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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 trait¹ 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 events³. 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–C5orf23*, *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 pathways⁴. 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 combining discovery and follow-up data (Fig. 1, Table 1, Supplementary Figs 2, 3 and Supplementary Tables 3–5). All 29 SNPs attained association $P < 5 \times 10^{-9}$, an order of magnitude beyond the standard genome-wide significance level for a single-stage experiment (Table 1).

Sixteen of these 29 associations were novel (Table 1). Two associations were near the *FURIN* and *GOSR2* genes; prior targeted analyses of variants in these genes suggested they may be blood pressure loci^{7,8}. At the *CACNB2* locus we validated association for a previously reported⁶ SNP, rs4373814, and detected a novel independent association for rs1813353 (pairwise $r^2 = 0.015$ in HapMap CEU). Of our 13 previously reported associations^{5,6}, only the association at *PLCD3*

was not supported by the current results (Supplementary Table 4). Some of the associations are in or near genes involved in pathways known to influence blood pressure (*NPR3*, *GUCY1A3–GUCY1B3*, *ADM*, *GNAS–EDN3*, *NPPA–NPPB* and *CYP17A1*; Supplementary Fig. 4). Twenty-two of the 28 loci did not contain genes that were a priori strong biological candidates.

As expected from prior blood pressure GWAS results, the effects of the novel variants on SBP and DBP were small (Fig. 1 and Table 1). For all variants, the observed directions of effects were concordant for SBP, DBP and hypertension (Fig. 1, Table 1 and Supplementary Fig. 3). 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 pressure⁹.

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 ($10^{-4} > P > 10^{-51}$; 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). The lack of significant association for individual SNPs may reflect small sample sizes, differences in allele frequencies or linkage disequilibrium patterns, imprecise imputation for some ancestries using existing reference samples, or a genuinely different underlying genetic architecture. Because of limited power to detect effects of individual variants in the smaller non-European samples, we created genetic risk scores for SBP and DBP incorporating all 29 blood pressure variants weighted according to effect sizes observed in the European samples. In each non-European ancestry group, risk scores were strongly associated with SBP ($P = 1.1 \times 10^{-40}$ in East Asian, $P = 2.9 \times 10^{-13}$ in South Asian, $P = 9.8 \times 10^{-4}$ in African

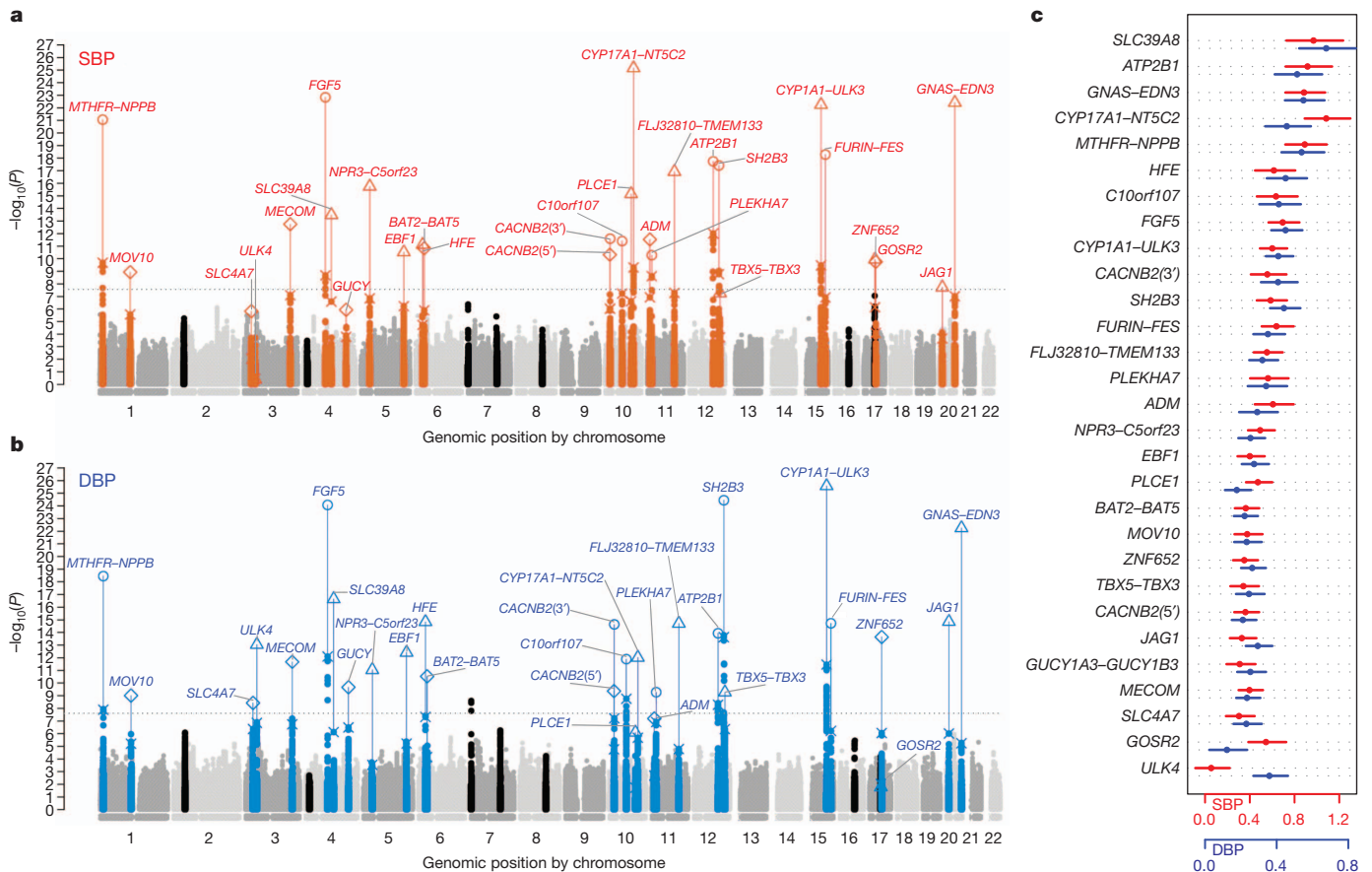


Figure 1 | Genome-wide $-\log_{10} P$ -value plots and effects for significant loci. a, b, Genome-wide $-\log_{10} P$ -value plots are shown for SBP (a) and DBP (b). SNPs within loci reaching genome-wide significance are labelled in red for SBP and blue for DBP (± 2.5 Mb of lowest P value) and lowest 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-

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 hypertensive complications including left ventricular mass, left ventricular wall thickness, incident heart failure, incident and prevalent stroke, prevalent coronary artery disease (CAD), kidney disease and measures of kidney function, using results from other GWAS consortia (Table 2, Supplementary Materials sections 10, 11 and Supplementary Table 14). The risk score was weighted using the average of SBP and DBP effects for the 29 SNPs. In an independent sample of 23,294 women¹⁰, an increase of one standard deviation in the genetic risk score was associated with a 23% increase in the odds of hypertension (95% confidence interval 19–28%; Table 2 and Supplementary Table 14). Among individuals in the top decile of the risk score, the prevalence of hypertension was 29% compared with 16% in the bottom decile (odds ratio 2.09, 95% confidence interval 1.86–2.36). Similar results were observed in an independent hypertension case-control sample (Table 2). In our study, individuals in the top compared to bottom quintiles of genetic risk score differed by 4.6 mm Hg SBP and 3.0 mm Hg DBP, differences that approach population-averaged blood pressure treatment effects for a single antihypertensive agent¹¹. Epidemiological data have shown that differences in SBP and DBP of this magnitude, across the population range of blood pressure, are associated with an increase in cardiovascular disease risk³. Consistent with this and in line with findings from randomized trials

analysis including the validation data are indicated as: circle (96,000–140,000), triangle ($>140,000$ –180,000) and diamond ($>180,000$ –220,000). SNPs near unconfirmed loci are in black. The horizontal dotted line is $P = 2.5 \times 10^{-8}$. GUCY denotes GUCY1A3–GUCY1B3. c, Effect size estimates and 95% confidence bars per blood-pressure-increasing allele of the 29 significant variants for SBP (red) and DBP (blue). Effect sizes are expressed in mm Hg per allele.

of blood-pressure-lowering medication in hypertensive patients^{12,13}, the genetic risk score was positively associated with left ventricular wall thickness ($P = 6.0 \times 10^{-6}$), 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 hypertension¹⁴. Thus, several lines of evidence converge to indicate that blood pressure elevation may in part be a consequence rather than a cause of sub-clinical kidney disease.

Our discovery meta-analysis (Supplementary Fig. 2) suggests an excess of modestly significant ($10^{-5} < P < 10^{-2}$) 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 estimate¹⁵ that there are 116 (95% confidence interval 57–174) independent blood pressure variants with effect sizes similar to those

Table 1 | Summary association results for 29 blood pressure SNPs

Locus	Index SNP	Chr	Position	CA/ NCA	CAF	nsSNP	eSNP	SBP			DBP			HTN	
								Beta	P value	Effect in EA/SA/A	Beta	P value	Effect in EA/SA/A	Beta	P value
<i>MOV10</i>	rs2932538	1	113,018,066	G/A	0.75	Y(p)	Y(p)	0.388	1.2×10^{-9}	+/+/-	0.240	9.9×10^{-10}	+/+*/-	0.049	2.9×10^{-7}
<i>SLC4A7</i>	rs13082711	3	27,512,913	T/C	0.78	Y(p)	Y(p)	-0.315	1.5×10^{-6}	-/-/+	-0.238	3.8×10^{-9}	-/-/+	-0.035	3.6×10^{-4}
<i>MECOM</i>	rs419076	3	170,583,580	T/C	0.47	-	-	0.409	1.8×10^{-13}	+/+/+	0.241	2.1×10^{-12}	+/+/-	0.031	3.1×10^{-4}
<i>SLC39A8</i>	rs13107325	4	103,407,732	T/C	0.05	Y	Y(+)	-0.981	3.3×10^{-14}	?/+/+	-0.684	2.3×10^{-17}	?/+/+	-0.105	4.9×10^{-7}
<i>GUCY1A3- GUCY1B3</i>	rs13139571	4	156,864,963	C/A	0.76	-	-	0.321	1.2×10^{-6}	+/-/+	0.260	2.2×10^{-10}	+/-/+	0.042	2.5×10^{-5}
<i>NPR3- C5orf23</i>	rs1173771	5	32,850,785	G/A	0.60	-	-	0.504	1.8×10^{-16}	+*/+/+	0.261	9.1×10^{-12}	+*/+/-	0.062	3.2×10^{-10}
<i>EBF1</i>	rs11953630	5	157,777,980	T/C	0.37	-	-	-0.412	3.0×10^{-11}	+/+/+	-0.281	3.8×10^{-13}	+/+/+	-0.052	1.7×10^{-7}
<i>HFE</i>	rs1799945	6	26,199,158	G/C	0.14	Y	-	0.627	7.7×10^{-12}	+/+/-	0.457	1.5×10^{-15}	+/+/-	0.095	1.8×10^{-10}
<i>BAT2-BAT5</i>	rs805303	6	31,724,345	G/A	0.61	Y(p)	Y(+)	0.376	1.5×10^{-11}	-/-/?	0.228	3.0×10^{-11}	-/-/+	0.054	1.1×10^{-10}
<i>CACNB2(5')</i>	rs4373814	10	18,459,978	G/C	0.55	-	-	-0.373	4.8×10^{-11}	+/+/-	-0.218	4.4×10^{-10}	+/-/-	-0.046	8.5×10^{-8}
<i>PLCE1</i>	rs932764	10	95,885,930	G/A	0.44	-	-	0.484	7.1×10^{-16}	+/+/-	0.185	8.1×10^{-7}	+/+/-	0.055	9.4×10^{-9}
<i>ADM</i>	rs7129220	11	10,307,114	G/A	0.89	-	-	-0.619	3.0×10^{-12}	?/+/+	-0.299	6.4×10^{-8}	?/+/+	-0.044	1.1×10^{-3}
<i>FLJ32810- TMEM133</i>	rs633185	11	100,098,748	G/C	0.28	-	-	-0.565	1.2×10^{-17}	+*/+/+	-0.328	2.0×10^{-15}	+*/+/-	-0.070	5.4×10^{-11}
<i>FURIN-FES</i>	rs2521501	15	89,238,392	T/A	0.31	-	Y(-)	0.650	5.2×10^{-19}	+*/+/+	0.359	1.9×10^{-15}	+*/+/+	0.059	7.0×10^{-7}
<i>GOSR2</i>	rs17608766	17	42,368,270	T/C	0.86	-	Y(+)	-0.556	1.1×10^{-10}	+/-/+	-0.129	0.017	+/-/+	-0.025	0.08
<i>JAG1</i>	rs1327235	20	10,917,030	G/A	0.46	-	-	0.340	1.9×10^{-8}	+*/+/+	0.302	1.4×10^{-15}	+*/+/+	0.034	4.6×10^{-4}
<i>GNAS-EDN3</i>	rs6015450	20	57,184,512	G/A	0.12	Y(p)	-	0.896	3.9×10^{-23}	?/+/+	0.557	5.6×10^{-23}	?/+/+	0.110	4.2×10^{-14}
<i>MTHFR- NPPB</i>	rs17367504	1	11,785,365	G/A	0.15	-	Y(-/r)	-0.903	8.7×10^{-22}	+/+/+	-0.547	3.5×10^{-19}	+/+/+	-0.103	2.3×10^{-10}
<i>ULK4</i>	rs3774372	3	41,852,418	T/C	0.83	Y	Y(r/p)	-0.067	0.39	-/-/+	-0.367	9.0×10^{-14}	+/+/+	-0.017	0.18
<i>FGF5</i>	rs1458038	4	81,383,747	T/C	0.29	-	-	0.706	1.5×10^{-23}	+*/+/+	0.457	8.5×10^{-25}	+*/+/+	0.072	1.9×10^{-7}
<i>CACNB2(3')</i>	rs1813353	10	18,747,454	T/C	0.68	-	-	0.569	2.6×10^{-12}	+/+/+	0.415	2.3×10^{-15}	+/+/+	0.078	6.2×10^{-10}
<i>C10orf107</i>	rs4590817	10	63,137,559	G/C	0.84	-	Y(r)	0.646	4.0×10^{-12}	-/+/-	0.419	1.3×10^{-12}	-/-/-	0.096	9.8×10^{-9}
<i>CYP17A1- NT5C2</i>	rs11191548	10	104,836,168	T/C	0.91	-	Y(-)	1.095	6.9×10^{-26}	+*/+/+	0.464	9.4×10^{-13}	+*/+/+	0.097	1.4×10^{-5}
<i>PLEKHA7</i>	rs381815	11	16,858,844	T/C	0.26	-	-	0.575	5.3×10^{-11}	+*/+/+	0.348	5.3×10^{-10}	+*/+/-	0.062	3.4×10^{-6}
<i>ATP2B1</i>	rs17249754	12	88,584,717	G/A	0.84	-	-	0.928	1.8×10^{-18}	+*/+*/-	0.522	1.2×10^{-14}	+*/+*/-	0.126	1.1×10^{-14}
<i>SH2B3</i>	rs3184504	12	110,368,991	T/C	0.47	Y	Y(+)	0.598	3.8×10^{-18}	-/-/+	0.448	3.6×10^{-25}	-/-/+	0.056	2.6×10^{-6}
<i>TBX5-TBX3</i>	rs10850411	12	113,872,179	T/C	0.7	-	-	0.354	5.4×10^{-8}	-/+/-	0.253	5.4×10^{-10}	-/-/-	0.045	5.2×10^{-6}
<i>CYP1A1- ULK3</i>	rs1378942	15	72,864,420	C/A	0.35	-	Y(+)	0.613	5.7×10^{-23}	+*/+/+	0.416	2.7×10^{-26}	+*/+/-	0.073	1.0×10^{-8}
<i>ZNF652</i>	rs12940887	17	44,757,806	T/C	0.38	-	Y(-)	0.362	1.8×10^{-10}	+/-/+	0.27	2.3×10^{-14}	+/-/+	0.046	1.2×10^{-7}

Summary association statistics, based on combined discovery and follow-up data, for 29 independent SNPs in individuals of European ancestry are shown. New genome-wide significant findings (17 SNPs) are presented in the top half of the table, data on 12 previously published signals are presented in the lower half. Y indicates that the blood pressure index SNP is a non-synonymous (ns)SNP, Y(p) indicates a proxy SNP is a nsSNP. Y(+/-) indicates that the blood pressure index SNP is the strongest known eSNP for a transcript; Y(-) indicates that the blood pressure index SNP is an eSNP but not the strongest known eSNP for any transcript. Y(r) indicates that the blood pressure index SNP is the strongest known eSNP in a targeted real-time PCR experiment. Y(p) indicates that a proxy SNP ($r^2 > 0.8$) to a blood pressure SNP is an eSNP but not the strongest known eSNP. Observed effect directions in East Asian (EA), South Asian (SA) and African (A) ancestry individuals are coded + or - if concordant or discordant with directions in European ancestry results. Effect size estimates (beta) correspond to mm Hg per coded allele for SBP and DBP and ln(odds) per coded allele for hypertension (HTN). CA, coded allele; CAF, coded allele frequency; NCA, non-coded allele. ? denotes missing data. Genomic positions use NCBI Build 36 coordinates.

* Significant, controlling the FDR at 5% over 58 tests per ancestry (Supplementary Tables 5 and 12).

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 Fig. 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 B-type natriuretic peptides (ANP, BNP), and previous work has identified SNPs—modestly 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 pathways^{17,18}, both of which act to regulate cyclic guanosine monophosphate. The first locus contains *NPR3*, which encodes the natriuretic peptide clearance receptor (NPR-C). *NPR3* 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, *SLC4A7* is an electro-neutral sodium bicarbonate co-transporter expressed in the nephron and in vascular smooth muscle²². At the second locus, *PLCE1* (phospholipase-C-epsilon-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 His/Asp change at amino acid 63 (H63D) in *HFE* 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

Phenotype	Source	Effect	s.e.	P value	No. SNPs	Contrast top versus bottom		N case/control or total
						(per s.d. of genetic risk score)	Quintiles	
Blood pressure phenotypes								
SBP (mm Hg)	WGHS	1.645	0.098	(a) 6.5×10^{-63}	29	4.61	5.77	(a) 23,294
DBP (mm Hg)	WGHS	1.057	0.067	(a) 8.4×10^{-57}	29	2.96	3.71	(a) 23,294
Prevalent hypertension	WGHS	0.211	0.018	(b) 3.1×10^{-33}	29	1.80	2.09	(b) 5,018/18,276
Prevalent hypertension	BRIGHT	0.287	0.031	(b) 7.7×10^{-21}	29	2.23	2.74	(b) 2,406/1,990
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-CHARGE	0.103	0.028	(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 3.3×10^{-5}	NA	NA	NA	NA 3,017/19,540
Prevalent CAD	CARDIoGRAM	0.092	0.010	(b) 1.6×10^{-19}	28	1.29	1.38	(b) 22,233/64,726
Prevalent CAD	C4D ProCARDIS	0.132	0.022	(b) 2.2×10^{-9}	29	1.45	1.59	(b) 5,720/4,381
Prevalent CAD	C4D HPS	0.083	0.027	(b) 0.002	29	1.26	1.34	(b) 2,704/2,804
Prevalent CAD (combined)	CARDIoGRAM & C4D	0.100	0.009	(b) 8.1×10^{-29}	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)	EchoGen	0.822	0.317	(a) 0.01	29	2.30	2.89	(a) 12,612
Left ventricular wall thickness (cm)	EchoGen	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. (a) Units are the unit of phenotypic measurement, either per standard deviation (s.d.) of genetic risk score, or as a difference between top/bottom quintiles or deciles. (b) Units are ln(odds) per s.d. of genetic risk score, or odds 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(phenotype) 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.

derived from the 29 variants was significantly associated with blood-pressure-related organ damage and clinical 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* locus²⁸.

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 and cardiovascular disease, estimation of numbers of undiscovered variants, measurement of natriuretic peptides, and brief literature reviews and GWAS database lookups of all validated blood pressure loci. Full GWAS results for ≈ 2.5 million SNPs are also provided.

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Author Contributions Full author contributions and roles are listed in Supplementary Materials section 19.

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