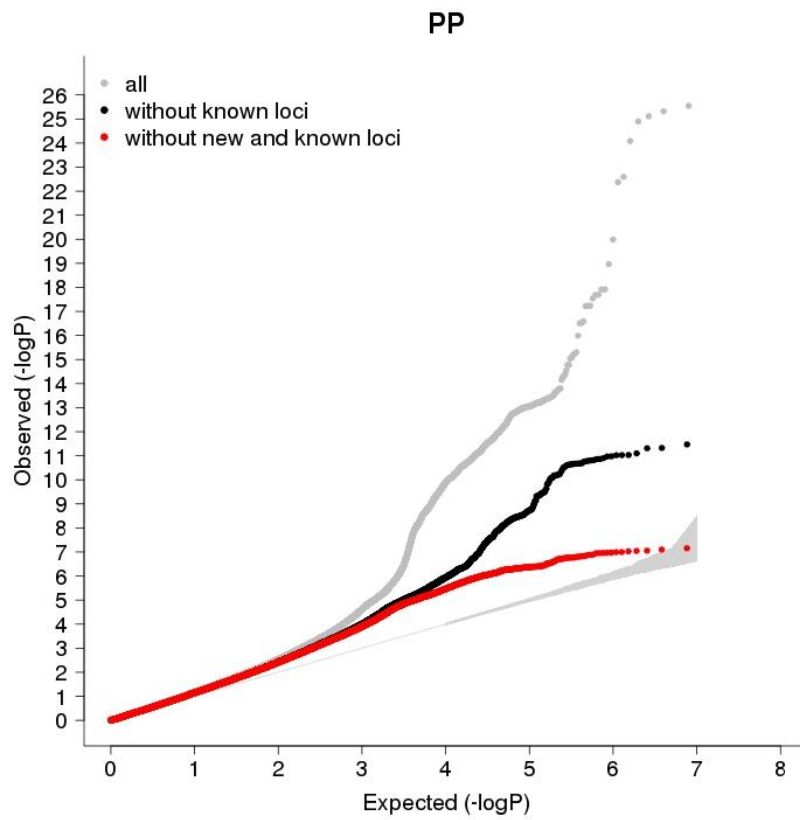


DBP



DBP

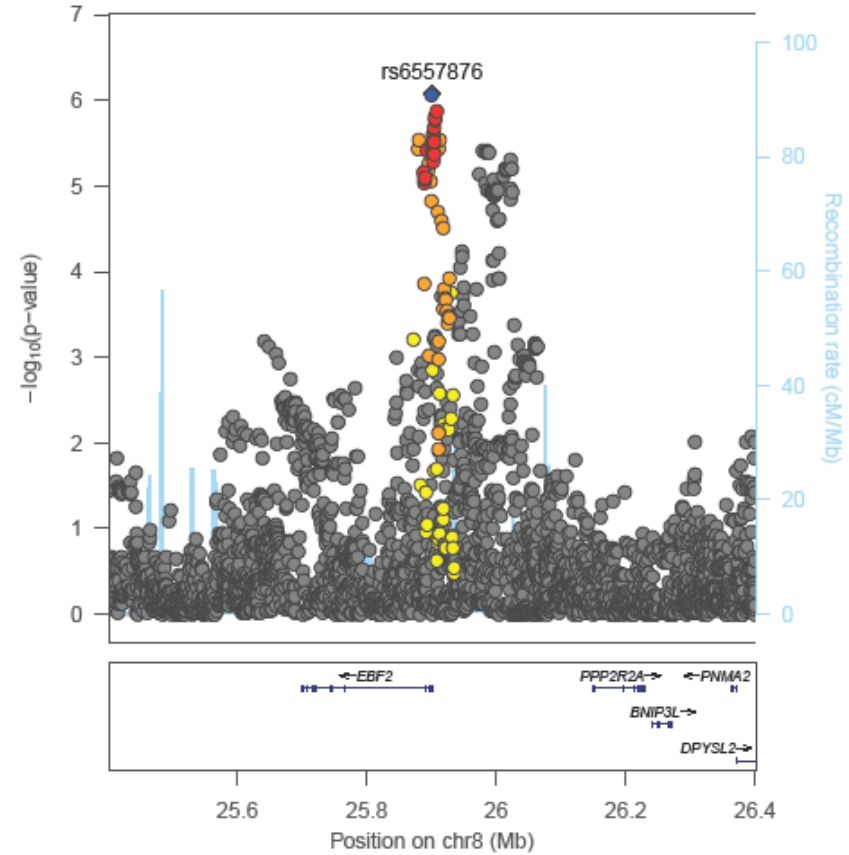
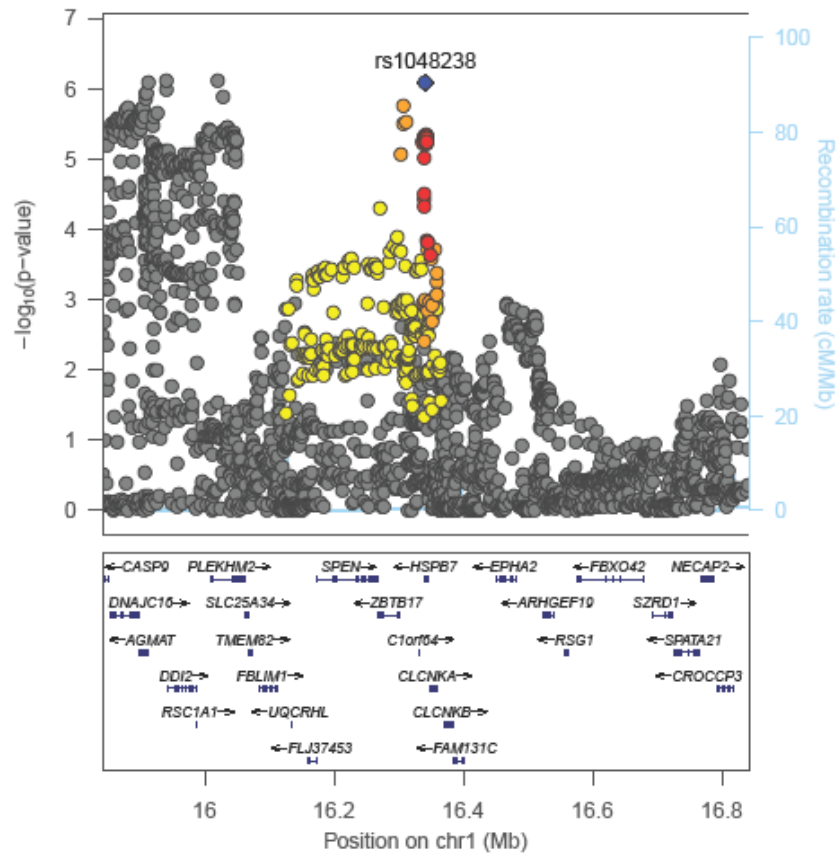


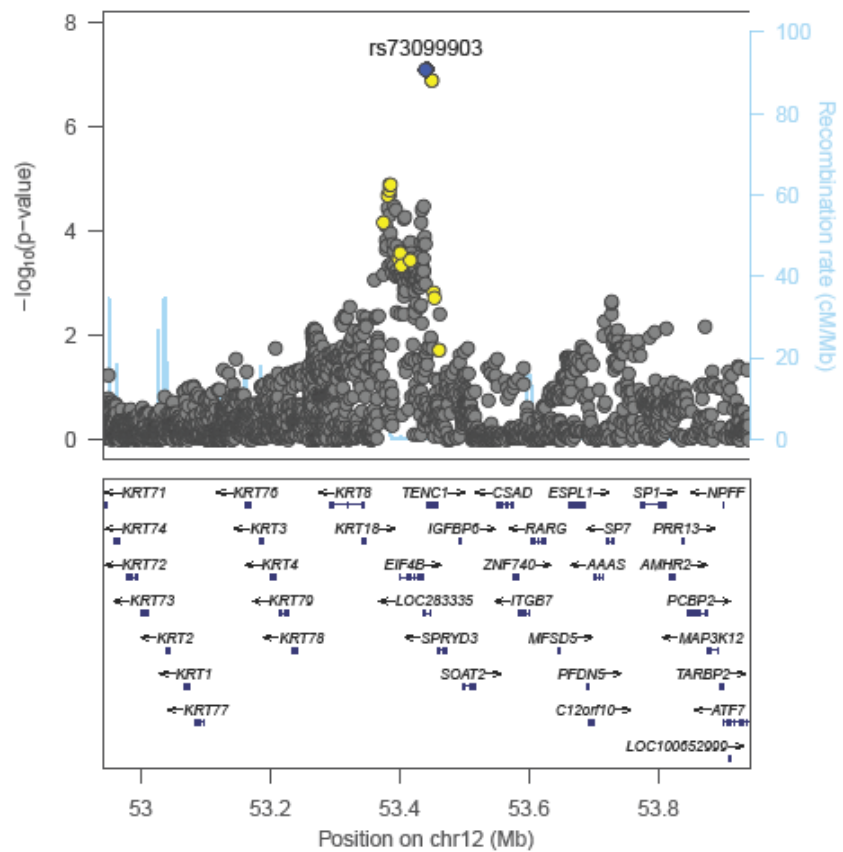
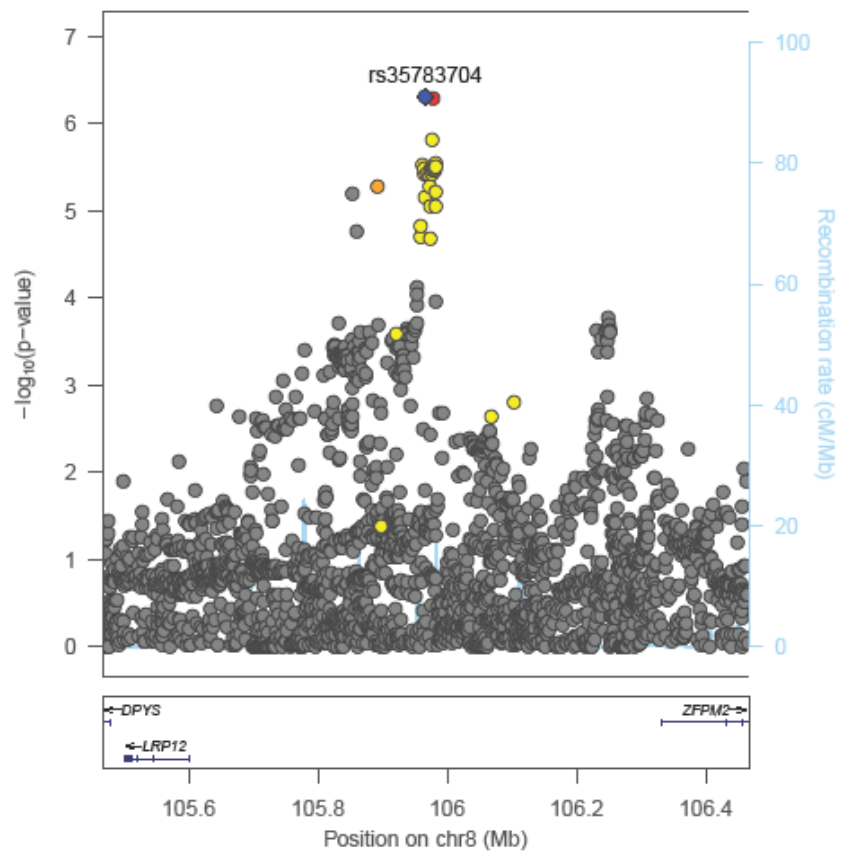


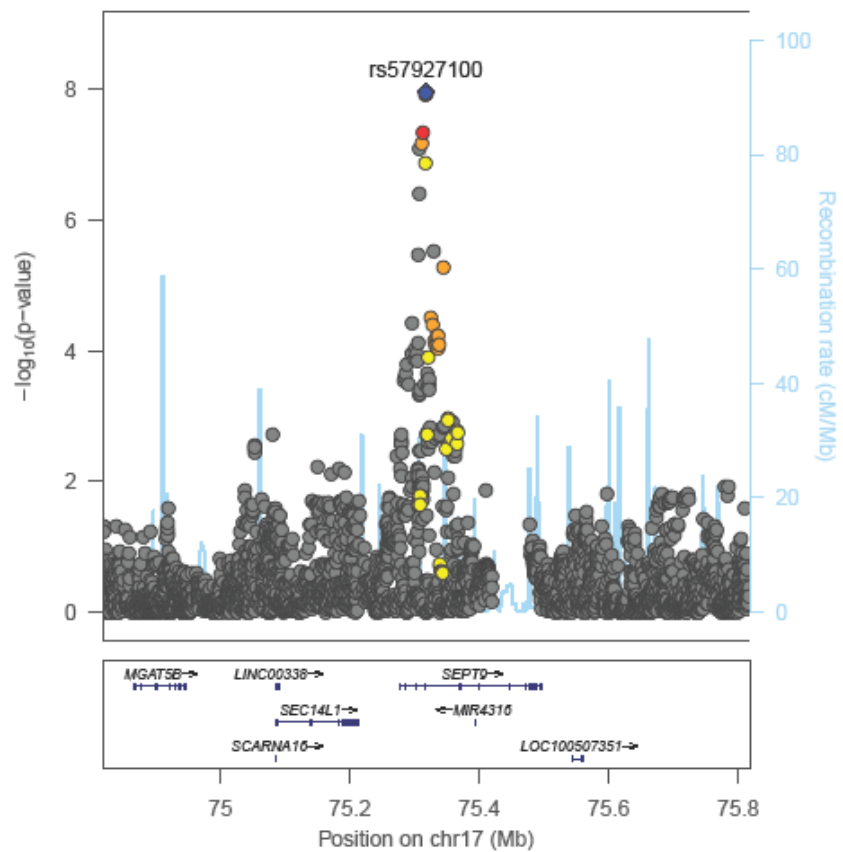
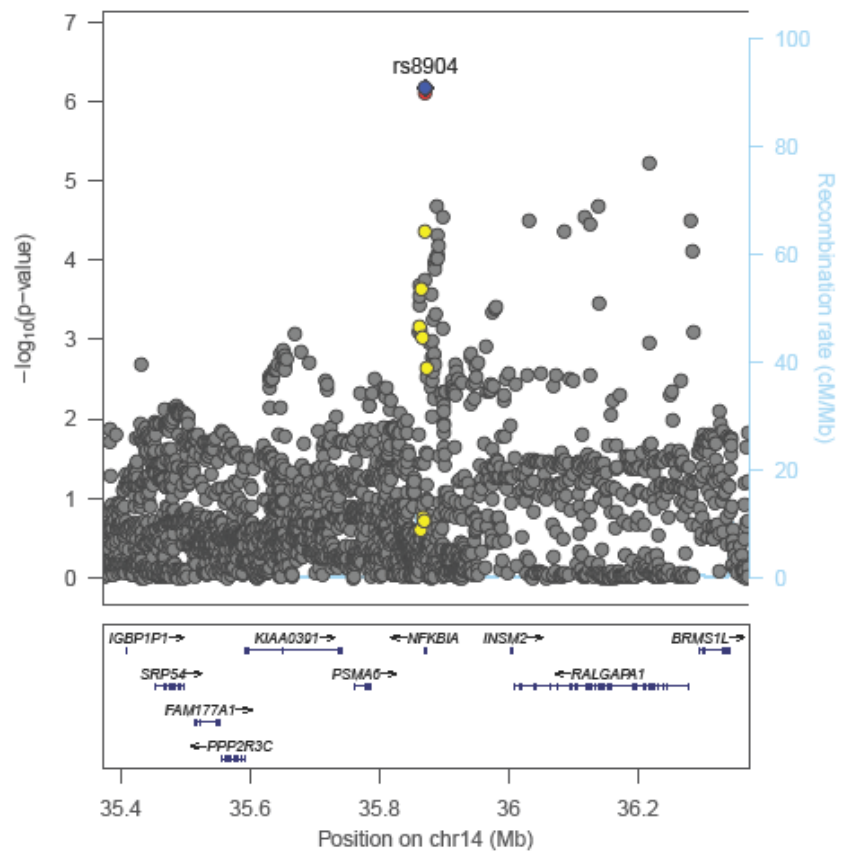
Known loci refers to signals published prior to this study. New includes signals that were initially identified as novel in this study but were subsequently reported in Warren et al 2017 and Hoffman et al 2016.

Supplementary Figure 3 (Figure S3): Region plots for 8 novel signals representing 7 novel regions of association for SBP (A), DBP (B) and PP (C).

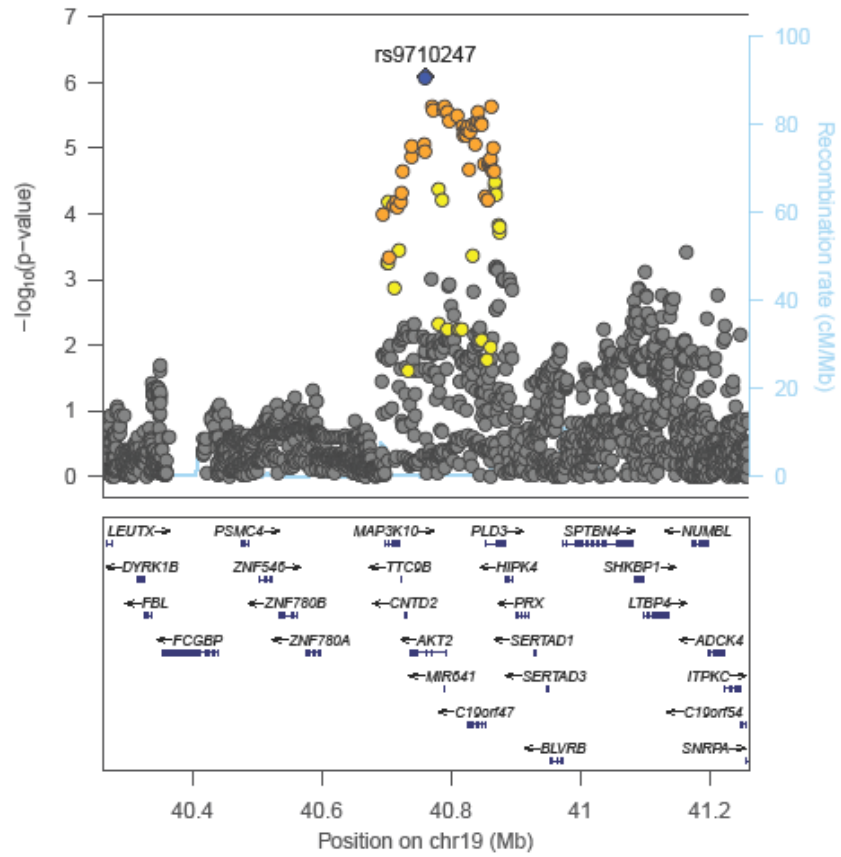
A) SBP





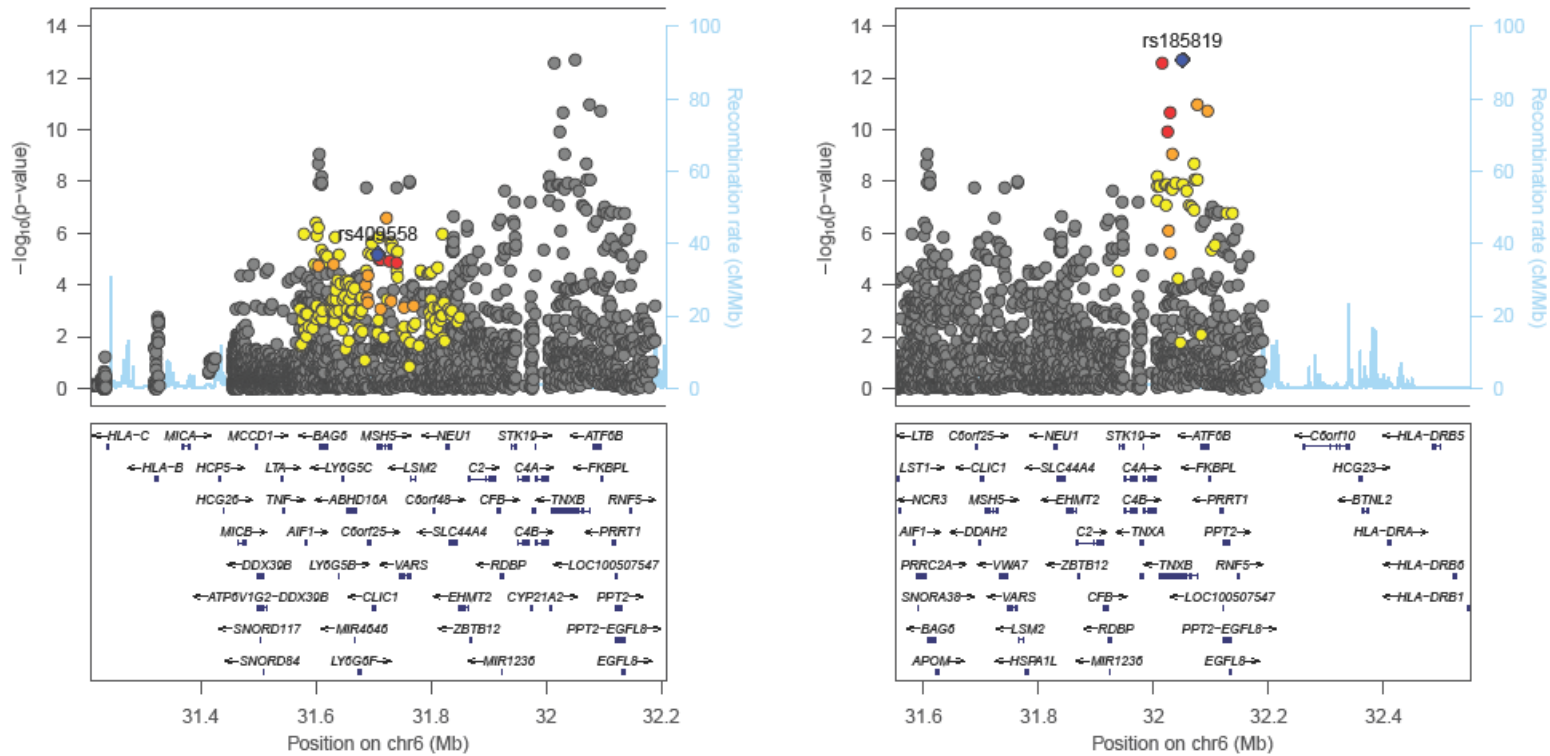


B) DBP



Supplementary Figure 4 (Figure S4): Region plots for a novel signal at a previously reported region of association.

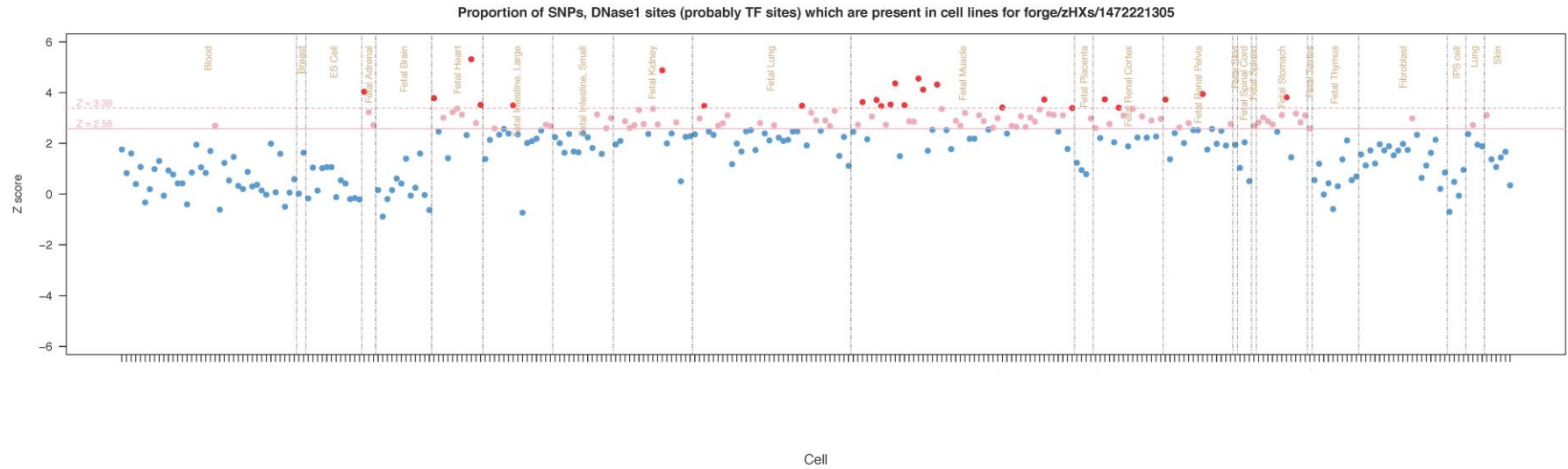
SBP: rs185819 (novel signal reported in this study)



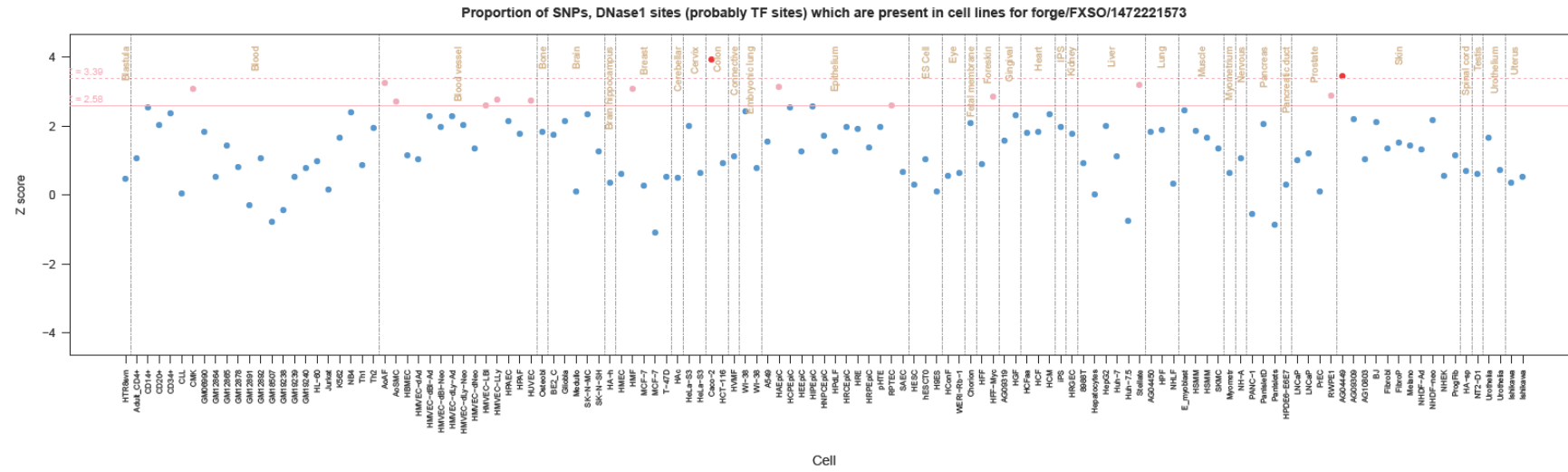
The region plot for the previously reported signal is shown (left) alongside the region plot for the novel signal. Results for association of the novel signal after conditioning on the previously reported signal are shown in **Supplementary Table 8 (S8)**.

Supplementary Figure 5 (Figure S5): Enrichment of overlap of DNase1 site in Roadmap (a) and ENCODE (b) tissues and cell lines.

a)



b)



Competing financial interests

Mike A. Nalls' participation is supported by a consulting contract between Data Tecnica International and the National Institute on Aging, NIH, Bethesda, MD, USA, as a possible conflict of interest Dr. Nalls also consults for Illumina Inc, the Michael J. Fox Foundation and University of California Healthcare among others.

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