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Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk

The International Consortium for Blood Pressure Genome-Wide Association Studies

Blood pressure is a heritable trait influenced by several biological pathways and responsive to environmental stimuli. Over one billion people worldwide have hypertension (≥140 mm Hg systolic blood pressure or ≥90 mm Hg diastolic blood pressure)\(^2\). Even small increments in blood pressure are associated with an increased risk of cardiovascular events\(^3\). This genome-wide association study of systolic and diastolic blood pressure, which used a multi-stage design in 200,000 individuals of European descent, identified sixteen novel loci: six of these loci contain genes previously known or suspected to regulate blood pressure (GUCY1A3–GUCY1B3, NPR3–CSor223, ADM, FURIN–FES, GOSR2, GNAS–EDN3); the other ten provide new clues to blood pressure physiology. A genetic risk score based on 29 genome-wide significant variants was associated with hypertension, left ventricular wall thickness, stroke and coronary artery disease, but not kidney disease or kidney function. We also observed associations with blood pressure in East Asian, South Asian and African ancestry individuals. Our findings provide new insights into the genetics and biology of blood pressure, and suggest potential novel therapeutic pathways for cardiovascular disease prevention.

Genetic approaches have advanced the understanding of biological pathways underlying inter-individual variation in blood pressure. For example, studies of rare Mendelian blood pressure disorders have identified multiple defects in renal sodium handling pathways\(^4\). More recently two genome-wide association studies (GWAS), each of >25,000 individuals of European ancestry, identified 13 loci associated with systolic blood pressure (SBP), diastolic blood pressure (DBP) and hypertension\(^5,6\). We now report results of a new meta-analysis of GWAS data that includes staged follow-up genotyping to identify additional blood pressure loci.

Primary analyses evaluated associations between 2.5 million genotyped or imputed single nucleotide polymorphisms (SNPs) and SBP and DBP in 69,395 individuals of European ancestry from 29 studies (Supplementary Materials sections 1–3 and Supplementary Tables 1 and 2). Following GWAS meta-analysis, we conducted a three-stage validation experiment that made efficient use of available genotyping resources, to follow up top signals in up to 133,661 additional individuals of European descent (Supplementary Fig. 1 and Supplementary Materials section 4). Twenty-nine independent SNPs at 28 loci were significantly associated with SBP, DBP, or both in the meta-analysis (Fig. 1, Table 1, Supplementary Materials section 4). Among the genes at the genome-wide significant loci, only CYP17A1, previously implicated in Mendelian congenital adrenal hyperplasia and hypertension, is known to harbour rare variants that have large effects on blood pressure\(^7\).

We performed several analyses to identify potential causal alleles and mechanisms. First, we looked up the 29 genome-wide significant index SNPs and their close proxies (\(r^2 > 0.8\)) among cis-acting expression SNP (eSNP) results from multiple tissues (Supplementary Materials section 5). For 13/29 index SNPs, we found an association between nearby eSNP variants and the expression levels of at least one gene transcript (\(10^{-4} > P > 10^{-3}\)) (Supplementary Table 6). In five cases, the index blood pressure SNP and the best eSNP from a genome-wide survey were identical, highlighting potential mediators of the SNP–blood pressure associations.

Second, because changes in protein sequence are a priori strong functional candidates, we sought non-synonymous coding SNPs that were in high linkage disequilibrium (\(r^2 > 0.8\)) with the 29 index SNPs. We identified such SNPs at eight loci (Table 1, Supplementary Materials section 6 and Supplementary Table 7). In addition we performed analyses testing for differences in genetic effect according to body mass index (BMI) or sex, and analyses of copy number variants, pathway enrichment and metabolomic data, but we did not find any statistically significant results (Supplementary Materials sections 7–9 and Supplementary Tables 8–10).

We evaluated whether the blood pressure variants we identified in individuals of European ancestry were associated with blood pressure in individuals of East Asian (\(N = 29,719\)), South Asian (\(N = 23,977\)) and African (\(N = 19,775\)) ancestries (Table 1 and Supplementary Tables 11–13). We found significant associations in individuals of East Asian ancestry for SNPs at nine loci and in individuals of South Asian ancestry for SNPs at six loci; some have been reported previously (Supplementary Tables 12 and 15). We did not find any statistically significant results (Supplementary Materials sections 7–9 and Supplementary Tables 8–10).

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Consistent with this and in line with findings from randomized trials of this magnitude, across the population range of blood pressure, ancestry individuals) and DBP ($P = 2.9\times 10^{-48}$, $P = 9.5\times 10^{-15}$ and $P = 5.3\times 10^{-5}$, respectively; Supplementary Table 13).

We also created a genetic risk score to assess association of the variants in aggregate with hypertension and with clinical measures of kidney function, using results from other GWAS consortia (Table 2, Supplementary Materials sections 10, 11 and 12). We sequenced our principal GWAS data set into non-overlapping discovery and measures of kidney function, using results from other GWAS consortia (Table 2, Supplementary Materials sections 10, 11 and 12). We sequenced our principal GWAS data set into non-overlapping discovery and validation ($N = 56,000$ and validation ($N = 14,000$) subsets, we found robust evidence for the existence of such undetected common variants (Supplementary Fig. 5 and Supplementary Materials section 12). We estimate that there are 116 (95% confidence interval 57–174) independent blood pressure variants with effect sizes similar to those of blood-pressure-lowering medication in hypertensive patients$^{12,13}$, the genetic risk score was positively associated with left ventricular wall thickness ($P = 6.0\times 10^{-4}$), occurrence of stroke ($P = 3.3\times 10^{-5}$) and CAD ($P = 8.1\times 10^{-29}$). The same genetic risk score was not, however, significantly associated with chronic kidney disease or measures of kidney function, even though these renal outcomes were available in a similar sample size as for the other outcomes (Table 2). The absence of association with kidney phenotypes could be explained by a weaker causal relationship between blood pressure and kidney phenotypes than with CAD and stroke. This finding is consistent with the mismatch between observational data that show a positive association of blood pressure with kidney disease, and clinical trial data that show inconsistent evidence of a benefit from blood pressure lowering on kidney disease prevention in patients with hypertension$^{14}$. Thus, several lines of evidence converge to indicate that blood pressure elevation may in part be a consequence rather than a cause of subclinical kidney disease.

Our discovery meta-analysis (Supplementary Fig. 2) suggests an excess of modestly significant ($10^{-5} < P < 10^{-3}$) associations probably arising from common blood pressure variants of small effect. By dividing our principal GWAS data set into non-overlapping discovery ($N \approx 56,000$) and validation ($N \approx 14,000$) subsets, we found robust evidence for the existence of such undetected common variants (Supplementary Fig. 5 and Supplementary Materials section 12). We estimate that there are 116 (95% confidence interval 57–174) independent blood pressure variants with effect sizes similar to those

**Figure 1** | Genome-wide $-\log_{10}P$-value plots and effects for significant loci. a, b, Genome-wide $-\log_{10}P$-value plots are shown for SBP (a) and DBP (b). SNPs within loci reaching genome-wide significance are labelled in red for SBP and blue for DBP ($\pm 2.5\text{ Mb of lowest }P\text{ value}$) and lowest $P$ values in the initial genome-wide analysis as well as the results of analysis including validation data are labelled separately. The lowest $P$ values in the initial GWAS are denoted with a X. The range of different sample sizes in the final meta-
reported here, which collectively can explain ~2.2% of the phenotypic variance for SBP and DBP, compared with 0.9% explained by the 29 associations discovered thus far (Supplementary Table 6 and Supplementary Materials section 13).

Most of the 28 blood pressure loci harbour multiple genes (Supplementary Table 15 and Supplementary Fig. 4), and although substantial research is required to identify the specific genes and variants responsible for these associations, several loci contain highly plausible biological candidates. The NPPA and NPPB genes at the MTHFR–NPPB locus encode precursors for atrial- and β-type natriuretic peptides (ANP, BNP), and previous work has identified SNPs—moderately correlated with our index SNP—at this locus—which are associated with plasma ANP, BNP and blood pressure16. We found the index SNP at this locus was associated with opposite effects on blood pressure and on ANP/BNP levels, consistent with a model in which the variants act through increased ANP/BNP production to lower blood pressure16 (Supplementary Materials section 14).

Two other loci identified in the current study harbour genes involved in natriuretic peptide and related nitric oxide signalling pathways17,18, both of which act to regulate cyclic guanosine monophosphate. The first locus contains NRP3, which encodes the natriuretic peptide clearance receptor (NPR-C). NRP3 knockout mice exhibit reduced clearance of circulating natriuretic peptides and lower blood pressure19. The second locus includes GUCY1A3 and GUCY1B3, encoding the α and β subunits of soluble guanylate cyclase; knockout of either gene in murine models results in hypertension20.

Another locus contains ADM—encoding adrenomedullin—which has natriuretic, vasodilatory and blood-pressure-lowering properties21. At the GNAS–EDN3 locus, ZNF831 is closest to the index SNP, but GNAS and EDN3 are two nearby compelling biological candidates (Supplementary Fig. 4 and Supplementary Table 15).

We identified two loci with plausible connections to blood pressure via genes implicated in renal physiology or kidney disease. At the first locus, SLCA47 is an electro–neutral sodium bicarbonate co-transporter expressed in the nephron and in vascular smooth muscle22. At the second locus, PLCE1 (phospholipase-C-episol-1 isoform) is important for normal podocyte development in the glomerulus; sequence variation in PLCE1 has been implicated in familial nephrotic syndromes and end-stage kidney disease23.

Missense variants in two genes involved in metal ion transport were associated with blood pressure in our study. The first encodes a Hist/Asp change at amino acid 63 (H63D) in HIFE and is a low-penetrance allele for hereditary hemochromatosis24. The second is an Ala/Thr polymorphism located in exon 7 of SLC39A8, which encodes a zinc transporter that also transports cadmium and manganese25. The same allele of SLC39A8 associated with blood pressure in our study has recently been associated with high-density lipoprotein cholesterol levels26 and BMI27 (Supplementary Table 15).

We have shown that 29 independent genetic variants influence blood pressure in people of European ancestry. The variants reside in 28 loci, 16 of which were novel, and we confirmed association of several of them in individuals of non-European ancestry. A risk score
Table 2 | Genetic risk score and cardiovascular outcome association results

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Source</th>
<th>Effect</th>
<th>s.e.</th>
<th>P value</th>
<th>No. SNPs</th>
<th>Contrast top versus bottom</th>
<th>N case/control or total</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mm Hg)</td>
<td>WGHS</td>
<td>1.645</td>
<td>0.098</td>
<td>(a) 6.5 × 10^{-6}</td>
<td>29</td>
<td>4.61</td>
<td>5.77 (a)</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>WGHS</td>
<td>1.057</td>
<td>0.067</td>
<td>(a) 8.4 × 10^{-7}</td>
<td>29</td>
<td>2.96</td>
<td>3.71 (a)</td>
</tr>
<tr>
<td>Prevalent hypertension</td>
<td>WGHS</td>
<td>0.211</td>
<td>0.018</td>
<td>(b) 3.1 × 10^{-3}</td>
<td>29</td>
<td>1.80</td>
<td>2.09 (b)</td>
</tr>
<tr>
<td>Prevalent hypertension</td>
<td>BRIGHT</td>
<td>0.287</td>
<td>0.031</td>
<td>(b) 7.7 × 10^{-2}</td>
<td>29</td>
<td>2.23</td>
<td>2.74 (b)</td>
</tr>
</tbody>
</table>

Dichotomous endpoints

- Incident heart failure | CHARGE-HF | 0.035 | 0.021 | (c) 0.10 | 29 | 1.10 | 1.13 (c) | 2,526/18,400 |
- Incident stroke | NEURO-CHE | 0.103 | 0.037 | (c) 0.0002 | 28 | 1.34 | 1.44 (c) | 1,544/18,058 |
- Prevalent stroke | SCG | 0.075 | 0.037 | (b) 0.05 | 29 | 1.23 | 1.30 (b) | 1,473/1,482 |
- Stroke (combined, incident and prevalent) | CHARGE & SCG | NA NA | NA | NA | 3,017/19,540 |
- Prevalent CAD | CARDiGRAM | 0.092 | 0.010 | (b) 1.6 × 10^{-9} | 28 | 1.29 | 1.38 (b) | 22,233/64,726 |
- Prevalent CAD | CARDiGRAM & C4D | 0.132 | 0.022 | (b) 2.2 × 10^{-9} | 29 | 1.45 | 1.59 (b) | 5,720/4,381 |
- Prevalent CAD (combined) | CARDiGRAM & C4D | 0.100 | 0.009 | (b) 8.1 × 10^{-9} | 29 | 1.32 | 1.42 (b) | 30,657/71,911 |
- Prevalent chronic kidney disease | CKDGen | 0.014 | 0.015 | (b) 0.35 | 29 | 1.04 | 1.05 (b) | 5,807/61,286 |
- Prevalent microalbuminuria | CKDGen | 0.008 | 0.019 | (b) 0.68 | 29 | 1.02 | 1.03 (b) | 3,698/27,882 |

Continuous measures of target organ damage

- Left ventricular mass (g) | ECHO Gen | 0.822 | 0.317 | (a) 0.05 | 29 | 2.30 | 2.89 (a) | 12,612 |
- Left ventricular wall thickness (cm) | ECHO Gen | 0.009 | 0.002 | (a) 6.0 × 10^{-6} | 29 | 0.03 | 0.03 (a) | 12,612 |
- Serum creatinine | KidneyGen | -0.001 | 0.001 | (d) 0.24 | 29 | 1.00 | 1.00 (d) | 23,812 |
- eGFR (four-parameter MDRD equation) | CKDGen | -0.0001 | 0.0009 | (d) 0.93 | 29 | 1.00 | 1.00 (d) | 67,093 |
- Urinary albumin/creatinine ratio | CKDGen | 0.005 | 0.007 | (d) 0.43 | 29 | 1.01 | 1.02 (d) | 31,580 |

Association of genetic risk score (using all 29 SNPs at 28 loci, parameterized using the average of SBP and DBP effects (=SBP effect + DBP effect)2) from the discovery analysis, tested in results from other GWAS consortia. Units are the unit of phenotypic measurement, or as a difference between top/bottom quintiles or deciles. (a) Units are ln(phenotype) per s.d. of genetic risk score, or odds ratio between top/bottom quintiles or deciles. (b) Units are ln(phenotype) per s.d. of genetic risk score, or hazard ratio between top/bottom quintiles or deciles. (c) Units are ln(hazard) per s.d. of genetic risk score, or hazard ratio between top/bottom quintiles or deciles. (d) Units are ln(hazard) per s.d. of genetic risk score, or phenotypic ratio between top/bottom quintiles or deciles. s.e., standard error. SCG, UK-US Stroke Collaborative Group; see Supplementary Materials sections 1.79 and 11 for further detail on consortia and studies.

METHODS SUMMARY

Supplementary Materials provide complete methods and include the following sections: study recruitment and phenotyping, adjustment for antihypertensive medications, genotyping, data quality control, genotype imputation, within-cohort association analyses, meta-analyses of discovery and validation stages, stratified analyses by sex and BMI, identification of eSNPs and non-synonymous SNPs, metabolomic and lipidomic analyses, CNV analyses, pathway analyses, analyses for non-European ancestries, association of a risk score with hypertension SNPs, metabolomic and lipidomic analyses, CNV analyses, pathway analyses, stratified analyses by sex and BMI, identification of eSNPs and non-synonymous SNPs, metabolomic and lipidomic analyses, CNV analyses, pathway analyses, analyses for non-European ancestries, association of a risk score with hypertension and the prevention of cardiovascular disease, but not kidney disease. These loci improve our understanding of the genetic architecture of blood pressure, provide new biological insights into blood pressure control and may identify novel targets for the treatment of hypertension and the prevention of cardiovascular disease.

Note added in proof: Since this manuscript was submitted, Kato et al. published a blood pressure GWAS in East Asians that identified a SNP highly correlated to the SNP we report at the NPR3/C5orf23 locus.28

METHODOLOGICAL ASSUMPTIONS

- Assumptions for the analysis of genetic risk scores and cardiovascular outcomes are outlined.
- The study used a genome-wide association approach to identify variants associated with blood pressure and cardiovascular disease.
- The results suggest a genetic contribution to blood pressure and cardiovascular disease risk, highlighting potential targets for future intervention and prevention.

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Meta-analysis of genome-wide association studies identifies common variants associated with blood pressure variation.