

## 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:e4-e19. 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,<sup>1</sup> and there is clear unmet need for novel therapeutic strategies to treat individuals with hypertension.<sup>2</sup> Several large studies have described blood pressure (BP) variant identification by genome-wide and targeted association approaches.<sup>3–19</sup> 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,<sup>20</sup> 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.<sup>21</sup> 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, age<sup>2</sup>, 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.<sup>22</sup> 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<sup>−6</sup> 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)<sup>23</sup> 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  $\chi^2$  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<sup>−6</sup> 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*<sup>2</sup>>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*>5×10<sup>−8</sup> were excluded. Of the signals with a final *P*<5×10<sup>−8</sup>,

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)<sup>16,18,24</sup> in 3 whole-blood data sets, 1 kidney data set, and the GTEx (Genotype-Tissue Expression) multiple tissue data resource, which included whole blood.<sup>25</sup> 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.<sup>26</sup> Full details of each data set can be found in the [online-only Data Supplement](#). The source transcriptomic renal data as described<sup>26</sup> 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.<sup>22</sup>  $r^2$  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).<sup>27,28</sup> Annotation was performed using the ANNOVAR software package.<sup>29</sup>

## 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<sup>30</sup> 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.<sup>31</sup> We used the Cytoscape<sup>32</sup> software platform extended by the GeneMANIA<sup>33</sup> plugin (Data Version: August 12, 2014).<sup>34</sup> 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<sup>35</sup> to identify the most relevant GO terms using the same plugin.<sup>34</sup>

## DNase1 Hypersensitivity Overlap Enrichment Across Tissue and Cell Types

The functional element overlap analysis of the results of GWAS experiments (Forge tool v1.1)<sup>36</sup> 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  $\geq 3.39$  (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).<sup>37</sup> 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/](http://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 design<sup>38</sup> 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 Biobank<sup>19</sup> (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<sup>17,19</sup> which presented genome-wide significant associations with evidence of replication. A further 2 were highlighted as putative novel signals in one of those studies<sup>17</sup> 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	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<sup>17,19</sup> and 22 novel signals of association identified and confirmed in this study and 2 contemporaneous studies<sup>3-19,24</sup> (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.<sup>39</sup> 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.<sup>3,15</sup> 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,<sup>40,41</sup> SABRe,<sup>15</sup> the BIOS resource,<sup>42</sup> and GTEx<sup>25</sup> (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.<sup>16,18</sup> For a total of 369 genes, gene expression was associated with the BP SNP in  $\geq 1$  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.<sup>43</sup>

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>	NY		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>	NY		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.<sup>15,16,18</sup> 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),<sup>26</sup> 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 *AS1C1*) and confirm a previously reported kidney eQTL signal for an antisense RNA for *PSMD5*.<sup>15</sup> The same SNP was also an eQTL for *PSMD5* itself in both blood and kidney. *AS1C1* 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.<sup>44</sup> 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 DGIdb<sup>37</sup> (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/](http://www.ebi.ac.uk/chembl/db/); version 22.1).

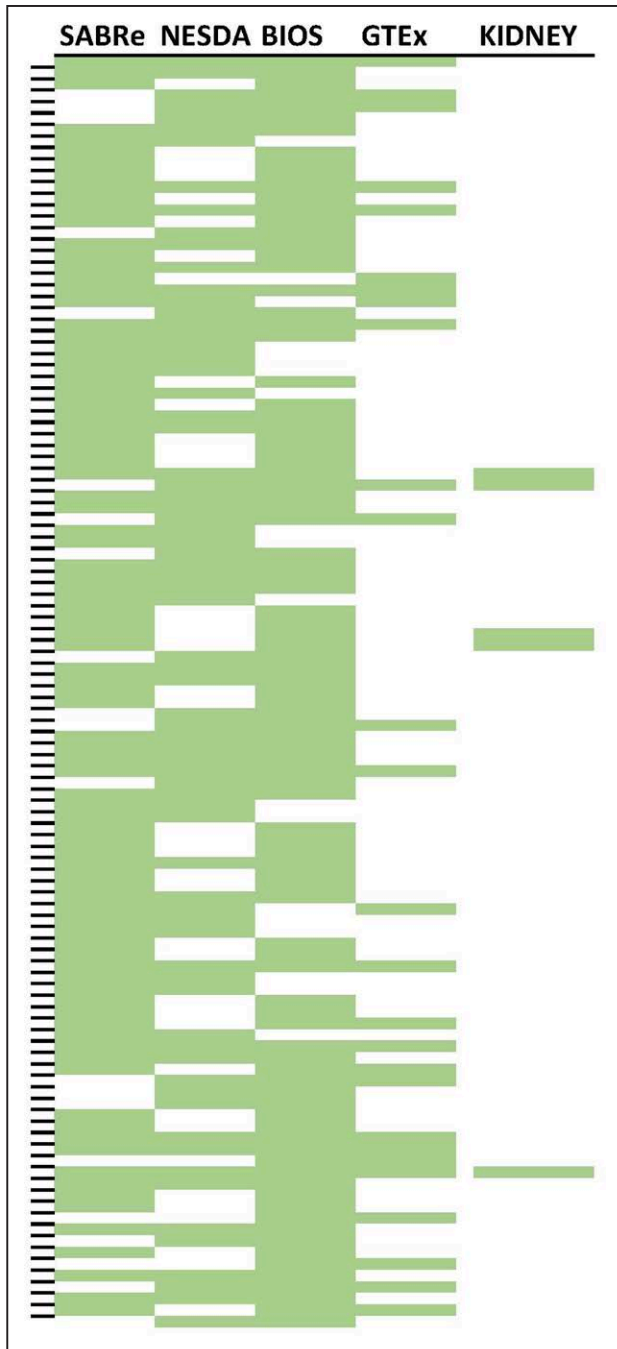
## Discussion

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.<sup>17</sup> 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.<sup>15</sup> 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 rs7103648<sup>15</sup> 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.<sup>45</sup>

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

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**INGI-VB:** The INGI-Val Borbera population is a collection of 1664 genotyped samples collected in the Val Borbera Valley, a geographically isolated valley located within the Appennine Mountains in Northwest Italy. The valley is inhabited by ≈3000 descendants from the original population, living in 7 villages along the valley and in the mountains. Participants were healthy people aged 18 to 102 years who had at least one grandfather living in the valley. The study plan and the informed consent form were reviewed and approved by the institutional

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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.