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, TNXB, LRP12, LOC283335, SEPT9, and AKT2, and provide new replication evidence for a further 2 signals in EFB2 and NKFBIA. 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:e4-e19. DOI: 10.1161/HYPERTENSIONAHA.117.09438.)

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

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.
Genetic support for a drug target increases the likelihood of success in drug development, and there is clear unmet need for novel therapeutic strategies to treat individuals with hypertension. Several large studies have described blood pressure (BP) variant identification by genome-wide and targeted association approaches. 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, reflecting arterial stiffness. Using these 3 traits, we undertook a meta-analysis of 150134 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 150134 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), EGCGUT (n=6395), EGCGUT2 (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), MICS (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). Full study names and gen-
support for independent replication within the stage 2 studies only was sought. Any signals that had $P<5 \times 10^{-4}$ and evidence for independent replication in stage 2 alone indicated by $P<8.2 \times 10^{-6}$ (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) in 3 whole-blood data sets, 1 kidney data set, and the GTEx (Genotype-Tissue Expression) multiple tissue data resource, which included whole blood. 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), NESDIA-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. Full details of each data set can be found in the online only Data Supplement. The source transcriptomic renal data as described 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, $r^2$ 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). Annotation was performed using the ANNOVAR software package.

**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 ConsensusPathDB 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. We used the Cytoscape software platform extended by the GeneMANIA plugin (Data Version: August 12, 2014). 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 terms to identify the most relevant GO terms using the same plugin.

**DNaS1 Hypersensitivity Overlap Enrichment Across Tissue and Cell Types**

The functional element overlap analysis of the results of GWAS experiments (Forge tool v1.1) 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 10000 background repetitions were run. A Z score threshold of $\geq 2.39$ (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 targeted genes using DGI-db (drug gene interaction database). Known drug–gene interactions were interrogated across 15 source databases in DGI-db 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 drug compounds using Chembli (www.ebi.ac.uk/chembl; version 22.1).

**Results**

The stage 1 discovery meta-analysis included 150134 individuals (Tables S1 through S4 and Figures S1 and S2) and 7994604 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 design 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 228245 individuals from 15 independent studies for replication, including 140886 individuals from UK Biobank (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 378376 individuals (Table 1 and Table S7). Of these, 14 were subsequently published in 2 other studies and presented genome-wide significant associations with evidence of replication. A further 2 were highlighted as putative novel signals in one of those studies but had not been confirmed by replication. In our study, we report the 6 remaining novel signals, and the 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 378376 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...
The 4 blood eQTL data sets were NESDA-NTR, SABRe, the BIOS resource, and GTEx (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. 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 3 out of the 4 resources (Table 2), suggesting robustness of the SNP–gene expression

reported prior to these studies and 22 novel signals of association identified and confirmed in this study and 2 contemporaneous studies (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. 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. 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).

### Table 1. Novel Genome-Wide Significant Signals of Association

<table>
<thead>
<tr>
<th>Variant ID (Wncoded/Coded Allele), Chr:Position, Nearest Gene(s) (Type*)</th>
<th>CAF</th>
<th>Beta (SE)</th>
<th>P Value</th>
<th>Neff</th>
<th>Beta (SE)</th>
<th>P Value</th>
<th>Neff</th>
<th>Beta (SE)</th>
<th>P Value</th>
<th>Neff</th>
<th>Stage 1+Stage 2 Meta-Analysis P Values for All Traits</th>
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<td></td>
<td></td>
<td></td>
<td>SBP</td>
</tr>
<tr>
<td>rs1048238 (C/T), 1:16341649, HSPB7 (UTR)</td>
<td>0.571</td>
<td>0.366 (0.074)</td>
<td>8.09E-07</td>
<td>140299</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>rs848309 (proxy) (T/C), 1:16388447</td>
<td>0.567</td>
<td>0.347 (0.072)</td>
<td>1.70E-06</td>
<td>146755</td>
<td>0.347 (0.071)</td>
<td>9.10E-07</td>
<td>140462</td>
<td>0.347 (0.051)</td>
<td>7.07E-12</td>
<td>287217</td>
<td>7.07E-12</td>
</tr>
<tr>
<td>rs185819 (T/C), 6:32,050,067, TNXB (ns)</td>
<td>0.513</td>
<td>0.534 (0.073)</td>
<td>1.93E-13‡</td>
<td>142397</td>
<td>0.277 (0.053)</td>
<td>1.49E-07</td>
<td>221748</td>
<td>0.365 (0.043)</td>
<td>1.04E-17‡</td>
<td>364144</td>
<td>1.04E-17</td>
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<td>rs6557876 (C/T), 8:25,900,675, EBF2</td>
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<td>−0.411 (0.089)</td>
<td>8.50E-07</td>
<td>143653</td>
<td>−0.350 (0.060)</td>
<td>5.66E-09‡</td>
<td>225803</td>
<td>−0.371 (0.049)</td>
<td>2.85E-14‡</td>
<td>369457</td>
<td>2.85E-14‡</td>
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<tr>
<td>rs35783704 (G/A), 8:105,966,258, LRP12/ZFPM2</td>
<td>0.109</td>
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<td>4.96E-07</td>
<td>133924</td>
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<td>4.78E-04</td>
<td>215528</td>
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<td>7.08E-09‡</td>
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<td>rs73099003 (C/T), 12:53,440,779, LOC283335</td>
<td>0.074</td>
<td>0.768 (0.143)</td>
<td>8.05E-08</td>
<td>136624</td>
<td>−0.220 (0.072)</td>
<td>5.66E-05</td>
<td>207253</td>
<td>0.515 (0.081)</td>
<td>1.95E-10</td>
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*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<5×10−8).

---

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.

---

The 4 blood eQTL data sets were NESDA-NTR, SABRe, the BIOS resource, and GTEx (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. 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 (r2> 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.

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

<table>
<thead>
<tr>
<th>Sentinel SNP</th>
<th>Chr</th>
<th>Position</th>
<th>Gene</th>
<th>Blood Data Sets</th>
<th>Top eQTL</th>
<th>Signal in Other Tissue(s) in GTEx</th>
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(Continued)
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 PSMD5.15 The same SNP was also reported BP association signals.

Table 2. Continued

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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, r²>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.

clinically approved drugs using DGIdb (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/; 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
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. 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.

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.

**Acknowledgments**

We thank all the study participants of this study for their contributions. Detailed acknowledgment of funding sources is provided in the Sources of Funding section.

**Author Contributions**

**Secondary Analyses**


**Discovery**

WGHS: Study phenotyping, P.M. Ridker; Genotyping or analysis, D.I. Chasman and L.M. Rose; Study PI, D.I. Chasman and P.M. Ridker.

RS: Study phenotyping, G.C. Verwoert; Genotyping or analysis, G.C. Verwoert and A.G. Uitterlinden; Study PI, O.H. Franco, A. Heijmans, and A.G. Uitterlinden.

NTR: Study phenotyping, E.J. de Geus and G. Willemsen; Genotyping or analysis: J-J. Hottenga, E.J. de Geus, and G. Willemsen; Study PI, D.I. Boomsma and E.J. de Geus.

STR: Study phenotyping, E. Ingelsson; Genotyping or analysis, R.J. Strawbridge and M. Fränberg; Study PI, E. Ingelsson and A. Hamsten.

EUCUT: Genotyping or analysis, T. Esko; Study PI, A. Metspalu.

ARIC: Genotyping or analysis, D.E. Arking, A.C. Morrison, and P. Nandakumar; Study PI, A. Chakravarti.

FHS: Study phenotyping, D. Levy; Genotyping or analysis, S.-I. Hwang; Study PI, D. Levy.

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

B5SC: 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.

PROSPER: Study phenotyping, J.W. Jukema and D.J. Stott; Genotyping or analysis, S. Trompet and J. Deelen; Study PI, J.W. Jukema.

BHS: Study phenotyping, A. James; Genotyping or analysis, N. Shrine, J. Hui, and J. Beilby.

SHIP: Study phenotyping, M. Dörr; Genotyping or analysis, A. Teumer, M. Dörr, and U. Völker; Study PI, R. Trettig.

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

CHS: Study phenotyping, B.M. Psaty; Genotyping or analysis, J.C. Bis, K. Rice, and K.D. Taylor; Study PI, B.M. Psaty.

AGES-Reykjavik: Genotyping or analysis, A.V. Smith; Study PI, A.V. Smith.

ERF: Study phenotyping, C.M. van Duijn and B.A. Oostra; Genotyping or analysis, N. Amin; Study PI, C.M. van Duijn and B.A. Oostra.

NESDA: Study phenotyping, B.W.J.H. Penninx; Genotyping or analysis, I.M. Nolte and Y. Milaneschi; Study PI, H. Snieder and W.B.J.H. Penninx.

YFS: Study phenotyping, T. Lehtimäki, M. Kähönen, and O.T. Raitakari; Genotyping or analysis, T. Lehtimäki, L.-P. Lyytikäinen, M. Kähönen, and O.T. Raitakari; Study PI, T. Lehtimäki, M. Kähönen, and O.T. Raitakari.

EPIC: Genotyping or analysis, N.J. Wareham; Study PI, J.H. Zhao.

ASPS: Study phenotyping, R. Schmidt; Genotyping or analysis, H. Schmidt, E. Hofer, Y. Saba, and R. Schmidt; Study PI, H. Schmidt and R. Schmidt.


FINRISK (COROGENE_CTRL): Study phenotyping, P. Jousilahti; Genotyping or analysis, K. Kristiansson and A.P. Sarin; Study PI, M. Perola and P. Jousilahti.

INGI-VB: Study phenotyping, C.F. Sala; Genotyping or analysis, M. Traglia, C.M. Barbierri, and C.F. Sala; Study PI, D. Tonioło.

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TRAILS: Study phenotyping, H. Riese; Genotyping or analysis, P.J. van der Most; Study PI, C.A. Hartman and A.J. Oldehinkel.

PROCARDS: Study phenotyping, A. Goel; Genotyping or analysis, A. Goel; Study PI, H. Watkins, and M. Farrall.

HABC: Study phenotyping, Y. Liu and T.B. Harris; Genotyping or analysis, M.A. Nalls; Study PI, Y. Liu and T.B. Harris.

KORA S3: Study phenotyping, C. Gieger; Genotyping or analysis, S. Söber, C. Gieger, and E. Org; Study PI, M. Laan.

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

Fenland: Study phenotyping, R.A. Scott, J. Luan, C. Langenberg, and N.J. Wareham; Genotyping or analysis, R.A. Scott, J. Luan, C. Langenberg, and N.J. Wareham; Study PI, R.A. Scott, C. Langenberg, and N.J. Wareham.

MICROS: Genotyping or analysis, A.A. Hicks, F. Del Greco M., and A. Saint Pierre; Study PI, F. Del Greco M. and P.P. Pramstaller.

HTO: Study phenotyping, B.D. Keavney; Genotyping or analysis, B.D. Keavney, K.L. Ayers, and C. Mamasoula; Study PI, B.D. Keavney and H.J. Cordell.

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

ULSAM: Study phenotyping, V. Giedraitis and E. Ingelsson; Genotyping or analysis, A.P. Morris and A. Mahajan; Study PI, A.P. Morris, V. Giedraitis, and E. Ingelsson.

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


CROATIA_Vis: Study phenotyping, I. Rudan; Genotyping or analysis, V. Vitart and J.E. Huffman; Study PI, V. Vitart and I. Rudan.

PIVUS: Study phenotyping, L. Lind and J. Sundström; Genotyping or analysis, C.M. Lindgren and A. Mahajan; Study PI, C.M. Lindgren, L. Lind, and J. Sundström.


CROATIA_Korcula: Genotyping or analysis, C. Hayward and J. Martens; Study PI, C. Hayward and A.F. Wright.

INGI-CARL: Genotyping or analysis, D. Vuckovic, M. Brumat, and I. Kolcic; Genotyping or analysis, O. Polasek and T. Zemunik; Study PI, O. Polasek.

BioMe (formerly IPM): Genotyping or analysis, Y. Lu; Study PI, R.J.F. Loos and E.P. Bottinger.

**Replication**


GoDARTS: Study phenotyping, C.N.A. Palmer and A.S.F. Doney; Genotyping or analysis, C.N.A. Palmer and N. Shah; Study PI, C.N.A. Palmer and A.D. Morris.

Lifelines: Study phenotyping, M.H. de Borst; Genotyping or analysis, M. Swertz; Study PI, P. van der Harst.

 TwinsUK: Study phenotyping, C. Mamasoula and T. Zemunik; Study PI, E. Evangelou.

The UK Household Longitudinal Study (UKHLS): Genotyping or analysis, B.P. Prins; Study PI, E. Zeggini.
Sources of Secondary Analyses
eQTL kidney: Study phenotyping, J.J. Dammann and M.A. Seelen; Genotyping or analysis, P.J. van der Most; Study PI, H. Snieder.
eQTL BIOS: Design of secondary analysis, R. Jansen; Computation of secondary analysis, R. Jansen; Study PI, R. Jansen.
SABRe: Study phenotyping, Y. Demirkale, P.J. Munson, and Q.T. Nguyen; Genotyping or analysis, R. Joehanes; Design of secondary analysis, D. Levy; Study PI, D. Levy.

ICBP-Steering Committee

Resources for Secondary Analyses

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Disclosures
We declare competing financial interests (see corresponding entry in the online-only Data Supplement).


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.
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≥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 (PEER^2), 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 1968^2. 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. 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/m²), 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 data 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 data. 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 previously. SNP genotype pre-imputation quality control, haplotype phasing and 1000 Genomes imputation were performed as described previously. Imputed SNP genotypes were coded into reference allele dosage format, and filtered at MAF>0.01 and HW P>1E−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 MatrixeQTL 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 by to account for large LD blocks with strong eQTL effects that inflate the FDR when using the first method. Similar as what was observed previously 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 < 1M 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 previously. The method described in these papers are summarized below. Genotype data were harmonized towards the Genome of the Netherlands (GoNL) using Genotype Hamonizer 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 >15M 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 permutations\textsuperscript{12}. 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 previously\textsuperscript{14}. 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 panel\textsuperscript{15} using Impute2\textsuperscript{16}. 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 R\textsuperscript{17} to account for multiple samples from a donor (package lme3 version 1.1.12\textsuperscript{18}). 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 variation\textsuperscript{8} were used as dependent variable. Probes with a false discovery rate <5% were considered statistically significant.
Supplemental references


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:I 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 (r² > 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 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).

**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 (r²>0.50) with the sentinel BP associated SNPs (**Supplementary Table 13 (S13)**).
Supplementary Figures

Supplementary Figure 1 (Figure S1): Study design.

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).

Potentially novel signals $P<10^{-6}$ for any trait

Confirmed NOVEL signals: $P<5\times10^{-8}$ in meta-analysis of stage 1 and stage 2

AND

Independent replication in stage 2 ($P<0.05$/number of signals followed up in stage 2)

Follow-up of variants for most significant trait from stage 1

Meta-analysis of GWAS of SBP, DBP and PP

*Max n for any SNP was 150,100

20
Supplementary Figure 2 (Figure S2): Manhattan and QQ plots

- **Manhattan plot**: The plot shows the relationship between the observed and expected values of logP for SBP. The x-axis represents the expected logP values, while the y-axis shows the observed logP values.
  - The gray line with circles represents all loci.
  - The black line with squares represents loci without known loci.
  - The red line with diamonds represents loci without new and known loci.

- **QQ plot**: The QQ plot compares the observed logP values against the expected logP values.
  - The black line represents all loci.
  - The gray line represents loci without known loci.
  - The red line represents loci without new and known loci.
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

![Graph showing recombination rate and position on chr19 Mb for DBP genes.]

Position on chr19 (Mb) vs. Recombination rate (cM/Mb) for DBP genes.
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)
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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