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

Ehret, Georg Benedikt

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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

Abstract

Blood pressure (BP) is a heritable trait[1] influenced by multiple biological pathways and is responsive to environmental stimuli. Over one billion people worldwide have hypertension (BP ≥140 mm Hg systolic [SBP] or ≥90 mm Hg diastolic [DBP])[2]. Even small increments in BP are associated with increased risk of cardiovascular events[3]. This genome-wide association study of SBP and DBP, which used a multi-stage design in 200,000 individuals of European descent, identified 16 novel loci: six of these loci contain genes previously known or suspected to regulate BP (*GUCY1A3-GUCY1B3; NPR3-C5orf23; ADM; FURIN-FES; GOSR2; GNAS-EDN3*); the other 10 provide new clues to BP 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 BP in East Asian, South Asian, and African ancestry individuals. Our findings provide new insights into the genetics and biology of BP, and suggest novel potential therapeutic pathways for cardiovascular disease prevention.

Genetic approaches have advanced the understanding of biological pathways underlying inter-individual variation in BP. For example, studies of rare Mendelian BP 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 SBP, 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 BP 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, Supplementary Tables 1–2). 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, Supplementary Tables 3–5). All 29 SNPs attained association $P<5\times10^{-9}$, 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

Note added in proof: Since this manuscript was submitted, Kato et al published a BP GWAS in East Asians that identified a SNP highly correlated to the SNP we report at the *NPR3-c5orf23* locus[28].

Author contributions
Full author contributions and roles are listed in the Supplementary Materials Section 19.

may be BP loci[7,8]. At the *CACNB2* locus we validated association for a previously reported[6] 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 BP (*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 BP 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, 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 BP[9].

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 association between nearby eSNP variants and expression level of at least one gene transcript ($10^{-4} > p > 10^{-51}$, Supplementary Table 6). In 5 cases, the index BP SNP and the best eSNP from a genome-wide survey were identical, highlighting potential mediators of the SNP-BP associations.

Second, because changes in protein sequence are strong *a priori* candidates to be functional, we sought non-synonymous coding SNPs that were in high LD (r^2 >0.8) with the 29 index SNPs. We identified such SNPsat 8 loci (Table 1, Supplementary Materials Section 6, 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, Supplementary Tables 8–10).

We evaluated whether the BP variants we identified in Europeans were associated with BP in individuals of East Asian (N=29,719), South Asian (N=23,977), and African (N=19,775) ancestries (Table 1, Supplementary Tables 11–13). We found significant associations in individuals of East Asian ancestry for SNPs at 9 loci and in individuals of South Asian ancestry for SNPs at 6 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 LD 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 BP variants weighted according to effect sizes observed in the European samples. In each non-European ancestry group, risk scores were strongly associated with SBP ($P=1.1\times10^{-40}$ in East Asian, $P=2.9\times10^{-13}$ in South Asian, $P=9.8\times10^{-4}$ in African ancestry individuals) and DBP ($P=2.9\times10^{-48}$, $P=9.5\times10^{-15}$, and $P=5.3\times10^{-5}$, 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, 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 women[10], an increase of 1 standard deviation in the genetic risk score was associated with a 21% increase in the odds of hypertension (95% CI 19%–28%; Table 2, 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% CI 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 BP treatment effects for a single antihypertensive agent[11]. Epidemiologic data have shown that differences in SBP and DBP of this magnitude, across the population range of BP, are associated with an increase in cardiovascular disease risk[3]. Consistent with this and in line with findings from randomized trials of BP-lowering medication in hypertensive patients[12,13], the genetic risk score was positively associated with left ventricular wall thickness (P=6.0×10^{-6}), occurrence of stroke (P=3.3×10^{-5}) and CAD (P=8.1×10^{-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 relation of BP with kidney phenotypes than with CAD and stroke. This finding is consistent with the mismatch between observational data that show a positive association of BP with kidney disease, and clinical trial data that show inconsistent evidence of benefit of BP lowering on kidney disease prevention in patients with hypertension[14]. Thus, several lines of evidence converge to suggest that BP 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 likely arising from common BP variants of small effect. By dividing our principal GWAS dataset into non-overlapping discovery (N≈56,000) and validation (N≈14,000) subsets, we found robust evidence for the existence of such undetected common variants (Supplementary Fig. 5, Supplementary Materials Section 12). We estimate[15] that there are 116 (95% CI 57–174) independent BP variants with effect sizes similar to those reported here, which collectively 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, Supplementary Materials Section 13).

Most of the 28 BP loci harbour multiple genes (Supplementary Table 15, 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, that are associated with plasma ANP, BNP, and BP[16]. We found the index SNP at this locus was associated with opposite effects on BP and on ANP/BNP levels, consistent with a model in which the variants act through increased ANP/BNP production to lower BP[16] (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 (cGMP). 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 BP[19]. The second locus includes *GUCY1A3* and *GUCY1B3,* encoding the alpha and beta subunits of soluble guanylatecyclase (sGC); knockout of either gene in murine models results in hypertension[20].

Another locus contains *ADM*, encoding adrenomedullin, which has natriuretic, vasodilatory, and BP-lowering properties[21]. 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, Supplementary Table 15).

We identified two loci with plausible connections to BP 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 muscle[22]. 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 disease[23].

Missense variants in two genes involved in metal ion transport were associated with BP 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 hemochromatosis[24]. The second is an Ala/Thr polymorphism located in exon 7 of *SLC39A8*, which encodes a zinc transporter that also transports cadmium and manganese[25]. The same allele of *SLC39A8* associated with BP in our study has recently been associated with high-density lipoprotein (HDL) cholesterol levels[26] and BMI[27] (Supplementary Table 15).

In conclusion, we have shown that 29 independent genetic variants influence BP 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 derived from the 29 variants was significantly associated with BP-related organ damage and clinical cardiovascular disease, but not kidney disease. These loci improve our understanding of the genetic architecture of BP, provide new biological insights into BP control and may identify novel targets for the treatment of hypertension and the prevention of cardiovascular disease.

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 nsSNPs, 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 BP loci.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Authors

Georg B. Ehret[1,2,3*], Patricia B. Munroe[4*#], Kenneth M. Rice[5*], Murielle Bochud[2*], Andrew D. Johnson[6,7*], Daniel I. Chasman[8,9*], Albert V. Smith[10,11*], Martin D. Tobin[12], Germaine C. Verwoert[13,14,15], Shih-Jen Hwang[6,16,7], Vasyl Pihur[1], Peter Vollenweider[17], Paul F. O'Reilly[18], Najaf Amin[13], Jennifer L Bragg-Gresham[19], Alexander Teumer[20], Nicole L. Glazer[21], Lenore Launer[22], Jing Hua Zhao[23], Yurii Aulchenko[13], Simon

[1]Center for Complex Disease Genomics, McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA
[2]Institute of Social and Preventive Medicine (IUMSP), Centre Hospitalier Universitaire Vaudois and University of Lausanne, Bugnon 17, 1005 Lausanne, Switzerland
[3]Cardiology, Department of Specialties of Internal Medicine, Geneva University Hospital, Rue Gabrielle-Perret-Gentil 4, 1211 Geneva 14, Switzerland
[*]contributed equally
[4]Clinical Pharmacology and The Genome Centre, William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London EC1M 6BQ, UK
[#]to whom correspondence should be addressed: aravinda@jhmi.edu; m.j.caulfield@qmul.ac.uk; levyd@nhlbi.nih.gov; p.b.munroe@qmul.ac.uk; cnewtoncheh@partners.org
[5]Department of Biostatistics, University of Washington, Seattle, WA, USA
[6]Framingham Heart Study, Framingham, MA, USA
[7]National Heart Lung, and Blood Institute, Bethesda, MD, USA
[8]Division of Preventive Medicine, Brigham and Women's Hospital, 900 Commonwealth Avenue East, Boston MA 02215, USA
[9]Harvard Medical School, Boston, MA, USA
[10]Icelandic Heart Association, Kopavogur, Iceland
[11]University of Iceland, Reykajvik, Iceland
[12]Department of Health Sciences, University of Leicester, University Rd, Leicester LE1 7RH, UK
[13]Department of Epidemiology, Erasmus Medical Center, PO Box 2040, 3000 CA, Rotterdam, The Netherlands
[14]Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands
[15]Netherlands Consortium for Healthy Aging (NCHA), Netherland Genome Initiative (NGI), The Netherlands
[16]Center for Population Studies, National Heart Lung, and Blood Institute, Bethesda, MD, USA
[17]Department of Internal Medicine, Centre Hospitalier Universitaire Vaudois, 1011 Lausanne, Switzerland
[18]Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, Norfolk Place, London W2 1PG, UK
[19]Center forStatistical Genetics, Department of Biostatistics, University of Michigan School of Public Health, Ann Arbor, MI 48103, USA
[20]Interfaculty Institute for Genetics and Functional Genomics, Ernst-Moritz-Arndt-University Greifswald, 17487 Greifswald, Germany
[21]Cardiovascular Health Research Unit, Departments of Medicine, Epidemiology and Health Services, University of Washington, Seattle, WA, USA
[22]Laboratory of Epidemiology, Demography, Biometry, National Institute on Aging, National Institutes of Health, Bethesda, Maryland 20892, USA
[23]MRC Epidemiology Unit, Institute of Metabolic Science, Cambridge CB2 0QQ, UK

Heath[24], Siim Sõber[25], Afshin Parsa[26], Jian'an Luan[23], Pankaj Arora[27], Abbas Dehghan[13,14,15], Feng Zhang[28], Gavin Lucas[29], Andrew A. Hicks[30], Anne U. Jackson[31], John F Peden[32], Toshiko Tanaka[33], Sarah H. Wild[34], Igor Rudan[35,36], Wilmar Igl[37], Yuri Milaneschi[33], Alex N. Parker[38], Cristiano Fava[39,40], John C. Chambers[18,41], Ervin R. Fox[42], Meena Kumari[43], Min Jin Go[44], Pim van der Harst[45], Wen Hong Linda Kao[46], Marketa Sjögren[39], D. G. Vinay[47], Myriam Alexander[48], Yasuharu Tabara[49], Sue Shaw-Hawkins[4], Peter H. Whincup[50], Yongmei Liu[51], Gang Shi[52], Johanna Kuusisto[53], Bamidele Tayo[54], Mark Seielstad[55,56], Xueling Sim[57], Khanh-Dung Hoang Nguyen[1], Terho Lehtimäki[58], Giuseppe Matullo[59,60], Ying Wu[61], Tom R. Gaunt[62], N. Charlotte Onland-Moret[63,64], Matthew N. Cooper[65], Carl G.P. Platou[66], Elin Org[25], Rebecca

[24]Centre National de Génotypage, Commissariat à L'Energie Atomique, Institut de Génomique, Evry, France
[25]Institute of Molecular and Cell Biology, University of Tartu, Riia 23, Tartu 51010, Estonia
[26]University of Maryland School of Medicine, Baltimore, MD, USA, 21201, USA
[27]Center for Human Genetic Research, Cardiovascular Research Center, Massachusetts General Hospital, Boston, Massachusetts, 02114, USA
[28]Department of Twin Research & Genetic Epidemiology, King's College London, UK
[29]Cardiovascular Epidemiology and Genetics, Institut Municipal d'Investigacio Medica, Barcelona Biomedical Research Park, 88 Doctor Aiguader, 08003 Barcelona, Spain
[30]Institute of Genetic Medicine, European Academy Bozen/Bolzano (EURAC), Viale Druso 1, 39100 Bolzano, Italy -Affiliated Institute of the University of Lübeck, Germany
[31]Department of Biostatistics, Center for Statistical Genetics, University of Michigan, Ann Arbor, Michigan, 48109, USA
[32]Department of Cardiovascular Medicine, The Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, OX3 7BN, UK
[33]Clinical Research Branch, National Institute on Aging, Baltimore MD 21250, USA
[34]Centre for Population Health Sciences, University of Edinburgh, EH89AG, UK
[35]Centre for Population Health Sciences and Institute of Genetics and Molecular Medicine, College of Medicine and Vet Medicine, University of Edinburgh, EH8 9AG, UK
[36]Croatian Centre for Global Health, University of Split, Croatia
[37]Department of Genetics and Pathology, Rudbeck Laboratory, Uppsala University, SE-751 85 Uppsala, Sweden
[38]Amgen, 1 Kendall Square, Building 100, Cambridge, MA 02139, USA
[39]Department of Clinical Sciences, Lund University, Malmö, Sweden
[40]Department of Medicine, University of Verona, Italy
[41]Ealing Hospital, London, UB1 3HJ, UK
[42]Department of Medicine, University of Mississippi Medical Center, USA
[43]Genetic Epidemiology Group, Epidemiology and Public Health, UCL, London, WC1E 6BT, UK
[44]Center for Genome Science, National Institute of Health, Seoul, Korea
[45]Department of Cardiology, University Medical Center Groningen, University of Groningen, The Netherlands
[46]Departments of Epidemiology and Medicine, Johns Hopkins University, Baltimore MD, USA
[47]Centre for Cellular and Molecular Biology (CCMB), Council of Scientific and Industrial Research (CSIR), Uppal Road, Hyderabad 500 007, India
[48]Department of Public Health and Primary Care, University of Cambridge, CB1 8RN, UK
[49]Department of Basic Medical Research and Education, and Department of Geriatric Medicine, Ehime University Graduate School of Medicine, Toon, 791-0295, Japan
[50]Division of Community Health Sciences, St George's University of London, London, SW17 0RE, UK
[51]Epidemiology & Prevention, Division of Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, NC 27157, USA
[52]Division of Biostatistics and Department of Genetics, School of Medicine, Washington University in St. Louis, Saint Louis, Missouri 63110, USA
[53]Department of Medicine, University of Eastern Finland and Kuopio University Hospital, 70210 Kuopio, Finland
[54]Department of Preventive Medicine and Epidemiology, Loyola University Medical School, Maywood, IL, USA
[55]Department of Laboratory Medicine & Institute of Human Genetics, University of California San Francisco, 513 Parnassus Ave. San Francisco CA 94143, USA
[56]Genome Institute of Singapore, Agency for Science, Technology and Research, Singapore, 138672, Singapore
[57]Centre for Molecular Epidemiology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, 117597, Singapore
[58]Department of Clinical Chemistry, University of Tampere and Tampere University Hospital, Tampere, 33521, Finland
[59]Department of Genetics, Biology and Biochemistry, University of Torino, Via Santena 19, 10126, Torino, Italy
[60]Human Genetics Foundation (HUGEF), Via Nizza 52, 10126, Torino, Italy
[61]Department of Genetics, University of North Carolina, Chapel Hill, NC, 27599, USA
[62]MRC Centre for Causal Analyses in Translational Epidemiology, School of Social & Community Medicine, University of Bristol, Bristol BS8 2BN, UK
[63]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Heidelberglaan 100, 3508 GA Utrecht, The Netherlands
[64]Complex Genetics Section, Department of Medical Genetics -DBG, University Medical Center Utrecht, 3508 GA Utrecht, The Netherlands

Hardy[67], Santosh Dahgam[68], Jutta Palmen[69], Veronique Vitart[70], Peter S. Braund[71,72], Tatiana Kuznetsova[73], Cuno S.P.M. Uiterwaal[63], Adebowale Adeyemo[74], Walter Palmas[75], Harry Campbell[35], Barbara Ludwig[76], Maciej Tomaszewski[71,72], Ioanna Tzoulaki[77,78], Nicholette D. Palmer[79], CARDIoGRAM consortium[80], CKDGen Consortium[80], KidneyGen Consortium[80], EchoGen consortium[80], CHARGE-HF consortium[80], Thor Aspelund[10,11], Melissa Garcia[22], Yen-Pei C. Chang[26], Jeffrey R. O'Connell[26], Nanette I. Steinle[26], Diederick E. Grobbee[63], Dan E. Arking[1], Sharon L. Kardia[81], Alanna C. Morrison[82], Dena Hernandez[83], Samer Najjar[84,85], Wendy L. McArdle[86], David Hadley[50,87], Morris J. Brown[88], John M. Connell[89], Aroon D. Hingorani[90], Ian N.M. Day[62], Debbie A. Lawlor[62], John P. Beilby[91,92], Robert W. Lawrence[65], Robert Clarke[93], Rory Collins[93], Jemma C Hopewell[93], Halit Ongen[32], Albert W. Dreisbach[42], Yali Li[94], J H. Young[95], Joshua C. Bis[21], Mika Kähönen[96], Jorma Viikari[97], Linda S. Adair[98], Nanette R. Lee[99], Ming-Huei Chen[100], Matthias Olden[101,102], Cristian Pattaro[30], Judith A. Hoffman Bolton[103], Anna Köttgen[104,103], Sven Bergmann[105,106], Vincent Mooser[107], Nish Chaturvedi[108], Timothy M. Frayling[109],

[65]Centre for Genetic Epidemiology and Biostatistics, University of Western Australia, Crawley, WA, Australia
[66]HUNT Research Centre, Department of Public Health and General Practice, Norwegian University of Science and Technology, 7600 Levanger, Norway
[67]MRC Unit for Lifelong Health & Ageing, London, WC1B 5JU, UK
[68]Occupational and Environmental Medicine, Department of Public Health and Community Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, 40530 Gothenburg, Sweden
[69]Centre for Cardiovascular Genetics, University College London, London WC1E 6JF, UK
[70]MRC Human Genetics Unit and Institute of Genetics and Molecular Medicine, Edinburgh, EH2, UK
[71]Department of Cardiovascular Sciences, University of Leicester, Glenfield Hospital, Leicester, LE3 9QP, UK
[72]Leicester NIHR Biomedical Research Unit in Cardiovascular Disease, Glenfield Hospital, Leicester, LE3 9QP, UK
[73]Studies Coordinating Centre, Division of Hypertension and Cardiac Rehabilitation, Department of Cardiovascular Diseases, University of Leuven, Campus Sint Rafaël, Kapucijnenvoer 35, Block D, Box 7001, 3000 Leuven, Belgium
[74]Center for Research on Genomics and Global Health, National Human Genome Research Institute, Bethesda, MD 20892, USA
[75]Columbia University, NY, USA
[76]Department of Medicine III, Medical Faculty Carl Gustav Carus at the Technical University of Dresden, 01307 Dresden, Germany
[77]Epidemiology and Biostatistics, School of Public Health, Imperial College, London, W2 1PG, UK
[78]Clinical and Molecular Epidemiology Unit, Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina, Greece
[79]Wake Forest University Health Sciences, Winston-Salem, NC 27157, USA
[80]A list of consortium members is supplied in the Supplementary Materials
[81]Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, MI 48109, USA
[82]Division of Epidemiology, Human Genetics and Environmental Sciences, School of Public Health, University of Texas at Houston Health Science Center, 12 Herman Pressler, Suite 453E, Houston, TX 77030, USA
[83]Laboratory of Neurogenetics, National Institute on Aging, Bethesda, MD 20892, USA
[84]Laboratory of Cardiovascular Science, Intramural Research Program, National Institute on Aging, NIH, Baltimore, Maryland, USA
[85]Washington Hospital Center, Division of Cardiology, Washington DC, USA
[86]ALSPAC Laboratory, University of Bristol, Bristol, BS8 2BN, UK
[87]Pediatric Epidemiology Center, University of South Florida, Tampa, FL, USA
[88]Clinical Pharmacology Unit, University of Cambridge, Addenbrookes Hospital, Hills Road, Cambridge CB2 2QQ, UK
[89]University of Dundee, Ninewells Hospital &Medical School, Dundee, DD1 9SY, UK
[90]Genetic Epidemiology Group, Department of Epidemiology and Public Health, UCL, London WC1E 6BT, UK
[91]Pathology and Laboratory Medicine, University of Western Australia, Crawley, WA, Australia
[92]Molecular Genetics, PathWest Laboratory Medicine, Nedlands, WA, Australia
[93]Clinical Trial Service Unit and Epidemiological Studies Unit, University of Oxford, Oxford, OX3 7LF, UK
[94]Department of Epidemiology and Biostatistics, Case Western Reserve University, 2103 Cornell Road, Cleveland, OH 44106, USA
[95]Department of Medicine, Johns Hopkins University, Baltimore, USA
[96]Department of Clinical Physiology, University of Tampere and Tampere University Hospital, Tampere, 33521, Finland
[97]Department of Medicine, University of Turku and Turku University Hospital, Turku, 20521, Finland
[98]Department of Nutrition, University of North Carolina, Chapel Hill, NC, 27599, USA
[99]Office of Population Studies Foundation, University of San Carlos, Talamban, Cebu City 6000, Philippines
[100]Department of Neurology and Framingham Heart Study, Boston University School of Medicine, Boston, MA, 02118, USA
[101]Department of Internal Medicine II, University Medical Center Regensburg, 93053 Regensburg, Germany
[102]Department of Epidemiology and Preventive Medicine, University Medical Center Regensburg, 93053 Regensburg, Germany
[103]Department of Epidemiology, Johns Hopkins University, Baltimore MD, USA
[104]Renal Division, University Hospital Freiburg, Germany
[105]Département de Génétique Médicale, Université de Lausanne, 1015 Lausanne, Switzerland
[106]Swiss Institute of Bioinformatics, 1015 Lausanne, Switzerland
[107]Division of Genetics, GlaxoSmithKline, Philadelphia, Pennsylvania 19101, USA

Muhammad Islam[110], Tazeen H. Jafar[110], Jeanette Erdmann[111], Smita R. Kulkarni[112], Stefan R. Bornstein[76], Jürgen Grässler[76], Leif Groop[113,114], Benjamin F. Voight[115], Johannes Kettunen[116,126], Philip Howard[117], Andrew Taylor[43], Simonetta Guarrera[60], Fulvio Ricceri[59,60], Valur Emilsson[118], Andrew Plump[118], Inês Barroso[119,120], Kay-Tee Khaw[48], Alan B. Weder[121], Steven C. Hunt[122], Yan V. Sun[81], Richard N. Bergman[123], Francis S. Collins[124], Lori L. Bonnycastle[124], Laura J. Scott[31], Heather M. Stringham[31], Leena Peltonen[119,125,126,127], Markus Perola[125], Erkki Vartiainen[125], Stefan-Martin Brand[128,129], Jan A. Staessen[73], Thomas J. Wang[6,130], Paul R. Burton[12,72], Maria Soler Artigas[12], Yanbin Dong[131], Harold Snieder[132,131], Xiaoling Wang[131], Haidong Zhu[131], Kurt K. Lohman[133], Megan E. Rudock[51], Susan R Heckbert[134,135], Nicholas L Smith[134,136,135], Kerri L Wiggins[137], Ayo Doumatey[74], Daniel Shriner[74], Gudrun Veldre[25,138], Margus Viigimaa[139,140], Sanjay Kinra[141], Dorairajan Prabhakaran[142], Vikal Tripathy[142], Carl D. Langefeld[79], Annika Rosengren[143], Dag S. Thelle[144], Anna Maria Corsi[145], Andrew Singleton[83], Terrence Forrester[146], Gina Hilton[1], Colin A. McKenzie[146],

[108]International Centre for Circulatory Health, National Heart & Lung Institute, Imperial College, London, UK
[109]Genetics of Complex Traits, Peninsula Medical School, University of Exeter, UK
[110]Department of Community Health Sciences & Department of Medicine, Aga Khan University, Karachi, Pakistan
[111]Medizinische Klinik II, Universität zu Lübeck, Lübeck, Germany
[112]Diabetes Unit, KEM Hospital and Research Centre, Rasta Peth, Pune-411011, Maharashtra, India
[113]Department of Clinical Sciences, Diabetes and Endocrinology Research Unit, University Hospital, Malmö, Sweden
[114]Lund University, Malmö 20502, Sweden
[115]Program in Medical and Population Genetics, Broad Institute of Harvard and MIT, Cambridge, Massachusetts, 02139, USA
[116]Department of Chronic Disease Prevention, National Institute for Health and Welfare, FIN-00251 Helsinki, Finland
[126]FIMM, Institute for Molecular Medicine, Finland, Biomedicum, P.O. Box 104, 00251 Helsinki, Finland
[117]William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London EC1M 6BQ, UK
[118]Merck Research Laboratory, 126 East Lincoln Avenue, Rahway, NJ 07065, USA
[119]Wellcome Trust Sanger Institute, Hinxton, CB10 1SA, UK
[120]University of Cambridge Metabolic Research Labs, Institute of Metabolic Science Addenbrooke's Hospital, CB2 OQQ, Cambridge, UK
[121]Division of Cardiovascular Medicine, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, MI, USA
[122]Cardiovascular Genetics, University of Utah School of Medicine, Salt Lake City, UT, USA
[123]Department of Physiology and Biophysics, Keck School of Medicine, University of Southern California, Los Angeles, California 90033, USA
[124]National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland 20892, USA
[125]National Institute for Health and Welfare, 00271 Helsinki, Finland
[127]Broad Institute, Cambridge, Massachusetts 02142, USA
[128]Leibniz-Institute for Arteriosclerosis Research, Department of Molecular Genetics of Cardiovascular Disease, University of Münster, Münster, Germany
[129]Medical Faculty of the Westfalian Wilhelms University Muenster, Department of Molecular Genetics of Cardiovascular Disease, University of Muenster, Muenster, Germany
[130]Division of Cardiology, Massachusetts General Hospital, Boston, MA, USA
[131]Georgia Prevention Institute, Department of Pediatrics, Medical Collegeof Georgia, Augusta, GA, USA
[132]Unit of Genetic Epidemiology and Bioinformatics, Department of Epidemiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
[133]Department of Biostatical Sciences, Division of Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, NC 27157, USA
[134]Department of Epidemiology, University of Washington, Seattle, WA, 98195, USA
[135]Group Health Research Institute, Group Health Cooperative, Seattle, WA, USA
[136]Seattle Epidemiologic Research and Information Center, Veterans Health Administration Office of Research & Development, Seattle, WA 98108, USA
[137]Department of Medicine, University of Washington, 98195, USA
[138]Department of Cardiology, University of Tartu, L. Puusepa 8, 51014 Tartu, Estonia
[139]Tallinn University of Technology, Institute of Biomedical Engineering, Ehitajate tee 5, 19086 Tallinn, Estonia
[140]Centre of Cardiology, North Estonia Medical Centre, Sütiste tee 19, 13419 Tallinn, Estonia
[141]Division of Non-communicable disease Epidemiology, The London School of Hygiene and Tropical Medicine London, Keppel Street, London WC1E 7HT, UK
[142]South Asia Network for Chronic Disease, Public Health Foundation of India, C-1/52, SDA, New Delhi 100016, India
[143]Department of Emergency and Cardiovascular Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, 41685 Gothenburg, Sweden
[144]Department of Biostatistics, Institute of Basic Medical Sciences, University of Oslo, 0317 Oslo, Norway
[145]Tuscany Regional Health Agency, Florence, Italy

Tunde Salako[147], Naoharu Iwai[148], Yoshikuni Kita[149], Toshio Ogihara[150], Takayoshi Ohkubo[149,151], Tomonori Okamura[148], Hirotsugu Ueshima[152], Satoshi Umemura[153], Susana Eyheramendy[154], Thomas Meitinger[155,156], H.-Erich Wichmann[157,158,159], Yoon Shin Cho[44], Hyung-Lae Kim[44], Jong-Young Lee[44], James Scott[160], Joban S. Sehmi[160,41], Weihua Zhang[18], Bo Hedblad[39], Peter Nilsson[39], George Davey Smith[62], Andrew Wong[67], Narisu Narisu[124], Alena Stančáková[53], Leslie J. Raffel[161], Jie Yao[161], Sekar Kathiresan[162,27], Chris O'Donnell[163,27,9], Stephen M. Schwartz[134], M. Arfan Ikram[13,15], W. T. Longstreth Jr.[164], Thomas H. Mosley[165], Sudha Seshadri[166], Nick R.G. Shrine[12], Louise V. Wain[12], Mario A. Morken[124], Amy J. Swift[124], Jaana Laitinen[167], Inga Prokopenko[51,168], Paavo Zitting[169], Jackie A. Cooper[69], Steve E. Humphries[69], John Danesh[48], Asif Rasheed[170], Anuj Goel[32], Anders Hamsten[171], Hugh Watkins[32], Stephan J.L. Bakker[172], Wiek H. van Gilst[45], Charles S. Janipalli[47], K. Radha Mani[47], Chittaranjan S. Yajnik[112], Albert Hofman[13], Francesco U.S. Mattace-Raso[13,14], Ben A. Oostra[173], Ayse Demirkan[13], Aaron Isaacs[13], Fernando Rivadeneira[13,14], Edward G Lakatta[174], Marco Orru[175,176], Angelo Scuteri[174], Mika Ala-Korpela[177,178,179], Antti J Kangas[177], Leo-Pekka Lyytikäinen[58], Pasi Soininen[177,178], Taru Tukiainen[180,181,177], Peter Würtz[177,18,180], Rick Twee-Hee Ong[56,57,182], Marcus Dörr[183], Heyo K. Kroemer[184],

[146]Tropical Medicine Research Institute, University of the West Indies, Mona, Kingston, Jamaica
[147]University of Ibadan, Ibadan, Nigeria
[148]Department of Genomic Medicine, and Department of Preventive Cardiology, National Cerebral and Cardiovascular Research Center, Suita, 565-8565, Japan
[149]Department of Health Science, Shiga University of Medical Science, Otsu, 520-2192, Japan
[150]Department of Geriatric Medicine, Osaka University Graduate School of Medicine, Suita, 565-0871, Japan
[151]Tohoku University Graduate School of Pharmaceutical Sciences and Medicine, Sendai, 980-8578, Japan
[152]Lifestyle-related Disease Prevention Center, Shiga University of Medical Science, Otsu, 520-2192, Japan
[153]Department of Medical Science and Cardiorenal Medicine, Yokohama City University School of Medicine, Yokohama, 236-0004, Japan
[154]Department of Statistics, Pontificia Universidad Catolicade Chile, Vicuña Mackena 4860, Santiago, Chile
[155]Institute of Human Genetics, Helmholtz Zentrum Munich, German Research Centre for Environmental Health, 85764 Neuherberg, Germany
[156]Institute of Human Genetics, Klinikum rechts der Isar, Technical University of Munich, 81675 Munich, Germany
[157]Institute of Epidemiology, Helmholtz Zentrum Munich, German Research Centre for Environmental Health, 85764 Neuherberg, Germany
[158]Chair of Epidemiology, Institute of Medical Informatics, Biometry and Epidemiology, Ludwig-Maximilians-Universität, 81377 Munich, Germany
[159]Klinikum Grosshadern, 81377 Munich, Germany
[160]National Heart and Lung Institute, Imperial College London, London, UK, W12 0HS, UK
[161]Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA
[162]Medical Population Genetics, Broad Institute of Harvard and MIT, 5 Cambridge Center, Cambridge MA 02142, USA
[163]National Heart, Lung and Blood Institute and its Framingham Heart Study, 73 Mount Wayte Ave., Suite #2, Framingham, MA 01702, USA
[164]Department of Neurology and Medicine, University of Washington, Seattle, USA
[165]Department of Medicine (Geriatrics), University of Mississippi Medical Center, Jackson, MS, USA
[166]Department of Neurology, Boston University School of Medicine, USA
[167]Finnish Institute of Occupational Health, Finnish Institute of Occupational Health, Aapistie 1, 90220 Oulu, Finland
[168]Wellcome Trust Centre for Human Genetics, University of Oxford, UK
[169]Lapland Central Hospital, Department of Physiatrics, Box 8041, 96101 Rovaniemi, Finland
[170]Center for Non-Communicable Diseases Karachi, Pakistan
[171]Atherosclerosis Research Unit, Department of Medicine, Karolinska Institute, Stockholm, Sweden
[172]Department of Internal Medicine, University Medical Center Groningen, University of Groningen, The Netherlands
[173]Department of Medical Genetics, Erasmus Medical Center, Rotterdam, The Netherlands
[174]Gerontology Research Center, National Institute on Aging, Baltimore, MD 21224, USA
[175]Istituto di Neurogenetica e Neurofarmacologia, Consiglio Nazionale delle Ricerche, Cittadella Universitaria di Monserrato, Monserrato, Cagliari, Italy
[176]Unita' Operativa Semplice Cardiologia, Divisione di Medicina, Presidio Ospedaliero Santa Barbara, Iglesias, Italy
[177]Computational Medicine Research Group, Institute of Clinical Medicine, University of Oulu and Biocenter Oulu, 90014 University of Oulu, Oulu, Finland
[178]NMR Metabonomics Laboratory, Department of Biosciences, University of Eastern Finland, 70211 Kuopio, Finland
[179]Department of Internal Medicine and Biocenter Oulu, Clinical Research Center, 90014 University of Oulu, Oulu, Finland
[180]Institute for Molecular Medicine Finland FIMM, 00014 University of Helsinki, Helsinki, Finland
[181]Department of Biomedical Engineering and Computational Science, School of Science and Technology, Aalto University, 00076 Aalto, Espoo, Finland

Uwe Völker[20], Henry Völzke[185], Pilar Galan[186], Serge Hercberg[186], Mark Lathrop[24], Diana Zelenika[24], Panos Deloukas[119], Massimo Mangino[28], Tim D. Spector[28], Guangju Zhai[28], James F. Meschia[187], Michael A. Nalls[83], Pankaj Sharma[188], Janos Terzic[189], M. J. Kranthi Kumar[47], Matthew Denniff[71], Ewa Zukowska-Szczechowska[190], Lynne E. Wagenknecht[79], F. Gerald R. Fowkes[191], Fadi J. Charchar[192], Peter E.H. Schwarz[193], Caroline Hayward[70], Xiuqing Guo[161], Charles Rotimi[74], Michiel L. Bots[63], Eva Brand[194], Nilesh J. Samani[71,72], Ozren Polasek[195], Philippa J. Talmud[69], Fredrik Nyberg[68,196], Diana Kuh[67], Maris Laan[25], Kristian Hveem[66], Lyle J. Palmer[197,198], Yvonne T. van der Schouw[63], Juan P. Casas[199], Karen L. Mohlke[61], Paolo Vineis[200,60], Olli Raitakari[201], Santhi K. Ganesh[202], Tien Y. Wong[203,204], E Shyong Tai[205,57,206], Richard S. Cooper[54], Markku Laakso[53], Dabeeru C. Rao[207], Tamara B. Harris[22], Richard W. Morris[208], Anna F. Dominiczak[209], Mika Kivimaki[210], Michael G. Marmot[210], Tetsuro Miki[49], Danish Saleheen[170,48], Giriraj R. Chandak[47], Josef Coresh[211], Gerjan Navis[212], Veikko Salomaa[125], Bok-Ghee Han[44], Xiaofeng Zhu[94], Jaspal S. Kooner[160,41], Olle Melander[39], Paul M Ridker[8,213,9], Stefania Bandinelli[214], Ulf B. Gyllensten[37], Alan F. Wright[70], James F. Wilson[34], Luigi Ferrucci[33], Martin Farrall[32], Jaakko Tuomilehto[215,216,217,218], Peter P. Pramstaller[30,219], Roberto Elosua[29,220], Nicole Soranzo[119,28], Eric J.G. Sijbrands[13,14],

[182]NUS Graduate School for Integrative Sciences & Engineering (NGS) Centre for Life Sciences (CeLS), Singapore, 117456, Singapore
[183]Department of Internal Medicine B, Ernst-Moritz-Arndt-University Greifswald, 17487 Greifswald, Germany
[184]Institute of Pharmacology, Ernst-Moritz-Arndt-University Greifswald, 17487 Greifswald, Germany
[185]Institute for Community Medicine, Ernst-Moritz-Arndt-University Greifswald, 17487 Greifswald, Germany
[186]U557 Institut National de la Santé et de la Recherche Médicale, U1125 Institut National de la Recherche Agronomique, Université Paris 13, Bobigny, France
[187]Department of Neurology, Mayo Clinic, Jacksonville, FL, USA
[188]Imperial College Cerebrovascular Unit (ICCRU), Imperial College, London, W6 8RF, UK
[189]Faculty of Medicine, University of Split, Croatia
[190]Department of Internal Medicine, Diabetology, and Nephrology, Medical University of Silesia, 41-800, Zabrze, Poland
[191]Public Health Sciences section, Division of Community Health Sciences, University of Edinburgh, Medical School, Teviot Place, Edinburgh, EH8 9AG, UK
[192]School of Science and Engineering, University of Ballarat, 3353 Ballarat, Australia
[193]Prevention and Care of Diabetes, Department of Medicine III, Medical Faculty Carl Gustav Carus at the Technical University of Dresden, 01307 Dresden, Germany
[194]University Hospital Münster, Internal Medicine D, Münster, Germany
[195]Department of Medical Statistics, Epidemiology and Medical Informatics, Andrija Stampar School of Public Health, University of Zagreb, Croatia
[196]AstraZeneca R&D, 431 83 Mölndal, Sweden
[197]Genetic Epidemiology & Biostatistics Platform, Ontario Institute for Cancer Research, Toronto
[198]Samuel Lunenfeld Institute for Medical Research, University of Toronto, Canada
[199]Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, UK
[200]Department of Epidemiology and Public Health, Imperial College, Norfolk Place London W2 1PG, UK
[201]Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku and the Department of Clinical Physiology, Turku University Hospital, Turku, 20521, Finland
[202]Department of Internal Medicine, Division of Cardiovascular Medicine, University of Michigan Medical Center, Ann Arbor, Michigan, USA
[203]Singapore Eye Research Institute, Singapore, 168751, Singapore
[204]Department of Ophthalmology, National University of Singapore, Singapore, 119074, Singapore
[205]Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, 119074, Singapore
[206]Duke-National University of Singapore Graduate Medical School, Singapore, 169857, Singapore
[207]Division of Biostatistics, Washington University School of Medicine, Saint Louis, MO, 63110, USA
[208]Department of Primary Care & Population Health, UCL, London, UK, NW3 2PF, UK
[209]BHF Glasgow Cardiovascular Research Centre, University of Glasgow, 126 University Place, Glasgow, G12 8TA, UK
[210]Epidemiology Public Health, UCL, London, UK, WC1E 6BT, UK
[211]Departments of Epidemiology, Biostatistics, and Medicine, Johns Hopkins University, Baltimore MD, USA
[212]Division of Nephrology, Department of Internal Medicine, University Medical Center Groningen, University of Groningen, The Netherlands
[213]Division of Cardiology, Brigham and Women's Hospital, 900 Commonwealth Avenue East, Boston MA 02215, USA
[214]Geriatric Rehabilitation Unit, Azienda Sanitaria Firenze (ASF), Florence, Italy
[215]National Institute for Health and Welfare, Diabetes Prevention Unit, 00271 Helsinki, Finland
[216]Hjelt Institute, Department of Public Health, University of Helsinki, 00014 Helsinki, Finland
[217]South Ostrobothnia Central Hospital, 60220 Seinäjoki, Finland
[218]Red RECAVA Grupo RD06/0014/0015, Hospital UniversitarioLa Paz, 28046 Madrid, Spain

David Altshuler[221,115], Ruth J.F. Loos[23], Alan R. Shuldiner[26,222], Christian Gieger[157], Pierre Meneton[223], Andre G. Uitterlinden[13,14,15], Nicholas J. Wareham[23], Vilmundur Gudnason[10,11], Jerome I. Rotter[161], Rainer Rettig[224], Manuela Uda[175], David P. Strachan[50], Jacqueline C.M. Witteman[13,15], Anna-Liisa Hartikainen[225], Jacques S. Beckmann[105,226], Eric Boerwinkle[227], Ramachandran S. Vasan[6,228], Michael Boehnke[31], Martin G. Larson[6,229], Marjo-Riitta Järvelin[18,230,231,232,233], Bruce M. Psaty[21,135*], Gonçalo R Abecasis[19*], Aravinda Chakravarti[1*#], Paul Elliott[18,233*], Cornelia M. van Duijn[13,234*], Christopher Newton-Cheh[27,115*#], Daniel Levy[6,16,7*#], Mark J. Caulfield[4*#], Toby Johnson[4*]

[219]Department of Neurology, General Central Hospital, 39100 Bolzano, Italy
[220]CIBER Epidemiología y Salud Pública, 08003 Barcelona
[221]Department of Medicine and Department of Genetics, Harvard Medical School, Boston, Massachusetts 02115, USA
[222]Geriatric Research and Education Clinical Center, Veterans Administration Medical Center, Baltimore, MD, USA
[223]U872 Institut National de la Santé et de la Recherche Médicale, Centre de Recherche des Cordeliers, Paris, France
[224]Institute of Physiology, Ernst-Moritz-Arndt-University Greifswald, 17487 Greifswald, Germany
[225]Institute of Clinical Medicine/Obstetrics and Gynecology, University of Oulu, Finland
[226]Service of Medical Genetics, Centre Hospitalier Universitaire Vaudois, 1011 Lausanne, Switzerland
[227]Human Genetics Center, 1200 Hermann Pressler, Suite E447 Houston, TX 77030, USA
[228]Division of Epidemiology and Prevention, Boston University School of Medicine, Boston, MA, USA
[229]Department of Mathematics, Boston University, Boston, MA, USA
[230]Institute of Health Sciences, University of Oulu, BOX 5000, 90014 University of Oulu, Finland
[231]Biocenter Oulu, University of Oulu, BOX 5000, 90014 University of Oulu, Finland
[232]National Institute for Health and Welfare, Box 310, 90101 Oulu, Finland
[233]MRC-HPA Centre for Environment and Health, School of Public Health, Imperial College London, Norfolk Place, London W2 1PG, UK
[234]Centre of Medical Systems Biology (CMSB 1-2), NGI Erasmus Medical Center, Rotterdam, The Netherlands

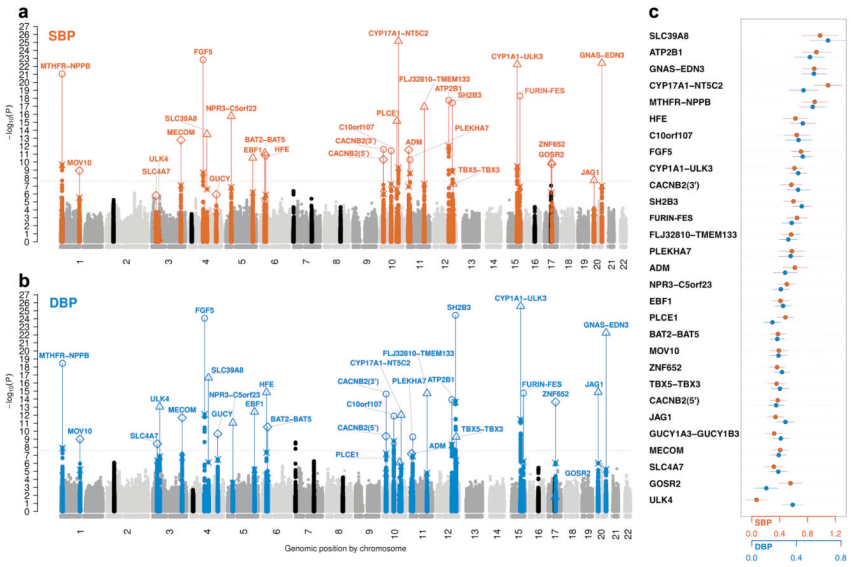

Fig. 1.

Genome-wide $-\log_{10}$ *P*-value plots and effects for significant loci.

Genome-wide $-\log_{10}$ *P*-value plots are shown for systolic (SBP: panel a) and diastolic (DBP: panel b). SNPs within loci reaching genome-wide significance are labeled in red for SBP and blue for DBP (±2.5Mb 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 labeled separately. The lowest *P*-values in the initial GWAS are denoted as an X. The range of different sample sizes in the final meta-analysis including the validation data are indicated as: circle (96–140k), triangle (>140–180k), and diamond (>180–220k). SNPs near unconfirmed loci are in black. The horizontal dotted line is $P=2.5 \times 10^{-8}$. Panel c shows the effect size estimates and 95% confidence bars per BP-increasing allele of the 29 significant variants for SBP (red) and DBP (blue). Effect sizes are expressed in mmHg/allele. GUCY = *GUCY1A3-GUCY1B3*.

Table 1

Summary association results for 29 BP SNPs

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.

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
MOV10	rs2932538	1	113,018,066	G/A	0.75	Y(p)	Y(p)	0.388	$1.2*10^{-9}$	+/+/−	0.24	$9.9*10^{-10}$	+/+*/−	0.049	$2.9*10^{-7}$
SLC4A7	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	$3.6*10^{-4}$
NEUROD1	rs419076	3	170,583,580	T/C	0.47	-	-	0.409	$1.8*10^{-13}$	+/+/+	0.241	$2.1*10^{-12}$	+/+/−	0.031	$3.1*10^{-4}$
SLC39A8	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	$4.9*10^{-7}$
GUCY1A3-GUCY1B3	rs13139571	4	156,864,963	C/A	0.76	-	-	0.321	$1.2*10^{-6}$	+/−/+	0.26	$2.2*10^{-10}$	+/−/+	0.042	$2.5*10^{-5}$
EPR3-C5orf23	rs1173771	5	32,850,785	G/A	0.6	-	-	0.504	$1.8*10^{-16}$	+*/+/+	0.261	$9.1*10^{-12}$	+*/+/−	0.062	$3.2*10^{-10}$
EBF1	rs11953630	5	157,777,980	T/C	0.37	-	-	−0.412	$3.0*10^{-11}$	+/+/+	−0.281	$3.8*10^{-13}$	+/+/+	−0.052	$1.7*10^{-7}$
HFE	rs1799945	6	26,199,158	G/C	0.14	Y	-	0.627	$7.7*10^{-12}$	+/+/−	0.457	$1.5*10^{-15}$	+/+/−	0.095	$1.8*10^{-10}$
BAT2-BAT5	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	$1.1*10^{-10}$
CACNB2(5′)	rs4373814	10	18,459,978	G/C	0.55	-	-	−0.373	$4.8*10^{-11}$	+/+/−	−0.218	$4.4*10^{-10}$	−/+/−	−0.046	$8.5*10^{-8}$
PLCE1	rs932764	10	95,885,930	G/A	0.44	-	-	0.484	$7.1*10^{-16}$	+/+/−	0.185	$8.1*10^{-7}$	+/+/−	0.055	$9.4*10^{-9}$
ADM	rs7129220	11	10,307,114	G/A	0.89	-	-	−0.619	$3.0*10^{-12}$	?/−/+	−0.299	$6.4*10^{-8}$	?/−/+	−0.044	$1.1*10^{-3}$
FLJ32810-TMEM133	rs633185	11	100,098,748	G/C	0.28	-	-	−0.565	$1.2*10^{-17}$	+*/+/+	−0.328	$2.0*10^{-15}$	+*/+/−	−0.07	$5.4*10^{-11}$
FURIN-FES	rs2521501	15	89,238,392	T/A	0.31	-	Y(−)	0.65	$5.2*10^{-19}$	+*/+/+	0.359	$1.9*10^{-15}$	+*/+/+	0.059	$7.0*10^{-7}$
GOSR2	rs17608766	17	42,368,270	T/C	0.86	-	Y(+)	−0.556	$1.1*10^{-10}$	+/−/+	−0.129	0.017	+/−/+	−0.025	0.08

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
JAG1	rs1327235	20	10,917,030	G/A	0.46	-	-	0.34	$1.9*10^{-8}$	+*/+/+	0.302	$1.4*10^{-15}$	+*/+*/+	0.034	$4.6*10^{-4}$
GNAS-EDN3	rs6015450	20	57,184,512	G/A	0.12	Y(p)	-	0.896	$3.9*10^{-23}$	?/+/+	0.557	$5.6*10^{-23}$	?/+*/+	0.11	$4.2*10^{-14}$
MTHFR-NPPB	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	$2.3*10^{-10}$
ULK4	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
FGF5	rs1458038	4	81,383,747	T/C	0.29	-	-	0.706	$1.5*10^{-23}$	+*/+/+	0.457	$8.5*10^{-25}$	+*/+*/+	0.072	$1.9*10^{-7}$
CACNB2(3′)	rs1813353	10	18,747,454	T/C	0.68	-	-	0.569	$2.6*10^{-12}$	+/+/+	0.415	$2.3*10^{-15}$	+/+/+	0.078	$6.2*10^{-10}$
C10orf107	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	$9.8*10^{-9}$
CYP17A1-NT5C2	rs11191548	10	104,836,168	T/C	0.91	-	Y(−)	1.095	$6.9*10^{-26}$	+*/+*/+	0.464	$9.4*10^{-13}$	+*/+*/+	0.097	$1.4*10^{-5}$
PLEKHA7	rs381815	11	16,858,844	T/C	0.26	-	-	0.575	$5.3*10^{-11}$	+*/+/+	0.348	$5.3*10^{-10}$	+*/−/+	0.062	$3.4*10^{-6}$
ATP2B1	rs17249754	12	88,584,717	G/A	0.84	-	-	0.928	$1.8*10^{-18}$	+*/+*/−	0.522	$1.2*10^{-14}$	+*/+*/−	0.126	$1.1*10^{-14}$
SH2B3	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	$2.6*10^{-6}$
TBX5-TBX3	rs10850411	12	113,872,179	T/C	0.7	-	-	0.354	$5.4*10^{-8}$	−/+/−	0.253	$5.4*10^{-10}$	−/−/−	0.045	$5.2*10^{-6}$
CYP1A1-ULK3	rs1378942	15	72,864,420	C/A	0.35	-	Y(+)	0.613	$5.7*10^{-23}$	+*/+/+	0.416	$2.7*10^{-26}$	+*/+/−	0.073	$1.0*10^{-8}$
ZNF652	rs12940887	17	44,757,806	T/C	0.38	-	Y(−)	0.362	$1.8*10^{-10}$	+/−/+	0.27	$2.3*10^{-14}$	+/−/+	0.046	$1.2*10^{-7}$

Y indicates the BP index SNP is a nsSNP, Y(p) indicates a proxy SNP is a nsSNP. Y(+): indicatesBP index SNP is the strongest known eSNP for a transcript; Y(−): indicates BP index SNP is an eSNP but not strongest known eSNP for any transcript. Y(r): indicates BP index SNP is strongest known eSNP in a regional SNP-RTPCR experiment. Y(p): indicates a proxy SNP ($r^2 > 0.8$) to BP 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;

*denotes significance controlling the FDR at 5% over 58 tests per ancestry (Supplementary Tables 5 and 12). Effect size estimates (beta) correspond to mmHg per coded allele for SBP and DBP and ln(odds) per coded allele for HTN.

CA = coded allele; NCA = non-coded allele; CAF = coded allele frequency; ? denotes missing data. Genomic positions use NCBI Build 36 coordinates.

Table 2

Genetic risk score and cardiovascular outcome association results

Association of genetic risk score (using all 29 SNPs at 28 loci, parameterised using the average of SBP and DBP effects [=(SBP effect + DBP effect)/2] from the discovery analysis), tested in results from other GWAS consortia.

		Effect	SE				Contrast top vs. bottom			
Phenotype	**Source**	**(per SD of genetic risk score)**			***P*-value**	**# SNPs**	**quintiles**	**deciles**		**N case/control or total**
Blood pressure phenotypes										
SBP [mmHg]	WGHS	1.645	0.098	*(a)*	$6.5*10^{-63}$	29	4.61	5.77	*(a)*	23,294
DBP [mmHg]	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	UK-US Stroke Collaborative Group(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 oftarget organ damage										

Phenotype	Source	Effect (per SD of genetic risk score)	SE (per SD of genetic risk score)		*P*-value	# SNPs	Contrast top vs. bottom quintiles	Contrast top vs. bottom deciles		N case/control or total
Blood pressure phenotypes										
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 (4 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

(a) Units are the unit of phenotypic measurement, either per SD of genetic risk score, or as a difference between top/bottom quintiles or deciles.

(b) Units are ln(odds) per SD of genetic risk score, or odds ratio between top/bottom quintiles or deciles.

(c) Units are ln(hazard) per SD of genetic risk score, or hazard ratio between top/bottom quintiles or deciles.

(d) Units are ln(phenotype) per SD of genetic risk score, or phenotypic ratio between top/bottom quintiles or deciles.