WAIN, Louise, et al. Genome-wide association study identifies six new loci influencing pulse pressure and mean arterial pressure. *Nature Genetics*, 2011, vol. 43, p. 1005

DOI: 10.1038/ng.922
PMID: 21909110
Genome-wide association study identifies six new loci influencing pulse pressure and mean arterial pressure

Louise V Wain1,2,180, Germaine C Verwoert3,4,180, Paul F O’Reilly5,180, Gang Shi6,7,180, Toby Johnson8,180, Andrew D Johnson9,10, Murielle Bochud11,12, Kenneth M Rice13, Peter Henneman14, Albert V Smith15,16, Georg B Ehret17,18,19, Najaf Amin20, Martin G Larson9,21, Vincent Mooser22, David Hadley23,24, Marcus Dörr25, Joshua C Bis26, Thor Aspelund15,16, Tõnu Esko27,28,29, A Cecile JW Janssens20, Jing Hua Zhao30, Simon Heath31, Maris Laan29, Jingyuansu32,33, Giorgio Pistis34, Jian’an Luan30, Pankaj Arora35, Gavin Lucas36, Nicola Pirastu37, Irene Pilcher38, Anne U Jackson39, Rebecca J Webster40, Feng Zhang41, John F Peden42,43, Helena Schmidt44, Toshiko Tanaka45, Harry Campbell46, Wilmar Ig47, Yuri Milaneschi48, Jouke-Jan Hottenga48, Veronique Vitart49, Daniel I Chasman50,51, Stella Trompet52,53, Jennifer L Bragg-Gresham54, Behrooz Z Alizadeh55, John C Chambers56, Xiaqing Guo55, Terho Lehtimäki56, Brigitte Kühnel57, Lorna M Lopez58,59, Ozren Polašek60, Milad Boban61, Christopher P Nelson62, Alanna C Morrison63, Vasil Pihiur7, Santhi K Ganesh64, Albert Hofman20, Suman Kundu20, Francesco US Mattace-Raso20,3, Fernando Rivadeneira3,4, Eric JG Sijbrands20,3, Andre G Uitterlinden3,4, Shih-Jen Hung9,65,10, Ramachandran S Vasan9,66, Thomas J Wang9,67, Sven Bergmann68,69, Peter Vollenweider70, Gérard Waerber70, Jaana Laitinen71, Anneli Pouta72, Paavo Zitting73, Wendy L McArdle74, Heyo K Kroemer75, Uwe Völker76, Henry Völzke77, Nicole L Glazer78, Kent D Taylor75, Tamara B Harris79, Helene Alavere27, Toomas Haller27, Alme Keis79, Mari-Liis Tammesoo27, Yuri Aulchenko20, Inês Barroso101, Kay-Tee Khaw92, Pilar Galan83,84,85, Serge Hercberg83,84,85, Mark Lathrop81, Susana Eyheramendy86, Elin Org93, Slim Söber29, Xiaowen Lu32, Ilja M Nolte32, Brenda W Penninx37,88,89, Tanguy Corre34, Corrado Masciullo34, Cinzia Sala34, Leif Groop90, Benjamin F Voight91, Olle Melander92, Christopher J O’Donnell93, Veikko Salomaa94, Adamo Pio d’Adamo37, Antonella Fabretto95, Flavio Faletra95, Sheila Ulliy83,7, M Fabiola Del Greco38, Maurizio Facheris38, Francis S Collins96, Richard N Bergman97, John P Beilby98,99,100, Joseph Hung101,100, A William Musk100,102,103, Massimo Mangino41, So-Youn Shin80,41, Nicole Soranzo80,41, Hugh Watkins82,43, Anuj Goel42,43, Anders Hamsten104, Pierre Gider44, Marisa Loitfelder105, Marion Zeginig44, Dorota Nadalin106, Samer S Najjar107,108, Pau Navarro49, Sarah H Wild46, Anna Maria Corsi109, Andrew Singleton106, ECO JC de Gueus110, Gonneke Willemse110, Alex N Parker111, Lynda M Rose50, Brendan Buckley112, David Stott113, Marco Orru114, Manuela Uda114, LifeLines Cohort Study, Melanie M van der Klauw115, Weiheua Zhang5,54, Xinzhong Li5, James Scott116, Yi-Der Ida Chen55, Gregory L Burke117, Mika Kähönen118, Jorma Viikari119, Angela Döring120,121, Thomas Meitinger122,123, Gail Davies59, John M Starr58,124, Valur Emilsson15, Andrew Plump125, Janet H Lindeman126, Peter AC ’t Hoen127,128, Inke R König129, EchoGen consortium179, Janine F Felix20,4,130, Robert Clarke131, Jemma C Hopewell131, Halit Ongen42, Monique Breteler20, Stéphanie

Correspondence to: Martin D Tobin; Paul Elliott; Cornelia M van Duijn.

179 A list of consortium members is supplied in the Supplementary Note.

180 These authors contributed equally.

Competing Financial Interests
A.C. is managed by Johns Hopkins Medicine. I.B. and spouse own stock in Incyte Ltd and GlaxoSmithKline. A.N.P is an employee of Amgen. G.F.M. is owner of Cardiovascular Engineering, Inc, a company that designs and manufactures devices that measure vascular stiffness. The company uses these devices in clinical studies that evaluate the effects of diseases and interventions on vascular stiffness. V.M. is an employee of GlaxoSmithKline plc. A.Plump is an employee of Merck and Co, Inc.
Debette, Anita L DeStefano, Myriam Fornage, AortaGen Consortium, Gary F Mitchell, CHARGE Consortium, Heart Failure Working Group, Nicholas L Smith, KidneyGen consortium, Hilma Holm, Kari Stefansson, Gudmar Thorleifsson, Unnur Thorsteinsdottir, CKDG consortium, CardioGenics consortium, CardioGram, Niles J Samani, Michael Preuss, Igor Rudan, Caroline Hayward, Ian J Deary, E-Herich Wichmann, Olli T Raitakari, Walter Palmer, Jaspal S Kooner, Ronald P Stolk, J Wouter Jukema, Alan F Wright, Dorret I Boomsma, Stefania Bandinelli, Ulf B Gyllensten, James F Wilson, Luigi Ferrucci, Reinhold Schmidt, Martin Farrall, Tim D Spector, Lyle J Palmer, Jaakko Tuomilehto, Arne Pfeuf, Paolo Gasparini, David Siscovick, David Altschuler, Ruth JF Loos, Daniela Toniolo, Harold Snieder, Christian Gieger, Pierre Meneton, Nicholas J Wareham, Ben A Oostra, Andres Metspalu, Lenore Launer, Rainer Rettig, David P Strachan, Jacques S Beckmann, Jacqueline CM Witteman, Jeanette Erdmann, Ko Willems van Dijk, Eric Boerwinkle, Michael Boehnke, Paul M Ridker, Marjo-Riitta Jarvelin, Aravinda Chakravarti, Goncalo R Abecasis, Vilmundur Gudnason, Christopher Newton-Cheh, Daniel Levy, Patricia B Munroe, Bruce M Psaty, Mark J Caulfield, Dabeeru C Rao, Martin D Tobin, Paul Elliott, and Cornelia M van Duijn.

1Department of Health Sciences, University of Leicester, Leicester, UK 2Department of Genetics, University of Leicester, Leicester, UK 3Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands 4Netherlands Genomics Initiative (NGI)-sponsored Netherlands Consortium for Healthy Aging (NCHA) 5Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, UK 6Division of Biostatistics, Washington University in St. Louis, School of Medicine, Saint Louis, Missouri, USA 7Department of Genetics, Washington University in St. Louis, School of Medicine, Saint Louis, Missouri, USA 8Clinical Pharmacology and The Genome Centre, William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK 9Framingham Heart Study, Framingham, Massachusetts, USA 10National Heart, Lung and Blood Institute, Bethesda, Maryland, USA 11Institute of Social and Preventive Medicine (IUMSP), Centre Hospitalier Universitaire Vaudois, 1005 Lausanne, Switzerland 12University of Lausanne, Lausanne, Switzerland 13Department of Biostatistics, University of Washington, Seattle, Washington, USA 14Department of Human Genetics, Leiden University Medical Center, Leiden, the Netherlands 15Icelandic Heart Association, Kopavogur, Iceland 16University of Iceland, Reykjavik, Iceland 17Center for Complex Disease Genomics, McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA 18Institute of Social and Preventive Medicine, Lausanne University Hospital, Lausanne, Switzerland 19Cardiology, Department of Medicine, Geneva University Hospital, Geneva, Switzerland 20Department of Epidemiology, Erasmus University Medical Center, Rotterdam, The Netherlands 21Department of Mathematics, Boston University, Boston, Massachusetts, USA 22Genetics Division R&D, GlaxoSmithKline, King of Prussia, Pennsylvania, USA 23Division of Community Health Sciences, St George’s, University of London, London, UK 24Pediatric Epidemiology Center, University of South Florida, Tampa, Florida, USA 25Department of Internal Medicine B, Ernst-Moritz-Arndt-University Greifswald, Greifswald, Germany 26Cardiovascular Health Research Unit, Division of Internal Medicine, Department of Medicine, University of Washington, Seattle, Washington, USA 27Estonian Genome Center, University of Tartu, Tartu, Estonia 28Estonian Biocenter, Tartu, Estonia 29Institute of Molecular and Cell Biology, University of Tartu, Tartu, Estonia 30MRC Epidemiology Unit, Institute of Metabolic Science, Cambridge, UK 31Centre National de Génopuce, Commissariat à L’Energie Atomique, Institut de Génomique, Evry, France 32Unit of Genetic Epidemiology and Bioinformatics.
Department of Epidemiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands 33Department of Genetics, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands 34Division of Genetics and Cell Biology, San Raffaele Scientific Institute, Milano, Italy 35Center for Human Genetic Research, Cardiovascular Research Center, Massachusetts General Hospital, Boston, Massachusetts, USA 36Cardiovascular Epidemiology and Genetics, Institut Municipal d'Investigacio Medica, Barcelona Biomedical Research Park, Barcelona, Spain 37Medical Genetics IRCCS Burlo Garofolo/Università degli Studi di Trieste, Trieste, Italy 38Institute of Genetic Medicine, European Academy Bozen/Bolzano (EURAC), Bolzano, Italy, Affiliated Institute of the University of Lübeck, Lübeck, Germany 39Department of Biostatistics, Center for Statistical Genetics, University of Michigan, Ann Arbor, Michigan, USA 40Centre for Genetic Epidemiology and Biostatistics, University of Western Australia, Crawley, Western Australia, Australia 41Department of Twin Research and Genetic Epidemiology, King's College London, London, UK 42Department of Cardiovascular Medicine, The Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK 43Department of Cardiovascular Medicine, University of Oxford, John Radcliffe Hospital, Headington, Oxford, UK 44Institute of Molecular Biology and Biochemistry, Medical University Graz, Graz, Austria 45Clinical Research Branch, National Institute on Aging, Baltimore, Maryland, USA 46Centre for Population Health Sciences, University of Edinburgh, Edinburgh, UK 47Department of Genetics and Pathology, Rudbeck Laboratory, Uppsala University, Uppsala, Sweden 48NCA institute, Department of Biological Psychology, VU University, Amsterdam, The Netherlands 49MRC Human Genetics Unit, Institute of Genetics and Molecular Medicine, Western General Hospital, Edinburgh, UK 50Division of Preventive Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA 51Harvard Medical School, Boston, Massachusetts, USA 52Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands 53Department of Gerontology and Geriatrics, Leiden University Medical Center, Leiden, The Netherlands 54Ealing Hospital NHS Trust, Middlesex, UK 55Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles, California, USA 56Department of Clinical Chemistry, University of Tampere and Tampere University Hospital, Tampere, Finland 57Institute of Genetic Epidemiology, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany 58Centre for Cognitive Ageing and Cognitive Epidemiology, The University of Edinburgh, Edinburgh, Edinburgh, UK 59Department of Psychology, The University of Edinburgh, Edinburgh, UK 60Department of Public Health, Medical School, University of Split, Split, Croatia 61Department of Pharmacology, Medical School, University of Split, Split, Croatia 62Department of Cardiovascular Sciences, University of Leicester, Glenfield Hospital, Leicester, UK 63Division of Epidemiology, Human Genetics and Environmental Sciences, School of Public Health, University of Texas at Houston Health Science Center, Houston, Texas, USA 64Department of Internal Medicine, Division of Cardiovascular Medicine, University of Michigan Medical Center, Ann Arbor, Michigan, USA 65Center for Population Studies, National Heart Lung, and Blood Institute, Bethesda, Maryland, USA 66Division of Epidemiology and Prevention, Boston University School of Medicine, Boston, Massachusetts, USA 67Division of Cardiology, Massachusetts General Hospital, Boston, Massachusetts, USA 68Département de Génétique Médicale, Université de Lausanne, Lausanne, Switzerland 69Swiss Institute of Bioinformatics, Lausanne, Switzerland 70Department of Internal Medicine, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland 71Finnish Institute of Occupational Health, Oulu, Finland 72National Institute for Health and Welfare, Oulu, Finland 73Department of Physiatrics, Lapland Central Hospital, Rovaniemi, Finland 74ALSPAC Laboratory, Department of Social Medicine, University of Bristol, Bristol, UK 75Institute of Pharmacology, Ernst-Moritz-Arndt-University Greifswald, Greifswald, Germany 76Institute for Genetics and Functional Genomics, Ernst-Moritz-Arndt-University Greifswald, Greifswald, Germany 77Institute for Community Medicine, Ernst-Moritz-Arndt-University Greifswald, Greifswald, Germany 78Section of Preventive Medicine and Epidemiology, Department of Medicine, Boston University School of Medicine, Boston,
Massachusetts, USA 79National Institute of Aging’s Laboratory for Epidemiology, Demography and Biometry, Bethesda, Maryland, USA 80Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge, UK 81University of Cambridge Metabolic Research Labs, Institute of Metabolic Science, Addenbrooke’s Hospital, Cambridge, UK 82Department of Public Health and Primary Care, Institute of Public Health, University of Cambridge, Cambridge, UK 83U557 Institut National de la Santé et de la Recherche Médicale, Paris, France 84U1125 Institut National de la Recherche Agronomique, Paris, France 85Université Paris 13, Bobigny, France 86Department of Statistics, Pontificia Universidad Catolica de Chile, Santiago, Chile 87Department of Psychiatry/EMGO Institute/Neuroscience Campus, VU University Medical Centre, Amsterdam, The Netherlands 88Department of Psychiatry, Leiden University Medical Centre, Leiden, The Netherlands 89Department of Psychiatry, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands 90Department of Clinical Sciences, Diabetes and Endocrinology Research Unit, Lund University, University Hospital Malmö, Malmö, Sweden 91Program in Medical and Population Genetics, Broad Institute of Harvard and MIT, Cambridge, Massachusetts, USA 92Department of Clinical Sciences, Hypertension and Cardiovascular Diseases, University Hospital, Malmö, Lund University, Malmö 20502, Sweden 93National Heart, Lung and Blood Institute and its Framingham Heart Study, 73 Mount Wayte Ave., Suite 94Department of Chronic Disease Prevention, THL-National Institute for Health and Welfare, Helsinki, Finland 95IRCSS Burlo Garofolo Medical Genetics, Trieste, Italy 96National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland, USA 97Department of Physiology and Biophysics, Keck School of Medicine, University of Southern California, Los Angeles, California, USA 98Pathology and Laboratory Medicine, University of Western Australia, Crawley, Western Australia, Australia 99Molecular Genetics, PathWest Laboratory Medicine, Nedlands, Western Australia, Australia 100Busselton Population Medical Research Foundation, Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia 101School of Medicine and Pharmacology, University of Western Australia, Crawley, Western Australia, Australia 102School of Medicine and Pharmacology, University of Western Australia, Crawley, Western Australia, Australia 103Department of Respiratory Medicine, Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia 104Atherosclerosis Research Unit, Department of Medicine, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden 105Department of Neurology Section of Special Neurology, Medical University Graz, Graz, Austria 106National Institute of Aging’s Laboratory of Neurogenetics, Bethesda, Maryland, USA 107Laboratory of Cardiovascular Science, Intramural Research Program, National Institute on Aging, NIH, Baltimore, Maryland, USA 108Cardiovascular Research Institute, MedStar Health Research Institute, Washington Hospital Center, Washington DC, USA 109Tuscany Regional Health Agency, Florence, Italy 110EMGO+ institute, Department of Biological Psychology, VU University, Amsterdam, The Netherlands 111Amgen, Cambridge, Massachusetts, USA 112Department of Pharmacology and Therapeutics, University College Cork, Cork, Ireland 113Institute of Cardiovascular and Medical Sciences, School of Medicine, University of Glasgow, UK 114Istituto di Neurogenetica e Neurofarmacologia, Consiglio Nazionale delle Ricerche, Monserrato, Italy 115Department of Endocrinology, University Medical Center Groningen, University of Groningen, The Netherlands 116National Heart and Lung Institute, Imperial College London, Hammersmith Hospital, London, UK 117Division of Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA 118Department of Clinical Physiology, University of Tampere and Tampere University Hospital, Tampere, Finland 119Department of Medicine, University of Turku and Turku University Hospital, Turku, Finland 120Institute of Epidemiology I, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany 121Institute of Epidemiology II, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany 122Institute of Human Genetics, Helmholtz Zentrum München, German Research Centre for Environmental Health, Neuherberg, Germany 123Institute of Human Genetics, Technische Universität München,
Munich, Germany 124Geriatric Medicine Unit, The University of Edinburgh, Royal Victoria, Edinburgh, UK 125Cardiovascular Disease Franchise, Merck Research Laboratory, Rahway, New Jersey, USA 126Department of Vascular Surgery, Leiden University Medical Center, Leiden, The Netherlands 127Department of Human Genetics, Leiden University Medical Center, Leiden, The Netherlands 128Leiden Genome Technology Center, Leiden University Medical Center, Leiden, The Netherlands 129Institut für Medizinische Biometrie und Statistik, Universität zu Lübeck, Lübeck, Germany 130German Cancer Research Center, Division of Clinical Epidemiology and Aging Research, Heidelberg, Germany 131Clinical Trial Service Unit and Epidemiological Studies Unit, University of Oxford, Oxford, UK 132Department of Neurology, Boston University School of Medicine, Boston, Massachusetts, USA 133Boston University School of Public Health, Boston, Massachusetts, USA 134Brown Foundation Institute of Molecular Medicine and Human Genetics Center, University of Texas Health Science Center at Houston, Houston, Texas, USA 135Cardiovascular Engineering, Inc., Norwood, Massachusetts, USA 136Department of Epidemiology, University of Washington, Seattle, Washington, USA 137Seattle Epidemiologic Research and Information, Center of the Department of Veterans Affairs Office of Research and Development, Seattle, Washington, USA 138Group Health Research Institute, Group Health Cooperative, Seattle, Washington, USA 139deCODE genetics Inc, Reykjavik, Iceland 140Faculty of Medicine, University of Iceland, Reykjavik, Iceland 141Leicester NIHR Biomedical Research Unit in Cardiovascular Disease, Glenfield Hospital, Leicester, UK 142Medizinische Klinik II, Universität zu Lübeck, Lübeck, Germany 143Croatian Centre for Global Health, University of Split Medical School, Split, Croatia 144Institute of Medical Informatics, Biometry and Epidemiology, Ludwig-Maximilians-Universität und Klinikum Grosshadern, Munich, Germany 145Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku and the Department of Clinical Physiology, Turku University Hospital, Turku, Finland 146Columbia University, New York, New York, USA 147Department of Epidemiology, University Medical Center Groningen, University of Groningen, The Netherlands 148Durrer Center for Cardiogenetic Research, Amsterdam, The Netherlands 149Interuniversity Cardiology Institute of the Netherlands, Utrecht, the Netherlands 150Geriatric Unit, Azienda Sanitaria Firenze (ASF), Florence, Italy 151Ontario Institute for Cancer Research, Toronto, Canada 152Samuel Lunenfeld Research Institute, Toronto, Canada 153National Institute for Health and Welfare, Diabetes Prevention Unit, Helsinki, Finland 154Hjelt Institute, Department of Public Health, University of Helsinki, 00014 Helsinki, Finland 155South Ostrobothnia Central Hospital, Seinäjoki, Finland 156Institute of Human Genetics, Klinikum rechts der Isar der Technischen Universität München, Munich, Germany 157Institute of Human Genetics, Helmholtz Zentrum München, Neuherberg, Germany 158Department of Medicine, University of Washington, Seattle, Washington, USA 159Department of Medicine, Harvard Medical School, Boston, Massachusetts, USA 160Department of Genetics, Harvard Medical School, Boston, Massachusetts, USA 161Diabetes Unit, Massachusetts General Hospital, Boston, Massachusetts, USA 162Institute of Molecuar Genetics_CNR, Pavia, Italy 163I872 Institut National de la Santé et de la Recherche Médicale, Centre de Recherche des Cordeliers, Paris, France 164Department of Clinical Genetics, Erasmus University Medical Center, Rotterdam, The Netherlands 165National Institute of Aging’s Laboratory for Epidemiology, Demography and Biometry, Bethesda, Maryland, USA 166Institute of Physiology, Ernst-Moritz-Arndt-University Greifswald, Greifswald, Germany 167Service of Medical Genetics, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland 168Department of Internal Medicine, Leiden University Medical Center, Leiden, the Netherlands 169Human Genetics Center, Houston, Texas, USA 170Division of Cardiology, Brigham and Women’s Hospital, Boston, Massachusetts, USA 171Department of Biostatistics and Epidemiology, School of Public Health, Imperial College London, Norfolk Place, London, UK 172Institute of Health Sciences, University of Oulu, University of Oulu, Finland 173Biocenter, University of Oulu, Oulu, Finland 174Department of Health Services, University of Washington, Seattle, Washington, USA 175Department of Psychiatry, Washington University in St. Louis, School of Medicine, Saint Louis, Missouri, USA 176Department of Mathematics, Washington
Abstract

Numerous genetic loci influence systolic blood pressure (SBP) and diastolic blood pressure (DBP) in Europeans. We now report genome-wide association studies of pulse pressure (PP) and mean arterial pressure (MAP). In discovery (N=74,064) and follow-up studies (N=48,607), we identified at genome-wide significance (P=2.7×10^{-8} to P=2.3×10^{-13}) four novel PP loci (at 4q12 near CHIC2/PDGFRAI, 7q22.3 near PIK3CG, 8q24.12 in NOV, 11q24.3 near ADAMTS-8), two novel MAP loci (3p21.31 in MAP4, 10q25.3 near ADRB1) and one locus associated with both traits (2q24.3 near FIGN) which has recently been associated with SBP in east Asians. For three of the novel PP signals, the estimated effect for SBP was opposite to that for DBP, in contrast to the majority of common SBP- and DBP-associated variants which show concordant effects on both traits. These findings indicate novel genetic mechanisms underlying blood pressure variation, including pathways that may differentially influence SBP and DBP.

High blood pressure is a major risk factor for coronary heart disease and stroke. Large genome-wide association studies in Europeans have reported 29 novel loci for systolic and diastolic blood pressure (SBP and DBP) where alleles have effect sizes of up to 0.5-1mm Hg. Even small increments in blood pressure levels have important effects on cardiovascular morbidity and mortality at the population level. We undertook a genome-wide association study of two further blood pressure phenotypes, pulse pressure (PP, the difference between SBP and DBP), a measure of stiffness of the main arteries, and mean arterial pressure (MAP), a weighted average of SBP and DBP. Both PP and MAP are predictive of hypertension and cardiovascular disease.

This study was undertaken by the International Consortium of Blood Pressure Genome-Wide Association Studies (ICBP-GWAS) which aims to further the understanding of the genetic architecture underlying blood pressure. The initial publication by this consortium studied SBP and DBP with discovery GWAS among 69,395 people and a combined sample of ~200,000 Europeans. The two blood pressure phenotypes reported here, namely PP and MAP, were not previously analysed. All but one study that was included in the discovery GWAS of the study of SBP and DBP were included in the discovery GWAS stage of this study. In addition, a further 6 studies not included in the previous study were included here bringing our discovery GWAS sample size to 74,064.

We first conducted a genome-wide association meta-analysis of PP and MAP in 74,064 individuals of European ancestry from 35 studies (Supplementary Table 1A). Genotypes were imputed using HapMap. To account for effects of anti-hypertensive treatments, we imputed underlying SBP and DBP by adding a constant to each. Associations were adjusted for age, age^{2}, sex and body mass index. We combined results across studies using an inverse variance weighted meta-analysis and, to correct for residual test statistic inflation, applied genomic control (GC) both to study-level association statistics and to the meta-analysis (λ_{GC}=1.08 for PP, λ_{GC}=1.12 for MAP). The QQ plots show an excess of extreme values largely accounted for by a modest number of genomic regions (Supplementary Figures 1 (a) – (b)). Independent follow-up analyses were performed in 48,607 individuals of European ancestry (Online Methods and Supplementary Note).

SNPs in 12 regions showed genome-wide significant association (P<5×10^{-8}) with either PP or MAP in our discovery data (Stage 1) (Supplementary Figures 1 (c) – (d)), including two
novel regions for PP (7q22.3 near \( \text{PIK3CG} \), \( P=1.2 \times 10^{-10} \) and 11q24.3 near \( \text{ADAMTS8} \), \( P=8.5 \times 10^{-11} \); Table 1) and 10 regions previously associated with SBP and DBP (Supplementary Table 2A for PP, Supplementary Table 2B for MAP)\(^1-3\). For follow-up in a series of independent cohorts we selected 99 SNPs comprising those with \( P<1 \times 10^{-5} \) for either PP or MAP and SNPs reported in recent large genome-wide association studies of SBP and DBP\(^1-3\) to evaluate their effects on PP and MAP (Stage 2: Online Methods, Supplementary Note).

After meta-analysis of the Stage 1 and Stage 2 data (Supplementary Table 2C), the two novel regions showing genome-wide association with PP after Stage 1 (near \( \text{PIK3CG} \) and near \( \text{ADAMTS8} \)) remained genome-wide significant. In addition, we found genome-wide significant associations for SNPs at two further novel loci for PP (at 4q12 near \( \text{CHIC2/ PDGFR\( \alpha \)} \) and 8q24.12 in \( \text{NOV} \)), two novel loci for MAP (3p21.31 in \( \text{MAP4} \), 10q25.3 near \( \text{ADRB1} \)), and one locus for both traits (2q24.3 near \( \text{FIGN} \)) (Table 1 and Figure 1) which has not previously shown an association with SBP or DBP in Europeans but which has recently been associated with SBP in east Asians (see Supplementary Note)\(^11\). Forest plots of the Stage 1 effect sizes and standard errors are shown in Supplementary Figure 2. The novel signals for MAP were strongly associated with both SBP and DBP (\( P=7.7 \times 10^{-7} \) to \( P=1.8 \times 10^{-12} \)), reflecting the high inter-correlations among these three blood pressure traits\(^12,13\). For the sentinel SNPs in three of the novel PP loci, the estimated effects on SBP were in the opposite direction to the effects on DBP (Table 1, Figure 2, Supplementary Tables 2D and 2E). Our findings show that analyses of PP and MAP reveal loci influencing blood pressure phenotypes which may not be detectable by studying SBP and DBP separately. Identification of novel genetic associations could help inform understanding about possible distinct mechanisms underlying relationships of PP with vascular risk\(^14,15\).

Five additional loci for PP and 19 loci for MAP reaching genome-wide significance (\( P<5 \times 10^{-8} \), Stage 1 and Stage 2 combined) were recently shown to be associated with SBP/DBP\(^1-3\) (Supplementary Tables 2A and 2B). We used sentinel SNPs from both the novel and known regions showing genome-wide significant associations with PP or MAP in the combined Stage 1 and 2 data to create weighted risk scores for: i) PP (10 independent SNPs) and; ii) MAP (22 SNPs) (Supplementary Table 2F). We studied the associations of both risk scores with hypertension and blood pressure related outcomes including coronary heart disease, heart failure, stroke, echocardiographic measures of left ventricular structure, pulse wave velocity, renal function and renal failure. Adjusting for multiple testing for the 12 traits evaluated (\( P<0.05/12=4.1 \times 10^{-3} \)), the PP SNP risk score was associated with prevalent hypertension (\( P=7.9 \times 10^{-6} \)), incident stroke (\( P=4.9 \times 10^{-4} \)) and coronary heart disease (\( P=4.3 \times 10^{-4} \)), and the MAP SNP risk score was associated with hypertension (\( P=5.1 \times 10^{-16} \)), coronary heart disease (\( P=4.0 \times 10^{-20} \)), stroke (\( P=0.0019 \)) and left ventricular wall thickness (\( P=2.1 \times 10^{-4} \)) (Supplementary Table 3A), confirming the clinical relevance of these measures of blood pressure phenotype\(^8,9\). For a range of blood pressure related outcomes (see Supplementary Note), we compared \( P \) values for the PP risk score and a series of 1000 permutations of SBP risk scores, each based on 10 of the 26 blood pressure SNPs associated with SBP but not PP, constraining the selection of SNPs to have similar sized effects for SBP as those of the 10 PP SNPs. The PP risk score had a significantly (\( P<0.05 \)) greater association with risk of ischemic stroke than the SBP risk score (Supplementary Note and Supplementary Table 3B).

None of the genes in the identified novel regions is a strong candidate for blood pressure regulation, although several are implicated in mechanisms that may influence blood pressure. The most significant association with PP is within a putative mRNA clone (AF086203) spanning \(-13.7\)kb at 7q22.3, 94kb upstream of \( \text{PIK3CG} \) (rs17477177, \( P=2.3 \times 10^{-13} \), Table 1 and Figure 1a). \( \text{PIK3CG} \) encodes the phosphoinositide-3-kinase,
catalytic, gamma polypeptide protein which phosphorylates phosphoinositides and modulates extracellular signals. This region was earlier associated with mean platelet volume, platelet count, and platelet aggregation\textsuperscript{16-18}, but the sentinel SNPs reported in those studies are independent of SNP rs17477177 reported here ($r^2<0.01$). Mice lacking the catalytic subunit of PI3K\textsubscript{γ} have shown resistance to SBP-lowering effects of beta-adrenergic receptor agonists\textsuperscript{19}; PI3K\textsubscript{γ} activity is increased in the failing human heart and associated with down-regulation of beta-adrenergic receptors in the plasma membrane\textsuperscript{20}.

The second locus for PP located at 11q24.3 spans 35.5kb with the top-ranking SNP (rs1122084, $P=1.9\times10^{-11}$, Figure 1b) lying 1.6kb downstream of \textit{ADAMTS-8}. This gene is highly expressed in macrophage-rich areas of human atherosclerotic plaques and may affect extracellular matrix remodeling\textsuperscript{21}. The third locus for PP spans 28.5kb at 8q24.12 with the sentinel SNP (rs2071518, $P=3.7\times10^{-9}$, Figure 1c) located in the 3’UTR of \textit{NOV} which encodes the nephroblastoma overexpressed (CCN3) protein, associated with angiogenesis, proliferation, and inhibition of vascular smooth muscle cell growth and migration\textsuperscript{22}, and with reduced neointimal thickening in mice null for CCN3\textsuperscript{23}. Mice with mutations in \textit{NOV} that truncate the NOV protein exhibit abnormal cardiac development\textsuperscript{24}. Of the genes evaluated for expression in human aortic samples at the novel PP loci, \textit{NOV} showed by far the highest expression levels (Supplementary Note and Supplementary Figure 3).

For MAP we identified two novel loci. The first locus for MAP is at 10q25.3, 22.3kb upstream of \textit{ADRB1} (rs2782980, $P=2.5\times10^{-9}$, Figure 1e). \textit{ADRB1} encodes the beta-1-adrenergic receptor, which mediates the effects of the stimulatory G protein and cAMP/protein kinase A pathway to increase heart rate and myocardial contraction. Polymorphisms in this gene have been associated with resting heart rate, response to beta-blockers\textsuperscript{27}, and hypertension\textsuperscript{28}. \textit{ADRB1} knockout mice have no difference in heart rate or blood pressure compared with the wild type but do exhibit a significant reduction in the response of both phenotypes to catecholamines\textsuperscript{29}. SNP rs2782980 is associated with expression of an \textit{ADRB1} transcript in brain tissue (Supplementary Note and Supplementary Figure 4A). The second locus for MAP spans over 300kb at 3p21.31 with the top-ranking SNP (rs319690, $P=2.7\times10^{-8}$, Figure 1f) lying within an intron of the microtubule associated protein 4 gene, \textit{MAP4}. Coating of microtubules by MAP4 may inhibit beta adrenergic receptor recycling and number, as seen in cardiac hypertrophy and failure\textsuperscript{30}. \textit{MAP4} was detectably expressed in human aortic samples (Supplementary Note and Supplementary Figure 3).

The locus associated both with PP (SNP rs13002573, $P=1.8\times10^{-8}$, Figure 1g) and MAP (rs1446468, $P=6.5\times10^{-12}$, Figure 1h) is in an intergenic region spanning ~280kb at 2q24.3. Although the two signals are ~50kb apart and statistically independent ($r^2=0.075$), rs13002573 is highly correlated ($r^2=1$ in HapMap CEU population, $r^2=0.87$ in HapMap JPT +CHB) with rs16849225 which has recently been reported as showing association with SBP in a GWAS of 19,608 subjects of east Asian origin with follow-up in a further 30,765 individuals (combined result: $P=3.5\times10^{-11}$)\textsuperscript{11} (see Supplementary Note). In our combined dataset in 116,998 Europeans, the association $P$ value for rs13002573 with SBP was $P=3.25\times10^{-7}$. The top PP SNP lies ~320kb upstream of \textit{FIGN} and ~430kb downstream of \textit{GRB14} (growth factor receptor-bound protein 14). Relatively little is known regarding \textit{FIGN} (fidgetin).
We report six novel loci associated with PP and MAP based on genome-wide discovery and follow-up in over ~120,000 individuals, and a further locus (near FIGN) not previously reported in Europeans. Our results expand knowledge of the genetic architecture of blood pressure and PP regulation and may give clues as to possible novel targets for blood pressure therapies.

**Online Methods**

Pulse pressure was defined as systolic minus diastolic pressure and MAP as 2/3 diastolic plus 1/3 systolic pressure. A two-staged analysis was used to discover genes associated with PP and MAP.

**Stage 1 samples and analyses**

Stage 1 was a meta-analysis of directly genotyped and imputed SNPs from population-based or control samples from case-control studies, in the International Consortium of Blood Pressure Genome-wide Association Studies (ICBP-GWAS). The characteristics of the 35 studies, including demographics, genotyping arrays, quality control filters and statistical analysis methods used are listed in Supplementary Tables 1A and 1B. Imputation of allele dosage of ungenotyped SNPs in HapMap CEU v21a or v22 was carried out by each of the studies using MACH\(^{31}\), IMPUTE\(^{32}\) or BIMBAM\(^{33}\) with parameters and pre-imputation filters as specified in Supplementary Table 1B. SNPs were excluded from analysis if the study-specific imputation quality (r\(^2\)hat in MACH or .info in IMPUTE) was <0.3. In total, up to 2652054 genotyped or imputed autosomal SNPs were analyzed. Full details of the models, methods, and corrections for antihypertensive treatment are provided in the Supplementary methods. All analyses assumed an additive genetic model and were adjusted for sex, age, age\(^2\), body mass index and ancestry principal components. In related individuals, regression methods that account for relatedness were applied. All study-specific effect estimates and coded alleles were oriented to the forward strand of the HapMap release 22 with the alphabetically higher allele as the coded allele. To capture loss of power due to imperfect imputation, we estimated “N effective” as the sum of the study-specific products of the imputation quality metric and the sample size. No filtering on minor allele frequency was done. Genomic control was carried out on study-level data and inverse variance weighting was used for meta-analysis of Stage 1. The meta-analysis results were subject to genomic control. Lambda estimates are given in Supplementary Table 1A.

**Selection of SNPs for Stage 2**

We aimed in Stage 2 to follow up SNPs which had evidence of association with PP or MAP and, for completeness, to evaluate the effects on PP and MAP of SNPs reported in recent large genome-wide association studies of SBP and DBP\(^{1-3}\). All SNPs with P<1×10\(^{-5}\) for association with either PP or MAP (or both) were divided into independent regions based on LD and the most significant SNP was selected from each region. Within the FIGN region, different SNPs were associated with PP and with MAP and both SNPs were followed up in Stage 2. For SNPs with an N effective ≤75% of total N, a proxy was also included if it had P ≤1×10\(^{-5}\) and an r\(^2\)>0.6 with the top SNP (this occurred for one SNP). For all regions that had previously shown association with SBP or DBP\(^{1-3}\), the sentinel SNP for PP and MAP and the previously reported SNP for SBP and DBP were followed up. In all, 99 SNPs were followed up in Stage 2 (Supplementary Note), comprising: 44 SNPs from 22 loci with PP or MAP associations (P<1×10\(^{-5}\)) in Stage 1 data and with previously reported SBP or DBP associations; 47 SNPs from 45 loci with PP or MAP associations (P<1×10\(^{-5}\)) in Stage 1 data only and; 8 SNPs from 7 loci with previously reported SBP or DBP associations and no association (P≥1×10\(^{-5}\)) with PP or MAP in the Stage 1 data.
Stage 2

The characteristics of the Stage 2 studies, including the genotyping and imputation approaches, are described in Supplementary Tables 1A and 1B and the details of corrections for treatment described in the Supplementary Note. For the 99 SNPs selected for follow-up, the Stage 2 studies followed the analysis approach adopted in the Stage 1 analyses. Meta-analysis was done using the inverse variance weights method.

Pooled analysis of first and second stage samples

Meta-analysis from stages 1 and 2 was conducted using inverse variance weighting and genomic control applied. A threshold of $5 \times 10^{-8}$ was taken for genome-wide significance.

Calculation of risk scores

We calculated risk scores based on the most significantly associated SNP from all regions which were genome-wide significant after meta-analysis of Stages 1 and 2 for i) PP (10 SNPs) and ii) MAP (22 SNPs) (Supplementary Table 2F). Each risk score was constructed using an approach described in the Supplementary Note and was tested for association with hypertension, coronary artery disease, stroke, hypertension, chronic kidney disease, heart failure, microalbuminuria, and with continuous traits left ventricular mass, left ventricular wall thickness, pulse wave velocity, serum creatinine, eGFR and urinary albumin:creatinine ratio (Supplementary Table 3).

Additional analyses

Identification of potentially functional SNPs in LD with the reported sentinel SNPs, eQTL analyses and expression analyses in human aortic samples were also carried out as discussed in the Supplementary Note and Supplementary Figures 3 and 4.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

A number of the participating studies and authors are members of the CHARGE and Global BPgen consortia. Many funding mechanisms by NIH/NHLBI, European, and private funding agencies contributed to this work and a full list is provided in the Supplementary Note.

Contributions

ICBP-GWAS PP/MAP Working and Writing Sub-Group (alphabetical order) M.J.C., P.E. (co-chair), T.J., P.B.M., P.F.O’R., M.D.T. (co-chair), C.M.V. (co-chair), G.C.V., L.V.W. ICBP-GWAS Steering Committee (alphabetical order) G.R.A., M.Bochud, M.Boehnke, M.J.C. (co-chair), A.C., G.B.E., P.E., T.B.H., M-R.J., A.D.J., T.J., M.G.L., L.L., D.L. (co-chair), P.B.M.(co-chair), C.N-C. (co-chair), B.M.P., K.M.R., A.V.S., M.D.T., C.M.V., G.C. V. Analysis L.V.W., G.C.V., P.F.O’R., T.J. Expression analyses V.E., P.H., A.D.J., D.L., J.H.L., C.P.N, A.Plump, P.A.C’t H., K.W.V. Cohort contributions (alphabetical order): Study concept/design: AGES: T.A., V.G., T.B.H., L.L., A.V.S., AortaGen Consortium: G.F.M., ARIC: E.B., A.C., S.K.G., ASPS: H.Schmidt, R.S., BLSA: L.F., B58C-T1DGC: D.P.S., B58C-WTCCC: D.P.S., BHS: L.J.P., CardioGram Consortium: N.J.S., C4D Consortium: R.Clarke, R.Collins, CHS: J.C.B., N.L.G., B.M.P., K.M.R., K.D.T., CHARGE Consortium Heart Failure Working Group: N.L.S., CoLaus: V.M., P.Vollenweider, G.Waebcr, CROATIA-Korcula: C.H., CROATIA-Split: M.Boban, I.R., CROATIA-Vis: A.F.W., DeCode Genetics: H.H., K.S., G.T., U.T., DGI controls: D.A.
L.G., C.N-C., ENGAGE: J.E., I.R.K., EGUCUT: H.A., A.M., EPIC: K-T.K., ERF: B.A.O., Fenland: N.J.W., FUSION: M.Boehnke, F.S.C., R.N.B., J.T., INGI CARL: A.P.d'A., P.Gasparini, INGI-FVG: A.P.d'A., P.Gasparini, INCHIANTI: S.Bandinelli., Y.M., KORA S3: C.G., M.Laan, E.O., KORA F4: T.M, H-E.W., LifeLines: R.P.S., M.M.V., LOLIPOP: J.C.C., P.E., J.S.K., LBC1921/LBC1936: I.J.D., J.M.S., MICROs: A.Pfeufer, MESA: X.G., W.P., MiGen controls: O.M., C.J.O., V.S., D.Siscovick, NESDA: B.W.P., H.Snieder, NEURO-CHARGE Consortium: M.Breteler M.Fornage, NFBC1966: M-R.J, B.S.N., NSPHS: U.B.G., S.E.H., NTR: D.I.B., E. J.C. deG., ORCADES: H.C., J.F.W., PROCARDIS controls: M.Farrall, A.Hamsten, J.F.W., PROSPER: PHASE: B.B., J.W.J., D.Stott, RSI/RSII/RSIII: A. Hofman, C. M.V., SardiNIA: G.A., M.U., SHIP: M.D., H.K.K., R.R., U. V., H.V., SUVIMAX: P.Gilan, S.Herberg, P.M., TwinsUK: T.D.S., WGHS: P.M.R., YFS: M.K., T.L., O.T.R., J.V. Phenotype data acquisition/QC: AGES: T.A., V.G., T.B.H., L.L., ARIC: A.C., S.K.G., A.C.M, D.C.R., ASPS: M.Bochud, M.V., BLSA: S.N., B58C-T1DGC: D.P.S., B58C-WTCCC: D.P.S., BHS: J.P.B., J.H., C4D Consortium: R.Clarke, R.Collins, J.C.H., CHS: B.M.P., CoLaus: M.Bochud, V.M., P.Vollenweider, CROATIA-Korcula: C.H., O.P., CROATIA-Split: M.Boban, I.R., DGI controls: L.G., C.N-C., EGUCUT: H.A., A.K., A.M., M.L.T., EPIC: N.J.W., Fenland: N.J.W., FHS: S.-J.H., M.G.L., D.L., R.S.V., T.J.W., FUSION: I.T., INGI CARL: A.F., F.F., P.Gasparini, S.U., INGI FVG: A.F., F.F., P.Gasparini, S.U., INGI-Val Borbera: C.Masciullo, C.S., D.T., INCHIANTI: A.M.C., KORA S3: C.G., KORA F4: A.D., LifeLines: M.M.V., LOLIPOP: J.C.C., J.S.K., J.S., LBC1921/LBC1936: I.J.D., J.M.L., J.M.S., MICROs: M.Facheris, A.Pfeufer, MESA: X.G., W.P., MiGen controls: G.L., O.M., C.J.O., V.S., D.Siscovick, NESDA: X.Lu, I.M.N., B.W.P., H.Snieder, NEURO-CHARGE Consortium: M.Breteler, S.D., A.L.D., M.Fornage, NFBC1966: P.E., M.R-J., J.Laitinen, A.Pouta, P.Z., NSPHS: J.A.C, U.B.G., S.E.H., P.J.T., NTR: D.I.B., E.J.C.deG., G.Willemsen, ORCADES: S.H.W., J.F.W., PROCARDIS controls: J.F.P., PROSPER/PHASE: D.Stott, S.T., RSI/RSII/RSIII: F.U.S.M.R., E.J.G.S., C.M.V., G.C.V., J.C.W., SardiNIA: M.O., M.U., SHIP: M.D., R.R., H.V., SUVIMAX: P.Gilan, M.Lathrop, TwinsUK: T.D.S., WGHS: D.I.C., A.N.P., YFS: M.K., T.L., O.T.R., J.V. Genotype data acquisition/QC: AGES: A.V.S., ARIC: A.C., G.B.E., S.K.G., A.C.M., D.C.R, G.S., ASPS: P.Gider, H. Schmidt, M.Z., BLSA: D.Hernandez, B58C-T1DGC: S.Heath, W.L.Mca., B58C-WTCCC: W.L.Mca., BHS: J.P.B., J.R.W., C4D Consortium: J.C.H., H.O., CHS: J.C.B., N.L.G., K.D.T., CoLaus: V.M., P.Vollenweider, CROATIA-Korcula: C.H., O.P., CROATIA-Split: I.R., CROATIA-Vis: V.V., DGI controls: D.A., B.F.V., EGUCUT: T.E., T.H., EPIC: N.J.W., Fenland: R.J.F.L., J.Luan, N.J.W., FHS: S.-J.H., M.G.L., D.L., R.S.V., T.J.W., FUSION: F.S.C., INGI CARL: A.P.d'A., INGI FVG: A.P.d'A., INGI Val Borbera: C.Masciullo, C.S., D.T., INCHIANTI: A.S., KORA S3: C.G., KORA F4: T.M, H-E.W., LifeLines: B.Z.A., LOLIPOP: J.C.C., J.S.K., J.S., W.Z., LBC1921/LBC1936: G.D., I.J.D., MICROs: I.P., MESA: X.G., MiGen controls: G.L., O.M., C.J.O., V.S., D.S., NESDA: J.F., X.Lu, I.M.N., B.W.P., H.Snieder, NFBC1966: P.E., M.R-J., J.Laitinen, P.Z., NSPHS: J.P.T., NTR: D.I.B., E.J.C.deG., J.J.H., G.Willemsen, ORCADES: H.C., J.F.W., PROCARDIS controls: A.G., J.F.P., PROSPER/PHASE: S.T., RSI/RSII/RSIII: F.R., A.G.U., SardiNIA: G.A., SHIP: H.K.K., U.V., H.V., SUVIMAX: S.Heath, M.Lathrop, TwinsUK: M.M., S.-Y.S.N.S., F.Z., WGHS: P.M.R., YFS: T.L., O.T.R. Data analysis: AGES: T.A., A.V.S, ARIC: A.C., G.B.E., A.C.M., V.P., D.C.R, G.S., ASPS: P.Gider, H. Schmidt, M.Z., BLSA: T.T. B58C-T1DGC: D.P.S., B58C-WTCCC: D.Hadley, D.P.S., BHS: W.A.M., L.I.P., J.R.W., C4D Consortium: J.C.H., H.O., CHS: J.C.B., N.L.G., K.M.R., CoLaus: S.Bergmann, M.Bochud, TJ., CROATIA-Korcula: C.H., O.P., CROATIA-Split: C.H., CROATIA-Vis: V.V., DGI controls: P.A., C.N-C., B.F.V., EchoGen Consortium: J.F.F., EGUCUT: T.E., T.H., ENGAGE: M.P., EPIC: I.B., R.J.F.L., N.J.W., J.H.Z., ERF: A.C.J.W.J., Y.A., Fenland: R.J.F.L., J.Luan., FHS: S.-J.H., M.G.L., FUSION: A.U.J., INGI CARL: N.P., INGI FVG: N.P., INGI Val Borbera: T.C., G.P., C.S., D.T., Nat Genet. Author manuscript; available in PMC 2012 September 18.
References

1. Ehret G, et al. Genetic Variants in Novel Pathways Influence Blood Pressure and Cardiovascular Disease Risk. Nature. 2011
2. Levy D, et al. Genome-wide association study of blood pressure and hypertension. Nat Genet. 2009; 41:677–87. [PubMed: 19430479]
3. Newton-Cheh C, et al. Genome-wide association study identifies eight loci associated with blood pressure. Nat Genet. 2009; 41:666–76. [PubMed: 19430483]
4. Lawes CM, et al. Blood pressure and the global burden of disease 2000. Part II: estimates of attributable burden. J Hypertens. 2006; 24:423–30. [PubMed: 16467640]
5. Rose, G. Strategies of prevention: the individual and the population. In: Marmot, M.; E, P., editors. Coronary heart disease epidemiology: From aetiology to Public health. Oxford University Press; Oxford: 2005. p. 631-41.
6. Domanski MJ, et al. Independent prognostic information provided by sphygmomanometrically determined pulse pressure and mean arterial pressure in patients with left ventricular dysfunction. J Am Coll Cardiol. 1999; 33:951–8. [PubMed: 10091821]
7. Domanski M, et al. Pulse pressure and cardiovascular disease-related mortality: follow-up study of the Multiple Risk Factor Intervention Trial (MRFIT). Jama. 2002; 287:2677–83. [PubMed: 12020303]
8. Franklin SS, et al. Single versus combined blood pressure components and risk for cardiovascular disease: the Framingham Heart Study. Circulation. 2009; 119:243–50. [PubMed: 19118251]
9. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002; 360:1903–13. [PubMed: 12493255]
10. Devlin B, Roeder K. Genomic control for association studies. Biometrics. 1999; 55:997–1004. [PubMed: 11315092]
11. Kato N, et al. Meta-analysis of genome-wide association studies identifies common variants associated with blood pressure variation in east Asians. Nat Genet. May 15.2011 published online.
12. Sesso HD, et al. Systolic and diastolic blood pressure, pulse pressure, and mean arterial pressure as predictors of cardiovascular disease risk in Men. Hypertension. 2000; 36:801–7. [PubMed: 11082146]
13. Darne B, Girerd X, Safar M, Cambien F, Guize L. Pulsatile versus steady component of blood pressure: a cross-sectional analysis and a prospective analysis on cardiovascular mortality. Hypertension. 1989; 13:392–400. [PubMed: 2522417]
14. Blacher J, Safar ME. Large-artery stiffness, hypertension and cardiovascular risk in older patients. Nat Clin Pract Cardiovasc Med. 2005; 2:450–5. [PubMed: 16265885]
15. Dart AM, Kingwell BA. Pulse pressure--a review of mechanisms and clinical relevance. J Am Coll Cardiol. 2001; 37:975–84. [PubMed: 11263624]
16. Johnson AD, et al. Genome-wide meta-analyses identifies seven loci associated with platelet aggregation in response to agonists. Nat Genet. 2010; 42:608–13. [PubMed: 20526338]
17. Soranzo N, et al. A novel variant on chromosome 7q22.3 associated with mean platelet volume, counts, and function. Blood. 2009; 113:3831–7. [PubMed: 19221038]
18. Soranzo N, et al. A genome-wide meta-analysis identifies 22 loci associated with eight hematological parameters in the HaemGen consortium. Nat Genet. 2009; 41:1182–90. [PubMed: 19820697]
19. Oudit GY, et al. Phosphoinositide 3-kinase gamma-deficient mice are protected from isoproterenol-induced heart failure. Circulation. 2003; 108:2147–52. [PubMed: 12963636]
20. Perrino C, et al. Dynamic regulation of phosphoinositide 3-kinase-gamma activity and beta-adrenergic receptor trafficking in end-stage human heart failure. Circulation. 2007; 116:2571–9. [PubMed: 17998459]
21. Wagsater D, et al. ADAMTS-4 and -8 are inflammatory regulated enzymes expressed in macrophage-rich areas of human atherosclerotic plaques. Atherosclerosis. 2008; 196:514–22. [PubMed: 17606262]
22. Ellis PD, Chen Q, Barker PJ, Metcalfe JC, Kemp PR. Nov gene encodes adhesion factor for vascular smooth muscle cells and is dynamically regulated in response to vascular injury. Arterioscler Thromb Vasc Biol. 2000; 20:1912–9. [PubMed: 10938011]
23. Shimoyama T, et al. CCN3 inhibits neointimal hyperplasia through modulation of smooth muscle cell growth and migration. Arterioscler Thromb Vasc Biol. 2010; 30:675–82. [PubMed: 20139355]
24. Heath E, et al. Abnormal skeletal and cardiac development, cardiomyopathy, muscle atrophy and cataracts in mice with a targeted disruption of the Nov (Ccn3) gene. BMC Dev Biol. 2008; 8:18. [PubMed: 18289368]
25. Cools J, et al. Fusion of a novel gene, BTL, to ETV6 in acute myeloid leukemias with a t(4;12)(q11-q12;p13). Blood. 1999; 94:1820–4. [PubMed: 10477709]
26. Kamatani Y, et al. Genome-wide association study of hematological and biochemical traits in a Japanese population. Nat Genet. 2010; 42:210–5. [PubMed: 20139978]
27. Dorn GW 2nd. Adrenergic signaling polymorphisms and their impact on cardiovascular disease. Physiol Rev. 2010; 90:1013–62. [PubMed: 20664078]
28. Kitsios GD, Zintzaras E. Synopsis and data synthesis of genetic association studies in hypertension for the adrenergic receptor family genes: the CUMAGAS-HYPERT database. Am J Hypertens. 2010; 23:305–13. [PubMed: 20044737]
29. Rohrer DK, Chruscinski A, Schauble EH, Bernstein D, Kobilka BK. Cardiovascular and metabolic alterations in mice lacking both beta1- and beta2-adrenergic receptors. J Biol Chem. 1999; 274:16701–8. [PubMed: 10358009]
30. Cheng G, Qiao F, Gallien TN, Kuppuswamy D, Cooper Gt. Inhibition of beta-adrenergic receptor trafficking in adult cardiocytes by MAP4 decoration of microtubules. Am J Physiol Heart Circ Physiol. 2005; 288:H1193–202. [PubMed: 15528234]
31. Li Y, Abecasis GR. Mach 1.0: Rapid haplotype reconstruction and missing genotype inference. Am J Hum Genet S. 2006; 79:2290.
32. Marchini J, Howie B, Myers S, McVean G, Donnelly P. A new multipoint method for genome-wide association studies by imputation of genotypes. Nat Genet. 2007; 39:906–13. [PubMed: 17572673]
33. Servin B, Stephens M. Imputation-based analysis of association studies: candidate regions and quantitative traits. PLoS Genet. 2007; 3:e114. [PubMed: 17676998]
Figure 1.
Regional association plots of the 8 SNPs at 7 loci showing genome-wide significant association ($P<5\times10^{-8}$) with pulse pressure and/or mean arterial pressure. Statistical significance of each SNP shown on the $-\log_{10}$ scale as a function of chromosome position (NCBI build 36) in the meta-analysis of stage 1 only. The sentinel SNP at each locus is shown in blue; the correlations ($r^2$) of each of the surrounding SNPs to the sentinel SNP are shown in the colours indicated in the key. Fine-scale recombination rate is shown in blue. Gene positions are indicated at the bottom.
Figure 2.
Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) effect sizes (beta coefficients) for all BP SNPs identified in the present study and Ehret et al.\(^1\), obtained from follow-up samples only. Beta coefficients are shown as standard deviation (s.d.) differences so that SBP and DBP are measured on comparable scales. Points are colour-coded according to whether they are genome-wide significant (\(P<5\times10^{-8}\)) for Pulse Pressure (PP) (red), Mean Arterial Pressure (MAP) (blue) or both PP and MAP (purple) in stages 1 and 2 of the present study, while those that are significant only for SBP and/or DBP from Ehret et al.\(^1\) are shown in black. The novel SNPs found in the present study are labelled with their rs-numbers. For illustration purposes the effect allele for each SNP is defined such that the direction of the SBP effect is always positive.
Table 1

Summary of Pulse Pressure (PP) and Mean Arterial Pressure (MAP) association results from Stages 1 and 2 and the combined analysis for all SNPs that showed genome-wide significant ($P<5\times10^{-8}$) association with PP and/or MAP on combined analysis and which had not previously been reported for Systolic (SBP) or Diastolic Blood Pressure (DBP). SBP and DBP combined Stage 1 and Stage 2 association results, based on the same sample set as for PP and MAP are also shown (full SBP and DBP results are in Supplementary Tables 2D and 2E). Genome-wide significant associations ($P<5\times10^{-8}$) are shown in bold.

| Locus                              | Coded allele & freq | Stage 1 | Stage 2 | Stage 1 + 2 | SBP Stage 1 + 2 | DBP Stage 1 + 2 |
|------------------------------------|---------------------|---------|---------|-------------|----------------|-----------------|
|                                    | N eff               | Beta (Se)| P       | N eff       | Beta (Se) | P        | N eff       | Beta (Se) | P       | N eff       | Beta (Se) | P       |
| Pulse Pressure                     |                     |         |         |             |           |          |             |           |          |             |           |          |
| rs13002573 near FIGN chr2: 164623454 | G 0.203             | 73043   | -0.320 (0.089) | 5.43x10^{-6} | 43953 | -0.206 (0.089) | 8.58x10^{-4} | 116998 | -0.310 (0.055) | 1.76x10^{-8} | -0.416 (0.081) | 1.25x10^{-7} | -0.107 (0.052) | 4.02x10^{-2} |
| rs871606 near CHIC2 chr4: 54494002 | T 0.85              | 71444   | 0.428 (0.096) | 9.28x10^{-6} | 44082 | 0.431 (0.121) | 3.75x10^{-4} | 115525 | 0.429 (0.075) | 1.32x10^{-6} | 0.403 (0.112) | 3.04x10^{-5} | -0.010 (0.072) | 8.85x10^{-1} |
| rs17717177 near PIG3CG chr7: 66199004 | T 0.717             | 72097   | -0.344 (0.094) | 1.40x10^{-6} | 39999 | 0.401 (0.075) | 2.72x10^{-4} | 113996 | -0.345 (0.057) | 2.27x10^{-6} | 0.437 (0.084) | 1.67x10^{-5} | -0.001 (0.055) | 1.40x10^{-3} |
| rs2071538 NOV (3' UTR) chr8: 129504903 | T 0.167             | 73252   | 0.323 (0.086) | 1.60x10^{-6} | 45804 | 0.332 (0.086) | 1.36x10^{-6} | 119096 | 0.312 (0.053) | 6.6x10^{-11} | 0.181 (0.078) | 2.08x10^{-4} | -0.015 (0.059) | 3.89x10^{-5} |
| rs11222084 near ADAMTS-8 chr11: 129778440 | T 0.375             | 67334   | 0.211 (0.081) | 9.17x10^{-6} | 40391 | 0.337 (0.05)  | 1.90x10^{-11} | 108095 | 0.337 (0.05)  | 2.63x10^{-6} | 0.263 (0.074) | 4.00x10^{-5} | -0.101 (0.048) | 3.44x10^{-3} |
| Mean Arterial Pressure              |                     |         |         |             |           |          |             |           |          |             |           |          |
| rs1446468 near FIGN chr2: 164671732 | T 0.534             | 69364   | -0.418 (0.082) | 1.68x10^{-6} | 39680 | -0.418 (0.082) | 3.80x10^{-4} | 108914 | -0.306 (0.049) | 6.46x10^{-12} | -0.499 (0.071) | 3.82x10^{-12} | -0.265 (0.046) | 6.88x10^{-5} |
| rs216960 MAPN (3' UTR) chr3: 37924988 | T 0.751             | 50137   | 0.280 (0.059) | 1.80x10^{-6} | 34359 | 0.280 (0.059) | 1.80x10^{-6} | 93496  | 0.297 (0.033) | 2.69x10^{-6} | 0.423 (0.077) | 4.74x10^{-6} | 0.282 (0.055) | 1.84x10^{-8} |
| rs2782980 near ADRB1 chr10: 115711517 | T 0.198             | 61284   | -0.326 (0.094) | 1.14x10^{-6} | 37388 | -0.326 (0.094) | 5.55x10^{-4} | 99072  | -0.338 (0.057) | 2.46x10^{-6} | -0.406 (0.082) | 7.66x10^{-7} | -0.283 (0.053) | 9.60x10^{-5} |