# The genetics of blood pressure regulation and its target organs from association studies in 342,415 individuals

**To dissect the genetic architecture of blood pressure and assess effects on target organ damage, we analyzed 128,272 SNPs from targeted and genome-wide arrays in 201,529 individuals of European ancestry, and genotypes from an additional 140,886 individuals were used for validation. We identified 66 blood pressure–associated loci, of which 17 were new; 15 harbored multiple distinct association signals. The 66 index SNPs were enriched for *cis*-regulatory elements, particularly in vascular endothelial cells, consistent with a primary role in blood pressure control through modulation of vascular tone across multiple tissues. The 66 index SNPs combined in a risk score showed comparable effects in 64,421 individuals of non-European descent. The 66-SNP blood pressure risk score was significantly associated with target organ damage in multiple tissues but with minor effects in the kidney. Our findings expand current knowledge of blood pressure–related pathways and highlight tissues beyond the classical renal system in blood pressure regulation.**

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There are considerable physiological, clinical and genetic data that point to the kidney as the major regulator of blood pressure and to renal damage as a consequence of long-term blood pressure elevation. However, alternative hypotheses, such as increased systemic vascular resistance, are also serious contenders to explain the rise of blood pressure with increasing age, but these hypotheses currently have limited genetic support. The genetic basis of elevated blood pressure, or hypertension (HTN), involves many loci that have been identified using large-scale analyses of candidate genes[1,2], linkage studies and genome-wide association studies (GWAS)[3–12]. Identification of the genes underlying blood pressure regulation can help resolve many of the open questions regarding blood pressure (patho)physiology. Although ~40–50% of variability in blood pressure is heritable[13,14], the associated genetic variation identified thus far explains only ~2% (refs. 1–12).

The Cardio-Metabochip is a custom genotyping microarray designed to facilitate cost-effective follow-up of nominal associations for metabolic and cardiovascular traits, including blood pressure. This array comprises 196,725 variants, including ~5,000 SNPs with nominal ($P < 0.016$) evidence of association with blood pressure in our previous GWAS meta-analysis[5]. Furthermore, the array includes several dense scaffolds for fine-mapping of selected loci spanning, on average, genomic regions of 350 kb[5,15], of which 24 include genome-wide significant blood pressure associations in the current study[5,16].

## RESULTS

### New genetic loci associated with systolic and diastolic blood pressure

We performed meta-analyses of association summary statistics from a total of 201,529 individuals of European (EUR) ancestry from 74 studies: (i) 109,096 individuals from 46 studies genotyped on the Cardio-MetaboChip and (ii) 92,433 individuals from 28 studies with imputed genotype data from genome-wide genotyping at variants included on the Cardio-MetaboChip. Twenty-four of the 28 studies with genome-wide genotyping data had contributed to previous analyses (**Supplementary Tables 1–3**)[5,7].

Blood pressure was measured using standardized protocols in all studies[5,17] (Online Methods and **Supplementary Table 1**). Association statistics for systolic and diastolic blood pressure (SBP and DBP) in models adjusting for age, age$^2$, sex and body mass index (BMI) were obtained for each study separately, with study-specific genomic control applied to correct for possible population structure. Fixed-effects meta-analysis was carried out in four stages, separately for the following SNP associations: stage 1, meta-analysis using results based on 46 studies with Cardio-MetaboChip genotypes of 109,096 participants; stage 2, meta-analysis using additional results based on imputed genotypes from genome-wide genotyping arrays in 4 previously unpublished studies; stage 3, meta-analysis using imputed genotypes from genome-wide genotyping arrays in 24 previously published studies[5]; and stage 4, joint meta-analysis of stages 1–3 including a total of 201,529 independent individuals (**Supplementary Fig. 1, Supplementary Tables 2** and **3**, and **Supplementary Note**). To account for population structure across studies in stages 1–3 of our meta-analysis, genomic control correction was applied to meta-analysis results from each of these stages considered independently[18,19]. Association statistics (*P* values) are available as **Supplementary Data**, and full association results are available via the database of Genotypes and Phenotypes (dbGaP) (phs000585.v2.p1).

After stage 4, 67 loci attained genome-wide significance ($P < 5 \times 10^{-8}$), 18 of which were not previously reported in the literature (**Supplementary Table 4**). Quantile–quantile plots of the stage 4 meta-analysis showed an excess of small *P* values, with an elevated genomic control $\lambda$ estimate that was persistent, albeit attenuated, after excluding all 66 loci (**Supplementary Fig. 2**). This observation is compatible with either residual uncorrected population stratification or the presence of a large number of variants that are truly associated with blood pressure but fail to achieve genome-wide significance in the current meta-analysis. The Cardio-MetaboChip array's inclusion of SNPs

A full list of authors and affiliations appears at the end of the paper.

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**Figure 1** Manhattan plots for SBP and DBP from the stage 4 Cardio-MetaboChip-wide meta-analysis. $P$ values (expressed as $-\log_{10} P$) are plotted by physical genomic position, labeled by chromosome. SNPs in new loci, identified in this study, are labeled in red (SBP) or dark blue (DBP); SNPs in previously known loci are labeled in orange (SBP) or light blue (DBP). Locus names are given. Gray X's represent genomic positions at which the $y$ axis was truncated (SNPs with $P < 1 \times 10^{-15}$). A horizontal dashed line is drawn at the genome-wide significance threshold of $P = 5 \times 10^{-8}$.

from an earlier blood pressure GWAS[5] does not seem to be the sole explanation, as we did not observe a significant decrease in the excess of small $P$ values after exclusion of all SNPs that were included on the Cardio-MetaboChip because of nominal association with blood pressure (**Supplementary Figs. 3** and **4**). Because the quantile–quantile plots continued to show deviation from the null expectation, we sought additional validation for 18 variants attaining genome-wide significance but without previous support in the literature in up to 140,886 individuals of European ancestry from UK Biobank[20]. For these SNPs, we performed a stage 5 meta-analysis combining the association summary statistics from stage 4 and UK Biobank, in a total of up to 342,415 individuals (**Supplementary Table 5**).

After stage 5 meta-analysis, 17 of 18 variants retained genome-wide significance for the primary trait (SBP or DBP result with the lower $P$ value). The one variant that was not genome-wide significant had a borderline $P$ value of $4.49 \times 10^{-8}$ in stage 4. These findings are consistent with appropriate calibration of the association test statistics at stage 4 in that observing one failure among 18 validation tests is consistent with the use of a significance threshold ($P < 5 \times 10^{-8}$) designed to have a 1 in 20 chance of yielding a result as or more extreme than one solely due to chance. In total, 66 loci attained genome-wide significance: 13 loci for SBP only, 12 loci for DBP only and 41 loci for both traits. Of these, 17 blood pressure loci were new, whereas 49 were previously reported at genome-wide significance (**Fig. 1** and **Table 1**).

In comparison with previously reported blood pressure–associated variants[5,7,21], the newly discovered variants had a smaller average absolute effect size, with comparable minor allele frequency (MAF), presumably owing to the increased power of a larger sample size (**Table 2**).

**Table 1 New and known blood pressure–associated loci**

| Locus number | Locus name | Lead SNP | Chr. | Position (hg19) | CA/NC | CAF | Trait | SBP | | | | DBP | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Effect | SE | *P* value | Total *n*[b] | Effect | SE | *P* value | Total *n*[b] |
| **New loci** | | | | | | | | | | | | | | | |
| 1 | *HIVEP3* | rs7515635 | 1 | 42,408,070 | T/C | 0.468 | SBP | 0.307 | 0.0444 | $4.81 \times 10^{-12}$ | 340,969 | 0.1365 | 0.0263 | $2.05 \times 10^{-7}$ | 340,934 |
| 2 | *PNPT1* | rs1975487 | 2 | 55,809,054 | A/G | 0.464 | DBP | –0.2107 | 0.045 | $2.81 \times 10^{-6}$ | 337,522 | –0.1602 | 0.0266 | $1.75 \times 10^{-9}$ | 337,517 |
| 3 | *FGD5* | rs11128722 | 3 | 14,958,126 | A/G | 0.563 | SBP + DBP | –0.3103 | 0.0469 | $3.61 \times 10^{-11}$ | 310,430 | –0.1732 | 0.0279 | $5.16 \times 10^{-10}$ | 310,429 |
| 4 | *ADAMTS9* | rs918466 | 3 | 64,710,253 | A/G | 0.406 | DBP | –0.0865 | 0.0459 | $5.94 \times 10^{-2}$ | 336,671 | –0.1819 | 0.027 | $1.73 \times 10^{-11}$ | 336,653 |
| 5 | *TBC1D1–FLJ13197* | rs2291435 | 4 | 38,387,395 | T/C | 0.524 | SBP + DBP | –0.3441 | 0.0449 | $1.90 \times 10^{-14}$ | 331,382 | –0.156 | 0.0266 | $4.26 \times 10^{-9}$ | 331,389 |
| 6 | *TRIM36* | rs10077885 | 5 | 114,390,121 | A/C | 0.501 | SBP + DBP | –0.284 | 0.0444 | $1.64 \times 10^{-10}$ | 338,328 | –0.1735 | 0.0263 | $3.99 \times 10^{-11}$ | 338,323 |
| 7 | *CSNK1G3* | rs6891344 | 5 | 123,136,656 | A/G | 0.819 | DBP | 0.2811 | 0.058 | $1.24 \times 10^{-6}$ | 338,688 | 0.2311 | 0.0343 | $1.58 \times 10^{-11}$ | 338,678 |
| 8 | *CHST12–LFNG* | rs2969070 | 7 | 2,512,545 | A/G | 0.639 | SBP + DBP | –0.2975 | 0.0464 | $1.44 \times 10^{-10}$ | 335,991 | –0.1821 | 0.0274 | $2.92 \times 10^{-11}$ | 335,972 |
| 9 | *ZC3HC1* | rs11556924a | 7 | 129,663,496 | T/C | 0.384 | SBP + DBP | –0.2705 | 0.0468 | $7.64 \times 10^{-9}$ | 325,929 | –0.2141 | 0.0276 | $8.15 \times 10^{-15}$ | 325,963 |
| 10 | *PSMD5* | rs10760117 | 9 | 123,586,737 | T/G | 0.415 | SBP | 0.283 | 0.0457 | $6.10 \times 10^{-10}$ | 333,377 | 0.0999 | 0.0269 | $2.08 \times 10^{-4}$ | 333,377 |
| 11 | *DBH* | rs6271[a] | 9 | 136,522,274 | T/C | 0.072 | SBP + DBP | –0.5911 | 0.0899 | $4.89 \times 10^{-11}$ | 306,394 | –0.4646 | 0.0532 | $2.42 \times 10^{-18}$ | 306,463 |
| 12 | *RAPSN, PSMC3, SLC39A13* | rs7103648 | 11 | 47,461,783 | A/G | 0.614 | SBP + DBP | –0.3349 | 0.0462 | $4.43 \times 10^{-13}$ | 335,614 | –0.2409 | 0.0272 | $9.03 \times 10^{-19}$ | 335,592 |
| 13 | *LRRC10B* | rs751984 | 11 | 61,278,246 | T/C | 0.879 | SBP + DBP | 0.4074 | 0.0691 | $3.80 \times 10^{-9}$ | 334,583 | 0.3755 | 0.0409 | $4.20 \times 10^{-20}$ | 334,586 |
| 14 | *SETBP1* | rs12958173 | 18 | 42,141,977 | A/C | 0.306 | SBP + DBP | 0.3614 | 0.0489 | $1.43 \times 10^{-13}$ | 331,007 | 0.1789 | 0.0289 | $5.87 \times 10^{-10}$ | 331,010 |
| 15 | *INSR* | rs4247374 | 19 | 7,252,756 | T/C | 0.143 | SBP + DBP | –0.5933 | 0.0673 | $1.23 \times 10^{-18}$ | 302,458 | –0.3852 | 0.0396 | $2.08 \times 10^{-22}$ | 302,459 |
| 16 | *ELAVL3* | rs17638167 | 19 | 11,584,818 | T/C | 0.047 | DBP | –0.4784 | 0.1066 | $7.13 \times 10^{-6}$ | 333,137 | –0.3479 | 0.0632 | $3.71 \times 10^{-8}$ | 333,107 |
| 17 | *CRYAA–SIK1* | rs12627651 | 21 | 44,760,603 | A/G | 0.288 | SBP + DBP | 0.3905 | 0.0513 | $2.69 \times 10^{-14}$ | 310,738 | 0.2037 | 0.0301 | $1.36 \times 10^{-11}$ | 310,722 |
| **Established loci** | | | | | | | | | | | | | | | |
| 1 | *CASZ1* | rs880315 | 1 | 10,796,866 | T/C | 0.641 | SBP + DBP | –0.475 | 0.062 | $2.09 \times 10^{-14}$ | 184,226 | –0.257 | 0.038 | $1.34 \times 10^{-11}$ | 184,212 |
| 2 | *MTHFR–NPPB* | rs17037390a | 1 | 11,860,843 | A/G | 0.155 | SBP + DBP | –0.908 | 0.081 | $5.95 \times 10^{-29}$ | 195,493 | –0.499 | 0.05 | $1.20 \times 10^{-23}$ | 195,481 |
| 3 | *ST7L–CAPZA1–MOV10* | rs1620668 | 1 | 113,023,980 | A/G | 0.822 | SBP + DBP | –0.535 | 0.076 | $1.45 \times 10^{-12}$ | 197,966 | –0.285 | 0.047 | $9.00 \times 10^{-10}$ | 197,948 |
| 4 | *MDM4* | rs4245739 | 1 | 204,518,842 | A/C | 0.737 | DBP | 0.326 | 0.068 | $1.37 \times 10^{-6}$ | 191,594 | 0.243 | 0.041 | $4.63 \times 10^{-9}$ | 191,578 |
| 5 | *AGT* | rs2493134a | 1 | 230,849,359 | T/C | 0.579 | SBP + DBP | –0.413 | 0.058 | $9.65 \times 10^{-13}$ | 199,505 | –0.275 | 0.036 | $9.53 \times 10^{-15}$ | 199,502 |
| 6 | *KCNK3* | rs2586886 | 2 | 26,932,031 | T/C | 0.599 | SBP + DBP | –0.404 | 0.059 | $5.94 \times 10^{-12}$ | 197,269 | –0.254 | 0.036 | $1.92 \times 10^{-12}$ | 197,272 |
| 7 | *NCAPH* | rs772178 | 2 | 96,963,684 | A/G | 0.64 | DBP | –0.072 | 0.061 | $2.39 \times 10^{-1}$ | 192,513 | –0.208 | 0.038 | $3.58 \times 10^{-8}$ | 192,501 |
| 8 | *FIGN–GRB14* | rs1371182 | 2 | 165,099,215 | T/C | 0.443 | SBP + DBP | –0.444 | 0.058 | $1.89 \times 10^{-14}$ | 196,262 | –0.252 | 0.036 | $1.50 \times 10^{-12}$ | 196,240 |
| 9 | *HRH1–ATG7* | rs2594992 | 3 | 11,360,997 | A/C | 0.607 | SBP | –0.334 | 0.06 | $2.31 \times 10^{-8}$ | 189,895 | –0.136 | 0.037 | $2.20 \times 10^{-4}$ | 189,854 |
| 10 | *SLC4A7* | rs711737 | 3 | 27,543,655 | A/C | 0.604 | SBP | 0.334 | 0.058 | $9.93 \times 10^{-9}$ | 200,282 | 0.17 | 0.036 | $2.24 \times 10^{-6}$ | 200,260 |
| 11 | *ULK4* | rs2272007[a] | 3 | 41,996,136 | T/C | 0.18 | DBP | –0.11 | 0.077 | $1.52 \times 10^{-1}$ | 193,915 | 0.328 | 0.047 | $3.94 \times 10^{-12}$ | 193,900 |
| 12 | *MAP4* | rs6442101[a] | 3 | 48,130,893 | T/C | 0.692 | SBP + DBP | 0.396 | 0.062 | $1.62 \times 10^{-10}$ | 200,543 | 0.303 | 0.038 | $1.60 \times 10^{-15}$ | 200,534 |
| 13 | *MECOM* | rs6779380 | 3 | 169,111,915 | T/C | 0.539 | SBP + DBP | –0.439 | 0.06 | $1.85 \times 10^{-13}$ | 186,535 | –0.239 | 0.037 | $6.87 \times 10^{-11}$ | 186,521 |
| 14 | *FGF5* | rs1458038 | 4 | 81,164,723 | T/C | 0.3 | SBP + DBP | 0.659 | 0.065 | $5.36 \times 10^{-24}$ | 188,136 | 0.392 | 0.04 | $7.36 \times 10^{-23}$ | 188,088 |
| 15 | *ARHGAP24* | rs17010957 | 4 | 86,719,165 | T/C | 0.857 | SBP | –0.498 | 0.082 | $1.51 \times 10^{-9}$ | 196,325 | –0.173 | 0.051 | $6.63 \times 10^{-4}$ | 196,292 |
| 16 | *SLC39A8* | rs13107325a | 4 | 103,188,709 | T/C | 0.07 | SBP + DBP | –0.837 | 0.127 | $4.69 \times 10^{-11}$ | 175,292 | –0.602 | 0.078 | $1.63 \times 10^{-14}$ | 175,372 |
| 17 | *GUCY1A3–GUCY1B3* | rs4691707 | 4 | 156,441,314 | A/G | 0.652 | SBP | –0.349 | 0.06 | $7.10 \times 10^{-9}$ | 198,246 | –0.163 | 0.037 | $1.08 \times 10^{-5}$ | 198,226 |
| 18 | *NPR3–C5orf23* | rs12656497 | 5 | 32,831,939 | T/C | 0.403 | SBP + DBP | –0.487 | 0.06 | $3.85 \times 10^{-16}$ | 194,831 | –0.228 | 0.037 | $4.73 \times 10^{-10}$ | 194,829 |
| 19 | *EBF1* | rs11953630 | 5 | 157,845,402 | T/C | 0.366 | SBP + DBP | –0.38 | 0.065 | $3.91 \times 10^{-9}$ | 167,698 | –0.23 | 0.04 | $8.07 \times 10^{-9}$ | 167,708 |
| 20 | *HFE* | rs1799945[a] | 6 | 26,091,179 | C/G | 0.857 | SBP + DBP | –0.598 | 0.086 | $3.28 \times 10^{-12}$ | 185,306 | –0.43 | 0.053 | $3.10 \times 10^{-16}$ | 185,273 |
| 21 | *BAT2–BAT5* | rs2187668 | 6 | 32,605,884 | T/C | 0.126 | DBP | –0.291 | 0.092 | $1.60 \times 10^{-3}$ | 189,806 | –0.372 | 0.057 | $4.31 \times 10^{-11}$ | 189,810 |
| 22 | *ZNF318–ABCC10* | rs6919440 | 6 | 43,352,898 | A/G | 0.57 | SBP | –0.337 | 0.058 | $4.92 \times 10^{-9}$ | 200,733 | –0.125 | 0.035 | $4.25 \times 10^{-4}$ | 200,730 |
| 23 | *RSPO3* | rs1361831 | 6 | 127,181,089 | T/C | 0.541 | SBP + DBP | –0.482 | 0.058 | $7.38 \times 10^{-17}$ | 197,027 | –0.271 | 0.036 | $2.34 \times 10^{-14}$ | 197,012 |
| 24 | *PLEKHG1* | rs17080093 | 6 | 150,997,440 | T/C | 0.075 | DBP | –0.564 | 0.111 | $3.83 \times 10^{-7}$ | 194,728 | –0.411 | 0.068 | $1.71 \times 10^{-9}$ | 194,734 |
| 25 | *HOTTIP–EVX* | rs3735533 | 7 | 27,245,893 | T/C | 0.081 | SBP + DBP | –0.798 | 0.106 | $6.48 \times 10^{-14}$ | 197,881 | –0.445 | 0.065 | $1.09 \times 10^{-11}$ | 197,880 |
| 26 | *PIK3C G* | rs12705390 | 7 | 106,410,777 | A/G | 0.227 | SBP | 0.619 | 0.069 | $2.69 \times 10^{-19}$ | 198,297 | 0.059 | 0.042 | $1.63 \times 10^{-1}$ | 198,290 |
| 27 | *BLK–GATA4* | rs2898290 | 8 | 11,433,909 | T/C | 0.491 | SBP | 0.377 | 0.058 | $8.85 \times 10^{-11}$ | 197,759 | 0.167 | 0.036 | $3.17 \times 10^{-6}$ | 197,726 |
| 28 | *CACNB2* | rs12243859 | 10 | 18,740,632 | T/C | 0.326 | SBP + DBP | –0.402 | 0.061 | $6.13 \times 10^{-11}$ | 199,136 | –0.335 | 0.038 | $8.11 \times 10^{-19}$ | 199,124 |

(continued)

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**Table 1 New and known blood pressure–associated loci (Contd.)**

| Locus number | Locus name | Lead SNP | Chr. | Position (hg19) | CA/NC | CAF | Trait | SBP Effect | SBP SE | SBP *P* value | SBP Total *n*[b] | DBP Effect | DBP SE | DBP *P* value | DBP Total *n*[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 29 | *C10orf107* | rs7076398 | 10 | 63,533,663 | A/T | 0.188 | SBP + DBP | −0.563 | 0.076 | $1.72 \times 10^{-13}$ | 187,013 | −0.409 | 0.047 | $2.55 \times 10^{-18}$ | 187,024 |
| 30 | *SYNPO2L* | rs12247028 | 10 | 75,410,052 | A/G | 0.611 | SBP | −0.364 | 0.063 | $8.16 \times 10^{-9}$ | 180,194 | −0.159 | 0.039 | $3.89 \times 10^{-5}$ | 180,094 |
| 31 | *PLCE1* | rs932764[a] | 10 | 95,895,940 | A/G | 0.554 | SBP + DBP | −0.495 | 0.059 | $6.88 \times 10^{-17}$ | 195,577 | −0.224 | 0.036 | $6.28 \times 10^{-10}$ | 195,547 |
| 32 | *CYP17A1–NT5C2* | rs943037 | 10 | 104,835,919 | T/C | 0.087 | SBP + DBP | −1.133 | 0.105 | $2.35 \times 10^{-27}$ | 193,818 | −0.482 | 0.064 | $4.48 \times 10^{-14}$ | 193,799 |
| 33 | *ADRB1* | rs740746 | 10 | 115,792,787 | A/G | 0.73 | SBP + DBP | 0.486 | 0.067 | $4.59 \times 10^{-13}$ | 184,835 | 0.32 | 0.041 | $8.63 \times 10^{-15}$ | 184,868 |
| 34 | *LSP1–TNNT3* | rs592373 | 11 | 1,890,990 | A/G | 0.64 | SBP + DBP | 0.484 | 0.063 | $2.02 \times 10^{-14}$ | 177,149 | 0.282 | 0.039 | $3.61 \times 10^{-13}$ | 177,134 |
| 35 | *ADM* | rs1450271 | 11 | 10,356,115 | T/C | 0.468 | SBP + DBP | 0.413 | 0.059 | $3.40 \times 10^{-12}$ | 191,246 | 0.199 | 0.036 | $4.11 \times 10^{-8}$ | 191,221 |
| 36 | *PLEKHA7* | rs1156725 | 11 | 16,307,700 | T/C | 0.804 | SBP + DBP | −0.447 | 0.072 | $5.65 \times 10^{-10}$ | 200,889 | −0.292 | 0.044 | $3.67 \times 10^{-11}$ | 200,899 |
| 37 | *SIPA1* | rs3741378[a] | 11 | 65,408,937 | T/C | 0.137 | SBP | −0.486 | 0.084 | $8.04 \times 10^{-9}$ | 194,563 | −0.183 | 0.052 | $4.17 \times 10^{-4}$ | 194,551 |
| 38 | *FLJ32810–TMEM133* | rs633185 | 11 | 100,593,538 | C/G | 0.715 | SBP + DBP | 0.522 | 0.067 | $6.97 \times 10^{-15}$ | 183,845 | 0.288 | 0.041 | $2.38 \times 10^{-12}$ | 183,825 |
| 39 | *PDE3A* | rs3752728 | 12 | 20,192,972 | A/G | 0.737 | DBP | 0.331 | 0.066 | $4.32 \times 10^{-7}$ | 200,440 | 0.319 | 0.04 | $2.35 \times 10^{-15}$ | 200,408 |
| 40 | *ATP2B1* | rs11105354 | 12 | 90,026,523 | A/G | 0.84 | SBP + DBP | 0.909 | 0.081 | $3.88 \times 10^{-29}$ | 195,206 | 0.459 | 0.05 | $2.61 \times 10^{-20}$ | 195,195 |
| 41 | *SH2B3* | rs3184504[a] | 12 | 111,884,608 | T/C | 0.475 | SBP + DBP | 0.498 | 0.062 | $9.97 \times 10^{-16}$ | 177,067 | 0.362 | 0.038 | $1.28 \times 10^{-21}$ | 177,122 |
| 42 | *TBX5–TBX3* | rs2891546 | 12 | 115,552,499 | A/G | 0.11 | DBP | −0.529 | 0.1 | $1.36 \times 10^{-7}$ | 172,012 | −0.38 | 0.061 | $4.71 \times 10^{-10}$ | 171,980 |
| 43 | *CYP1A1–ULK3* | rs936226 | 15 | 75,069,282 | T/C | 0.722 | SBP + DBP | −0.549 | 0.067 | $3.06 \times 10^{-16}$ | 187,238 | −0.363 | 0.041 | $1.03 \times 10^{-18}$ | 187,221 |
| 44 | *FURIN–FES* | rs2521501 | 15 | 91,437,388 | A/T | 0.684 | SBP + DBP | −0.639 | 0.069 | $3.35 \times 10^{-20}$ | 164,272 | −0.358 | 0.042 | $1.85 \times 10^{-17}$ | 164,255 |
| 45 | *PLCD3* | rs7213273 | 17 | 43,155,914 | A/G | 0.658 | SBP | −0.413 | 0.066 | $4.71 \times 10^{-10}$ | 164,795 | −0.185 | 0.041 | $7.23 \times 10^{-6}$ | 164,788 |
| 46 | *GOSR2* | rs17608766 | 17 | 45,013,271 | T/C | 0.854 | SBP | −0.658 | 0.083 | $2.27 \times 10^{-15}$ | 188,895 | −0.218 | 0.051 | $1.95 \times 10^{-5}$ | 188,928 |
| 47 | *ZNF652* | rs12940887 | 17 | 47,402,807 | T/C | 0.38 | DBP | 0.321 | 0.06 | $7.06 \times 10^{-8}$ | 192,546 | 0.261 | 0.037 | $1.07 \times 10^{-12}$ | 192,524 |
| 48 | *JAG1* | rs1327235 | 20 | 10,969,030 | A/G | 0.542 | SBP + DBP | −0.395 | 0.059 | $2.23 \times 10^{-11}$ | 192,680 | −0.308 | 0.036 | $1.78 \times 10^{-17}$ | 192,659 |
| 49 | *GNAS–EDN3* | rs6026748 | 20 | 57,745,815 | A/G | 0.125 | SBP + DBP | 0.867 | 0.089 | $3.15 \times 10^{-22}$ | 192,338 | 0.552 | 0.055 | $4.86 \times 10^{-24}$ | 192,327 |

Meta-analysis results of up to 342,415 individuals of European ancestry for SBP and DBP (some individuals were missing genotypes for individual SNPs). Established and new loci are grouped separately. Nearest genes are given as locus labels, but this should not be interpreted as support of the nearest gene as the causal gene. The SNP with the lowest *P* value for either blood pressure trait is shown as the lead SNP, and both SBP and DBP results are presented even if a SNP is genome-wide significant for only one of these traits. SNP effects are shown according to the effect in mm Hg per copy of the coded allele (that is, the allele coded 0, 1 or 2) under an additive genetic model. Chr., chromosome; CA, coded allele; NC, non-coded allele; CAF, coded allele frequency.
[a]Nonsynonymous coding SNP (either the SNP itself or another SNP having $r^2$ >0.8 with it). [b]Established loci have smaller total sample sizes than new loci (**Supplementary Note**).

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As expected from the high correlation between effects on SBP and DBP, the observed directions of effect for the two traits were generally concordant (**Supplementary Fig. 5**). The absolute effect sizes were inversely correlated with MAF (**Table 1** and **Supplementary Fig. 6**). The 66 blood pressure–associated SNPs explained 3.46% and 3.36% of variance in SBP and DBP, respectively, a modest increase from the 2.95% and 2.78% explained by the 49 previously reported SNPs (**Supplementary Note**). The low percentage variance explained is consistent with estimates that large numbers of common variants with weak effects at a large number of loci influence blood pressure[5].

## Signal refinement at the 66 blood pressure loci

To identify distinct signals of association at the 66 blood pressure loci and the variants most likely to be causal for each, we started with an approximate conditional analysis using a model selection procedure implemented in the GCTA-COJO package[22,23] as well as a detailed literature review of all published blood pressure association studies. GCTA-COJO analysis was performed using the association summary statistics for SBP and DBP from the stage 4 EUR-ancestry meta-analyses, with linkage disequilibrium (LD) between variants estimated on the basis of Cardio-MetaboChip genotype data from 7,006 individuals of EUR ancestry from the GoDARTS cohort[24]. More than one distinct blood pressure association signal was identified for 13 loci at $P < 5 \times 10^{-8}$ (**Supplementary Fig. 7**, **Supplementary Table 6** and **Supplementary Note**). At six loci, the distinct signals were identified for SBP and DBP when these traits were analyzed separately; these trait-specific associations were represented by the same or highly correlated ($r^2$ >0.8) SNPs at five of the six loci (**Supplementary Tables 7** and **8**). We repeated GCTA-COJO analyses using the same summary association results but with a different reference sample for LD estimates (WTCCC1-T2D/58BC, $n$ = 2,947; **Supplementary Note**) and observed minimal differences arising from minor fluctuations in the association *P* value in the joint regression models (**Supplementary Tables 7** and **8**). LD-based comparisons of published association signals at established blood pressure loci and the current study's findings suggested that, at ten loci, the signals identified by the single-SNP and GCTA-COJO analyses were distinct from those reported in the literature (**Supplementary Table 9**).

We then performed multivariate regression modeling in a single large cohort (Women's Genome Health Study, WGHS; $n$ = 23,047) with simultaneous adjustment for (i) all combinations of putative index SNPs for each distinct signal from the GCTA-COJO conditional analyses and (ii) all index SNPs for all potential distinct signals identified by our literature review (**Supplementary Table 9** and **Supplementary Note**). Although WGHS is very large as a single study, power is lower in a single sample than in the overall meta-analysis (23,000 versus 342,000 individuals) and, consequently, the failure to reach significance does not represent non-replication for individual SNPs. The WGHS analysis supported two distinct association signals at 8 of the 13 loci identified in the GCTA-COJO analysis but could not provide

**Table 2 Overview of variant properties for new and known blood pressure–associated variants**

| | 17 new loci | 49 established loci | 66 total loci |
|---|---|---|---|
| Minor allele frequency (mean, range) | 32.1%, 5–50% | 28.9%, 7–49% | 29.8%, 5–50% |
| Effect size SBP in mm Hg (mean, range) | 0.34, 0.09–0.59 | 0.5, 0.07–1.13 | 0.46, 0.07–1.13 |
| Effect size DBP in mm Hg (mean, range) | 0.23, 0.1–0.46 | 0.3, 0.06–0.60 | 0.28, 0.06–0.6 |
| Variance explained SBP | 0.52% | 2.95% | 3.46% |
| Variance explained DBP | 0.58% | 2.78% | 3.36% |

Key characteristics of the new and established blood pressure loci are shown. MAF and effect size estimates are derived from the Cardio-MetaboChip data. Estimates of variance explained are derived from one large study (**Supplementary Note**).

support for the remaining 5 (**Supplementary Table 10**). The joint SNP modeling in WGHS additionally supported two distinct signals of association at three other loci (*GUCY1A3–GUCY1B3*, *SYNPO2L* and *TBX5–TBX3*) at which the SNP identified in the current study is distinct from that previously reported in the literature[5,11].

We sought to refine the localization of likely functional variants in loci with high-density coverage on the Cardio-MetaboChip. We followed a Bayesian approach to define, for each signal, credible sets of variants that had 99% probability of containing or tagging the causal variant (**Supplementary Note**). To improve the resolution of the method, the analyses were restricted to 24 regions selected to fine-map genetic associations and that included at least one SNP reaching genome-wide significance in the current meta-analyses (**Supplementary Table 11**). Twenty-one of the Cardio-MetaboChip fine-mapped regions were designated blood pressure loci in the original design, and three of the newly discovered blood pressure loci corresponded to fine-mapped regions originally selected for other, non–blood pressure traits. We observed that the 99% credible SNP sets at five blood pressure loci spanned <20 kb. The greatest refinement was observed at the *SLC39A8* locus for SBP and DBP and at the *ZC3HC1* and *PLCE1* loci for DBP, where the 99% credible sets included only the index variants (**Supplementary Table 12**). Although SNPs in credible sets were primarily noncoding, they included one synonymous and seven nonsynonymous variants that attained high posterior probability of driving seven distinct association signals in six blood pressure loci (**Supplementary Table 12**). Of these, three variants by themselves accounted for more than 95% of the posterior probability of driving the association signal observed at each of three loci (**Supplementary Tables 12** and **13**). Despite reduced statistical power, the analyses restricted to only the samples with Cardio-MetaboChip genotypes ($n$ = 109,096) identified the majority of SNPs identified in the GWAS + Cardio-MetaboChip data (**Supplementary Table 12**). The full lists of SNPs in the 99% credible sets are given in **Supplementary Table 13**.

## Functional annotation of blood pressure variants

Index SNPs or their proxies ($r^2$ >0.8) altered amino acid sequence at 11 of 66 blood pressure loci (**Table 1**). Thus, the majority of blood pressure association signals are likely driven by noncoding variants hypothesized to regulate expression of some nearby gene in *cis*. To characterize their effects, we first sought SNPs associated with gene expression (eSNPs) from a range of available expression data that included HTN target end organs and cells of the circulatory system (heart tissue, kidney tissue, brain tissue, aortic endothelial cells and blood vessels) as well as other tissue and cell types ($CD4^+$ macrophages, monocytes, lymphoblastoid cell lines, skin tissue, fat tissue and liver tissue). Fourteen blood pressure–associated SNPs at the *MTHFR–NPPB*, *MDM4*, *ULK4*, *CYP1A1–ULK3*, *ADM*, *FURIN–FES*, *FIGN* and *PSMD5* loci were eSNPs across different tissues (**Supplementary Table 14**). Of these 14 eSNPs, 3 were also predicted to alter amino acid sequence at the *MTHFR–NPPB*, *MAP4* and *ULK4* loci, providing two potential mechanisms to explore in functional studies. Second, we used gene expression levels measured in whole blood in two different samples each including >5,000 individuals of EUR descent. We tested whether the lead blood pressure SNP was associated with expression of any transcript in *cis* (<1 Mb from the lead SNP at each locus) at a false discovery rate (FDR) of <0.05, accounting for all possible *cis* transcript association tests across the genome. It is likely that we did not genotype the causal genetic variant underlying each blood pressure association signal; a nearby SNP–transcript association, identified by LD, may therefore reflect an independent genetic effect on expression that is unrelated to the effect on blood pressure. Consequently, we required that the lead blood pressure SNP and the most significant eSNP for a given transcript be highly correlated ($r^2$ >0.7). Furthermore, we required that the significance of the transcript association with the lead blood pressure SNP be substantially reduced in a conditional model adjusting for the best eSNP for a given transcript. Eighteen SNPs at 15 loci were associated with 22 different transcripts, with a total of 23 independent SNP–transcript associations (3 SNPs were associated with 2 transcripts each; **Supplementary Table 15** and **Supplementary Note**). The genes expressed in an allele-specific manner with respect to blood pressure SNPs are clearly high-priority candidates to mediate the association with blood pressure. In whole blood, these genes included obvious biological candidates such as *GUCY1A3*, encoding the α subunit of the soluble guanylate cyclase protein, and *ADM*, encoding adrenomedullin, both of which are known to induce vasodilation[25,26]. There was some overlap of eSNPs between the whole blood and other tissue data sets at the *MTHFR–NPPB*, *MDM4*, *PSMD5*, *ULK4* and *CYP1A1–ULK3* loci.

An alternative method to prioritize noncoding variants at blood pressure loci that are most likely to be causal is to determine whether they fall within DNase I hypersensitivity sites (DHSs). We performed two analyses to investigate whether blood pressure SNPs or their LD proxies ($r^2$ >0.8) were enriched in DHSs in a cell-type-specific manner (**Supplementary Note**). First, we used Epigenomics Roadmap and Encyclopedia of DNA Elements (ENCODE) DHS data from 123 cell lines or tissues derived from adults[27–29] to estimate the fold increase in the proportion of blood pressure SNPs mapping to DHSs as compared to SNPs associated at genome-wide significance with non–blood pressure phenotypes from the National Human Genome Research Institute (NHGRI) GWAS catalog[30]. We observed that 7 of the 10 cell types with the greatest relative enrichment of blood pressure SNPs mapping to DHSs were from blood vessels (vascular or microvascular endothelial cell lines or cells), and 11 of the 12 endothelial cell types were among the top 25% most enriched among the 123 cell types (**Fig. 2** and **Supplementary Table 16**). In a second analysis of an expanded set of tissues and cell lines, in which cell types were grouped into tissues (**Supplementary Table 17**), blood pressure–associated SNP enrichment in DHSs in blood vessels was again observed ($P = 1.2 \times 10^{-9}$), as well as in heart samples ($P = 5.3 \times 10^{-8}$; **Supplementary Table 18**).

We next tested whether there was enrichment of blood pressure SNPs among sites with trimethylation of histone H3 at lysine 4 (H3K4me3)[31], a methylation mark associated with both promoters and enhancers. We observed significant enrichment in a range of cell types including $CD34^+$ primary cells, adult kidney cells and muscle satellite cultured cells (**Supplementary Table 19**). Enrichment of blood pressure SNPs in regions with predicted strong and weak enhancer

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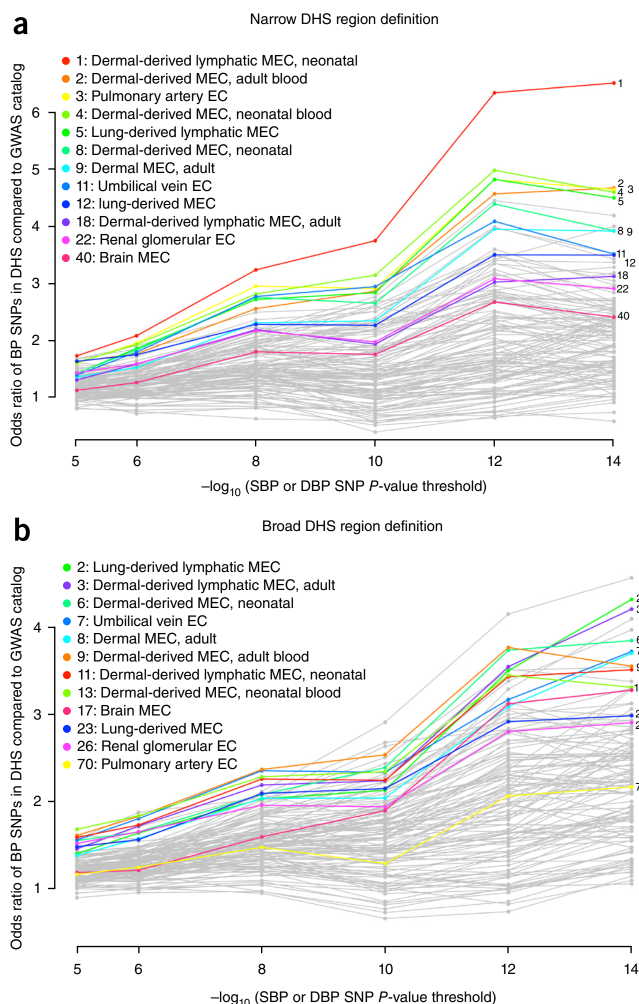


**Figure 2** Enrichment of DNase I–hypersensitive sites among blood pressure loci in 123 different cell types. (**a**,**b**) Enrichment analyses of SBP- or DBP-associated loci according to discovery $P$ value using narrow peaks (**a**) or broad peaks (**b**). SNPs were selected according to different $P$-value cutoffs ($x$ axis), and fold enrichment of overlap with DHSs as compared to unrelated GWAS SNPs was calculated ($y$ axis) (**Supplementary Note**). The 12 endothelial cell lines are indicated in color, and for each endothelial cell type the rank using the $P$-value cutoff of $1 \times 10^{-14}$ is given. BP, blood pressure; EC, endothelial cells; MEC, microvascular endothelial cells.

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states and in active promoters[32] in a range of cell types was also observed (**Supplementary Fig. 8** and **Supplementary Table 20**).

We used Meta-Analysis Gene Set Enrichment of Variant Associations (MAGENTA)[33] to attempt to identify pathways over-represented in the blood pressure association results. No gene sets meeting experiment-wide significance for enrichment for blood pressure association were identified by MAGENTA after correction for multiple testing, although some attained nominal significance (**Supplementary Table 21** and **Supplementary Note**). We also adapted the Data-Driven Expression Prioritized Integration for Complex Traits (DEPICT)[34] pathway analysis tool to identify assembled gene sets that were enriched for genes near associated variants and to assess whether genes from associated loci were highly expressed in particular tissues or cell types. Using the extended blood pressure locus list based on genome-wide significant loci from this analysis and previously published SNPs that might not have reached genome-wide significance in the current analysis (**Supplementary Table 9**), we identified five significant (FDR 5%) gene sets: abnormal cardiovascular system physiology, $G_{\alpha12,13}$ signaling events, embryonic growth retardation, prolonged QT interval and abnormal vitelline vasculature morphology. We also found that suggestive SBP and DBP associations ($P < 1 \times 10^{-5}$) were enriched for reconstituted gene sets at DBP loci (mainly related to developmental pathways) but not at SBP loci (**Supplementary Table 22** and **Supplementary Note**). In a final analysis, we assessed Cardio-MetaboChip SNPs at the fine-mapping loci using formaldehyde-assisted isolation of regulatory elements (FAIRE-gen) in lymphoblastoid cell lines[35]. Our results provided support for two SNPs, one of which (rs7961796 in the *TBX5*–*TBX3* locus) was located in a regulatory site. Although the other SNP (rs3184504 in the *SH2B3* locus) is a nonsynonymous variant, there was also a regulatory site indicated by DNase I and monomethylation at histone H3 at lysine 4 (H3K4me1) signatures at the locus, making the SNP a potential regulatory variant (**Supplementary Table 23**)[36]. Both SNPs were included in the list of 99% credible SNPs at each locus.

### Asian- and African-ancestry blood pressure SNP association

We tested the 66 lead SNPs at the established and new loci for association with blood pressure in up to 20,875 individuals of South Asian (SAS) ancestry (PROMIS and RACE studies), 9,637 individuals of East Asian (EAS) ancestry (HEXA, HALST, CLHNS, DRAGON and TUDR studies) and 33,909 individuals of African (AFR) ancestry (COGENT-BP Consortium, Jupiter, SPT, Seychelles, GXE and TANDEM studies). As expected, effect allele frequencies were very similar across studies of the same ancestry group but were markedly different across different ancestry groups (**Supplementary Fig. 9**). Many associations for individual SNPs failed to reach $P < 0.05$ for the blood pressure trait with the lower $P$ value (**Supplementary Table 24**), which could potentially be because of the much lower statistical power at the sample sizes available, different patterns of LD at each locus across ancestry groups, variability in allele frequency or true lack of association in individuals of a given non-European ancestry. The low statistical power for the great majority of SNPs tested was apparent when considering SNP-by-SNP power calculations using European-ancestry effect sizes (**Supplementary Table 24**). However, concordant directions of allelic effect for both SBP and DBP were observed for 45 of 66 SNPs in SAS samples, 36 of 60 SNPs in EAS samples and 42 of 66 SNPs in AFR samples; the strongest concordance with SAS samples may not be surprising because South Asians are more closely related to Europeans than are East Asians or Africans. Moreover, strong correlation of effect sizes was observed for EUR samples with SAS, EAS and AFR samples ($r = 0.55$, 0.60 and 0.48, respectively). SBP and DBP risk scores composed of 66 SNPs were significant predictors of SBP and DBP, respectively, in all samples. SBP and DBP risk scores that were 1 mm Hg higher in EUR samples were associated with increases of 0.58 and 0.50 mm Hg in SBP and DBP, respectively, in SAS samples (SBP $P = 1.5 \times 10^{-19}$, DBP $P = 3.2 \times 10^{-15}$), increases of 0.49 and 0.50 mm Hg in SBP and DBP in EAS samples (SBP $P = 1.9 \times 10^{-10}$, DBP $P = 1.3 \times 10^{-7}$), and increases of 0.51 and 0.47 mm Hg in SBP and DBP in AFR samples (SBP $P = 2.2 \times 10^{-21}$, DBP $P = 6.5 \times 10^{-19}$). The attenuation of the genetic risk score estimates in non-European ancestries is presumably due to inclusion of a subset of variants that lack association in the non-European or admixed samples.

We subsequently performed a trans-ancestry meta-analysis of the 66 SNPs in all 64,421 samples from the three non-European ancestry groups. After correcting for 66 tests, 12 of the 66 SNPs were significantly associated with either SBP or DBP ($P < 7.6 \times 10^{-4}$), with correlation between EUR and non-EUR effect estimates of 0.77 for SBP

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**Table 3 Blood pressure risk score effects on disease outcomes and traits**

| Phenotype | Variant type | Ancestry | Consortium | Total *n* or cases/controls | Total SNPs | SBP score | | | | | DBP score | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Effect (all) | *P* (all) | $P_{het}$ (all) | *P* (p) | SNPs rem. | Effect (all) | *P* (all) | $P_{het}$ (all) | *P* (p) | SNPs rem. |
| **Heart** | | | | | | | | | | | | | | | |
| Coronary artery disease | Dichotomous | EUR_SAS | CARDIoGRAMplusC4D | 63,746/130,681 | 61 | 1.042 | $\mathbf{1.72 \times 10^{-44}}$ | $1.75 \times 10^{-25}$ | $\mathbf{4.08 \times 10^{-32}}$ | 10 | 1.069 | $\mathbf{1.19 \times 10^{-42}}$ | $6.63 \times 10^{-27}$ | $\mathbf{2.2 \times 10^{-38}}$ | 10 |
| Heart failure | Dichotomous | EUR | CHARGE | 2,526/18,400 | 66 | 1.021 | $2.77 \times 10^{-2}$ | $1.63 \times 10^{-1}$ | $2.77 \times 10^{-2}$ | 0 | 1.035 | $2.31 \times 10^{-2}$ | $1.70 \times 10^{-1}$ | $2.31 \times 10^{-2}$ | 0 |
| LV mass | Continuous | EUR | CHARGE | 11,273 | 66 | 0.480 | $\mathbf{6.43 \times 10^{-4}}$ | $3.58 \times 10^{-1}$ | $\mathbf{6.43 \times 10^{-4}}$ | 0 | 0.754 | $\mathbf{1.23 \times 10^{-3}}$ | $3.21 \times 10^{-1}$ | $\mathbf{1.23 \times 10^{-3}}$ | 0 |
| LV wall thickness | Continuous | EUR | CHARGE | 11,311 | 66 | 0.004 | $\mathbf{4.45 \times 10^{-6}}$ | $5.83 \times 10^{-2}$ | $\mathbf{4.45 \times 10^{-6}}$ | 0 | 0.007 | $\mathbf{3.19 \times 10^{-6}}$ | $6.40 \times 10^{-2}$ | $\mathbf{3.19 \times 10^{-6}}$ | 0 |
| **Kidney** | | | | | | | | | | | | | | | |
| CKD | Dichotomous | EUR | CHARGE | 6,271/68,083 | 65 | 1.010 | $1.37 \times 10^{-1}$ | $1.77 \times 10^{-3}$ | $2.65 \times 10^{-1}$ | 1 | 1.008 | $4.49 \times 10^{-1}$ | $1.25 \times 10^{-3}$ | $7.69 \times 10^{-1}$ | 1 |
| eGFR (based on creatinine) | Continuous | EUR | CHARGE | 74,354 | 65 | 0.000 | $7.07 \times 10^{-1}$ | $3.12 \times 10^{-5}$ | $3.22 \times 10^{-1}$ | 2 | 0.000 | $9.41 \times 10^{-1}$ | $3.02 \times 10^{-5}$ | $9.65 \times 10^{-1}$ | 2 |
| eGFR (based on cystatin) | Continuous | EUR | CHARGE | 74,354 | 65 | –0.001 | $9.05 \times 10^{-2}$ | $9.28 \times 10^{-6}$ | $4.11 \times 10^{-1}$ | 1 | –0.001 | $3.30 \times 10^{-1}$ | $5.64 \times 10^{-6}$ | $6.9 \times 10^{-1}$ | 1 |
| Creatinine | Continuous | EUR | KidneyGEN | 23,812 | 66 | 0.000 | $9.42 \times 10^{-1}$ | $6.31 \times 10^{-3}$ | $9.42 \times 10^{-1}$ | 0 | 0.000 | $4.11 \times 10^{-1}$ | $7.16 \times 10^{-3}$ | $4.11 \times 10^{-1}$ | 0 |
| Microalbuminuria | Dichotomous | EUR | CHARGE | 2,499/29,081 | 65 | 1.011 | $2.10 \times 10^{-1}$ | $4.79 \times 10^{-2}$ | $2.1 \times 10^{-1}$ | 0 | 1.023 | $1.02 \times 10^{-1}$ | $5.66 \times 10^{-2}$ | $1.02 \times 10^{-2}$ | 0 |
| Urinary albumin/creatinine ratio | Continuous | EUR | CHARGE | 31,580 | 65 | 0.009 | $\mathbf{2.52 \times 10^{-3}}$ | $3.02 \times 10^{-4}$ | $0.53 \times 10^{-3}$ | 1 | 0.015 | $\mathbf{2.40 \times 10^{-3}}$ | $3.08 \times 10^{-4}$ | $8.31 \times 10^{-3}$ | 1 |
| **Stroke** | | | | | | | | | | | | | | | |
| Stroke, all subtypes | Dichotomous | EUR | CHARGE | 1,544/18,058 | 66 | 1.058 | $\mathbf{6.11 \times 10^{-6}}$ | $8.26 \times 10^{-2}$ | $\mathbf{6.11 \times 10^{-6}}$ | 0 | 1.089 | $\mathbf{3.79 \times 10^{-5}}$ | $4.98 \times 10^{-2}$ | $\mathbf{3.79 \times 10^{-5}}$ | 0 |
| Stroke, ischemic subtype | Dichotomous | EUR | CHARGE | 1,164/18,438 | 66 | 1.069 | $\mathbf{3.33 \times 10^{-6}}$ | $1.75 \times 10^{-1}$ | $\mathbf{3.33 \times 10^{-6}}$ | 0 | 1.101 | $\mathbf{5.63 \times 10^{-5}}$ | $8.82 \times 10^{-2}$ | $\mathbf{5.63 \times 10^{-5}}$ | 0 |
| Stroke, ischemic subtype | Dichotomous | EUR | MetaStroke | 11,012/40,824 | 66 | 1.036 | $\mathbf{1.69 \times 10^{-10}}$ | $4.72 \times 10^{-2}$ | $\mathbf{1.69 \times 10^{-10}}$ | 0 | 1.058 | $\mathbf{1.29 \times 10^{-9}}$ | $2.51 \times 10^{-2}$ | $\mathbf{1.29 \times 10^{-9}}$ | 0 |
| **Vasculature** | | | | | | | | | | | | | | | |
| cIMT | Continuous | EUR | CHARGE | 27,610 | 66 | 0.004 | $\mathbf{4.80 \times 10^{-15}}$ | $5.06 \times 10^{-8}$ | $\mathbf{7.32 \times 10^{-10}}$ | 4 | 0.005 | $\mathbf{4.15 \times 10^{-11}}$ | $3.84 \times 10^{-10}$ | $\mathbf{6.2 \times 10^{-7}}$ | 5 |
| **Eye** | | | | | | | | | | | | | | | |
| Mild retinopathy | Dichotomous | EUR | CHARGE | 1,122/18,289 | 66 | 1.021 | $1.37 \times 10^{-1}$ | $6.01 \times 10^{-3}$ | $1.37 \times 10^{-1}$ | 0 | 1.046 | $5.78 \times 10^{-2}$ | $7.81 \times 10^{-3}$ | $5.78 \times 10^{-2}$ | 0 |
| Central retinal artery caliber | Continuous | EUR | CHARGE | 18,576 | 66 | –0.343 | $\mathbf{3.29 \times 10^{-14}}$ | $2.56 \times 10^{-6}$ | $\mathbf{2.06 \times 10^{-13}}$ | 2 | –0.570 | $\mathbf{3.61 \times 10^{-14}}$ | $2.44 \times 10^{-6}$ | $\mathbf{7.05 \times 10^{-13}}$ | 3 |
| Mild retinopathy | Dichotomous | EAS | SEED | 289/5,419 | 66 | 1.033 | $2.55 \times 10^{-1}$ | $2.42 \times 10^{-1}$ | $2.55 \times 10^{-1}$ | 0 | 1.087 | $8.55 \times 10^{-2}$ | $2.87 \times 10^{-1}$ | $8.55 \times 10^{-2}$ | 0 |
| Central retinal artery caliber | Continuous | EAS | SEED | 6,976 | 63 | –0.320 | $\mathbf{1.39 \times 10^{-4}}$ | $9.07 \times 10^{-1}$ | $\mathbf{1.39 \times 10^{-4}}$ | 0 | –0.533 | $\mathbf{2.19 \times 10^{-4}}$ | $8.91 \times 10^{-1}$ | $\mathbf{2.19 \times 10^{-4}}$ | 0 |

Shown are the estimated effects of a blood pressure risk score comprising up to 66 SNPs (actual number given in "Total SNPs" column) on risk of dichotomous outcome or increment in continuous measures per 1 mm Hg predicted from the SBP or DBP score. Effect sizes are expressed as the incremental change in the phenotype for quantitative traits and as the odds ratio for binary traits per a predicted increase of 1 mm Hg in SBP or DBP. *P* values are bolded if they meet an analysis-wide significance threshold (<0.05/18 = 0.0028). Results are shown for all SNPs ("all") and for pruned SNPs ("p"). The results for pruned SNPs were obtained by iterative removal of SNPs from the risk score, starting with the SNP with the lowest heterogeneity *P* value ($P_{het}$). Iterations to remove SNPs were continued until the heterogeneity *P* value was >0.0028 (**Supplementary Note**). The number of SNPs removed when calculating the pruned results is indicated in the "SNPs rem." column. The results for individual SNPs can be found in **Supplementary Table 15**. CAD, coronary artery disease; LV, left ventricle; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; cIMT, carotid intima:media thickness; EUR, European ancestry; SAS, South Asian ancestry; EAS, East Asian ancestry.

and 0.67 for DBP; the EUR-ancestry SBP and DBP risk scores were associated with increases of 0.53 and 0.48 mm Hg in blood pressure per 1 mm Hg of predicted SBP and DBP, respectively (SBP $P < 6.6 \times 10^{-48}$, DBP $P < 1.3 \times 10^{-38}$). For 7 of the 12 significant SNPs, no association has previously been reported in genome-wide studies of non-European ancestry. Some heterogeneity was observed between EUR and non-EUR effect estimates (**Supplementary Table 24**). Taken together, these findings suggest that, in aggregate, blood pressure loci identified using data from individuals of EUR ancestry are also predictive of blood pressure in non-EUR samples, but larger non-EUR sample sizes will be needed to establish precisely which individual SNPs are associated in a given ancestry group.

### Impact on hypertensive target organ damage

Long-term elevated blood pressure causes target organ damage, especially in the heart, kidney, brain, large blood vessels and retinal vessels[37]. Consequently, the genetic effect of the 66 SBP- and DBP-associated SNPs on end organ outcome can be tested directly using the risk score, although some outcomes lacked results for a small number of SNPs. Interestingly, blood pressure risk scores significantly predicted (**Supplementary Note**) coronary artery disease risk, left ventricular mass and wall thickness, stroke, urinary albumin/creatinine ratio, carotid intimamedial thickness and central retinal artery caliber, but not heart failure or other kidney phenotypes, after accounting for the number of outcomes examined (**Table 3**). Because outlier effects can influence risk scores, potentially due to pleiotropic effects, we repeated the risk score analysis while iteratively removing SNPs that contributed to statistical heterogeneity (SNP–trait effects relative to SNP–blood pressure effects). Heterogeneity was defined on the basis of a multiple-testing-adjusted significance threshold for Cochran's *Q* test of homogeneity of effects (**Supplementary Note**). The risk score analyses restricted to the subset of SNPs showing no heterogeneity of effect gave essentially identical results, with the exception that the urinary albumin/creatinine ratio was no longer significant. The results for each SNP are presented in **Supplementary Figure 10** and **Supplementary Table 25**. Because large-scale GWAS of non–blood pressure cardiovascular risk factors are available, we examined the blood pressure risk scores as predictors of other cardiovascular risk factors: LDL cholesterol, HDL cholesterol, triglycerides, type 2 diabetes, BMI and height. We observed nominal ($P < 0.05$) association of the blood pressure risk scores with these risk factors, although the effects were mostly in the opposite direction to the risk factor–cardiovascular disease association (**Supplementary Table 26**). The inability to demonstrate an effect of blood pressure risk scores on heart failure may reflect limited power from a modest sample size, but the lack of significant effects on renal measures despite adequate sample size suggests that the epidemiological relationship of higher blood pressure and worse renal function may not reflect direct consequences of blood pressure elevation.

## DISCUSSION

The study reported here is the largest thus far to investigate the genomics of blood pressure in multiple continental ancestry groups. Our results highlight four major features of between-individual variation in blood pressure: (i) we identified 66 (17 new) genome-wide significant loci for SBP and DBP by targeted genotyping in up to 342,415 individuals of EUR ancestry that cumulatively explain ~3.5% of the trait; (ii) the variants were enriched for *cis*-regulatory elements, particularly in vascular endothelial cells; (iii) the variants had broadly comparable effects on blood pressure in South Asians, East Asians and Africans, albeit in smaller sample sizes; and (iv) a 66-SNP risk score predicted target organ damage in the heart, cerebral vessels, carotid artery and eye with little evidence for an effect in the kidney. Overall, there was no enrichment of a single genetic pathway in our data; rather, our results are consistent with the effects of blood pressure arising from multiple tissues and organs.

Genetic and molecular analyses of Mendelian syndromes of HTN and hypotension point largely to a renal origin, involving multiple rare deleterious mutations of proteins that regulate salt–water balance[38]. This is strong support for Guyton's hypothesis that the regulation of sodium excretion by the kidney and its effects on extracellular volume are a prime pathway determining intra-arterial pressure[39]. However, our genetic data from unselected individuals in the general community argue against a single, dominant renal effect. The 66 SNPs we identified are not chance effects but have a global distribution and impact on blood pressure that are consistent as measured by their effects across the many studies on which meta-analysis was performed. That these sites are polymorphic across all continental ancestry groups argues for their origin and functional effects before human continental differentiation.

However, several of the 17 new loci contain strong positional biological candidates; these are described in greater detail in **Supplementary Table 27** and the **Supplementary Note**. The single most common feature we identified was the enrichment of regulatory elements for gene expression in vascular endothelial cells. The broad distribution of these cells across both large and small vessels and across all tissues and organs suggests that functional variation in these cells affects endothelial permeability or vascular smooth muscle cell contractility via multiple pathways. These hypotheses will need to be tested rigorously in appropriate models, to assess the contribution of these pathways to blood pressure control, and these pathways could also be targets for systemic antihypertensive therapy as they are for the pulmonary circulation[40].

In summary, these genetic observations may contribute to an improved understanding of blood pressure biology and a reevaluation of the pathways considered relevant for therapeutic blood pressure control.

**URLs.** ENCODE data (accessed 13 March 2013), http://hgdownload.cse.ucsc.edu/goldenPath/hg19/encodeDCC/wgEncodeUwDnase; NHGRI GWAS catalog (accessed 13 March 2013), http://www.genome.gov/gwastudies; ENCODE cell type data (accessed 13 March 2013), http://genome.ucsc.edu/ENCODE/cellTypes.html.

## METHODS

Methods and any associated references are available in the online version of the paper.

**Accession codes.** Summary statistics have been deposited in the database of Genotypes and Phenotypes (dbGaP) under accession phs000585.v2.p1.

*Note: Any Supplementary Information and Source Data files are available in the online version of the paper.*

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AUTHOR CONTRIBUTIONS

**Analysis group.** Design of secondary analyses: G.B.E., T. Ferreira, T.J., A.P.M., P.B.M., C.N.-C. Computation of secondary analyses: G.B.E., T. Ferreira, T.J., A.P.M., P.B.M., C.N.-C. Manuscript writing: A.C., G.B.E., T. Ferreira, T.J., A.P.M., P.B.M., C.N.-C. Study management: P.B.M., C.N.-C.

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**Cardio-MetaboChip or new GWAS. WGHS.** Study phenotyping: P.M.R., D.I.C., L.M.R. Genotyping or analysis: P.M.R., D.I.C., L.M.R., F. Giulianini. Study PI: P.M.R. **JUPITER.** Study phenotyping: P.M.R., D.I.C., L.M.R. Genotyping or analysis: D.I.C., L.M.R., F. Giulianini. Study PI: P.M.R., D.I.C. **deCODE.** Study phenotyping: G.B. Genotyping or analysis: G.T. Study PI: K.S., U.T. **GoDARTS.** Study phenotyping: C.N.A.P., L.A.D., A.D.M., A.S.F.D. Genotyping or analysis: C.N.A.P., L.A.D., A.D.M., M.I.M., C.J.G., N.W.R. Study PI: C.N.A.P., A.D.M. **KORA F3/F4.** Study phenotyping: A.D., H. Schunkert, J.E. Genotyping or analysis: A.-K.P., M.M.-N., N.K., T.I. Study PI: H.-E.W., A. Peters. **GLACIER.** Study phenotyping: F.R., G.H. Genotyping or analysis: P.W.F., D. Shungin, I.B., S. Edkins, F.R. Study PI: P.W.F. **B58C.** Genotyping or analysis: S. Kanoni, K.E.S., Wellcome Trust Case Control Consortium, E.M., T. Ferreira, T.J. Study PI: P.D. **MORGAM.** Study phenotyping: K. Kuulasmaa, F. Gianfagna, A. Wagner, J. Dallongeville. Genotyping or analysis: M.F.H., F. Gianfagna. Study PI: J.V., J.F., A.E. **SardiNIA.** Study phenotyping: E.G.L. Genotyping or analysis: E.G.L., O. Meirelles, S. Sanna, R.N., A. Mulas, K.V.T. **NFBC1986.** Study phenotyping: M.-R.J., S. Sebert, K.-H.H., A.-L.H. Genotyping or analysis: M. Kaakinen, A.-L.H. Study PI: M.-R.J. **DESIR.** Genotyping or analysis: N.B.-N., L.Y., S.L. Study PI: P.F., N.B.-N., B.B. **DILGOM.** Study phenotyping: S.M. Genotyping or analysis: K. Kristiansson, M.P., A.S.H. Study PI: V.S. **IMPROVE.** Study phenotyping: D.B. Genotyping or analysis: R.J.S., K.G. Study PI: A. Hamsten, E. Tremoli. **HyperGEN.** Study phenotyping: S.C.H., D.C.R. Genotyping or analysis: A.C., V.P., G.B.E. Study PI: S.C.H. **FENLAND (MetaboChip).** Study phenotyping: R.J.F.L., J. Luan, N.J.W., K.K.O. Genotyping or analysis: R.J.F.L., J. Luan, N.J.W., K.K.O. Study PI: N.J.W. **Whitehall II.** Study phenotyping: M. Kumari. Genotyping or analysis: M. Kumari, S. Shah, C.L. Study PI: A.D.H., M. Kivimaki. **LURIC.** Genotyping or analysis: M.E.K., G. Delgado. Study PI: W.M. **MESA.** Study phenotyping: W.P. Genotyping or analysis: W.P., X.G., J.Y., D.V., K.D.T., J.I.R., Y.-D.C. Study PI: W.P. **HUNT2.** Study phenotyping: K. Kvaløy, J.H., O.L.H. Genotyping or analysis: A.U.J. Study PI: K.H. **FINCAVAS.** Genotyping or analysis: T.L., L.-P.L., K.N., M. Kähönen. Study PI: T.L., M. Kähönen. **GenNet.** Study phenotyping: R.S.C., A.B.W. Genotyping or analysis: A.C., V.P., M.X.S., D.E.A., G.B.E. Study PI: A.C., R.S.C., A.B.W. **SCARFSHEEP.** Study phenotyping: B.G. Genotyping or analysis: R.J.S. Study PI: A. Hamsten, U.d.F. **DPS.** Study phenotyping: J. Lindström. Genotyping or analysis: A.U.J., P.S.C. Study PI: J.T., M.U. **DR's EXTRA.** Study phenotyping: P.K. Genotyping or analysis: A.U.J., M.H. Study PI: R. Rauramaa, T.A.L. **FIN-D2D 2007.** Genotyping or analysis: A.U.J., L.L.B. Study PI: J. Saltevo, L.M. **METSIM.** Study phenotyping: H.M.S. Genotyping or analysis: A.U.J., A.S. Study PI: M.L., J.K. **MDC-CVA.** Study phenotyping: O. Melander. Genotyping or analysis: O. Melander, C.F. Study PI: O. Melander. **BRIGHT.** Study phenotyping: A.F.D., M.J.B., N.J.S., J.M.C. Genotyping or analysis: T.J., P.B.M. Study PI: M.J.C., A.F.D., M.J.B., N.J.S., J.M.C., P.B.M. **NESDA.** Study phenotyping: J.H.S. Genotyping or analysis: H. Snieder, I.M.N. Study PI: B.W.P. **EPIC (MetaboChip).** Study phenotyping: R.J.F.L., J. Luan, N.J.W. Genotyping or analysis: J. Luan, N.J.W. Study PI: N.J.W., K.-T.K. **ELY.** Study phenotyping: C.L., J. Luan, N.J.W. Genotyping or analysis: C.L., J. Luan, N.J.W. Study PI: N.J.W. **DIAGEN.** Study phenotyping: J.G., G.M. Genotyping or analysis: A.U.J., G.M. Study PI: P.E.H.S., S.R.B. **GOSH.** Study phenotyping: P.K.M., N.L.P. Genotyping or analysis: E.I., P.K.M., N.L.P., T. Fall. Study PI: E.I. **Tromsø.** Study phenotyping: T.W. Genotyping or analysis: A.U.J., A.J.S., N.N. Study PI: I.N.N. **ADVANCE.** Study phenotyping: T.L.A., C.I. Genotyping or analysis: T.L.A., E.L.S., T.Q. Study PI: T.L.A., T.Q., C.I. **ULSAM.** Study phenotyping: E.I., J. Sundstrom. Genotyping or analysis: E.I., N.E., J. Sundstrom, A.-C.S. Study PI: J. Sundstrom. **PIVUS.** Study phenotyping: L. Lind, J. Sundstrom. Genotyping or analysis: L. Lind, N.E., J. Sundstrom, T.A. Study PI: L. Lind, J. Sundstrom. **MRC NSHD.** Study phenotyping: D.K. Genotyping or analysis: A. Wong, J. Luan, D.K., K.K.O. Study PI: D.K. **ASCOT.** Study phenotyping: A.V. Stanton, N.P. Genotyping or analysis: T.J., M.J.C., P.B.M., E.P.A.v.I. Study PI: P.S., M.J.C. **THISEAS.** Genotyping or analysis: L.S.R., S. Kanoni, E.M., G. Kolovou. Study PI: G. Dedoussis, P.D. **PARC.** Study phenotyping: R.M.K. Genotyping or analysis: K.D.T., E. Theusch, J.I.R., X.L., M.O.G., Y.-D.I.C. Study PI: R.M.K. **AMC-PAS.** Genotyping or analysis: G.K.H., P.D., E.P.A.v.I. Study PI: G.K.H. **CARDIOGENICS.** Genotyping or analysis: S. Kanoni, A.H.G. Study PI: P.D., A.H.G., J.E., N.J.S., H. Schunkert.

**Secondary analyses. Allele-specific FAIRE.** Design of secondary analysis: A.J.P.S. Computation of secondary analysis: A.J.P.S., F.D., P.H. **ASAP eQTL.** Design of secondary analysis: A.F.-C. Computation of secondary analysis: L. Folkersen, P. Eriksson. **CARDIOGENICS eQTL.** Computation of secondary analysis: L. Lataniotis. **Cardio-MetaboChip design.** P.B.M., C.N.-C., T.J., B.F.V., H.M.K. **Comprehensive literature review.** Design of secondary analysis: P.B.M. Computation of secondary analysis: K.W., P.B.M. **DEPICT.** Design of secondary analysis: L. Franke, T.H.P., J.N.H. Computation of secondary analysis: T.H.P. **DHS and methylation analysis by tissue.** Design of secondary analysis: C.J.W. Computation of secondary analysis: E.M.S. **DHS and methylation by cell line.** Design of secondary analysis: D.I.C. Computation of secondary analysis: D.I.C., F. Giulianini. **FHS eSNP.** Design of secondary analysis: R. Joehanes. Computation of secondary analysis: R. Joehanes. **ICBP SC.** C.N.-C., M.J.C., P.B.M., A.C., K.M.R., P.F.O'R., W.P., D.L., M.D.T., B.M.P., A.D.J., P. Elliott, C.M.v.D., D.I.C., A.V. Smith, M. Bochud, L.V.W., H. Snieder, G.B.E. **Kidney eQTL.** Computation of secondary analysis: H.J.G., S.K.K. **MAGENTA.** Design of secondary analysis: D.I.C. Computation of secondary analysis: D.I.C. **Miscellaneous.** Computation of secondary analysis: H. Warren. **MuTHER eQTL.** Design of secondary analysis: P.D. Computation of secondary analysis: L. Lataniotis, T.-P.Y. **NESDA eQTL.** Design of secondary analysis: R. Jansen. Computation of secondary analysis: R. Jansen, A.V. **NTR eQTL.** Design of secondary analysis: R. Jansen. Computation of secondary analysis: R. Jansen, J.-J.H. Study PI: D.I.B. **eQTL, EGCUT.** Design of secondary analysis: A. Metspalu. Computation of secondary analysis: T.E., A. Metspalu. **eQTL, Groningen.** Design of secondary analysis: L. Franke. Computation of secondary analysis: H.-J.W., L. Franke. **Public eSNP and methylation.** Design of secondary analysis: A.D.J., J.D.E. Computation of secondary analysis: A.D.J., J.D.E. **PubMed search.** Design of secondary analysis: G.B.E. Computation of secondary analysis: G.B.E., L. Lin. **WGHS conditional.** Design of secondary analysis: D.I.C. Computation of secondary analysis: D.I.C., F. Giulianini, L.M.R.

**Lookup of Cardio-MetaboChip variants. HEXA.** Genotyping or analysis: Y.J.K., Y.K.K., Y.-A.S. Study PI: J.-Y.L. **RACe.** Study phenotyping: D. Saleheen, W. Zhao, A.R. Genotyping or analysis: W. Zhao, A.R. Study PI: D. Saleheen. **HALST.** Study phenotyping: C.A.H. Genotyping or analysis: J.I.R., Y.-D.C., C.A.H., R.-H.C., I.-S.C. Study PI: C.A.H. **CLHNS.** Study phenotyping: N.R.L., L.S.A. Genotyping or analysis: Y.W., N.R.L., L.S.A. Study PI: K.L.M., L.S.A. **GxE/Spanish Town.** Study phenotyping: B.O.T., C.A.M., R.W. Genotyping or analysis: C.D.P. Study PI: R.S.C., C.A.M., R.W., T. Forrester, J.N.H. **DRAGON.** Study phenotyping: W.-J.L., W.H.-H.S., K.-W.L., I.-T.L. Genotyping or analysis: J.I.R., Y.-D.C., E.K., D.A., K.D.T., X.G. Study PI: W.H.-H.S. **SEY:** study phenotyping: P.B. Genotyping or analysis: M. Bochud, G.B.E., F.M. Study PI: P.B., M. Bochud, M. Burnier, F.P. **TUDR:** study phenotyping: W.H.-H.S., I.-T.L., W.-J.L. Genotyping or analysis: J.I.R., Y.-D.C., E.K., K.D.T., X.G. Study PI: W.H.-H.S. **TANDEM.** Study phenotyping: P.B., M. Bochud. Genotyping or analysis: G.B.E., F.M. Study PI: P.B., M. Bochud, M. Burnier, F.P.

**Imputed genotypes. FHS.** Study phenotyping: D.L. Genotyping or analysis: D.L. Study PI: D.L. **ARIC.** Study phenotyping: E.B. Genotyping or analysis: G.B.E., E.B., A.C.M., A.C., S.K.G. Study PI: E.B., A.C. **RS.** Genotyping or analysis: G.C.V., A.G.U. Study PI: A. Hofman, A.G.U., O.H.F. **CoLaus.** Study phenotyping: P.V. Genotyping or analysis: Z.K. Study PI: P.V. **NFBC1966.** Study phenotyping: M.-R.J. Genotyping or analysis: P.F.O'R. Study PI: M.-R.J. **SHIP.** Study phenotyping: R. Rettig. Genotyping or analysis: A.T. **CHS.** Study phenotyping: B.M.P. Genotyping or analysis: K.M.R. Study PI: B.M.P. **EPIC (GWAS).** Study phenotyping: N.J.W., R.J.F.L., J. Luan. Genotyping or analysis: N.J.W., J.H.Z., J. Luan. Study PI: N.J.W., K.-T.K. **SU.VI.MAX.** Study phenotyping: S.H. Genotyping or analysis: S.H., P.M. Study PI: P.M. **Amish.** Genotyping or analysis: M.E.M. Study PI: A. Parsa. **FENLAND (GWAS).** Study phenotyping: N.J.W., J. Luan, R.J.F.L., K.K.O. Genotyping or analysis: N.J.W., J. Luan, R.J.F.L., K.K.O. Study PI: N.J.W. **DGI.** Study phenotyping: C.N.-C. Genotyping or analysis: C.N.-C., G. Kosova. Study PI: C.N.-C. **ERF (EUROSPAN).** Genotyping or analysis: N.A. Study PI: C.M.v.D. **MIGEN.** Study phenotyping: S. Kathiresan, R.E. Genotyping or analysis: S. Kathiresan, R.E. Design of secondary analysis: S. Kathiresan, R.E. **MICROS.** Study phenotyping: P.P.P. Genotyping or analysis: A.A.H. Study PI: A.A.H., P.P.P. **FUSION.** Genotyping or analysis: A.U.J. Study PI: M. Boehnke, F.S.C., K.L.M., J. Saramies. **TwinsUK.** Genotyping or analysis: C.M. Study PI: T.D.S. **PROCARDIS.** Genotyping or analysis: M. Farrall, A.G. Study PI: M. Farrall. **BLSA.** Study phenotyping: L. Ferrucci. Genotyping or analysis: T.T. Study PI: L. Ferrucci. **ORCADES.** Study phenotyping: J.F.W. Genotyping or analysis: R.M.F. Study PI: J.F.W. **Croatia-Vis.** Genotyping or analysis: V.V., C.H. Study PI: V.V., C.H. **NSPHS.** Genotyping or analysis: S. Enroth. Study PI: U.G. **InCHIANTI.** Genotyping or analysis: T.T. Study PI: S. Bandinelli. **AGES Reykjavik.** Study phenotyping: V.G. Genotyping or analysis: A.V. Smith. Study PI: V.G.

**Lookup. CARDIoGRAMplusC4D.** Genotyping or analysis: P.D. Study PI: J. Danesh, H. Schunkert, T.L.A., J.E., S. Kathiresan, R. Roberts, N.J.S., P.D., H. Watkins. **CHARGE cIMT.** Genotyping or analysis: C.J.O'D., J.C.B. **CHARGE EYE.** Genotyping or analysis: T.Y.W., X.S., R.A.J. Study PI: T.Y.W. **CHARGE-HF Consortium.** Study phenotyping: R.S.V., J.F.F. Genotyping or analysis: H.L., J.F.F. Study PI: R.S.V. **CKDGen.** Genotyping or analysis: M.G., V.M. **COGENT-BP.** Study phenotyping: N.F., J.R. Genotyping or analysis: N.F., X.Z., B.J.K., B.O.T., J.R. **EchoGen Consortium.** Study phenotyping: R.S.V., J.F.F. Genotyping or analysis: H.L., J.F.F. Study PI: R.S.V. **KidneyGen Consortium.** Study phenotyping: J.C.C., J.S.K., P. Elliott. Genotyping or analysis: W. Zhang, J.C.C., J.S.K. Study PI: J.C.C., J.S.K. **MetaStroke.** Genotyping or analysis: S. Bevan, H.S.M. **NeuroCHARGE.** Genotyping or analysis: M. Fornage, M.A.I. Study PI: M.A.I.

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**PROMIS.** Study phenotyping: D. Saleheen, W. Zhao, J. Danesh. Genotyping or analysis: W. Zhao. Study PI: D. Saleheen. **SEED.** Study phenotyping: T.Y.W., C.-Y.C. Genotyping or analysis: E.-S.T., C.-Y.C., C.-Y.C. Study PI: C.-Y.C., T.Y.W. **UK Biobank.** BP group leaders: M.J.C., P. Elliott. Genotyping or analysis: M.R.B., H. Warren, C.P.C., E.E., H.G.

## COMPETING FINANCIAL INTERESTS

The authors declare competing financial interests: details are available in the online version of the paper.

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**Georg B Ehret[1,2,269], Teresa Ferreira[3,269], Daniel I Chasman[4,5], Anne U Jackson[6,7], Ellen M Schmidt[8], Toby Johnson[9,10], Gudmar Thorleifsson[11], Jian'an Luan[12], Louise A Donnelly[13], Stavroula Kanoni[14], Ann-Kristin Petersen[15], Vasyl Pihur[1], Rona J Strawbridge[16,17], Dmitry Shungin[18–20], Maria F Hughes[21], Osorio Meirelles[22], Marika Kaakinen[23], Nabila Bouatia-Naji[24,25], Kati Kristiansson[26,27], Sonia Shah[28], Marcus E Kleber[29], Xiuqing Guo[30], Leo-Pekka Lyytikäinen[31,32], Cristiano Fava[33,34], Niclas Eriksson[35], Ilja M Nolte[36], Patrik K Magnusson[37], Elias L Salfati[38], Loukianos S Rallidis[39], Elizabeth Theusch[40], Andrew J P Smith[41], Lasse Folkersen[16], Kate Witkowska[9,42], Tune H Pers[43–47], Roby Joehanes[48], Stuart K Kim[49], Lazaros Lataniotis[14], Rick Jansen[50], Andrew D Johnson[48,51], Helen Warren[9,42], Young Jin Kim[52], Wei Zhao[53], Ying Wu[54], Bamidele O Tayo[55], Murielle Bochud[56], CHARGE-EchoGen Consortium[57], CHARGE-HF Consortium[57], Wellcome Trust Case Control Consortium[57], Devin Absher[58], Linda S Adair[59], Najaf Amin[60], Dan E Arking[1], Tomas Axelsson[61], Damiano Baldassarre[62,63], Beverley Balkau[64], Stefania Bandinelli[65], Michael R Barnes[14,42], Inês Barroso[66–68], Stephen Bevan[69], Joshua C Bis[70], Gyda Bjornsdottir[11], Michael Boehnke[6,7], Eric Boerwinkle[71], Lori L Bonnycastle[72], Dorret I Boomsma[73], Stefan R Bornstein[74], Morris J Brown[75], Michel Burnier[76],**

Claudia P Cabrera[9,42], John C Chambers[77–79], I-Shou Chang[80], Ching-Yu Cheng[81–83], Peter S Chines[72], Ren-Hua Chung[84], Francis S Collins[72], John M Connell[85], Angela Döring[86,87], Jean Dallongeville[88], John Danesh[66,89,90], Ulf de Faire[91], Graciela Delgado[29], Anna F Dominiczak[92], Alex S F Doney[13], Fotios Drenos[41,93], Sarah Edkins[66], John D Eicher[48,51], Roberto Elosua[94], Stefan Enroth[95,96], Jeanette Erdmann[97,98], Per Eriksson[16], Tonu Esko[43,99,100], Evangelos Evangelou[77,101], Alun Evans[21], Tove Fall[102], Martin Farrall[3,103], Janine F Felix[104], Jean Ferrières[105], Luigi Ferrucci[106], Myriam Fornage[107], Terrence Forrester[108], Nora Franceschini[109], Oscar H Franco[104], Anders Franco-Cereceda[110], Ross M Fraser[111,112], Santhi K Ganesh[113], He Gao[77], Karl Gertow[16,17], Francesco Gianfagna[114,115], Bruna Gigante[91], Franco Giulianini[4], Anuj Goel[3,103], Alison H Goodall[116,117], Mark O Goodarzi[118], Mathias Gorski[119,120], Jürgen Gräßler[121], Christopher J Groves[122], Vilmundur Gudnason[123,124], Ulf Gyllensten[95,96], Göran Hallmans[18], Anna-Liisa Hartikainen[125,126], Maija Hassinen[127], Aki S Havulinna[26], Caroline Hayward[128], Serge Hercberg[129], Karl-Heinz Herzig[130–132], Andrew A Hicks[133], Aroon D Hingorani[28], Joel N Hirschhorn[43–45,134], Albert Hofman[104,135], Jostein Holmen[136], Oddgeir Lingaas Holmen[136,137], Jouke-Jan Hottenga[73], Phil Howard[41], Chao A Hsiung[84], Steven C Hunt[138,139], M Arfan Ikram[104,140,141], Thomas Illig[142–144], Carlos Iribarren[145], Richard A Jensen[70,146], Mika Kähönen[147,148], Hyun Min Kang[6,7], Sekar Kathiresan[45,149–152], Brendan J Keating[153,154], Kay-Tee Khaw[155], Yun Kyoung Kim[52], Eric Kim[30], Mika Kivimaki[28], Norman Klopp[142,143], Genovefa Kolovou[156], Pirjo Komulainen[127], Jaspal S Kooner[78,79,157], Gulum Kosova[100,149,150], Ronald M Krauss[158], Diana Kuh[159], Zoltan Kutalik[160,161], Johanna Kuusisto[162], Kirsti Kvaløy[136], Timo A Lakka[127,163,164], Nanette R Lee[165,166], I-Te Lee[167,168], Wen-Jane Lee[169], Daniel Levy[48,170], Xiaohui Li[30], Kae-Woei Liang[171,172], Honghuang Lin[48,173], Li Lin[2], Jaana Lindström[26], Stéphane Lobbens[174–176], Satu Männistö[26], Gabriele Müller[177], Martina Müller-Nurasyid[15,178,179], François Mach[2], Hugh S Markus[180], Eirini Marouli[14,181], Mark I McCarthy[3,122], Colin A McKenzie[108], Pierre Meneton[182], Cristina Menni[183], Andres Metspalu[99], Vladan Mijatovic[184], Leena Moilanen[185,186], May E Montasser[187], Andrew D Morris[13], Alanna C Morrison[188], Antonella Mulas[189], Ramaiah Nagaraja[22], Narisu Narisu[72], Kjell Nikus[190,191], Christopher J O'Donnell[48,152,192], Paul F O'Reilly[193], Ken K Ong[12], Fred Paccaud[56], Cameron D Palmer[43,45,194], Afshin Parsa[187], Nancy L Pedersen[37], Brenda W Penninx[195–197], Markus Perola[26,27,99], Annette Peters[87], Neil Poulter[198], Peter P Pramstaller[133,199,200], Bruce M Psaty[70,201–203], Thomas Quertermous[38], Dabeeru C Rao[204], Asif Rasheed[205], N William Rayner[3,66,122], Frida Renström[18,19,206], Rainer Rettig[207], Kenneth M Rice[208], Robert Roberts[209,210], Lynda M Rose[4], Jacques Rossouw[192], Nilesh J Samani[116,117], Serena Sanna[189], Jouko Saramies[211], Heribert Schunkert[212–215], Sylvain Sebert[131,164,216], Wayne H-H Sheu[167,168,217], Young-Ah Shin[52], Xueling Sim[6,7,218], Johannes H Smit[195], Albert V Smith[123,124], Maria X Sosa[1], Tim D Spector[183], Alena Stančáková[219], Alice V Stanton[220], Kathleen E Stirrups[14,221], Heather M Stringham[6,7], Johan Sundstrom[61], Amy J Swift[72], Ann-Christine Syvänen[61], E-Shyong Tai[82,218,222], Toshiko Tanaka[106], Kirill V Tarasov[223], Alexander Teumer[224], Unnur Thorsteinsdottir[11,124], Martin D Tobin[225], Elena Tremoli[62,63], Andre G Uitterlinden[104,226], Matti Uusitupa[227,228], Ahmad Vaez[36,229], Dhananjay Vaidya[230], Cornelia M van Duijn[104,231], Erik P A van Iperen[232,233], Ramachandran S Vasan[48,234,235], Germaine C Verwoert[104], Jarmo Virtamo[26], Veronique Vitart[128], Benjamin F Voight[236], Peter Vollenweider[237], Aline Wagner[238], Louise V Wain[225], Nicholas J Wareham[12], Hugh Watkins[3,103], Alan B Weder[239], Harm-Jan Westra[240], Rainford Wilks[241], Tom Wilsgaard[242,243], James F Wilson[111,128], Tien Y Wong[81–83], Tsun-Po Yang[14,244], Jie Yao[30], Loic Yengo[174–176], Weihua Zhang[77,78], Jing Hua Zhao[12], Xiaofeng Zhu[245], Pascal Bovet[56,246], Richard S Cooper[55], Karen L Mohlke[54], Danish Saleheen[205,247], Jong-Young Lee[52], Paul Elliott[77,248], Hinco J Gierman[49,249], Cristen J Willer[8,239,250], Lude Franke[251], G Kees Hovingh[252], Kent D Taylor[30], George Dedoussis[181], Peter Sever[198], Andrew Wong[159], Lars Lind[61], Themistocles L Assimes[38], Inger Njølstad[242,243], Peter E H Schwarz[74,253,254], Claudia Langenberg[12], Harold Snieder[36], Mark J Caulfield[9,42], Olle Melander[33], Markku Laakso[162], Juha Saltevo[255], Rainer Rauramaa[127,164], Jaakko Tuomilehto[26,256–258], Erik Ingelsson[38,102], Terho Lehtimäki[31,32], Kristian Hveem[136], Walter Palmas[259], Winfried März[260,261], Meena Kumari[28], Veikko Salomaa[26], Yii-Der I Chen[30], Jerome I Rotter[30], Philippe Froguel[123,174–176], Marjo-Riitta Jarvelin[131,216,248,262], Edward G Lakatta[223], Kari Kuulasmaa[26], Paul W Franks[18,19,263], Anders Hamsten[16,17], H-Erich Wichmann[86,179,264], Colin N A Palmer[13], Kari Stefansson[11,124], Paul M Ridker[4,5], Ruth J F Loos[12,265,266], Aravinda Chakravarti[1], Panos Deloukas[14,267], Andrew P Morris[3,268,270], Christopher Newton-Cheh[45,100,148,150,270] & Patricia B Munroe[9,42,270]

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[1]Center for Complex Disease Genomics, McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA. [2]Cardiology, Department of Medicine, Geneva University Hospital, Geneva, Switzerland. [3]Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK. [4]Division of Preventive Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA. [5]Harvard Medical School, Boston, Massachusetts, USA. [6]Department of Biostatistics, University of Michigan, Ann Arbor, Michigan, USA. [7]Center for Statistical Genetics, University of Michigan, Ann Arbor, Michigan, USA. [8]Department of Computational Medicine and Bioinformatics, University of Michigan, Ann Arbor, Michigan, USA. [9]Clinical Pharmacology, William Harvey Research Institute, Queen Mary University of London, London, UK. [10]GlaxoSmithKline, Stevenage, UK. [11]deCODE Genetics/Amgen, Inc., Reykjavik, Iceland. [12]MRC Epidemiology Unit, University of Cambridge School of Clinical Medicine, Institute of Metabolic Science, Cambridge Biomedical Campus, Cambridge, UK. [13]Medical Research Institute, University of Dundee, Ninewells Hospital and Medical School, Dundee, UK. [14]William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK. [15]Institute of Genetic Epidemiology, Helmholtz Zentrum München, Neuherberg, Germany. [16]Cardiovascular Research Unit, Center for Molecular Medicine, Department of Medicine, Karolinska Institutet, Stockholm, Sweden. [17]Center for Molecular Medicine, Karolinska University Hospital Solna, Stockholm, Sweden. [18]Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden. [19]Department of Clinical Sciences, Genetic and Molecular Epidemiology Unit, Lund University, Malmö, Sweden. [20]Department of Odontology, Umeå University, Umeå, Sweden. [21]Centre of Excellence for Public Health, Queens University Belfast, Belfast, UK. [22]Laboratory of Genetics, Intramural Research Program, National Institute on Aging, US National Institutes of Health, Baltimore, Maryland, USA. [23]Department of Genomics of Common Disease, School of Public Health, Imperial College London, Hammersmith Hospital, London, UK. [24]INSERM UMR 970, Paris Cardiovascular Research Center (PARCC), Paris, France. [25]University Paris-Descartes, Sorbonne Paris Cité, Paris, France. [26]National Institute for Health and Welfare, Helsinki, Finland. [27]Institute for Molecular Medicine Finland (FIMM), University of Helsinki, Helsinki, Finland. [28]Genetic Epidemiology Group, Department of Epidemiology and Public Health, University College London, London, UK. [29]Vth Department of Medicine, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany. [30]Institute for Translational Genomics and Population Sciences, Los Angeles Biomedical Research Institute and Department of Pediatrics at Harbor-UCLA Medical Center, Torrance, California, USA. [31]Department of Clinical Chemistry, Fimlab Laboratories, Tampere, Finland. [32]Department of Clinical Chemistry, University of Tampere School of Medicine, Tampere, Finland. [33]Department of Internal Medicine, University of Lund, Malmö, Sweden. [34]Department of Medicine, University of Verona, Verona, Italy. [35]Uppsala University, Uppsala Clinical Research Center, Uppsala, Sweden. [36]Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands. [37]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden. [38]Department of Medicine, Stanford University School of Medicine, Stanford, California, USA. [39]Second Department of Cardiology, Attikon Hospital, School of Medicine, University of Athens, Athens, Greece. [40]Children's Hospital Oakland Research Institute, Oakland, California, USA. [41]Centre for Cardiovascular Genetics, Institute of Cardiovascular Science, University College London, London, UK. [42]NIHR Barts Cardiovascular Biomedical Research Unit, Queen Mary University of London, London, UK. [43]Division of Endocrinology, Boston Children's Hospital, Boston, Massachusetts, USA. [44]Center for Basic and Translational Obesity Research, Boston Children's Hospital, Boston, Massachusetts, USA. [45]Program in Medical and Population Genetics, Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA. [46]Novo Nordisk Foundation Centre for Basic Metabolic Research, Section of Metabolic, Genetics, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark. [47]Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark. [48]National Heart, Lung, and Blood Institute's Framingham Heart Study, Framingham, Massachusetts, USA. [49]Department of Developmental Biology and Genetics, Stanford University Medical Center, Stanford, California, USA. [50]Department of Psychiatry, VU University Medical Center, Amsterdam, the Netherlands. [51]National Heart, Lung, and Blood Institute, Cardiovascular Epidemiology and Human Genomics Branch, Bethesda, Maryland, USA. [52]Center for Genome Science, National Institute of Health, Osong Health Technology Administration Complex, Chungcheongbuk-do, Republic of Korea. [53]Division of Translational Medicine and Human Genetics, Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA. [54]Department of Genetics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA. [55]Department of Public Health Sciences, Loyola University Chicago Stritch School of Medicine, Maywood, Illinois, USA. [56]Institute of Social and Preventive Medicine (IUMSP), Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland. [57]A list of members and affiliations appears in the **Supplementary Note**. [58]HudsonAlpha Institute for Biotechnology, Huntsville, Alabama, USA. [59]Department of Nutrition, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA. [60]Genetic Epidemiology Unit, Department of Epidemiology, Erasmus MC, Rotterdam, the Netherlands. [61]Department of Medical Sciences, Uppsala University, Uppsala, Sweden. [62]Dipartimento di Scienze Farmacologiche e Biomolecolari, Università di Milano, Milan, Italy. [63]Centro Cardiologico Monzino, IRCCS, Milan, Italy. [64]INSERM U1018, Centre for Research in Epidemiology and Population Health, University Paris-Sud, URMS 1018, Villejuif, France. [65]Geriatric Unit, Azienda Sanitaria Firenze (ASF), Florence, Italy. [66]Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, UK. [67]University of Cambridge Metabolic Research Laboratories, Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge, UK. [68]NIHR Cambridge Biomedical Research Centre, Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge, UK. [69]School of Life Science, University of Lincoln, Joseph Banks Laboratories, Lincoln, UK. [70]Cardiovascular Health Research Unit, Department of Medicine, University of Washington, Seattle, Washington, USA. [71]Human Genetics Center, School of Public Health, University of Texas Health Science Center at Houston, Houston, Texas, USA. [72]Medical Genomics and Metabolic Genetics Branch, National Human Genome Research Institute, US National Institutes of Health, Bethesda, Maryland, USA. [73]Department of Biological Psychology, VU University, Amsterdam, the Netherlands. [74]Department of Medicine III, University of Dresden, Medical Faculty Carl Gustav Carus, Dresden, Germany. [75]Barts Heart Centre, William Harvey Research Institute, Queen Mary University of London, London, UK. [76]Nephrology, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland. [77]Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, UK. [78]Department of Cardiology, Ealing Hospital NHS Trust, Southall, UK. [79]Imperial College Healthcare NHS Trust, London, UK. [80]National Institute of Cancer Research, National Health Research Institutes, Zhunan Town, Taiwan. [81]Singapore Eye Research Institute, Singapore National Eye Centre, Singapore. [82]Duke-NUS Graduate Medical School Singapore, Singapore. [83]Department of Ophthalmology, National University of Singapore and National University Health System, Singapore. [84]Division of Biostatistics and Bioinformatics, Institute of Population Health Sciences, National Health Research Institutes, Zhunan Town, Taiwan. [85]University of Dundee, Ninewells Hospital and Medical School, Dundee, UK. [86]Institute of Epidemiology I, Helmholtz Zentrum München, Neuherberg, Germany. [87]Institute of Epidemiology II, Helmholtz Zentrum München, Neuherberg, Germany. [88]INSERM UMR 1167, Lille 2 University, Institut Pasteur Lille, Lille, France. [89]Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK. [90]NIHR Blood and Transplant Research Unit in Donor Health and Genomics, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK. [91]Division of Cardiovascular Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden. [92]BHF Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK. [93]Medical Research Council Integrative Epidemiology Unit, School of Social and Community Medicine, University of Bristol, Oakfield House, Oakfield Grove, Bristol, UK. [94]Cardiovascular Epidemiology and Genetics, Institut Hospital del Mar d'Investigacions Mèdiques (IMIM), Barcelona, Spain. [95]Department of Immunology, Genetics and Pathology, University of Uppsala, Biomedical Center, Uppsala, Sweden. [96]Science for Life Laboratory, University of Uppsala, Biomedical Center, Uppsala, Sweden. [97]Institut für Integrative und Experimentelle Genomik, Universität zu Lübeck, Lübeck, Germany. [98]Deutsches Zentrum für Herz Kreislauf Forschung (DZHK), partner site Hamburg, Lübeck, Kiel, Germany. [99]Estonian Genome Center, University of Tartu, Tartu, Estonia. [100]Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA. [101]Department of Hygiene and Epidemiology, University of Ioannina Medical School, Ioannina, Greece. [102]Department of Medical Sciences, Molecular Epidemiology and Science for Life Laboratory, Uppsala University, Uppsala, Sweden. [103]Division of Cardiovascular Medicine, Radcliffe Department of Medicine, University of Oxford, Oxford, UK. [104]Department of Epidemiology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands. [105]Toulouse University School of Medicine, Rangueil University Hospital, INSERM UMR 1027, Toulouse, France. [106]Translational Gerontology Branch, National Institute on Aging, Baltimore, Maryland, USA. [107]Institute of Molecular Medicine, University of Texas Health Science Center at Houston, Houston, Texas, USA. [108]Tropical Metabolism Research Unit, Tropical Medicine Research Institute, University of the West Indies, Mona, Kingston, Jamaica. [109]Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA. [110]Cardiothoracic Surgery Unit, Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden. [111]Usher Institute for Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, UK. [112]Synpromics, Ltd, Edinburgh, UK. [113]Department of Cardiology, University of Michigan Medical School, Ann Arbor, Michigan, USA. [114]Epidemiology and Preventive Medicine (EPIMED) Research Centre, Department of Clinical and Experimental Medicine, University of Insubria, Varese, Italy. [115]Department of Epidemiology and Prevention, IRCCS, Istituto Neurologico Mediterraneo (NEUROMED), Pozzilli, Italy. [116]Department of Cardiovascular Sciences, University of Leicester, Glenfield Hospital, Leicester, UK. [117]NIHR Leicester Cardiovascular Biomedical Research Unit, Glenfield Hospital, Leicester, UK. [118]Division of Endocrinology, Diabetes and Metabolism, Cedars-Sinai Medical Center, Los Angeles, California, USA. [119]Department of Genetic Epidemiology, Institute of Epidemiology and Preventive Medicine, University of Regensburg, Regensburg, Germany. [120]Department of Nephrology, University Hospital Regensburg, Regensburg, Germany. [121]Division of Pathobiochemistry, Department of Medicine III, Technische Universität Dresden, Dresden, Germany. [122]Oxford Centre for

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Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, UK. [123]Icelandic Heart Association, Kopavogur, Iceland. [124]Faculty of Medicine, University of Iceland, Reykjavik, Iceland. [125]Institute of Clinical Medicine/Obstetrics and Gynaecology, University of Oulu, Oulu, Finland. [126]Medical Research Center, Oulu University Hospital, Oulu, Finland. [127]Kuopio Research Institute of Exercise Medicine, Kuopio, Finland. [128]Institute of Genetics and Molecular Medicine, Western General Hospital, Edinburgh, UK. [129]UREN, INSERM U557, INRA U1125, CNAM, SMBH, Sorbonne Paris Cité, Université Paris 13, Bobigny, France. [130]Institute of Biomedicine, University of Oulu, Medical Research Center Oulu and Oulu University Hospital, Oulu, Finland. [131]Biocenter Oulu, University of Oulu, Oulu, Finland. [132]Department of Gastroenterology and Metabolism, Poznan University of Medical Sciences, Poznan, Poland. [133]Center for Biomedicine, European Academy Bozen/Bolzano (EURAC), Bolzano, Italy (affiliated institute of the University of Lübeck, Lübeck, Germany). [134]Department of Genetics, Harvard Medical School, Boston, Massachusetts, USA. [135]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA. [136]HUNT Research Centre, Department of Public Health and General Practice, Norwegian University of Science and Technology, Levanger, Norway. [137]St. Olav Hospital, Trondheim University Hospital, Trondheim, Norway. [138]Cardiovascular Genetics Division, University of Utah School of Medicine, Salt Lake City, Utah, USA. [139]Department of Genetic Medicine, Weill Cornell Medical College Qatar, Doha, Qatar. [140]Department of Radiology, Erasmus MC, Rotterdam, the Netherlands. [141]Department of Neurology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands. [142]Research Unit of Molecular Epidemiology, Helmholtz Zentrum München, Neuherberg, Germany. [143]Hannover Unified Biobank, Hannover Medical School, Hannover, Germany. [144]Hannover Medical School, Institute for Human Genetics, Hanover, Germany. [145]Division of Research, Kaiser Permanente, Oakland, California, USA. [146]Department of Medicine, University of Washington, Seattle, Washington, USA. [147]Department of Clinical Physiology, Tampere University Hospital, Tampere, Finland. [148]Department of Clinical Physiology, University of Tampere School of Medicine, Tampere, Finland. [149]Center for Human Genetic Research, Massachusetts General Hospital, Boston, Massachusetts, USA. [150]Cardiovascular Research Center, Massachusetts General Hospital, Boston, Massachusetts, USA. [151]Department of Medicine, Harvard Medical School, Boston, Massachusetts, USA. [152]Cardiology Division, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA. [153]Division of Transplantation, Department of Surgery, University of Pennsylvania, Philadelphia, Pennsylvania, USA. [154]Department of Pediatrics, University of Pennsylvania, Philadelphia, Pennsylvania, USA. [155]Department of Public Health and Primary Care, Institute of Public Health, University of Cambridge, Cambridge, UK. [156]1st Cardiology Department, Onassis Cardiac Surgery Center, Athens, Greece. [157]National Heart and Lung Institute, Imperial College London, Hammersmith Hospital Campus, London, UK. [158]Department of Medicine, Children's Hospital Oakland Research Institute, Oakland, California, USA. [159]MRC Unit for Lifelong Health and Ageing at UCL, London, UK. [160]Department of Medical Genetics, University of Lausanne, Lausanne, Switzerland. [161]Swiss Institute of Bioinformatics, Lausanne, Switzerland. [162]Department of Medicine, University of Eastern Finland and Kuopio University Hospital, Kuopio, Finland. [163]Institute of Biomedicine/Physiology, University of Eastern Finland, Kuopio, Finland. [164]Department of Clinical Physiology and Nuclear Medicine, Kuopio University Hospital, Kuopio, Finland. [165]Office of Population Studies Foundation, Inc., Talamban, Cebu City, Philippines. [166]Department of Anthropology, Sociology and History, University of San Carlos, Talamban, Cebu City, Philippines. [167]Division of Endocrine and Metabolism, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan. [168]School of Medicine, National Yang-Ming University, Taipei, Taiwan. [169]Department of Medical Research, Taichung Veterans General Hospital, Taichung, Taiwan. [170]Population Sciences Branch, National Heart, Lung, and Blood Institute, US National Institutes of Health, Bethesda, Maryland, USA. [171]Cardiovascular Center, Taichung Veterans General Hospital, Taichung, Taiwan. [172]Institute of Clinical Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan. [173]Section of Computational Biomedicine, Department of Medicine, Boston University School of Medicine, Boston, Massachusetts, USA. [174]European Genomic Institute for Diabetes (EGID), Lille, France. [175]CNRS UMR 8199, Lille Pasteur Institute, Lille, France. [176]Lille 2 University, Lille, France. [177]Center for Evidence-Based Healthcare, University of Dresden, Medical Faculty Carl Gustav Carus, Dresden, Germany. [178]Department of Medicine I, University Hospital Großhadern, Ludwig Maximilians University, Munich, Germany. [179]Institute of Medical Informatics, Biometry and Epidemiology, Ludwig Maximilians Universität, Munich, Germany. [180]Neurology Unit, University of Cambridge, Cambridge Biomedical Campus, Cambridge, UK. [181]Department of Dietetics-Nutrition, Harokopio University, Athens, Greece. [182]INSERM U1142, LIMICS, UMRS 1142, Sorbonne Universités, UPMC Université Paris 06, Université Paris 13, Paris, France. [183]Department of Twin Research and Genetic Epidemiology, King's College London, London, UK. [184]Department of Life and Reproduction Sciences, University of Verona, Verona, Italy. [185]Department of Medicine, Kuopio University Hospital, Kuopio, Finland. [186]Unit of General Practice, Oulu University Hospital, Oulu, Finland. [187]Department of Medicine, Program for Personalized and Genomic Medicine, University of Maryland School of Medicine, Baltimore, Maryland, USA. [188]Department of Epidemiology, Human Genetics and Environmental Sciences, School of Public Health, University of Texas Health Science Center at Houston, Houston, Texas, USA. [189]Istituto di Ricerca Genetica e Biomedica (IRGB), Consiglio Nazionale delle Ricerche, Cittadella Universitaria di Monseratto, Monserrato, Cagliari, Italy. [190]Department of Cardiology, Heart Center, Tampere University Hospital, Tampere, Finland. [191]Department of Cardiology, University of Tampere School of Medicine, Tampere, Finland. [192]National Heart, Lung, and Blood Institute, Division of Cardiovascular Sciences, Bethesda, Maryland, USA. [193]Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK. [194]Genetics and Program in Genomics, Children's Hospital Boston, Boston, Massachusetts, USA. [195]Department of Psychiatry, EMGO Institute, Neuroscience Campus, VU University Medical Centre, Amsterdam, the Netherlands. [196]Department of Psychiatry, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands. [197]Department of Psychiatry, Leiden University Medical Centre, Leiden, the Netherlands. [198]International Centre for Circulatory Health, Imperial College London, London, UK. [199]Department of Neurology, General Central Hospital, Bolzano, Italy. [200]Department of Neurology, University of Lübeck, Lübeck, Germany. [201]Department of Epidemiology, University of Washington, Seattle, Washington, USA. [202]Department of Health Services, University of Washington, Seattle, Washington, USA. [203]Group Health Research Institute, Group Health Cooperative, Seattle, Washington, USA. [204]Division of Biostatistics, Washington University School of Medicine, St. Louis, Missouri, USA. [205]Center for Non-Communicable Diseases, Karachi, Pakistan. [206]Department of Biobank Research, Umeå University, Umeå, Sweden. [207]Institute of Physiology, University Medicine Greifswald, Greifswald, Germany. [208]Department of Biostatistics, University of Washington, Seattle, Washington, USA. [209]University of Ottawa Heart Institute, Cardiovascular Research Methods Centre Ontario, Ottawa, Ontario, Canada. [210]Ruddy Canadian Cardiovascular Genetics Centre, Ottawa, Ontario, Canada. [211]South Karelia Central Hospital, Lappeenranta, Finland. [212]Deutsches Herzzentrum München, Munich, Germany. [213]Technische Universität München, Munich, Germany. [214]Deutsches Zentrum für Herz Kreislauf Forschung (DZHK), Munich, Germany. [215]Munich Heart Alliance, Munich, Germany. [216]Center For Lifecourse Health Research, University of Oulu, Oulu, Finland. [217]College of Medicine, National Defense Medical Center, Taipei, Taiwan. [218]Saw Swee Hock School of Public Health, National University of Singapore and National University Health System, Singapore. [219]University of Eastern Finland and Kuopio University Hospital, Kuopio, Finland. [220]Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland, Dublin, Ireland. [221]Department of Haematology, University of Cambridge, Cambridge, UK. [222]Department of Medicine, National University of Singapore and National University Health System, Singapore. [223]Laboratory of Cardiovascular Science, Intramural Research Program, National Institute on Aging, US National Institutes of Health, Baltimore, Maryland, USA. [224]Institute for Community Medicine, University Medicine Greifswald, Greifswald, Germany. [225]Department of Health Sciences, University of Leicester, Leicester, UK. [226]Department of Internal Medicine, Erasmus MC, Rotterdam, the Netherlands. [227]Department of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio, Finland. [228]Research Unit, Kuopio University Hospital, Kuopio, Finland. [229]Research Institute for Primordial Prevention of Non-Communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran. [230]Johns Hopkins Medical Institutions, Baltimore, Maryland, USA. [231]Centre of Medical Systems Biology (CMSB 1-2), NGI Erasmus Medical Center, Rotterdam, the Netherlands. [232]Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Center, Amsterdam, the Netherlands. [233]Durrer Center for Cardiogenetic Research, ICIN–Netherlands Heart Institute, Utrecht, the Netherlands. [234]Section of Preventive Medicine, Department of Medicine, Boston University School of Medicine, Boston, Massachusetts, USA. [235]Cardiology, Department of Medicine, Boston University School of Medicine, Boston, Massachusetts, USA. [236]Department of Systems Pharmacology and Translational Therapeutics, Department of Genetics, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA. [237]Department of Internal Medicine, University Hospital Lausanne, Lausanne, Switzerland. [238]Department of Epidemiology and Public Health, EA3430, University of Strasbourg, Strasbourg, France. [239]Division of Cardiovascular Medicine, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, Michigan, USA. [240]University of Groningen, University Medical Center Groningen, Groningen, the Netherlands. [241]Epidemiology Research Unit, Tropical Medicine Research Institute, University of the West Indies, Mona, Kingston, Jamaica. [242]Department of Community Medicine, Faculty of Health Sciences, University of Tromsø, Tromsø, Norway. [243]Department of Clinical Medicine, Faculty of Health Sciences, University of Tromsø, Tromsø, Norway. [244]MRC Cancer Unit, University of Cambridge, Cambridge, UK. [245]Department of Epidemiology and Biostatistics, School of Medicine, Case Western Reserve University, Cleveland, Ohio, USA. [246]Ministry of Health, Victoria, Seychelles. [247]Department of Biostatistics and Epidemiology, University of Pennsylvania, Philadelphia, Pennsylvania, USA. [248]MRC-PHE Centre for Environment and Health, School of Public Health, Imperial College London, London, UK. [249]Enterprise Informatics, Illumina, Inc., Santa Clara, California, USA. [250]Department of Human Genetics, University of Michigan, Ann Arbor, Michigan, USA. [251]Department of Genetics, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands. [252]Department of Vascular Medicine, Academic Medical Center, Amsterdam, the Netherlands. [253]Paul Langerhans Institute Dresden of the Helmholtz Center Munich at University

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Hospital and Faculty of Medicine, TU Dresden, Dresden, Germany. [254]German Center for Diabetes Research (DZD), Neuherberg, Germany. [255]Department of Medicine, Central Finland Health Care District, Jyväskylä, Finland. [256]Dasman Diabetes Institute, Dasman, Kuwait. [257]Saudi Diabetes Research Group, King Abdulaziz University, Jeddah, Saudi Arabia. [258]Centre for Vascular Prevention, Danube University Krems, Krems, Austria. [259]Department of Medicine, Columbia University, New York, New York, USA. [260]Synlab Academy, Synlab Services, Mannheim, Germany. [261]Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University of Graz, Graz, Austria. [262]Unit of Primary Care, Oulu University Hospital, Oulu, Finland. [263]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA. [264]Institute of Medical Statistics and Epidemiology, Technical University Munich, Munich, Germany. [265]Charles Bronfman Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai, New York,, New York, USA. [266]Mindich Child Health Development Institute, Icahn School of Medicine at Mount Sinai, New York, New York, USA. [267]Princess Al-Jawhara Al-Brahim Centre of Excellence in Research of Hereditary Disorders (PACER-HD), King Abdulaziz University, Jeddah, Saudi Arabia. [268]Department of Biostatistics, University of Liverpool, Liverpool, UK. [269]These authors contributed equally to this work. [270]These authors jointly directed this work. Correspondence should be addressed to C.N.-C. (cnewtoncheh@mgh.harvard.edu) or P.B.M. (p.b.munroe@qmul.ac.uk).

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## ONLINE METHODS

**Cohorts contributing to systolic and diastolic blood pressure analyses.** Studies contributing to blood pressure association discovery, including community- and population-based collections as well as studies of non–blood pressure traits, were analyzed as case and control samples separately. Details on each of the studies, including study design and blood pressure measurement, are provided in **Supplementary Table 1**, genotyping information appears in **Supplementary Table 2** and participant characteristics are given in **Supplementary Table 3**. All participants provided written informed consent, and the studies were approved by local research ethics committees and/or institutional review boards.

**European-ancestry meta-analysis.** Blood pressure was measured using standardized protocols in all studies regardless of whether the primary focus was blood pressure or another trait. We initially analyzed affected and unaffected individuals from samples selected as cases (for example, type 2 diabetes) or controls separately. However, because sensitivity analyses did not show any significant difference in blood pressure effect size estimates between case and control samples (data not shown), we analyzed all samples together. When available, the average of two blood pressure measurements was used for association analyses (**Supplementary Table 1**). If an individual was taking a blood pressure–lowering treatment, the underlying SBP and DBP were estimated by adding 15 mm Hg and 10 mm Hg, respectively, to the measured values, as done in previous analyses.

A meta-analysis of 340,934 individuals of EUR descent was undertaken in four stages with subsequent validation in an independent cohort. Because stage 1 Cardio-MetaboChip samples included many SNPs selected on the basis of association with blood pressure in earlier GWAS, we performed genomic control using a set of putative null SNPs selected on the basis of $P > 0.10$ in earlier GWAS of SBP and DBP, or both. Stage 2 samples with genome-wide genotyping used the entire genome-wide set of SNPs for genomic control, given the lack of ascertainment. The study design is summarized in **Supplementary Figure 1**, and further details are provided in **Supplementary Tables 2–5** and the **Supplementary Note**.

**Systematic PubMed search of the region ±100 kb with respect to each newly discovered index SNP.** All genes with any overlap with a 200-kb region centered on each of the 17 newly discovered lead SNPs were identified using the UCSC Genome Browser. A search term was constructed for each gene including the short and long gene names and the terms "blood pressure" and "hypertension" (for example, for *NPPA* on chromosome 1: "NPPA OR natriuretic peptide A AND (blood pressure OR hypertension)"), and the search results for each search term from PubMed were individually reviewed.

**Trait variance explained.** The trait variance explained by 66 lead SNPs at new and known loci was evaluated in one study that contributed to the discovery effort: the Atherosclerosis Risk in Communities (ARIC) study. We constructed a linear regression model with all 66 SNPs or the subset of 49 known SNPs as a set of predictors of the blood pressure residual after adjustment for covariates of the adjusted treatment-corrected blood pressure phenotype (SBP or DBP). The $r^2$ value from the regression model was used as the estimate of trait variance explained.

**European-ancestry GCTA-COJO analysis.** To identify multiple distinct association signals at any given blood pressure locus, we undertook approximate conditional analyses using a model selection procedure implemented in the GCTA-COJO software package[22,23]. To evaluate the robustness of the GCTA-COJO results to the choice of reference data set, model selection was performed using the LD between variants in separate analyses from two data sets of EUR descent, both with individuals from the UK with Cardio-MetaboChip genotype data: GoDARTS with 7,006 individuals and WTCCC1-T2D/58BC with 2,947 individuals. Assuming that the LD between SNPs separated by more than 10 Mb or on different chromosomes is zero, we undertook GCTA-COJO stepwise model selection to select SNPs that were conditionally independently associated with SBP and DBP, in turn, at genome-wide significance given by $P < 5 \times 10^{-8}$ (**Supplementary Tables 6–8**) using the stage 4 combined EUR GWAS + Cardio-MetaboChip meta-analysis data.

**Conditional analyses in the Women's Genome Health Study.** Multivariate regression modeling was performed for each possible combination of putative independent SNPs from (i) model selection implemented in GCTA-COJO and (ii) a comprehensive manual review of the literature (**Supplementary Table 9**). Any SNP with $P < 5 \times 10^{-8}$ in a previously reported blood pressure GWAS was considered. A total of 46 SNPs were examined (**Supplementary Table 10**). Genome-wide genotyping data imputed to 1000 Genomes Project in the WGHS ($n$ = 23,047) were used. Regression modeling was performed in the R statistical language (**Supplementary Table 10**).

**Fine-mapping and determination of credible sets of causal SNPs.** The GCTA-COJO and WGHS conditional analyses identified multiple distinct signals of association at multiple loci (**Supplementary Tables 6** and **10**). Of the 24 loci considered in fine-mapping analyses, 16 had no evidence for the existence of multiple distinct association signals, so it is reasonable to assume that there is a single causal SNP and, therefore, the credible sets of variants could be constructed using the association summary statistics from the unconditioned meta-analyses. However, in the remaining eight loci, where evidence of secondary signals was observed from GCTA-COJO, we performed approximate conditional analyses across the region by conditioning on each index SNP (**Supplementary Table 11**). By adjusting for the other index SNPs at the locus, we can therefore assume that a single variant is driving each conditionally independent association signal and can construct the 99% credible set of variants on the basis of the approximate conditional analysis from GCTA-COJO (**Supplementary Tables 12** and **13**). At five of the eight loci with multiple distinct signals of association, one index SNP mapped outside the fine-mapping region, so a credible set could not be constructed.

**eQTL analysis: whole blood.** Whole-blood expression quantitative trait locus (eQTL) analyses were performed in samples from the Netherlands Study of Depression and Anxiety (NESDA)[41] and the Netherlands Twin Registry (NTR)[42] studies. RNA expression analysis was performed using statistical software R. The residuals resulting from linear regression analysis of the probe set intensity values onto the covariates sex, age, BMI (kg/m$^2$), smoking status coded as a categorical covariate, several technical covariates and three principal components were used. eQTL effects were detected using a linear mixed-model approach, including for each probe set the expression level (normalized, residualized and without the first 50 expression principal components) as dependent variable; the SNP genotype values as fixed effects; and family identifier and zygosity (in the case of twins) as random effects to account for family and twin relationships[43].

The eQTL effects were defined as being in *cis* when probe set–SNP pairs were separated by a distance of <1 Mb. At an FDR of 0.01 applied across the genome, not just for candidate SNPs, the *P*-value threshold was $1 \times 10^{-4}$ for the *cis*-eQTL analysis. For each probe set that displayed a statistically significant association with at least one SNP located within its *cis* region, we identified the most significantly associated SNP and denoted this as the top *cis*-eQTL SNP. See the **Supplementary Note** for details.

**eQTL analysis: selected published eQTL data sets.** Lead blood pressure SNPs and proxies ($r^2$ >0.8) were searched against a collected database of eSNP results. The reported eSNP results met criteria for statistical thresholds for association with gene transcript levels as described in the original papers. The non-blood-cell tissue eQTLs searched included aortic endothelial cells[44], left ventricle of the heart[45], CD14$^+$ monocytes[46] and brain[47]. The results are presented in **Supplementary Tables 14** and **15**.

**Enrichment analyses: analysis of cell-type-specific DHSs using an odds ratio method.** The overlap of Cardio-MetaboChip SNPs with DHSs was examined using publicly available data from the Epigenomics Roadmap Project and ENCODE, choosing different cutoffs of Cardio-MetaboChip *P* value. DHS mappings were available for 123 cell types and tissues mostly derived from adults[29]. The DHS mappings were specified as both 'narrow' and 'broad' peaks, referring to reduction of the experimental data to peak calls at 0.1% and 1.0% FDR thresholds, respectively. Thus, the narrow peaks are largely nested within the broad peaks. Experimental replicates of the DHS mappings (typically duplicates) were also available for the majority of cell types and tissues.

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SNPs from the Cardio-MetaboChip genome-wide scan were first clumped in PLINK in windows of 100 kb with maximum LD values of $r^2 = 0.1$ in 1000 Genomes Project EUR data. Then, the resulting index SNPs at each *P*-value threshold were tagged with $r^2 = 0.8$ in windows of 100 kb, again using LD relationships from the 1000 Genomes Project, restricted to SNPs with MAF >1% and also present in the HapMap 2 CEU (EUR-ancestry) population. A reference set of SNPs was constructed using the same clumping and tagging procedures applied to GWAS catalog SNPs[30] with discovery $P < 5 \times 10^{-8}$ in EUR populations. A small number of reference SNPs or their proxies overlapping the blood pressure SNPs or their proxies were excluded. After LD pruning and exclusions, there were a total of 1,196 reference SNPs. For each cell type and *P*-value threshold, the enrichment of SBP- or DBP-associated SNPs (or their LD proxies) mapping to DHSs was expressed as an odds ratio relative to the GWAS catalog reference SNPs (or their LD proxies), using logistic mixed-effect models treating the replicate peak determinations as random effects (glmer package in R). The significance of the enrichment odds ratios was derived from the significance of $\beta$ coefficients for the main effects in the mixed models (**Fig. 2** and **Supplementary Table 16**).

**Enrichment analyses: analysis of tissue-specific enrichment of blood pressure variants and H3K4me3 sites.** An analysis to test for significant cell-type-specific enrichment in the overlap of blood pressure SNPs (or their proxies) with H3K4me3 sites was performed as described in Trynka *et al.*[31]. The measure of overlap is a 'score' that is constructed by dividing the height of an H3K4me3 ChIP signal in a particular cell type by the distance to the nearest test SNP. The significance of the scores (*P* value) for all SNPs was determined by a permutation approach that compares the observed scores to the scores of SNPs with similar properties as the test SNPs, essentially in terms of LD and proximity to genes (**Supplementary Note**). The number of permutations determined the number of significant digits in the *P* values, and we conducted 10,000 iterations. Results are shown in **Supplementary Table 19**.

**Enrichment analyses: analysis of tissue-specific DHSs and chromatin states using GREGOR.** The DNase-seq ENCODE data for all available cell types were downloaded in the processed narrowPeak format. The local maxima of the tag density in broad, variable-sized 'hotspot' regions of chromatin accessibility were thresholded at FDR 1% with peaks set to a fixed width of 150 bp. Individual cell types were further grouped into 41 broad tissue categories by taking the union of DHSs for all related cell types and replicates. For each GWAS locus, a set of matched control SNPs was selected on the basis of three criteria: (i) number of variants in LD ($r^2 > 0.7$; ± 8 variants), (ii) MAF (±1%), and (iii) distance to the nearest gene (±11,655 bp). To calculate the distance to the nearest gene, the distances to the 5′ flanking gene (start and end positions) and to the 3′ flanking gene were calculated and the minimum of these four values was used. If the SNP fell within the transcribed region of a gene, the distance was set to 0. The probability that a set of GWAS loci overlap a regulatory feature more often than we expect by chance was estimated.

**Enrichment analyses: FAIRE analysis of blood pressure variants in fine-mapping regions in lymphoblastoid cell lines.** FAIRE analysis was performed on a sample of 20 lymphoblastoid cell lines of EUR origin. All samples were genotyped using the Cardio-MetaboChip genotyping array, and blood pressure SNPs and LD proxies ($r^2 > 0.8$) at the fine-mapping loci ($n = 24$; **Supplementary Table 23**) were assessed to identify heterozygous imbalance between unprocessed and FAIRE-processed chromatin. A paired *t* test was used to compare the B-allele frequency (BAF) arising from formaldehyde-fixed chromatin sheared by sonication and DNA purification to the BAF when the same chromatin sample underwent FAIRE to enrich for open chromatin. Three hundred and fifty-seven Cardio-MetaboChip blood pressure SNPs were directly genotyped across the fine-mapping regions. The Bonferroni-corrected threshold of significance was $P < 0.0001$ (0.05/357). The results for SNPs with $P < 0.05$ are reported in **Supplementary Table 23**. FAIRE results were not available for some SNPs with missing data owing to genotype failure or not having >3 heterozygous individuals for statistical analysis. Therefore, there are no results for three lower-frequency blood pressure loci (*SLC39A8*, *CYP17A1–NT5C2* and *GNAS–EDN3*) and for the second signal at the following loci: *MTHFR–NPPB* (rs2272803), *MECOM* (rs2242338) and *HFE* (rs1800562).

**Pathway analyses: MAGENTA.** MAGENTA tests for enrichment of gene sets from a precompiled library derived from GO, KEGG, Panther, Reactome, Ingenuity and BioCarta was performed as described by Segré *et al.*[33]. Enrichment of significant gene-wide *P* values in gene sets is assessed by (i) using LD and distance criteria to define the span of each gene, (ii) selecting the smallest *P* value among SNPs mapping to the gene span, and (iii) adjusting this *P* value using a regression method that accounts for the number of SNPs, the LD, etc. In the second step, MAGENTA examines the distribution of these adjusted *P* values and defines thresholds for the 75th and 95th percentiles. In the third step, MAGENTA calculates the enrichment for each gene set by comparing the number of genes in the gene set with *P* value less than either the 75th or 95th percentile to the number of genes in the gene set with *P* value greater than either the 75th or 95th percentile and then comparing this quotient to the same quotient among genes not in the gene set. This gene set quotient is assigned a *P* value on the basis of reference to a hypergeometric distribution. The results from our analyses are given in **Supplementary Table 21**.

**Pathway analyses: DEPICT.** We applied DEPICT[34] analysis separately on genome-wide significant loci from the overall blood pressure Cardio-MetaboChip analysis, including published blood pressure loci (**Supplementary Table 22**). SNPs at the *HFE* and *BAT2–BAT5* loci (rs1799945, rs1800562, rs2187668, rs805303 and rs9268977) could not be mapped. As a secondary analysis, we additionally included associated loci ($P < 1 \times 10^{-5}$) from the Cardio-MetaboChip stage 4 combined meta-analyses of SBP and DBP. DEPICT assigned genes to associated regions if they overlapped or resided within associated LD blocks with $r^2 > 0.5$ to a given associated SNP.

**Literature review for genes at the newly discovered loci.** Recognizing that the most significantly associated SNP at a locus may not be located in the causal gene and that the functional consequences of a SNP often extend beyond 100 kb, we conducted a literature review of genes in extended regions encompassing newly discovered blood pressure index SNPs. The genes for this extensive review were identified by DEPICT (**Supplementary Table 22**).

**Non-European meta-analysis.** To assess the association of the 66 significant loci from the EUR-ancestry meta-analysis in non-EUR ancestries, we obtained lookup results for the 66 index SNPs for participants of SAS ancestry (eight data sets, total $n = 20,875$), EAS ancestry (five data sets, total $n = 9,637$), and AFR and African-American ancestry (six data sets, total $n = 33,909$). The association analyses were all conducted with the same covariates (age, age$^2$, sex and BMI) and treatment correction (+15/10 mm Hg in the presence of any hypertensive medication) as the association analyses for the discovery effort in Europeans. Tests for heterogeneity across effect estimates in EUR, SAS, EAS and AFR samples were performed using GWAMA[48].

**Genetic risk score and cardiovascular outcomes.** The gtx package for the R statistical programming language was used to estimate the effect of the SNP risk scores on the response variable in a regression model, as described in ref. 5.

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