Novel Blood Pressure Locus and Gene Discovery Using Genome-Wide Association Study and Expression Data Sets From Blood and the Kidney

Louise V. Wain, Ahmad Vaez, Rick Jansen, Roby Joehanes, Peter J. van der Most, A. Mesut Erzurumluoglu, Paul F. O'Reilly, Claudia P. Cabrera, Helen R. Warren, Lynda M. Rose, Germaine C. Verwoert, Jouke-Jan Hottenga, Rona J. Strawbridge, Tonu Esko, Dan E. Arking, Shih-Jen Hwang, Xiuqing Guo, Zoltan Kutalik, Stella Trompet, Nick Shrine, Alexander Teumer, Janina S. Ried, Joshua C. Bis, Albert V. Smith, Najaf Amin, Ilja M. Nolte, Leo-Pekka Lyytikäinen, Anubha Mahajan, Nicholas J. Wareham, Edith Hofer, Peter K. Joshi, Kati Kristiansson, Michela Traglia, Aki S. Havulinna, Anuj Goel, Mike A. Nalls, Siim Sõber, Dragana Vuckovic, Jian'an Luan, Fabiola Del Greco M., Kristin L. Ayers, Jaume Marrugat, Daniela Ruggiero, Lorna M. Lopez, Teemu Niiranen, Stefan Enroth, Anne U. Jackson, Christopher P. Nelson, Jennifer E. Huffman, Weihua Zhang, Jonathan Marten, Ilaria Gandin, Sarah E. Harris, Tatijana Zemunik, Yingchang Lu, Evangelos Evangelou, Nabi Shah, Martin H. de Borst, Massimo Mangino, Bram P. Prins, Archie Campbell, Ruifang Li-Gao, Ganesh Chauhan, Christopher Oldmeadow, Gonçalo Abecasis, Maryam Abedi, Caterina M. Barbieri, Michael R. Barnes, Chiara Batini, John Beilby; BIOS Consortium*; Tineka Blake, Michael Boehnke, Erwin P. Bottinger, Peter S. Braund, Morris Brown, Marco Brumat, Harry Campbell, John C. Chambers, Massimiliano Cocca, Francis Collins, John Connell, Heather J. Cordell, Jeffrey J. Damman, Gail Davies, Eco J. de Geus, Renée de Mutsert, Joris Deelen, Yusuf Demirkale, Alex S.F. Doney, Marcus Dörr, Martin Farrall, Teresa Ferreira, Mattias Frånberg, He Gao, Vilmantas Giedraitis, Christian Gieger, Franco Giulianini, Alan J. Gow, Anders Hamsten, Tamara B. Harris, Albert Hofman, Elizabeth G. Holliday, Jennie Hui, Marjo-Riitta Jarvelin, Åsa Johansson, Andrew D. Johnson, Pekka Jousilahti, Antti Jula, Mika Kähönen, Sekar Kathiresan, Kay-Tee Khaw, Ivana Kolcic, Seppo Koskinen, Claudia Langenberg, Marty Larson, Lenore J. Launer, Benjamin Lehne, David C.M. Liewald; Lifelines Cohort Study*; Li Lin, Lars Lind, François Mach, Chrysovalanto Mamasoula, Cristina Menni, Borbala Mifsud, Yuri Milaneschi, Anna Morgan, Andrew D. Morris, Alanna C. Morrison, Peter J. Munson, Priyanka Nandakumar, Quang Tri Nguyen, Teresa Nutile, Albertine J. Oldehinkel, Ben A. Oostra, Elin Org, Sandosh Padmanabhan, Aarno Palotie,

Received March 24, 2017; first decision April 10, 2017; revision accepted June 30, 2017.

From the Department of Health Sciences (L.V.W., A.M.E., N. Shrine, C.B., T.B., M.D.T.), and Department of Cardiovascular Sciences and NIHR Leicester Biomedical Research Centre (C.P.N., P.S.B., N.J.S.), University of Leicester, United Kingdom; Department of Epidemiology (A.V., P.J.v.d.M., I.M.N., H. Snieder), Division of Nephrology, Department of Internal Medicine (M.H.d.B., M.A.S.), Interdisciplinary Center Psychopathology and Emotion Regulation (IPCE) (A.J.O., H.R., C.A.H.), Department of Genetics, (M.S.), and Department of Cardiology (P.v.d.H.), University of Groningen, University Medical Center Groningen, The Netherlands; Research Institute for Primordial Prevention of Non-Communicable Disease, Isfahan University of Medical Sciences, Iran (A.V.); Department of Psychiatry, VU University Medical Center, Neuroscience Campus Amsterdam, The Netherlands (R. Jansen); Hebrew SeniorLife, Harvard Medical School, Boston, MA (R. Joehanes); National Heart, Lung and Blood Institute's Framingham Heart Study, MA (R. Joehanes, A.D.J., M. Larson); Institute of Psychiatry, Psychology and Neuroscience (P.F.O.), and Department of Twin Research and Genetic Epidemiology (M.M., C. Menni, T.D.S.), King's College London, United Kingdom; Clinical Pharmacology, William Harvey Research Institute (C.P.C., H.R.W., M.R.B., M. Brown, B.M., M.R., P.B.M., M.J.C.) and NIHR Barts Cardiovascular Biomedical Research Unit (C.P.C., H.R.W., M.R.B., M. Brown, P.B.M., M.J.C.), Barts and The London School of Medicine and Dentistry, Queen Mary University of London, United Kingdom; Division of Preventive Medicine, Brigham and Women's Hospital, Boston, MA (L.M.R., F.G., P.M.R., D.I.C.); Department of Epidemiology (G.C.V., A. Hofman, A.G.U., O.H.F.), Genetic Epidemiology Unit, Department of Epidemiology (N.A., B.A.O., C.M.v.D.), and Department of Internal Medicine (A.G.U.), Erasmus MC, Rotterdam, The Netherlands; Department of Biological Psychology, Vrije Universiteit, Amsterdam, EMGO+ Institute, VU University Medical Center, The Netherlands (J.-J.H., E.J.d.G., G.W., D.I.B.); Cardiovascular Medicine Unit, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden (R.J.S., M. Frånberg, A. Hamsten); Centre for Molecular Medicine, Karolinska Universitetsjukhuset, Solna, Sweden (R.J.S., M. Frånberg, A. Hamsten); Estonian Genome Center (T.E., E.O., A. Metspalu), Institute of Biomedicine and Translational Medicine (S.S., M. Laan), and Estonian Genome Center (M.P.), University of Tartu, Estonia; Divisions of Endocrinology/Children's Hospital, Boston, MA (T.E.); Broad Institute of Harvard and MIT, Cambridge, MA (T.E., C.M.L., C.N.-C.); Center for Complex Disease Genomics, McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD (D.E.A., P.N., A. Chakravarti, G.B.E.); The Population Science Branch, Division of Intramural Research, National Heart Lung and Blood Institute (S.-J.H., D.L.), Laboratory of Neurogenetics, National Institute on Aging (M.A.N.), Medical Genomics and Metabolic Genetics Branch, National Human Genome Research Institute (F.C.),

Hypertension **is available at http://hyper.ahajournals.org** **DOI: 10.1161/HYPERTENSIONAHA.117.09438**

Guillaume Paré, Alison Pattie, Brenda W.J.H. Penninx, Neil Poulter, Peter P. Pramstaller, Olli T. Raitakari, Meixia Ren, Kenneth Rice, Paul M. Ridker, Harriëtte Riese, Samuli Ripatti, Antonietta Robino, Jerome I. Rotter, Igor Rudan, Yasaman Saba, Aude Saint Pierre, Cinzia F. Sala, Antti-Pekka Sarin, Reinhold Schmidt, Rodney Scott, Marc A. Seelen, Denis C. Shields, David Siscovick, Rossella Sorice, Alice Stanton, David J. Stott, Johan Sundström, Morris Swertz, Kent D. Taylor, Simon Thom, Ioanna Tzoulaki, Christophe Tzourio, André G. Uitterlinden; Understanding Society Scientific Group*; Uwe Völker, Peter Vollenweider, Sarah Wild, Gonneke Willemsen, Alan F. Wright, Jie Yao, Sébastien Thériault, David Conen, John Attia, Peter Sever, Stéphanie Debette, Dennis O. Mook-Kanamori, Eleftheria Zeggini, Tim D. Spector, Pim van der Harst, Colin N.A. Palmer, Anne-Claire Vergnaud, Ruth J.F. Loos, Ozren Polasek, John M. Starr, Giorgia Girotto, Caroline Hayward, Jaspal S. Kooner, Cecila M. Lindgren, Veronique Vitart, Nilesh J. Samani, Jaakko Tuomilehto, Ulf Gyllensten, Paul Knekt, Ian J. Deary, Marina Ciullo, Roberto Elosua, Bernard D. Keavney, Andrew A. Hicks, Robert A. Scott, Paolo Gasparini, Maris Laan, YongMei Liu, Hugh Watkins, Catharina A. Hartman, Veikko Salomaa, Daniela Toniolo,

and Center for Information Technology (Y.D., P.J.M., Q.T.N.), National Institutes of Health, Bethesda, MD; The Framingham Heart Study, Framingham, MA (S.-J.H., D.L.); The Institute for Translational Genomics and Population Sciences, Department of Pediatrics (X.G., J.Y.), and The Institute for Translational Genomics and Population Sciences, Departments of Pediatrics and Medicine (J.I.R.), LABioMed at Harbor-UCLA Medical Center, Torrance, CA; Institute of Social and Preventive Medicine, Lausanne University Hospital, Lausanne, Switzerland (Z.K., M. Bochud); Swiss Institute of Bioinformatics, Lausanne, Switzerland (Z.K.); Department of Cardiology (S. Trompet, J.W.J.) Department of Gerontology and Geriatrics (S. Trompet), Department of Clinical Epidemiology (R.L.-G., R.d.M., D.O.M.-K.), Department of Molecular Epidemiology (J.D.), and Department of Public Health and Primary Care (D.O.M.-K.), Leiden University Medical Center, The Netherlands; Institute for Community Medicine (A.T.), Department of Internal Medicine B (M.D.), and Interfaculty Institute for Genetics and Functional Genomics (U.V.), University Medicine Greifswald, Germany; DZHK (German Centre for Cardiovascular Research), partner site Greifswald, Germany (A.T., M.D., U.V.); Institute of Epidemiology II, Helmholtz Zentrum München, Neuherberg, Germany (J.S.R., A. Peters); Cardiovascular Health Research Unit, Department of Medicine (J.C.B., B.M.P.) and Departments of Biostatistics (K.R.), Epidemiology (B.M.P.), and Health Services (B.M.P.), University of Washington, Seattle; Icelandic Heart Association, Kopavogur, Iceland (A.V.S., V. Gudnason); Faculty of Medicine, University of Iceland, Reykjavik, Iceland (A.V.S., V. Gudnason); Department of Clinical Chemistry, Fimlab Laboratories, Tampere, Finland (L.-P.L., T.L.); Department of Clinical Chemistry, Faculty of Medicine and Life Sciences, University of Tampere, Finland (L.-P.L., T.L.); Wellcome Trust Centre for Human Genetics (A. Mahajan, A.G., M. Farrall, T.F., C.M.L., H.W., A.P.M.), and Division of Cardiovascular Medicine, Radcliffe Department of Medicine (A.G., M. Farrall, H.W.), University of Oxford, United Kingdom; MRC Epidemiology Unit, University of Cambridge School of Clinical Medicine, Institute of Metabolic Science, United Kingdom (N.J.W., J.L., C.L., R.J.F.L., R.A.S., J.H.Z.); Clinical Division of Neurogeriatrics, Department of Neurology (E.H., R. Schmidt), Institute of Medical Informatics, Statistics and Documentation (E.H.), and Department of Neurology (H. Schmidt), Medical University Graz, Austria; Centre for Global Health Research, Usher Institute of Population Health Sciences and Informatics (P.K.J., H.C., I.R., S.W., J.F.W.), Centre for Cognitive Ageing and Cognitive Epidemiology (L.M.L., S.E.H., G.D., A.J.G., D.C.M.L., J.M.S., I.J.D.), Medical Genetics Section, Centre for Genomic and Experimental Medicine, Institute of Genetics and Molecular Medicine (A. Campbell), Generation Scotland, Centre for Genomic and Experimental Medicine (A. Campbell, S.P., C.H.), Department of Psychology (G.D., D.C.M.L., A. Pattie, I.J.D.), Alzheimer Scotland Dementia Research Centre (J.M.S.), and Medical Research Council Human Genetics Unit, Institute of Genetics and Molecular Medicine (C.H.), University of Edinburgh, Scotland, United Kingdom; Department of Health (K.K., A.S.H., T. Niiranen, P.J., A.J., S. Koskinen, P.K., V.S., M.P.), and Chronic Disease Prevention Unit (J.T.), National Institute for Health and Welfare (THL), Helsinki, Finland; Division of Genetics and Cell Biology, San Raffaele Scientific Institute, Milano, Italy (M.T., C.M.B., C.F.S., D.T.); Data Tecnica International, Glen Echo, MD (M.A.N.); Medical Genetics, IRCCS-Burlo Garofolo Children Hospital, Trieste, Italy (D.V., G.G., P.G.); Department of Medical, Surgical and Health Sciences, University of Trieste, Italy (D.V., I.G., M. Brumat, M. Cocca, A. Morgan, G.G., P.G.); Institute for Biomedicine, Eurac Research, Affiliated Institute of the University of Lübeck, Bolzano, Italy (F.D.G.M., P.P.P., A.S.P., A.A.H.); Department of Genetics and Genomic Sciences (K.L.A.), The Charles Bronfman Institute for Personalized Medicine (Y.L., E.P.B., R.J.F.L.), and Mindich Child health Development Institute (R.J.F.L.), Icahn School of Medicine at Mount Sinai, New York; Cardiovascular Epidemiology and Genetics, IMIM, and CIBERCV, Barcelona, Spain (J. Marrugat, R.E.); Institute of Genetics and Biophysics A. Buzzati-Traverso, CNR, Napoli, Italy (D.R., T. Nutile, R. Sorice, M. Ciullo); Department of Psychiatry, Royal College of Surgeons in Ireland, Education and Research Centre, Beaumont Hospital, Dublin (L.M.L.); UCD Conway Institute, Centre for Proteome Research (L.M.L.), and School of Medicine, Conway Institute (D.C.S.), University College Dublin, Belfield, Ireland; Department of Immunology, Genetics and Pathology, Uppsala Universitet, Science for Life Laboratory, Sweden (S.E., Å. Johansson, U.G.); Department of Biostatistics and Center for Statistical Genetics, University of Michigan, Ann Arbor (A.U.J., M. Boehnke); NIHR Leicester Cardiovascular Biomedical Research Unit, Glenfield Hospital, Leicester United Kingdom (C.P.N., P.S.B., N.J.S.); MRC Human Genetics Unit, Institute of Genetics and Molecular Medicine (J.E.H., V.V., J. Marten, A.F.W., J.F.W.), and Medical Genetics Section, Centre for Genomic and Experimental Medicine and MRC Institute of Genetics and Molecular Medicine (S.E.H.), University of Edinburgh, Western General Hospital, Scotland, United Kingdom; Department of Epidemiology and Biostatistics, School of Public Health (W.Z., E.E., J.C.C., H.G., B.L., I.T., A.-C.V.), MRC-PHE Centre for Environment and Health, Department of Epidemiology and Biostatistics, School of Public Health (M.-R.J., P.E.), School of Public Health (N.P.), International Centre for Circulatory Health (S. Thom), and National Heart and Lung Institute (P.S.), Imperial College London, United Kingdom; Department of Cardiology, Ealing Hospital, London North West Healthcare NHS Trust, Southall, United Kingdom (W.Z., J.C.C., J.S.K.); Department of Medical Biology, Faculty of Medicine, University of Split, Croatia (T.Z.); Department of Hygiene and Epidemiology, University of Ioannina Medical School, Greece (E.E.); Medical Research Institute, University of Dundee, Ninewells Hospital and Medical School, Scotland, United Kingdom (N. Shah, A.S.F.D., C.N.A.P.); Department of Pharmacy, COMSATS Institute of Information Technology, Abbottabad, Pakistan (N. Shah); National Institute for Health Research Biomedical Research Centre, London, United Kingdom (M.M.); Department of Human Genetics, Wellcome Trust Sanger Institute, United Kingdom (B.P.P., E.Z.); INSERM U 1219, Bordeaux Population Health Center, France (G.C., C.T., S.D.); Bordeaux University, France (G.C., C.T., S.D.); Hunter Medical Research Institute, New Lambton, NSW, Australia (C.O., E.G.H., R. Scott, J.A.); Center for Statistical Genetics, Department of Biostatistics, Ann Arbor, MI (G.A.); Department of Genetics and Molecular Biology, Isfahan University of Medical Sciences, Iran (M.A.); Busselton Population Medical Research Institute, Western Australia (J.B., J.H.); PathWest Laboratory Medicine of Western Australia, Nedlands (J.B., J.H.); School of Pathology and Laboratory Medicine (J.B., J.H.), School of Population and Global Health (J.H.), and School of Medicine and Pharmacology (A. James), The University of Western Australia, Nedlands; Imperial College Healthcare NHS Trust, London, United Kingdom (J.C.C., J.S.K.); University of Dundee, Ninewells Hospital & Medical School, United Kingdom (J.C.); Institute of Genetic Medicine (H.J.C.), and Institute of Health and Society (C. Mamasoula), Newcastle University, Newcastle upon Tyne, United Kingdom; Department of Pathology, Amsterdam Medical Center, The Netherlands (J.J.D.); Department of Numerical Analysis and Computer Science, Stockholm University, Sweden (M. Frånberg); Department of Public Health and Caring Sciences, Geriatrics, Uppsala, Sweden (V. Giedraitis); Helmholtz Zentrum Muenchen, Deutsches

Markus Perola, James F. Wilson, Helena Schmidt, Jing Hua Zhao, Terho Lehtimäki, Cornelia M. van Duijn, Vilmundur Gudnason, Bruce M. Psaty, Annette Peters, Rainer Rettig, Alan James, J. Wouter Jukema, David P. Strachan, Walter Palmas, Andres Metspalu, Erik Ingelsson, Dorret I. Boomsma, Oscar H. Franco, Murielle Bochud, Christopher Newton-Cheh, Patricia B. Munroe, Paul Elliott, Daniel I. Chasman, Aravinda Chakravarti, Joanne Knight, Andrew P. Morris, Daniel Levy, Martin D. Tobin, Harold Snieder,† Mark J. Caulfield,† Georg B. Ehret†

Abstract—Elevated blood pressure is a major risk factor for cardiovascular disease and has a substantial genetic contribution. Genetic variation influencing blood pressure has the potential to identify new pharmacological targets for the treatment of hypertension. To discover additional novel blood pressure loci, we used 1000 Genomes Project–based imputation in 150 134 European ancestry individuals and sought significant evidence for independent replication in a further 228 245 individuals. We report 6 new signals of association in or near *HSPB7*, *TNXB*, *LRP12*, *LOC283335*, *SEPT9*, and *AKT2*, and provide new replication evidence for a further 2 signals in *EBF2* and *NFKBIA*. Combining large whole-blood gene expression resources totaling 12 607 individuals, we investigated all novel and previously reported signals and identified 48 genes with evidence for involvement in blood pressure regulation that are significant in multiple resources. Three novel kidney-specific signals were also detected. These robustly implicated genes may provide new leads for therapeutic innovation. **(*Hypertension*. 2017;70:e4-e19. DOI: 10.1161/HYPERTENSIONAHA.117.09438.)** ● **Online Data Supplement**

Key Words: blood pressure ■ cardiovascular risk ■ complex traits ■ eSNP ■ GWAS ■ hypertension

Forschungszentrum fuer Gesundheit und Umwelt (GmbH), Neuherberg, Germany (C.G.); Department of Psychology, School of Social Sciences, Heriot-Watt University, Edinburgh, United Kingdom (A.J.G.); Intramural Research Program, Laboratory of Epidemiology, Demography, and Biometry, National Institute on Aging (T.B.H., L.J.L.); Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA (A. Hofman); Center For Life-Course Health Research (M.-R.J.), and Biocenter Oulu (M.-R.J.), University of Oulu, Finland; Unit of Primary Care, Oulu University Hospital, Finland (M.-R.J.); National Heart, Lung and Blood Institute, Cardiovascular Epidemiology and Human Genomics Branch, Bethesda, MD (A.D.J.); Department of Clinical Physiology, Tampere University Hospital, Finland (M.K.); Department of Clinical Physiology, Faculty of Medicine and Life Sciences, University of Tampere, Finland (M.K.); Cardiovascular Research Center (S. Kathiresan, C.N.-C.); Center for Human Genetics (S. Kathiresan), and Center for Human Genetic Research (C.N.-C.), Massachusetts General Hospital, Boston; Program in Medical and Population Genetics, Broad Institute, Cambridge, MA (S. Kathiresan, C.N.-C.); Department of Public Health and Primary Care, Institute of Public Health, University of Cambridge, United Kingdom (K.-T.K.); Department of Public Health, Faculty of Medicine, University of Split, Croatia (I.K., O.P.); Cardiology, Department of Specialties of Medicine, Geneva University Hospital, Switzerland (L. Lin, F.M., G.B.E.); Department of Medical Sciences, Cardiovascular Epidemiology (L. Lind, J.S.), and Department of Medical Sciences, Molecular Epidemiology and Science for Life Laboratory (E.I.), Uppsala University, Sweden; Department of Psychiatry, EMGO Institute for Health and Care Research, VU University Medical Center, Amsterdam, The Netherlands (Y.M., B.W.J.H.P.); School of Molecular, Genetic and Population Health Sciences, University of Edinburgh, Medical School, Teviot Place, Scotland, United Kingdom (A.D.M.); Department of Epidemiology, Human Genetics and Environmental Sciences, School of Public Health, University of Texas Health Science Center at Houston (A.C.M.); British Heart Foundation Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, College of Medical, Veterinary and Life Sciences (S.P.), and Institute of Cardiovascular and Medical Sciences, Faculty of Medicine (D.J.S.), University of Glasgow, United Kingdom; Institute for Molecular Medicine Finland (FIMM), University of Helsinki, Finland (A. Palotie, S.R., A.-P.S., M.P.); Department of Pathology and Molecular Medicine, McMaster University, Hamilton, Canada (G.P., S. Thériault); Department of Neurology, General Central Hospital, Bolzano, Italy (P.P.P.); Department of Neurology, University of Lübeck, Germany (P.P.P.); Department of Clinical Physiology and Nuclear Medicine, Turku University Hospital, Finland (O.T.R.); Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku, Finland (O.T.R.); Department of Cardiology, Fujian Provincial Hospital, Fujian Medical University, Fuzhou, China (M.R.); Harvard Medical School, Boston, MA (P.M.R., D.I.C.); Institute for Maternal and Child Health IRCCS Burlo Garofolo, Trieste, Italy (A.R.); Institute of Molecular Biology and Biochemistry, Centre for Molecular Medicine, Medical University of Graz, Austria (Y.S., H. Schmidt); INSERM U1078, Etablissement Français du Sang, Brest Cedex, France (A.S.P.); Faculty of Health, University of Newcastle, Callaghan, NSW, Australia (R. Scott, J.A.); John Hunter Hospital, New Lambton, NSW, Australia (R. Scott, J.A.); The New York Academy of Medicine, New York (D.S.); IRCCS Neuromed, Pozzilli, Isernia, Italy (R. Sorice, M. Ciullo); Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland, Dublin 2, Ireland (A.S.); Institute for Translational Genomics and Population Sciences, Los Angeles BioMedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA (K.D.T.); Division of Genetic Outcomes, Department of Pediatrics, Harbor-UCLA Medical Center, Torrance, CA (K.D.T.); Department of Public Health (C.T.), and Department of Neurology (S.D.), Bordeaux University Hospital, France; Department of Internal Medicine, Lausanne University Hospital, CHUV, Switzerland (P.V.); Population Health Research Institute, McMaster University, Hamilton Ontario, Canada (D.C.); National Heart and Lung Institute, Imperial College London, Hammersmith Hospital Campus, United Kingdom (J.S.K.); Dasman Diabetes Institute, Kuwait (J.T.); Diabetes Research Group, King Abdulaziz University, Jeddah, Saudi Arabia (J.T.); Department of Neurosciences and Preventive Medicine, Danube-University Krems, Austria (J.T.); Division of Cardiovascular Sciences, The University of Manchester and Central Manchester University Hospitals NHS Foundation Trust, United Kingdom (B.D.K.); Division of Public Health Sciences, Wake Forest School of Medicine, Winston-Salem (Y.M.L.); Kaiser Permanent Washington Health Research Institute, Seattle, WA (B.M.P.); Institute of Physiology, University Medicine Greifswald, Karlsburg, Germany (R.R); Department of Pulmonary Physiology and Sleep, Sir Charles Gairdner Hospital, Nedlands, Western Australia (A. James); Population Health Research Institute, St George's, University of London, United Kingdom (D.P.S.); Department of Medicine, Columbia University Medical Center, New York (W.P.); Division of Cardiovascular Medicine, Department of Medicine, Stanford University School of Medicine, CA (E.I.); Data Science Institute and Lancaster Medical School, Lancaster University, United Kingdom (J.K.); and Department of Biostatistics, University of Liverpool, United Kingdom (A.P.M.).

*A list of contributing authors is given in the online-only Data Supplement.

This article was sent to Theodore A. Kotchen, Guest Editor, for review by expert referees, editorial decision, and final disposition.

†These authors contributed equally to this work.

The online-only Data Supplement is available with this article at http://hyper.ahajournals.org/lookup/suppl/doi:10.1161/HYPERTENSIONAHA.117.09438/-/DC1.

Correspondence to Georg B. Ehret, Cardiology, Department of Specialties of Medicine, Geneva University Hospital, 1205 Genève, Switzerland, E-mail georg@rhone.ch or Louise V. Wain, Department of Health Sciences, University of Leicester, Leicester LE1 7RH, United Kingdom, E-mail louisewain@le.ac.uk

Genetic support for a drug target increases the likelihood of success in drug development,[1] and there is clear unmet need for novel therapeutic strategies to treat individuals with hypertension.[2] Several large studies have described blood pressure (BP) variant identification by genome-wide and targeted association approaches.[3–19] Clinically, the most predictive BP traits for cardiovascular risk are systolic BP (SBP) and diastolic BP (DBP), reflecting roughly the peak and trough of the BP curve, and pulse pressure, the difference between SBP and DBP,[20] reflecting arterial stiffness. Using these 3 traits, we undertook a meta-analysis of 150 134 individuals from 54 genome-wide association studies (GWAS) of European ancestry with imputation based on the 1000 Genomes Project Phase 1. To minimize reporting of false-positive associations, we sought stringent evidence for significant independent replication in a further 228 245 individuals. We further followed up novel and previously reported association signals in multiple large gene expression databases and the largest kidney tissue gene expression resource currently available. Finally, we searched for enrichment of associated genes in biological pathways and gene sets and identified whether any of the genes were known drug targets or had tool molecules.

Materials and Methods

Studies Stage 1

Results from 54 independent European-ancestry studies, totaling 150 134 individuals, were included in the stage 1 meta-analysis: AGES (n=3215), ARIC (n=9402), ASPS (n=828), B58C (n=6458), BHS (n=4492), CHS (n=3254), Cilento study (n=999), COLAUS (n=5404), COROGENE-CTRL (n=1878), CROATIA-Vis (n=945), CROATIA-Split (n=494), CROATIA-Korcula (n=867), EGCUT (n=6395), EGCUT2 (n=1844), EPIC (n=2100), ERF (n=2617), Fenland (n=1357), FHS (n=8096), FINRISK-ctrl (n=861), FINRISK CASE (n=839), FUSION (n=1045), GRAPHIC (n=1010), H2000-CTRL (n=1078), HealthABC (n=1661), HTO (n=1000), INGI-CARL (n=456), INGI-FVG (n=746), INGI-VB (n=1775), IPM (n=300), KORAS3 (n=1590), KORAS4 (n=3748), LBC1921 (n=376), LBC1936 (n=800), LOLIPOP-EW610 (n=927), MESA (n=2678), MICROS (n=1148), MIGEN (n=1214), NESDA (n=2336), NSPHS (n=1005), NTR (n=1490), PHASE (n=4535), PIVUS (n=945), PROCARDIS (n=1652), SHIP (n=4068), ULSAM (n=1114), WGHS (n=23 049), YFS (n=1987), ORCADES (n=1908), RS1 (n=5645), RS2 (n=2152), RS3 (n=3018), TRAILS (n=1262), TRAILS-CC (n=282), and TWINGENE (n=9789). Full study names and general study information is given in Table S1 in the online-only Data Supplement.

Study-Level Genotyping and Association Testing

Three quantitative BP traits were analyzed: SBP, DBP, and pulse pressure (difference between SBP and DBP). Within each study, individuals known to be taking antihypertensive medication had 15 mm Hg added to their raw SBP value and 10 mm Hg added to their raw DBP values.[21] A summary of BP phenotypes in each study is given in Table S2. Association testing was undertaken according to a central analysis plan that specified the use of sex, age, age^2, and body mass index as covariates and optional inclusion of additional covariates to account for population stratification (Table S3). Trait residuals were calculated for each trait using a normal linear regression of the medication-adjusted trait values (mm Hg) onto all covariates. The genotyping array, preimputation quality control filters, imputation software, and association testing software used by each study are listed in Table S4. Each participating study imputed genotypes based on the 1000 Genomes Project Phase 1 integrated release version 3 (March 2012) all ancestry reference panel.[22] Imputed genotype dosages were used to take into account uncertainty in the imputation. Association testing was performed using linear regression of the trait residuals onto genotype dosages under an additive genetic model. Methods to account for relatedness within a study were used where appropriate (Table S3). Results for all variants (single nucleotide polymorphisms [SNPs] and insertion/deletion polymorphisms [INDELs]) were then returned to the central analysis group for further quality control checks and meta-analysis.

Stage 1 Meta-Analysis

Central quality control checks were undertaken across all results sets. This included checks to ensure allele frequency consistency (across studies and with reference populations), checks of effect size and standard error distributions (ie, to highlight phenotype issues), and generation of quantile–quantile plots and genomic inflation factor lambdas to check for over- or underinflation of test statistics. Genomic control was applied (if lambda >1) at study level. Variants with imputation quality <0.3 were excluded prior to meta-analysis. Inverse variance–weighted meta-analysis was undertaken. After meta-analysis, variants with a weighted minor allele frequency of <1% or N effective (product of study sample size and imputation quality summed across contributing studies) <60% were then excluded and meta-analysis genomic control lambda calculated and used to adjust the meta-analysis results.

Selection of Regions for Follow-Up

For each trait, regions of association were selected by ranking variants by P value, recording the variant with the lowest P value as a sentinel variant and then excluding all variants ±500 kb from the sentinel and reranking the remaining variants. This was undertaken iteratively until all sentinel variants representing 1 Mb regions containing associations with $P<10^{-6}$ had been identified. To identify additional signals represented by secondary sentinel variants within 500 kb of each of the sentinel variants, GCTA (the Genome-wide Complex Trait Analysis software)[23] was used to run conditional analyses (conditioned on the first sentinel variant) on each of the 1 Mb regions using GWAS summary statistics and linkage disequilibrium (LD) information from ARIC. This was done both for putatively novel regions and for regions that had previously been reported. A χ^2 test of heterogeneity of effect sizes across the 54 studies was run for each sentinel variant, and those with $P<0.05$ for heterogeneity were excluded from further follow-up. Variants with $P<10^{-6}$ after conditioning on the sentinel SNP (novel or known) in the region and for which any attenuation of the –log10 P value was <1.5 fold were also taken forward for replication.

Studies Stage 2

Data from 14 independent studies, totaling 87 360 individuals, and the first release of UK Biobank, totaling 140 886 individuals, were combined to replicate the findings from stage 1 (ie, totaling 228 245 individuals). Stage 2 study details, including full study names, are given in Table S6 and included 3C-Dijon (n=4061), Airwave (n=14 023), ASCOT-SC (n=2462), ASCOT-UK (n=3803), BRIGHT (n=1791), GAPP (n=1685), GoDARTs (n=7413), GS:SFHS (n=9749), HCS (n=2112), JUPITER (n=8718), LifeLines (n=13 376), NEO (n=5731), TwinsUK (n=4973), UK Biobank-CMC (n=140 886), and UKHLS (n=7462). Analysis was undertaken using the same methods as described for stage 1 studies. UK Biobank-CMC used a newer imputation reference panel than the other studies, and where a requested variant was not available, a proxy was used (next most significant P value with LD $r^2>0.6$ with original top variant). Results from all stage 2 studies were meta-analyzed using inverse variance–weighted meta-analysis. Two of the variants, rs1048238 and chr1:243458005:INDEL, were not available in the largest study in stage 2 (UK Biobank-CMC), and so proxy variants were selected (based on P value and LD).

Stage 1+Stage 2 Meta-Analysis

After meta-analysis of stage 1 and stage 2 results, signals with a $P>5\times10^{-8}$ were excluded. Of the signals with a final $P<5\times10^{-8}$,

support for independent replication within the stage 2 studies only was sought. Any signals that had $P<5\times10^{-8}$ and evidence for independent replication in stage 2 alone indicated by $P<8.2\times10^{-4}$ (Bonferroni correction for 61 tests) were reported as novel signals of association with BP. Any signals that were subsequently reported by other BP GWAS that were accepted for publication during the time this analysis was ongoing, or signals for which independence from another known signal could not be established, were removed from our list of novel signals at this stage (Table S5).

Genotype and Gene Expression

We searched for signals of association of genotype with gene expression for the 22 signals (including 8 novel) described in this study (Table S7) and all signals reported prior to our study (Table S10)[3–16,18,24] in 3 whole-blood data sets, 1 kidney data set, and the GTEx (Genotype-Tissue Expression) multiple tissue data resource, which included whole blood.[25] We selected cis signals of association, which were significant after controlling for 5% false discovery rate. The 3 whole-blood expression quantitative trait loci (eQTL) data sets were the National Heart, Lung, and Blood Institute SABRe (Systems Approach to Biomarker Research in Cardiovascular Disease) initiative whole-blood eQTL resource (microarray, n=5257), NESDA-NTR (microarray, n=4896), BIOS (RNAseq, n=2116). The whole-blood data from GTEx was based on data from 338 samples. The kidney data set comprised 236 donor kidney samples from 134 donors.[26] Full details of each data set can be found in the online-only Data Supplement. The source transcriptomic renal data as described[26] have been deposited in the GeneExpression Omnibus (NCBI) and are accessible online through GEO Series accession number GSE43974.

LD Lookup

The 1000 Genomes Project phase 3 release of variant calls was used (February 20, 2015) using 503 subjects of European ancestry.[22] r^2 between the sentinel SNPs and all other biallelic SNPs within the corresponding 2 Mb area were calculated using the Tabix and PLINK software package (v1.07).[27,28] Annotation was performed using the ANNOVAR software package.[29]

Gene-Based Pathway Analysis

All genes identified in 3 or 4 of the whole-blood eQTL resources above (Table 2) and genes containing a nonsynonymous variant with $r^2>0.5$ with the sentinel variant (Table S14) were tested for enrichment of biological pathways and gene ontology (GO) terms using ConsensusPathDB[30] using a false discovery rate <5% cutoff. Enriched pathways and GO terms containing genes only implicated by a single BP-associated variant were not reported.

Network Analysis

To construct a functional association network, we combined 2 prioritized candidate gene sets into a single query gene set as (1) genes mapping to the nonsynonymous SNPs in high LD ($r^2>0.5$) with the corresponding sentinel BP-associated SNP and (2) genes with eQTL evidence from 3 or 4 of the blood eQTL resources. Three sentinel SNPs (rs185819, rs926552, and rs805303) mapping to the HLA (human leukocyte antigen) region on chromosome 6 were excluded from downstream analyses. The single query gene set was then used as input for the functional network analysis.[31] We used the Cytoscape[32] software platform extended by the GeneMANIA[33] plugin (Data Version: August 12, 2014).[34] All the genes in the composite network, either from the query or the resulting gene sets, were then used for functional enrichment analysis against GO terms[35] to identify the most relevant GO terms using the same plugin.[34]

DNase1 Hypersensitivity Overlap Enrichment Across Tissue and Cell Types

The functional element overlap analysis of the results of GWAS experiments (Forge tool v1.1)[36] was used to test for enrichment of overlap of BP SNPs in tissues and cell lines from the Roadmap and ENCODE (Encyclopedia of DNA Elements) projects. All 164 SNPs were entered and 143 were included in the analysis. SNPs from 9 commonly used GWAS arrays were used to select background sets of SNPs for comparison, and 10 000 background repetitions were run. A Z score threshold of ≥3.39 (estimated false-positive rate of 0.5%) was used to declare significance.

Drug–Gene Interactions

Genes used for pathway and GO enrichment analyses were further investigated for potential druggable or drugged targets using DGIdb (drug gene interaction database).[37] Known drug–gene interactions were interrogated across 15 source databases in DGIdb and include all types of interactions. The analysis performed for druggability prediction included all 9 databases exclusively inspecting expert curated data only. We also evaluate genes for known tool compounds using Chembl (www.ebi.ac.uk/chembl/; version 22.1).

Results

The stage 1 discovery meta-analysis included 150 134 individuals (Tables S1 through S4 and Figures S1 and S2) and 7 994 604 variants with minor allele frequency >1% and an effective sample size of at least 60% of the total. We used the widely used 2-stage design[38] and identified 61 signals in the discovery analysis that were candidates for novel BP signals ($P<10^{-6}$ for any trait; Table S5). To ensure robustness of signals, we examined BP associations in an additional 228 245 individuals from 15 independent studies for replication, including 140 886 individuals from UK Biobank[19] (Table S6). We used the most significant (sentinel) SNP and trait for each locus in replication (61 tests). Twenty-two putatively novel association signals were initially confirmed, showing significant evidence of replication in the independent stage-2 studies ($P<8.2\times10^{-4}$, Bonferroni correction for 61 tests) and genome-wide significance ($P<5\times10^{-8}$) in a meta-analysis across all 378 376 individuals (Table 1 and Table S7). Of these, 14 were subsequently published in 2 other studies[17,19] which presented genome-wide significant associations with evidence of replication. A further 2 were highlighted as putative novel signals in one of those studies[17] but had not been confirmed by replication. In our study, we report the 6 remaining novel signals, and the 2 previously unconfirmed signals (in *EBF2* and in *NFKBIA*), as novel signals. The 8 novel signals included 7 signals at 7 independent loci (Figure S3) and 1 novel independent signal near a previously reported hit near *TNXB* (Table S8 and Figure S4). The novel signals show both significant evidence of replication in the independent stage-2 studies ($P<8.2\times10^{-4}$, Bonferroni correction for 61 tests) and genome-wide significance ($P<5\times10^{-8}$) in a meta-analysis across all 378 376 individuals. The sentinel variants at all 8 signals were common (minor allele frequency >5%), and the novel secondary signal at *TNXB* was in high linkage disequilibrium ($r^2>0.8$) with a nonsynonymous SNP. With the exception of rs9710247, which was only significant for association with DBP, all signals were significantly associated ($P<0.006$, Bonferroni corrected for 8 tests) with all 3 traits (Table 1 and Table S9).

We next sought to identify which genes might have expression levels that were associated with genotypes of the BP-associated variants reported in this study and others. Strong evidence of an association with expression of a specific gene may provide clues as to which gene(s) might be functionally relevant to that signal. We took the 139 BP association signals

Table 1. Novel Genome-Wide Significant Signals of Association

Variant ID (Noncoded/Coded Allele), Chr:Position, Nearest Gene(s) (Type*)	CAF	Results for Most Significant Trait									Stage 1+Stage 2 Meta-Analysis *P* Values for All Traits		
		Stage 1		Stage 2			Stage 1+Stage 2						
		Beta (SE)	*P* Value	Neff	Beta (SE)	*P* Value	Neff	Beta (SE)	*P* Value	Neff	SBP	DBP	PP
SBP													
rs1048238 (C/T), 1:16341649, *HSPB7* (3′UTR)	0.571	0.366 (0.074)	8.09E-07	140299	NA	NA	NA	NA	NA	NA	NA	NA	NA
rs848309 (proxy) (T/C), 1:16308447	0.567	0.347 (0.072)	1.70E-06	146755	0.347 (0.071)	9.10E-07	140462	0.347 (0.051)	7.07E-12‡	287217	7.07E-12‡	1.07E-10‡	5.48E-06
rs185819 (T/C),† 6:32,050,067, *TNXB* (ns)	0.513	0.534 (0.073)	1.93E-13‡	142397	0.277 (0.053)	1.49E-07	221748	0.365 (0.043)	1.04E-17‡	364144	1.04E-17‡	2.24E-11‡	8.50E-15‡
rs6557876 (C/T), 8:25,900,675, *EBF2*	0.252	−0.411 (0.084)	8.50E-07	143653	−0.350 (0.060)	5.66E-09‡	225803	−0.371 (0.049)	2.85E-14‡	369457	2.85E-14‡	2.50E-10‡	1.51E-08‡
rs35783704 (G/A), 8:105,966,258, *LRP12*/*ZFPM2*	0.109	−0.609 (0.121)	4.96E-07	133924	−0.310 (0.089)	4.78E-04	215528	−0.414 (0.072)	7.08E-09‡	349452	7.08E-09‡	1.60E-06	2.92E-07
rs73099903 (C/T), 12:53,440,779, *LOC283335*	0.074	0.768 (0.143)	8.05E-08	136064	0.396 (0.098)	5.32E-05	207253	0.515 (0.081)	1.95E-10‡	343318	1.95E-10‡	4.53E-06	5.46E-08
rs8904 (G/A), 14:35,871,217, *NFKBIA* (3′UTR)	0.375	0.377 (0.076)	6.76E-07	140424	0.278 (0.054)	2.31E-07	224771	0.311 (0.044)	1.31E-12‡	365195	1.31E-12‡	1.13E-04	3.44E-12‡
rs57927100 (C/G), 17:75,317,300, *SEPT9*	0.258	−0.489 (0.086)	1.10E-08‡	136624	−0.220 (0.061)	3.12E-04	210563	−0.310 (0.050)	4.04E-10‡	347188	4.04E-10‡	1.16E-10‡	1.81E-05
DBP													
rs9710247 (A/G), 19:40,760,449, *AKT2*	0.447	0.252 (0.051)	8.11E-07	109695	0.129 (0.032)	5.76E-05	198332	0.164 (0.027)	1.61E-09‡	308028	3.82E-02	1.61E-09‡	5.03E-01

Results from stage 1 and stage 2, and the meta-analysis of stage 1 and stage 2, for all novel genome-wide significant signals of association. *P* values of association for all 3 traits from a meta-analysis of stages 1 and 2 are also presented. Results from proxy SNPs are indicated by (proxy); rs848309 was a proxy SNP for rs1048238, and rs10926988 was a proxy SNP for chr1:243458005:INDEL. CAF indicates coded allele frequency; DBP, diastolic blood pressure; Neff, effective sample size; ns, nonsynonymous; PP, pulse pressure; s, synonymous; SBP, systolic blood pressure; and UTR, untranslated region.

*For intragenic variants, the nearest genes are listed; all other variants are intronic unless indicated otherwise.

†Novel signal at previously reported locus.

‡Genome-wide significant *P* values ($P<5\times10^{-8}$).

reported prior to these studies[17,19] and 22 novel signals of association identified and confirmed in this study and 2 contemporaneous studies[3–19,24] (Table S10) and searched for evidence of association with gene expression in whole blood (4 studies, total n=12 607; supporting information in the online-only Data Supplement) and in kidney tissue (n=134, the largest kidney eQTL resource currently available). Although of unclear direct relevance to BP, whole blood was studied because of the availability of large data sets enabling a powerful assessment of expression patterns that are likely present across multiple cell and tissue types. Similarly, circulating blood cells have been used for ion transport experiments in the past, and altered ion transport levels in erythrocytes were linked to hypertension.[39] Kidney was chosen because of the many renal pathways that regulate BP and outstanding questions about the relevance of kidney pathways to the genetic component of BP regulation in the general population.[3,15] eQTL signals were filtered by false discovery rate (<5%), and we examined *cis* (within 1 Mb) associations only (supporting information in the online-only Data Supplement).

The 4 blood eQTL data sets were NESDA-NTR,[40,41] SABRe,[15] the BIOS resource,[42] and GTEx[25] (supporting information in the online-only Data Supplement). The BIOS resource (n=2116) has not previously been used in the analysis of BP associations, and findings from NESDA-NTR and SABRe have been reported for a subset of the previously published signals.[16,18] For a total of 369 genes, gene expression was associated with the BP SNP in ≥1 of the 4 blood data sets at experiment-wide significance (Table S11). This included 14 genes for 6 of the 8 novel signals. For 110 genes, we found eQTL evidence in 2 out of 4 data sets (Figure), including 4 genes for 2 of the novel signals: *EIF4B* and *TNS2* for rs73099903 and *MAP3K10* and *PLD3* for rs9710247. SNP rs73099903 was in strong LD ($r^2>0.9$), with the SNP most strongly associated with *TNS2* expression in the BIOS resource. *TNS2* encodes a tensin focal adhesion molecule and may have a role in renal function.[43]

For 48 genes, we found evidence in 3 out of the 4 resources (Table 2), suggesting robustness of the SNP–gene expression

Table 2. BP-Associated SNPs Associated With Expression of the Same Gene Across 4 or 3 Independent Whole-Blood eQTL Resources and the Kidney Resource

Sentinel SNP	Chr	Position	Gene	Blood Data Sets	Top eQTL	Signal in Other Tissue(s) in GTEx	Signal in Kidney	eQTL Signal Previously Reported
Signal in 4 whole-blood eQTL resources								
rs17367504	1	11862778	*CLCN6*	YYYY		Y		Y
rs2169137	1	204497913	*MDM4*	YYYY	Y	Y		Y
rs10926988	1	243483279	*SDCCAG8*	YYYY		Y		
rs319690	3	47927484	*MAP4*	YYYY	Y	Y		Y
rs12521868	5	131784393	*SLC22A5*	YYYY		Y		
rs900145	11	13293905	*ARNTL*	YYYY		Y		Y
rs1060105	12	123806219	*CDK2AP1*	YYYY	Y	Y	Y	
rs1378942	15	75077367	*SCAMP2*	YYYY				
rs1126464	16	89704365	*CHMP1A*	YYYY		Y		Y
rs1126464	16	89704365	*FANCA*	YYYY				Y
rs12946454	17	43208121	*DCAKD*	YYYY		Y	Y	Y
Signal in 3 (out of 4) whole-blood eQTL resources								
rs17367504	1	11862778	*MTHFR*	YYYN		Y		Y
rs871524	1	38411445	*FHL3*	NYYY		Y		
rs871524	1	38411445	*SF3A3*	NYYY		Y		
rs4660293	1	40028180	*PABPC4*	YYYN	Y	Y		Y
rs6749447	2	169041386	*STK39*	YYYN	Y			
rs347591	3	11290122	*ATG7*	YYYN		Y		
rs319690	3	47927484	*ZNF589*	YYNY		Y		
rs12521868	5	131784393	*SLC22A4*	YYYN		Y		
rs1563788	6	43308363	*CRIP3*	YYYN	Y			Y
rs10943605	6	79655477	*PHIP*	YYYN	Y	Y		Y
rs4728142	7	128573967	*IRF5*	NYYY		Y	Y	Y
rs4728142	7	128573967	*TNPO3*	YYYN			Y	
rs2898290	8	11433909	*BLK*	YYYN		Y		
rs2898290	8	11433909	*FAM167A*	NYYY		Y		
rs2898290	8	11433909	*FDFT1*	YYYN		Y		
rs2071518	8	120435812	*NOV*	YYYN		Y		
rs76452347	9	35906471	*TPM2*	YYYN				
rs10760117	9	123586737	*MEGF9*	YYYN		Y		Y
rs4494250	10	96563757	*HELLS*	YYYN				Y
rs11191548	10	104846178	*NT5C2*	YYYN	Y			
rs661348	11	1905292	*TNNT3*	NYYY		Y		
rs2649044	11	9763969	*SBF2*	YYYN				
rs2649044	11	9763969	*SWAP70*	YYYN	Y	Y		?
rs7129220	11	10350538	*ADM*	YYYN				Y
rs7103648	11	47461783	*MYBPC3*	YYYN				
rs3741378	11	65408937	*CTSW*	YYYN				
rs7302981	12	50537815	*LIMA1*	YYYN				Y
rs7302981	12	50537815	*ATF1*	YYNY		Y		

(*Continued*)

Table 2. Continued

Sentinel SNP	Chr	Position	Gene	Blood Data Sets	Top eQTL	Signal in Other Tissue(s) in GTEx	Signal in Kidney	eQTL Signal Previously Reported
rs1036477	15	48914926	*FBN1*	YNYY				
rs1378942	15	75077367	*CSK*	YYYN	Y	Y		Y
rs1378942	15	75077367	*MPI*	NYYY		Y		
rs1378942	15	75077367	*ULK3*	YNYY		Y		Y
rs12946454	17	43208121	*NMT1*	YYYN				Y
rs2304130	19	19789528	*GATAD2A*	YYYN				
rs867186	20	33764554	*EIF6*	NYYY		Y		
rs6095241	20	47308798	*PREX1*	YYYN				
rs9306160	21	45107562	*RRP1B*	YNYY	Y	Y		

Signals of association of SNP genotype and gene expression in other nonblood tissues in GTEx and in kidney are also indicated. Blood data set order: (1) SABRe, (2) NESDA-NTR, (3) BIOS, and (4) GTEx (whole-blood). Top eQTL: top GWAS SNP is top eQTL SNP (or in high LD, r^2>0.9, with top eQTL SNP) in at least 1 data set. eQTL signal previously reported: Genes for which eQTL signals have been previously reported for that sentinel SNP.[15,16,18] For full list, see Table S12 in the online-only Data Supplement. eQTL indicates expression quantitative trait loci; GWAS, genome-wide association studies; GTEx, genotype-tissue expression; and LD, linkage disequilibrium; and SABRe, Systems Approach to Biomarker Research in Cardiovascular Disease.

correlation signal and highlighting those genes as potential candidates in genetic BP regulation. Of the 48 genes, 28 have not previously been described in eQTL analyses using BP-associated SNPs, and all were correlated with previously reported BP association signals.

In the kidney data set (TransplantLines),[26] there was association of gene expression and genotype for 9 SNPs and 13 genes (Table 2 and Figure; Table S12). Nine of the SNP–gene expression associations were also observed in the whole-blood eQTL data sets, suggesting that those signals may not be unique to the kidney. We report 3 signals that were unique to the kidney and not previously reported (*C4orf34*, *HIP2*, and *ASIC1*) and confirm a previously reported kidney eQTL signal for an antisense RNA for *PSMD5*.[15] The same SNP was also an eQTL for *PSMD5* itself in both blood and kidney. *ASIC1* encodes the acid sensing ion channel subunit 1, which may interact (and be coexpressed) with ENaC subunits, which mediate transepithelial Na transport in the distal nephron of the kidney.[44] The comparatively small number of signals using kidney tissue (Table 2 and Figure) compared with whole blood could be because of the small sample size. Complete GTEx results are given in Table S13.

For genes implicated by eQTL information from whole blood, we tested for enrichment of biological pathways and GOs. We noted enrichment of the 48 genes implicated by 3 or 4 blood eQTL resources (Table 2) and a further 54 genes containing a nonsynonymous variant with r^2>0.5 with the top SNP (Table S14) in pathways and ontology terms related to actin and striated muscle (Tables S15 and S16). Network analysis using the same genes highlighted further GO terms relating to muscle function, particularly cardiac muscle (Table S17). We tested the overlap of 161 non-HLA BP-associated variants with DNase hypersensitivity sites identified in the Roadmap and ENCODE cell lines and identified an overall enrichment in multiple cell and tissue types, including heart, kidney, and smooth muscle (Figure S5).

We next investigated these genes for potential suitability as drug targets (druggability), known tool compounds, and clinically approved drugs using DGIdb[37] (Table S18). Twelve genes had known drugs, including 4 genes with known antihypertensive drugs. We noted that drugs modulating all but 1 of the 12 drugged targets had a reported influence on BP, either as a primary antihypertensive indication or as a reported side effect of raised BP. Twenty additional genes were predicted druggable, among these 7 genes have known small molecule tool modulators, based on a query of the Chembl database (www.ebi.ac.uk/chembldb/; version 22.1).

Discussion

Enhanced discovery of BP loci increases the potential targets for therapeutic advances. After major advances in the number of BP loci known over the last years and months, we report 8 novel signals that implicate 5 regions of the genome not previously connected to BP regulation.

Six of the 8 novel signals we report had not previously been reported. Two signals (in *EBF2* and *NFKBIA*) have been suggested previously but without evidence for replication.[17] For these 2 signals, we present, for the first time, stringent evidence of replication, confirming their relevance to BP genetics.

The path from signal to genes is the essential next step toward realizing the therapeutic potential of a genetic locus and understanding the mechanisms of BP regulation. We have used several large eQTL resources as a first step to realize this objective. As expected, we observed that even across eQTL studies of the same tissue, there is limited overlap in experiment-wide significant signals, suggesting either biological variability (differences in the characteristics of the samples or in the methods for extraction and processing of mRNA in each of the studies), technology-specific differences in coverage of genes (use of RNAseq data for the BIOS blood data set and microarray-based expression levels for the kidney and other blood data sets), or the possibility of false-positive results despite stringent within-experiment significance thresholds. We were unable to distinguish these scenarios using the data available to us, but by selecting genes that were significant in at least 3

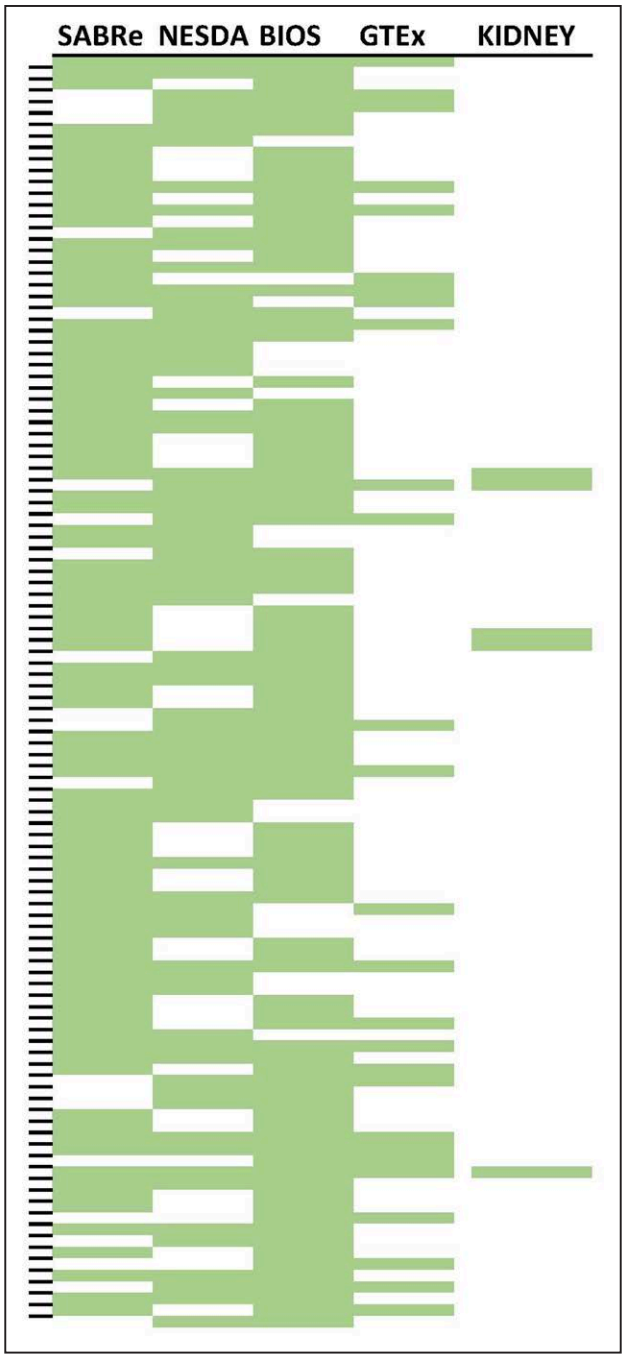

Figure. Overlap of expression quantitative trait loci (eQTL) evidence from 4 whole-blood and 1 kidney resource. The figure indicates overlap of evidence for eQTLs from 4 whole-blood studies (SABRe, NESDA-NTR, BIOS, and GTEx) and from 1 kidney resource (TransplantLines). Every colored line indicates that this gene was analysis-wide significant in a given resource. Only genes identified by at least 2 resources are shown. The genes are sorted by genomic position on the *y* axis.

resources, and therefore robust to these differences, we identified 48 genes as candidates for further study. These results are limited by the availability of large eQTL resources for whole blood only, which precludes well-powered comparisons across tissue types, particularly, as the origin of BP control is unlikely to be located in the blood. Enrichment and pathway analyses using these genes, and genes containing a correlated functional variant, highlight the potential relevance of muscular tissue and pathways, compatible with a vascular and cardiac origin of BP genetics, extending previous evidence.[15] We identify several drugged targets in the pathways identified, including 4 existing hypertension targets. Other drugs identified are not suitable candidates for repositioning to hypertension because most were reported in adverse events to raise BP; however, the targets would be valid for investigation using a reverse mechanism, for example, agonism in place of inhibition. We also identified 7 genes with small molecule tool modulators (mainly inhibitory or binding). These molecules and targets might be suitable candidates for further investigation to build a target validation case to support clinical investigation in hypertension.

Among the genes implicated in our eQTL, analyses were several for which there is already some evidence that they are relevant to BP regulation. The intronic SNP rs10926988 was independently associated with expression of *SDCCAG8* in all 4 whole-blood resources. Rare mutations in *SDCCAG8* cause Bardet–Biedl syndrome, which features hypertension. Expression levels of *MYBPC3* were correlated with rs7103648[15] in the 3 largest blood eQTL resources (ie, SABRe, NESDA-NTR, and BIOS). *MYBPC3* encodes the cardiac isoform of myosin-binding protein C, which is expressed in heart muscle, and mutations in *MYBPC3* are known to cause familial hypertrophic cardiomyopathy.[45]

This study has several limitations. Given the nature of statistical power for genome-wide association analyses, the sample size is limited, even though this is one of the largest efforts in BP GWAS undertaken to date. The study would clearly have benefited from the availability of larger eQTL resources on multiple tissues in sample sizes even larger than those available today. Our analyses were limited to *cis* signals, and future analyses, with larger sample sizes, might also consider *trans* signals.

Perspectives

Our study reports robust novel BP association signals and reports new candidate BP genes, contributing to the transition from variants to genes to explain BP variation. These genes now require further functional validation to establish their potential as drug targets. Our study additionally highlights the challenges of combining and interpreting data from multiple eQTL studies and emphasizes the need for harmonization of data and development of new eQTL resources for multiple tissue types.

In summary, our study reports novel BP association signals and reports new candidate BP genes, contributing to the transition from variants to genes to explain BP variation.

Acknowledgments

We thank all the study participants of this study for their contributions. Detailed acknowledgment of funding sources is provided in the Sources of Funding section.

Author Contributions

Secondary Analyses

Design of secondary analyses: L.V. Wain, G.B. Ehret, M.J. Caulfield, H. Snieder, M.D. Tobin, R. Joehanes, A. Vaez, R. Jansen, A.V. Smith,

J. Knight, P.F. O'Reilly, A.P. Morris, and C.P. Cabrera. Computation of secondary analysis: L.V. Wain, G.B. Ehret, A.P. Morris, A.M. Erzurumluoglu, T. Blake, L. Lin, R. Joehanes, A. Vaez, P.J. van der Most, R. Jansen, and C.P. Cabrera.

Discovery

WGHS: Study phenotyping, P.M. Ridker; Genotyping or analysis, D.I. Chasman and L.M. Rose; Study PI, D.I. Chasman and P.M. Ridker.

RS: Study phenotyping, G.C. Verwoert; Genotyping or analysis, G.C. Verwoert and A.G. Uitterlinden; Study PI, O.H. Franco, A. Hofman, and A.G. Uitterlinden.

NTR: Study phenotyping, E.J. de Geus and G. Willemsen; Genotyping or analysis: J.-J. Hottenga, E.J. de Geus, and G. Willemsen; Study PI, D.I. Boomsma and E.J. de Geus.

STR: Study phenotyping, E. Ingelsson; Genotyping or analysis, R.J. Strawbridge and M. Frånberg; Study PI, E. Ingelsson and A. Hamsten.

EGCUT: Genotyping or analysis, T. Esko; Study PI, A. Metspalu.

ARIC: Genotyping or analysis, D.E. Arking, A.C. Morrison, and P. Nandakumar; Study PI, A. Chakravarti.

FHS: Study phenotyping, D. Levy; Genotyping or analysis, S.-J. Hwang; Study PI: D. Levy.

MESA: Study phenotyping, J.I. Rotter; Genotyping or analysis, W. Palmas, X. Guo, J.I. Rotter, J. Yao; Study PI, W. Palmas.

B58C: Study phenotyping, D.P. Strachan; Genotyping or analysis, D.P. Strachan; Study PI, D.P. Strachan.

COLAUS: Study phenotyping, P. Vollenweider; Genotyping or analysis, M. Bochud and Z. Kutalik; Study PI, P. Vollenweider.

PROSPER: Study phenotyping, J.W. Jukema and D.J. Stott; Genotyping or analysis, S. Trompet and J. Deelen; Study PI, J.W. Jukema.

BHS: Study phenotyping, A. James; Genotyping or analysis, N. Shrine, J. Hui, and J. Beilby.

SHIP: Study phenotyping, M. Dörr; Genotyping or analysis, A. Teumer, M. Dörr, and U. Völker; Study PI, R. Rettig.

KORA S4: Genotyping or analysis, J.S. Ried; Study PI, A. Peters.

CHS: Study phenotyping, B.M. Psaty; Genotyping or analysis, J.C. Bis, K. Rice, and K.D. Taylor; Study PI, B.M. Psaty.

AGES-Reykjavik: Genotyping or analysis, A.V. Smith; Study PI, V. Gudnason, T.B. Harris, and L.J. Launer.

ERF: Study phenotyping, C.M. van Duijn and B.A. Oostra; Genotyping or analysis, N. Amin; Study PI, C.M. van Duijn and B.A. Oostra.

NESDA: Study phenotyping, B.W.J.H. Penninx; Genotyping or analysis, I.M. Nolte and Y. Milaneschi; Study PI, H. Snieder and B.W.J.H. Penninx.

YFS: Study phenotyping, T. Lehtimäki, M. Kähönen, and O.T. Raitakari; Genotyping or analysis, T. Lehtimäki, L.-P. Lyytikäinen, M. Kähönen, and O.T. Raitakari; Study PI, T. Lehtimäki, M. Kähönen, and O.T. Raitakari.

EPIC: Genotyping or analysis, N.J. Wareham; Study PI, J.H. Zhao.

ASPS: Study phenotyping, R. Schmidt; Genotyping or analysis, H. Schmidt, E. Hofer, Y. Saba, and R. Schmidt; Study PI, H. Schmidt and R. Schmidt.

ORCADES: Study phenotyping, J.F. Wilson, H. Campbell, and S. Wild; Genotyping or analysis, J.F. Wilson, P.K. Joshi, and S. Wild; Study PI, J.F. Wilson.

FINRISK (COROGENE_CTRL): Study phenotyping, P. Jousilahti; Genotyping or analysis, K. Kristiansson and A.P. Sarin; Study PI, M. Perola and P. Jousilahti.

INGI-VB: Study phenotyping, C.F. Sala; Genotyping or analysis, M. Traglia, C.M. Barbieri, and C.F. Sala; Study PI, D. Toniolo.

FINRISK_PREDICT_CVD: Study phenotyping, V. Salomaa and A.S. Havulinna; Study PI, V. Salomaa, A. Palotie, and S. Ripatti.

TRAILS: Study phenotyping, H. Riese; Genotyping or analysis, P.J. van der Most; Study PI, C.A. Hartman and A.J. Oldehinkel.

PROCARDIS: Study phenotyping, A. Goel; Genotyping or analysis, A. Goel; Study PI, H. Watkins, and M. Farrall.

HABC: Study phenotyping, Y. Liu and T.B. Harris; Genotyping or analysis, M.A. Nalls; Study PI, Y. Liu and T.B. Harris.

KORA S3: Study phenotyping, C. Gieger; Genotyping or analysis, S. Sõber, C. Gieger, and E. Org. Study PI, M. Laan.

INGI-FVG: Genotyping or analysis, D. Vuckovic, M. Brumat, and M. Cocca; Study PI, P. Gasparini.

Fenland: Study phenotyping, R.A. Scott, J. Luan, C. Langenberg, and N.J. Wareham; Genotyping or analysis, R.A. Scott, J. Luan, C. Langenberg, and N.J. Wareham; Study PI, R.A. Scott, C. Langenberg, and N.J. Wareham.

MICROS: Genotyping or analysis, A.A. Hicks, F. Del Greco M., and A. Saint Pierre; Study PI, F. Del Greco M. and P.P. Pramstaller.

HTO: Study phenotyping, B.D. Keavney; Genotyping or analysis, B.D. Keavney, K.L. Ayers, and C. Mamasoula; Study PI, B.D. Keavney and H.J. Cordell.

MIGEN: Study phenotyping, R. Elosua, J. Marrugat, S. Kathiresan, and D. Siscovick; Genotyping or analysis, R. Elosua, S. Kathiresan, and D. Siscovick; Study PI, S. Kathiresan.

ULSAM: Study phenotyping, V. Giedraitis and E. Ingelsson; Genotyping or analysis, A.P. Morris and A. Mahajan; Study PI, A.P. Morris, V. Giedraitis, and E. Ingelsson.

Cilento study: Study phenotyping, R. Sorice; Genotyping or analysis, D. Ruggiero, and T. Nutile; Study PI, M. Ciullo.

LBC1936: Study phenotyping, I.J. Deary and A.J. Gow; Genotyping or analysis, L.M. Lopez, G. Davies, and A.J. Gow; Study PI, I.J. Deary.

H2000_CTRL: Study phenotyping, T. Niiranen; Study PI, P. Knekt, A. Jula, and S. Koskinen.

NSPHS: Genotyping or analysis, S. Enroth and Å. Johansson; Study PI, U. Gyllensten.

FUSION: Genotyping or analysis, A.U. Jackson; Study PI, J. Tuomilehto, M. Boehnke, and F. Collins.

GRAPHIC: Study phenotyping, N.J. Samani, P.S. Braund, and M.D. Tobin. Genotyping or analysis: C.P. Nelson, P.S. Braund, and M.D. Tobin; Study PI, N.J. Samani.

CROATIA_Vis: Study phenotyping, I. Rudan; Genotyping or analysis, V. Vitart and J.E. Huffman; Study PI, V. Vitart and I. Rudan.

PIVUS: Study phenotyping, L. Lind and J. Sundström; Genotyping or analysis, C.M. Lindgren and A. Mahajan; Study PI, C.M. Lindgren, L. Lind, and J. Sundström.

LOLIPOP: Study phenotyping, J.S. Kooner and J.C. Chambers; Genotyping or analysis, J.S. Kooner, W. Zhang, J.C. Chambers, and B. Lehne; Study PI, J.S. Kooner and J.C. Chambers.

CROATIA_Korcula: Genotyping or analysis, C. Hayward and J. Marten; Study PI, C. Hayward and A.F. Wright.

INGI-CARL: Study phenotyping, G. Girotto; Genotyping or analysis, I. Gandin, A. Morgan, and A. Robino.

LBC1921: Study phenotyping, J.M. Starr and A. Pattie; Genotyping or analysis, J.M. Starr, S.E. Harris, D.C.M. Liewald, and A. Pattie; Study PI, J.M. Starr.

CROATIA_SPLIT: Study phenotyping, O. Polasek and I. Kolcic; Genotyping or analysis, O. Polasek and T. Zemunik; Study PI, O. Polasek.

BioMe (formerly IPM): Genotyping or analysis, Y. Lu; Study PI, R.J.F. Loos and E.P. Bottinger.

Replication

UKB-BP: Genotyping or analysis, H.R. Warren, M.R. Barnes, C.P. Cabrera, E. Evangelou, H. Gao, B. Mifsud, M. Ren, and I. Tzoulaki; Study PI, P. Elliott and M.J. Caulfield.

GoDARTS: Study phenotyping, C.N.A. Palmer and A.S.F. Doney; Genotyping or analysis, C.N.A. Palmer and N. Shah; Study PI, C.N.A. Palmer and A.D. Morris.

Lifelines: Study phenotyping: M.H. de Borst; Genotyping or analysis, M. Swertz; Study PI, P. van der Harst.

TwinsUK: Study phenotyping, C. Menni; Genotyping or analysis, M. Mangino and C. Menni; Study PI, T.D. Spector.

Airwave Health Monitoring Study: Genotyping or analysis, A.C. Vergnaud, E. Evangelou, H. Gao, and I. Tzoulaki; Study PI, E. Evangelou.

The UK Household Longitudinal Study (UKHLS): Genotyping or analysis, B.P. Prins; Study PI, E. Zeggini.

Generation Scotland (GS:SFHS): Study phenotyping, S. Padmanabhan; Genotyping or analysis, C. Hayward and A. Campbell.

JUPITER: Study phenotyping, P.M. Ridker; Genotyping or analysis, D.I. Chasman, L.M. Rose, F. Giulianini, and P.M. Ridker; Study PI, D.I. Chasman and P.M. Ridker.

NEO: Study phenotyping, R. de Mutsert; Genotyping or analysis, D.O. Mook-Kanamori and R. Li-Gao; Study PI, R. de Mutsert.

Three City-Dijon: Study phenotyping, S. Debette and C. Tzourio; Genotyping or analysis, G. Chauhan; Study PI, S. Debette and C. Tzourio.

ASCOT-UK: Study phenotyping: P. Sever and N. Poulter; Genotyping or analysis, P.B. Munroe and H.R. Warren; Study PI, P.B. Munroe, P. Sever, N. Poulter, and M.J. Caulfield.

ASCOT-SC: Study phenotyping, S. Thom and M.J. Caulfield; Genotyping or analysis, D.C. Shields, A. Stanton, H.R. Warren, and P.B. Munroe; Study PI, S. Thom, M.J. Caulfield, and P.B. Munroe.

Hunter Community Study: Study phenotyping, R. Scott; Genotyping or analysis, C. Oldmeadow and E.G. Holliday; Study PI, J. Attia.

GAPP: Study phenotyping, D. Conen; Genotyping or analysis, D. Conen, S. Thériault, and G. Paré; Study PI, D. Conen.

BRIGHT: Study phenotyping, M. Brown and J. Connell; Genotyping or analysis, M. Farrall, P.B. Munroe, and H.R. Warren; Study PI, M. Brown, J. Connell, M. Farrall, P.B. Munroe, and M.J. Caulfield.

Resources for Secondary Analyses

eQTL NESDA NTR: Design of secondary analysis, R. Jansen; Computation of secondary analysis, D.I. Boomsma, R. Jansen, and B.W.J.H. Penninx; Study PI, D.I. Boomsma and B.W.J.H. Penninx.

eQTL kidney: Study phenotyping, J.J. Damman and M.A. Seelen; Genotyping or analysis, P.J. van der Most; Study PI, H. Snieder.

eQTL BIOS: Design of secondary analysis, R. Jansen; Computation of secondary analysis, R. Jansen; Study PI, R. Jansen.

SABRe: Study phenotyping, Y. Demirkale, P.J. Munson, and Q.T. Nguyen; Genotyping or analysis, R. Joehanes; Design of secondary analysis, D. Levy; Study PI, D. Levy.

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Sources of Funding

This research used the ALICE and SPECTRE High Performance Computing Facilities at the University of Leicester. G.B. Ehret is supported by Geneva University Hospitals, Geneva University, de Reuter Foundation, the Swiss National Foundation project FN 33CM30-124087, and the Fondation pour Recherches Médicales, Geneva.

Airwave: We thank all participants of the Airwave Health Monitoring Study. The study is funded by the UK Home Office (Grant number 780-TETRA) with additional support from the National Institute for Health Research Imperial College Healthcare NHS Trust and Imperial College Biomedical Research Centre.

ARIC: The Atherosclerosis Risk in Communities Study is performed as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C), R01HL087641, R01HL59367, and R01HL086694; National Human Genome Research Institute contract U01HG004402; and National Institutes of Health contract HHSN268200625226C. Funding support for the Genetic Epidemiology of Causal Variants Across the Life Course (CALiCo) program was provided through the NHGRI PAGE program (U01 HG007416). We thank the staff and participants of the ARIC study for their important contributions.

ASCOT: This work was supported by Pfizer, New York, NY, for the ASCOT study and the collection of the ASCOT DNA repository; by Servier Research Group, Paris, France; and by Leo Laboratories, Copenhagen, Denmark. We thank all ASCOT trial participants, physicians, nurses, and practices in the participating countries for their important contribution to the study. In particular, we thank Clare Muckian and David Toomey for their help in DNA extraction, storage, and handling. This work forms part of the research programme of the NIHR Cardiovascular Biomedical Research Unit at Barts.

ASPS: The research reported in this article was funded by the Austrian Science Fond (FWF) grant number P20545-P05 and P13180. The Medical University of Graz supports the databank of the ASPS. We thank the staff and the participants of the ASPS for their valuable contributions. We thank Birgit Reinhart for her long-term administrative commitment and Ing Johann Semmler for the technical assistance at creating the DNA bank.

BRIGHT: This work was supported by the Medical Research Council of Great Britain (grant number G9521010D) and by the British Heart Foundation (grant number PG/02/128). The BRIGHT study is extremely grateful to all the patients who participated in the study and the BRIGHT nursing team. This work forms part of the research programme of the NIHR Cardiovascular Biomedical Research Unit at Barts.

B58C: We acknowledge use of phenotype and genotype data from the British 1958 Birth Cohort DNA collection, funded by the Medical Research Council grant G0000934 and the Wellcome Trust grant 068545/Z/02. Genotyping for the B58C-WTCCC subset was funded by the Wellcome Trust grant 076113/B/04/Z. The B58C-T1DGC genotyping used resources provided by the Type 1 Diabetes Genetics Consortium, a collaborative clinical study sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Allergy and Infectious Diseases (NIAID), National Human Genome Research Institute (NHGRI), National Institute of Child Health and Human Development (NICHD), and Juvenile Diabetes Research Foundation International (JDRF) and supported by U01 DK062418. B58C-T1DGC GWAS data were deposited by the Diabetes and Inflammation Laboratory, Cambridge Institute for Medical Research (CIMR), University of Cambridge, which is funded by Juvenile Diabetes Research Foundation International, the Wellcome Trust, and the National Institute for Health Research Cambridge Biomedical Research Centre; the CIMR is in receipt of a Wellcome Trust Strategic Award (079895). The B58C-GABRIEL genotyping was supported by a contract from the European Commission Framework Programme 6 (018996) and grants from the French Ministry of Research.

CHS: This CHS research was supported by National Heart, Lung, and Blood Institute (NHLBI) contracts HHSN268201200036C, HHSN268200800007C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086, and HHSN268200960009C and NHLBI grants U01HL080295, R01HL087652, R01HL105756, R01HL103612, R01HL120393, and R01HL130114, with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was provided through R01AG023629 from the National Institute on Aging (NIA). A full list of principal CHS investigators and institutions can be found at CHS-NHLBI.org. The provision of genotyping data was supported in part by the National Center for Advancing Translational Sciences, CTSI grant UL1TR000124, and the National Institute of Diabetes and Digestive and Kidney Disease Diabetes Research Center (DRC) grant DK063491 to the Southern California Diabetes Endocrinology Research Center. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Cilento study: The Cilento study was supported by the Italian Ministry of Education Universities and Research (Interomics Flagship Project, PON03PE_00060_7), FP6 (Vasoplus-037254), the Assessorato Ricerca Regione Campania, the Fondazione con il SUD (2011-PDR-13), and the Istituto Banco di Napoli-Fondazione to M. Ciullo. We address special thanks to the populations of Cilento for their participation in the study.

COLAUS: The CoLaus study was and is supported by research grants from GlaxoSmithKline (GSK), the Faculty of Biology and Medicine of Lausanne, and the Swiss National Science Foundation

(grants 3200B0-105993, 3200B0- 118308, 33CSCO-122661, and 33CS30-139468). We thank all participants, involved physicians, and study nurses to the CoLaus cohort.

COROGENE_CTRL: This study has been funded by the Academy of Finland (grant numbers 139635, 129494, 118065, 129322, and 250207), the Orion-Farmos Research Foundation, the Finnish Foundation for Cardiovascular Research, and the Sigrid Jusélius Foundation. We are grateful for the THL DNA laboratory for its skillful work to produce the DNA samples used in this study. We thank the Sanger Institute genotyping facilities for genotyping the samples.

CROATIA Studies: The CROATIA-Vis, CROATIA-Korcula, and CROATIA-Split studies in the Croatian islands of Vis and Korcula and mainland city of Split were supported by grants from the Medical Research Council (UK); the Ministry of Science, Education, and Sport of the Republic of Croatia (grant number 216-1080315-0302); the European Union framework program 6 European Special Populations Research Network project (contract LSHG-CT-2006–018947); the European Union framework program 7 project BBMRI-LPC (FP7 313010); and the Croatian Science Foundation (grant 8875). The CROATIA studies acknowledge the invaluable contributions of the recruitment teams (including those from the Institute of Anthropological Research in Zagreb) in Vis, Korcula, and Split, the administrative teams in Croatia and Edinburgh, and the people of Vis, Korcula, and Split. SNP genotyping of the CROATIA-Vis samples was performed by the Genetics Core Laboratory at the Wellcome Trust Clinical Research Facility, WGH, Edinburgh, Scotland. SNP genotyping for CROATIA-Korcula was performed by Helmholtz ZentrumMünchen, GmbH, Neuherberg, Germany. The SNP genotyping for the CROATIA-Split cohort was performed by AROS Applied Biotechnology, Aarhus, Denmark.

ERF: The ERF study as a part of EUROSPAN (European Special Populations Research Network) was supported by European Commission FP6 STRP grant number 018947 (LSHG-CT-2006-01947) and also received funding from the European Community's Seventh Framework Programme (FP7/2007–2013)/grant agreement HEALTH-F4-2007–201413 by the European Commission under the programme "Quality of Life and Management of the Living Resources" of 5th Framework Programme (no. QLG2-CT-2002-01254). High-throughput analysis of the ERF data was supported by a joint grant from the Netherlands Organization for Scientific Research and the Russian Foundation for Basic Research (NWO-RFBR 047.017.043). Exome sequencing analysis in ERF was supported by the ZonMw grant (project 91111025). Najaf Amin is supported by the Netherlands Brain Foundation (project number F2013(1)-28). We are grateful to all study participants and their relatives, general practitioners, and neurologists for their contributions and to P. Veraart for her help in genealogy, J. Vergeer for the supervision of the laboratory work, and P. Snijders for his help in data collection.

Fenland: J. Luan, C. Langenberg, R.A. Scott, and N.J. Wareham acknowledge support from the Medical Research Council (MC_U106179471 and MC_UU_12015/1). The Fenland Study is funded by the Wellcome Trust and the Medical Research Council (MC_U106179471). We are grateful to all the volunteers for their time and help and to the General Practitioners and practice staff for assistance with recruitment. We thank the Fenland Study Investigators, Fenland Study Co-ordination team and the Epidemiology Field, Data and Laboratory teams. We further acknowledge support from the Medical Research Council (MC_UU_12015/1).

FHS: The National Heart, Lung and Blood Institute's Framingham Heart Study is supported by contract N01-HC-25195.

FINRISK_PREDICT_CVD: This study has been funded by the Academy of Finland (grant numbers 139635, 129494, 118065, 129322, 250207, and 269517), the Orion-Farmos Research Foundation, the Finnish Foundation for Cardiovascular Research, and the Sigrid Jusélius Foundation. We are grateful for the THL DNA laboratory for its skillful work to produce the DNA samples used in this study. We thank the Sanger Institute genotyping facilities for genotyping the samples.

FUSION: Support for FUSION was provided by National Instituttes of Health (NIH) grants R01-DK062370 (to M. Boehnke) and intramural project number ZIA-HG000024 (to F. Collins). Genome-wide genotyping was conducted by the Johns Hopkins University Genetic Resources Core Facility SNP Center at the Center for Inherited Disease Research (CIDR), with support from CIDR NIH contract no. N01-HG-65403.

GAPP study: The GAPP study was supported by the Liechtenstein Government, the Swiss National Science Foundation, the Swiss Heart Foundation, the Swiss Society of Hypertension, the University of Basel, the University Hospital Basel, the Hanela Foundation, Schiller AG, and Novartis.

GS:SFHS: Generation Scotland received core support from the Chief Scientist Office of the Scottish Government Health Directorates (CZD/16/6) and the Scottish Funding Council (HR03006). Genotyping of the GS:SFHS samples was performed by the Genetics Core Laboratory at the Wellcome Trust Clinical Research Facility, Edinburgh, Scotland, and was funded by the Medical Research Council UK and the Wellcome Trust (Wellcome Trust Strategic Award "STratifying Resilience and Depression Longitudinally" (STRADL) Reference 104036/Z/14/Z). Ethics approval for the study was given by the NHS Tayside committee on research ethics (reference 05/S1401/89). We are grateful to all the families who took part, the general practitioners, and the Scottish School of Primary Care for their help in recruiting them and the whole Generation Scotland team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists, healthcare assistants, and nurses.

GoDARTS: GoDARTS was funded by The Wellcome Trust (072960/Z/03/Z, 084726/Z/08/Z, 084727/Z/08/Z, 085475/Z/08/Z, and 085475/B/08/Z) and as part of the EU IMI-SUMMIT program. We acknowledge the support of the Health Informatics Centre, University of Dundee, for managing and supplying the anonymized data and NHS Tayside, the original data owner. We are grateful to all the participants who took part in the Go-DARTS study, to the general practitioners, to the Scottish School of Primary Care for their help in recruiting the participants, and to the whole team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists, and nurses.

GRAPHIC: The GRAPHIC Study was funded by the British Heart Foundation (BHF/RG/2000004). C.P. Nelson and N.J. Samani are supported by the British Heart Foundation, and N.J. Samani is an NIHR Senior Investigator. This work falls under the portfolio of research supported by the NIHR Leicester Cardiovascular Biomedical Research Unit.

H2000: The Health 2000 Study was funded by the National Institute for Health and Welfare (THL), the Finnish Centre for Pensions (ETK), the Social Insurance Institution of Finland (KELA), the Local Government Pensions Institution (KEVA), and other organizations listed on the website of the survey (http://www.terveys2000.fi). We are grateful for the THL DNA laboratory for its skillful work to produce the DNA samples used in this study. We thank the Sanger Institute genotyping facilities for genotyping the GenMets subcohort.

HABC: The Health ABC Study was supported by NIA contracts N01AG62101, N01AG62103, and N01AG62106 and, in part, by the NIA Intramural Research Program. The genome-wide association study was funded by NIA grant 1R01AG032098-01A1 to Wake Forest University Health Sciences, and genotyping services were provided by the Center for Inherited Disease Research (CIDR). CIDR is fully funded through a federal contract from the National Institutes of Health to The Johns Hopkins University, contract number HHSN268200782096C. This study used the high-performance computational capabilities of the Biowulf Linux cluster at the National Institutes of Health, Bethesda, MD (http://biowulf.nih.gov).

HTO: The study was funded by the Wellcome Trust, Medical Research Council, and British Heart Foundation We thank all the families who participated in the study.

INGI-VB: The INGI-Val Borbera population is a collection of 1664 genotyped samples collected in the Val Borbera Valley, a geographically isolated valley located within the Appennine Mountains in Northwest Italy. The valley is inhabited by ≈3000 descendants from the original population, living in 7 villages along the valley and in the mountains. Participants were healthy people aged 18 to 102 years who had at least one grandfather living in the valley. The study plan and the informed consent form were reviewed and approved by the institutional

review boards of San Raffaele Hospital in Milan. The research was supported by funds from Compagnia di San Paolo, Torino, Italy; Fondazione Cariplo, Italy and Ministry of Health, Ricerca Finalizzata 2008 and CCM 2010, PRIN 2009, and Telethon, Italy, to D. Toniolo. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the article. We thank the inhabitants of the VB who made this study possible, the local administrations, the MD of the San Raffaele Hospital, and Prof Clara Camaschella for clinical data collection. We also thank Fiammetta Viganò for technical help, Corrado Masciullo and Massimiliano Cocca for building and maintaining the analysis platform.

INGI-CARL: Italian Ministry of Health RF2010 to P. Gasparini and RC2008 to P. Gasparini.

INGI-FVG: Italian Ministry of Health RF2010 to P. Gasparini and RC2008 to P. Gasparini.

JUPITER: Genetic analysis in the JUPITER trial was funded by a grant from AstraZeneca (D.I. Chasman and P.M. Ridker, Co-Pis).

KORA S3: KORA S3 500K blood pressure project was supported by Estonian Research Council, grant IUT34-12 (for M. Laan). The KORA Augsburg studies have been financed by the Helmholtz Zentrum Munchen, German Research Center for Environmental Health, Neuherberg, Germany, and supported by grants from the German Federal Ministry of Education and Research (BMBF). The KORA study group consists of H.-E. Wichmann (speaker), A. Peters, C. Meisinger, T. Illig, R. Holle, J. John, and coworkers who are responsible for the design and conduct of the KORA studies. Part of this work was financed by the German National Genome Research Network (NGFN-2 and NGFNPlus:01GS0823) and supported within the Munich Center of Health Sciences (MC Health) as part of LMUinnovativ.

LBC1921: Phenotype collection in the Lothian Birth Cohort 1921 was supported by the UK's Biotechnology and Biological Sciences Research Council (BBSRC), The Royal Society, and The Chief Scientist Office of the Scottish Government. Genotyping was funded by the BBSRC. The work was undertaken by The University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology, part of the cross council Lifelong Health and Wellbeing Initiative (MR/K026992/1). Funding from the BBSRC and Medical Research Council (MRC) is gratefully acknowledged. We thank the Lothian Birth Cohort 1921 participants and team members who contributed to these studies.

LBC1936: Phenotype collection in the Lothian Birth Cohort 1936 was supported by Age UK (The Disconnected Mind project). Genotyping was funded by the BBSRC. The work was undertaken by The University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology, part of the cross council Lifelong Health and Wellbeing Initiative (MR/K026992/1). Funding from the BBSRC and Medical Research Council (MRC) is gratefully acknowledged. We thank the Lothian Birth Cohort 1936 participants and team members who contributed to these studies.

Lifelines Cohort Study: The Lifelines Cohort Study and generation and management of GWAS genotype data for the Lifelines Cohort Study is supported by the Netherlands Organization of Scientific Research NWO (grant 175.010.2007.006), the Economic Structure Enhancing Fund (FES) of the Dutch government, the Ministry of Economic Affairs, the Ministry of Education, Culture and Science, the Ministry for Health, Welfare and Sports, the Northern Netherlands Collaboration of Provinces (SNN), the Province of Groningen, University Medical Center Groningen, the University of Groningen, Dutch Kidney Foundation, and Dutch Diabetes Research Foundation. We acknowledge the services of the Lifelines Cohort Study, the contributing research centers delivering data to Lifelines, and all the study participants.

LOLIPOP: The LOLIPOP study is funded by the British Heart Foundation (SP/04/002), the Medical Research Council (G0601966 and G0700931), the Wellcome Trust (084723/Z/08/Z), the NIHR (RP-PG-0407-10371), European Union FP7 (EpiMigrant, 279143), and Action on Hearing Loss (G51). The LOLIPOP study is supported by the National Institute for Health Research (NIHR) Comprehensive Biomedical Research Centre Imperial College Healthcare NHS Trust. The work was performed in part at the NIHR/Wellcome Trust Imperial Clinical Research Facility. We thank the participants and research staff who made the study possible.

MESA: This research was supported by the Multi-Ethnic Study of Atherosclerosis (MESA) contracts N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, and N01-HC-95169 and by grants UL1-TR-000040 and UL1-RR-025005 from NCRR. Funding for MESA SHARe genotyping was provided by NHLBI Contract N02-HL-6-4278. The provision of genotyping data was supported in part by the National Center for Advancing Translational Sciences, CTSI grant UL1TR000124, and the National Institute of Diabetes and Digestive and Kidney Disease Diabetes Research Center (DRC) grant DK063491 to the Southern California Diabetes Endocrinology Research Center.

MICROS: The MICROS study was supported by the Ministry of Health and Department of Innovation, Research and University of the Autonomous Province of Bolzano, the South Tyrolean Sparkasse Foundation, and the European Union framework program 6 EUROSPAN project (contract no. LSHG-CT-2006–018947). For the MICROS study, we thank the primary care practitioners Raffaela Stocker, Stefan Waldner, Toni Pizzecco, Josef Plangger, Ugo Marcadent, and the personnel of the Hospital of Silandro (Department of Laboratory Medicine) for their participation and collaboration in the research project.

MIGEN: The MIGEN Consortium was funded by grant R01 HL087676 (NIH, USA), CIBERCV (Instituto Carlos III, Spain), and AGAUR (Generalitat de Catalunya, Spain).

NEO: The NEO study is supported by the participating Departments, the Division, and the Board of Directors of the Leiden University Medical Center and by the Leiden University, Research Profile Area Vascular and Regenerative Medicine. D.O. Mook-Kanamori is supported by Dutch Science Organization (ZonMW-VENI Grant 916.14.023). The authors of the NEO study thank all individuals who participated in the Netherlands Epidemiology in Obesity study, all participating general practitioners for inviting eligible participants, and all research nurses for collection of the data. We thank the NEO study group, Pat van Beelen, Petra Noordijk, and Ingeborg de Jonge for the coordination, laboratory, and data management of the NEO study. The genotyping in the NEO study was supported by the Centre National de Génotypage (Paris, France), headed by Jean-Francois Deleuze.

NESDA: Funding was obtained from the Netherlands Organization for Scientific Research (Geestkracht program grant 10-000-1002); the Center for Medical Systems Biology (CSMB, NOW Genomics), Biobanking and Biomolecular Resources Research Infrastructure (BBMRI-NL), VU University's Institutes for Health and Care Research (EMGO+) and Neuroscience Campus Amsterdam, University Medical Center Groningen, Leiden University Medical Center, and National Institutes of Health (NIH, R01D0042157-01A, MH081802, Grand Opportunity grants 1RC2 MH089951 and 1RC2 MH089995). Part of the genotyping and analyses were funded by the Genetic Association Information Network (GAIN) of the Foundation for the National Institutes of Health. Computing was supported by BiG Grid, the Dutch e-Science Grid, which is financially supported by NWO.

NSPHS: The Northern Swedish Population Health Study (NSPHS) was funded by the Swedish Medical Research Council (Project Number K2007-66X-20270-01-3, 2011–5252, 2012–2884, and 2011–2354), the Foundation for Strategic Research (SSF). NSPHS as part of EUROSPAN (European Special Populations Research Network) was also supported by the European Commission FP6 STRP grant number 01947 (LSHG-CT-2006-01947). This work has also been supported by the Swedish Society for Medical Research (SSMF) and the Swedish Medical Research Council (No. 2015–03327) We are grateful for the contribution of district nurse Svea Hennix for data collection and Inger Jonasson for logistics and coordination of the health survey. We also thank all the participants from the community for their interest and willingness to contribute to this study.

NTR: Funding was obtained from the Netherlands Organization for Scientific Research (NWO) and The Netherlands Organisation for Health Research and Development (ZonMW) grants 904-61-090, 985-10-002, 904-61-193,480-04-004, 400-05-717, Addiction-31160008, Middelgroot-911-09-032, Spinozapremie 56-464-14192, Biobanking, and Biomolecular Resources Research Infrastructure (BBMRI –NL,

184.021.007); the Netherlands Heart Foundation grants 86.083 and 88.042 and 90.313; the VU Institute for Health and Care Research (EMGO+); the European Community's Seventh Framework Program (FP7/2007–2013), ENGAGE (HEALTH-F4-2007–201413); the European Research Council (ERC Advanced, 230374), the Rutgers University Cell and DNA Repository (NIMH U24 MH068457-06), the Avera Institute, Sioux Falls, South Dakota (USA), and the National Institutes of Health (NIH, R01D0042157-01A, MH081802; Grand Opportunity grant 1RC2 MH089951). Part of the genotyping and analyses were funded by the Genetic Association Information Network (GAIN) of the Foundation for the National Institutes of Health. Computing was supported by BiG Grid, the Dutch e-Science Grid, which is financially supported by NWO.

ORCADES: ORCADES was supported by the Chief Scientist Office of the Scottish Government, the Royal Society, the MRC Human Genetics Unit, Arthritis Research UK, and the European Union framework program 6 EUROSPAN project (contract no. LSHG-CT-2006–018947). DNA extractions were performed at the Wellcome Trust Clinical Research Facility in Edinburgh. We acknowledge the invaluable contributions of Lorraine Anderson and the research nurses in Orkney, the administrative team in Edinburgh, and the people of Orkney.

PIVUS: This project was supported by Knut and Alice Wallenberg Foundation (Wallenberg Academy Fellow), European Research Council (ERC Starting Grant), Swedish Diabetes Foundation (grant no. 2013–024), Swedish Research Council (grant no. 2012-1397), and Swedish Heart-Lung Foundation (20120197). The computations were performed on resources provided by SNIC through Uppsala Multidisciplinary Center for Advanced Computational Science (UPPMAX) under Project b2011036. Genetic data analysis was funded by the Wellcome Trust under awards WT098017 and WT090532. We thank the SNP&SEQ Technology Platform in Uppsala (www.genotyping.se) for excellent genotyping.

PROCARDIS: PROCARDIS was supported by the European Community Sixth Framework Program (LSHM-CT-2007–037273), AstraZeneca, the British Heart Foundation, the Swedish Research Council, the Knut and Alice Wallenberg Foundation, the Swedish Heart-Lung Foundation, the Torsten and Ragnar Söderberg Foundation, the Strategic Cardiovascular Program of Karolinska Institutet and Stockholm County Council, the Foundation for Strategic Research, and the Stockholm County Council (560283). M. Farrall and H. Watkins acknowledge the support of the Wellcome Trust core award (090532/Z/09/Z) and the BHF Centre of Research Excellence (RE/13/1/30181). A. Goel and H. Watkins acknowledge European Union Seventh Framework Programme FP7/2007–2013 under grant agreement no. HEALTH-F2-2013–601456 (CVGenes@Target) and A. Goel acknowledge the Wellcome Trust Institutional strategic support fund.

PROSPER: The PROSPER study was supported by an investigator-initiated grant obtained from Bristol-Myers Squibb. Dr J. W. Jukema is an Established Clinical Investigator of the Netherlands Heart Foundation (grant 2001 D 032). Support for genotyping was provided by the seventh framework program of the European commission (grant 223004) and by the Netherlands Genomics Initiative (Netherlands Consortium for Healthy Aging grant 050-060-810).

RS: The generation and management of GWAS genotype data for the Rotterdam Study (RS I, RS II, RS III) was executed by the Human Genotyping Facility of the Genetic Laboratory of the Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands. The GWAS data sets are supported by the Netherlands Organisation of Scientific Research NWO Investments (no. 175.010.2005.011, 911-03-012), the Genetic Laboratory of the Department of Internal Medicine, Erasmus MC, the Research Institute for Diseases in the Elderly (014-93-015; RIDE2), the Netherlands Genomics Initiative (NGI)/Netherlands Organisation for Scientific Research (NWO) Netherlands Consortium for Healthy Aging (NCHA), project no. 050-060-810. The Rotterdam Study is funded by Erasmus Medical Center and Erasmus University, Rotterdam, Netherlands, Organization for the Health Research and Development (ZonMw), the Research Institute for Diseases in the Elderly (RIDE), the Ministry of Education, Culture and Science, the Ministry for Health, Welfare and Sports, the European Commission (DG XII), and the Municipality of Rotterdam. We thank Pascal Arp, Mila Jhamai, Marijn Verkerk, Lizbeth Herrera, and Marjolein Peters, MSc, and Carolina Medina-Gomez, MSc, for their help in creating the GWAS database, and Karol Estrada, PhD, Yurii Aulchenko, PhD, and Carolina Medina-Gomez, MSc, for the creation and analysis of imputed data. We are grateful to the study participants, the staff from the Rotterdam Study, and the participating general practitioners and pharmacists.

SHIP: SHIP is part of the Community Medicine Research net of the University of Greifswald, Germany, which is funded by the Federal Ministry of Education and Research (grants no. 01ZZ9603, 01ZZ0103, and 01ZZ0403), the Ministry of Cultural Affairs, as well as the Social Ministry of the Federal State of Mecklenburg-West Pomerania, and the network 'Greifswald Approach to Individualized Medicine (GANI_MED)' funded by the Federal Ministry of Education and Research (grant 03IS2061A). Genome-wide data have been supported by the Federal Ministry of Education and Research (grant no. 03ZIK012) and a joint grant from Siemens Healthcare, Erlangen, Germany, and the Federal State of Mecklenburg-West Pomerania. The University of Greifswald is a member of the Caché Campus program of the InterSystems GmbH.

Three City-Dijon: The 3-City Study is conducted under a partnership agreement among the Institut National de la Santé et de la Recherche Médicale (INSERM), the University of Bordeaux, and Sanofi-Aventis. The Fondation pour la Recherche Médicale funded the preparation and initiation of the study. The 3C Study is also supported by the Caisse Nationale Maladie des Travailleurs Salariés, Direction Générale de la Santé, Mutuelle Générale de l'Education Nationale (MGEN), Institut de la Longévité, Conseils Régionaux of Aquitaine and Bourgogne, Fondation de France, and Ministry of Research–INSERM Programme "Cohortes et collections de données biologiques." This work was supported by the National Foundation for Alzheimer's Disease and Related Disorders, the Institut Pasteur de Lille, the Centre National de Génotypage, and the LABEX (Laboratory of Excellence program investment for the future) DISTALZ—Development of Innovative Strategies for a Transdisciplinary approach to Alzheimer's disease. G. Chauhan, C. Tzourio, and S. Debette are supported by a grant from the Fondation Leducq. We thank Philippe Amouyel and the UMR1167 Inserm Univ Lille Institut Pasteur de Lille for providing the 3C Dijon cohort SNP replication data funded by a grant from the French National Foundation on Alzheimer's disease and related disorders.

UKHLS: These data are from Understanding Society: The UK Household Longitudinal Study, which is led by the Institute for Social and Economic Research at the University of Essex and funded by the Economic and Social Research Council. The data were collected by NatCen, and the genome-wide scan data were analyzed by the Wellcome Trust Sanger Institute. The Understanding Society DAC have an application system for genetics data, and all use of the data should be approved by them. The application form is available at https://www.understandingsociety.ac.uk/about/health/data.

TRAILS: This research is part of the Tracking Adolescents' Individual Lives Survey (TRAILS). Participating centers of TRAILS include the University Medical Center and University of Groningen, the Erasmus University Medical Center Rotterdam, the University of Utrecht, the Radboud Medical Center Nijmegen, and the Parnassia Bavo group, all in The Netherlands. TRAILS has been financially supported by various grants from the Netherlands Organization for Scientific Research NWO (Medical Research Council program grant GB-MW 940-38-011; ZonMW Brainpower grant 100-001-004; ZonMw Risk Behavior and Dependence grants 60-60600-97-118; ZonMw Culture and Health grant 261-98-710; Social Sciences Council medium-sized investment grants GB-MaGW 480-01-006 and GB-MaGW 480-07-001; Social Sciences Council project grants GB-MaGW 452-04-314 and GB-MaGW 452-06-004; NWO large-sized investment grant 175.010.2003.005; NWO Longitudinal Survey and Panel Funding 481-08-013 and 481-11-001), the Dutch Ministry of Justice (WODC), the European Science Foundation (EuroSTRESS project FP-006), Biobanking and Biomolecular Resources Research Infrastructure BBMRI-NL (CP 32), and the participating universities. Statistical analyses were performed on the Genetic Cluster Computer (http://www.geneticcluster.org) hosted by SURFsara and financially supported by the Netherlands Scientific Organization (NWO 480-05-003 PI: Posthuma) along with a supplement from the Dutch Brain Foundation and the VU University Amsterdam.

TwinGene: This project was supported by grants from the Ministry for Higher Education, the Swedish Research Council (M-2005-1112 and 2009–2298), GenomEUtwin (EU/QLRT-2001-01254; QLG2-CT-2002-01254), NIH grant DK U01-066134, Knut and Alice Wallenberg Foundation (Wallenberg Academy Fellow), European Research Council (ERC Starting Grant), Swedish Diabetes Foundation (grant no. 2013–024), Swedish Research Council (grant no. 2012-1397), and Swedish Heart-Lung Foundation (20120197). We thank the SNP&SEQ Technology Platform in Uppsala (www.genotyping.se) for excellent genotyping. The computations were performed on resources provided by SNIC through Uppsala Multidisciplinary Center for Advanced Computational Science (UPPMAX) under Project b2011036.

TwinsUK: The study was funded by the Wellcome Trust; European Community's Seventh Framework Programme (FP7/2007–2013). The study also receives support from the National Institute for Health Research (NIHR) BioResource Clinical Research Facility and Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London (guysbrc-2012-1). We thank the staff from the Genotyping Facilities at the Wellcome Trust Sanger Institute for sample preparation, quality control, and genotyping; Le Centre National de Génotypage, France, for genotyping; Duke University, NC, for genotyping; and the Finnish Institute of Molecular Medicine, Finnish Genome Center, University of Helsinki. Genotyping was also done by CIDR as part of an NEI/NIH project grant.

UK Biobank_Cardiometabolic Consortium: The UKB-CMC received support from the British Heart Foundation (grant SP/SP/13/2/30111). This research has been conducted using the UK Biobank Resource under application number 236. H.R. Warren, C.P. Cabrera, and M.R. Barnes were funded by the National Institutes for Health Research (NIHR) as part of the portfolio of translational research of the NIHR Biomedical Research Unit at Barts. M. Ren was funded by the National Institute for Health Research (NIHR) Biomedical Research Unit in Cardiovascular Disease at Barts. M. Ren is recipient from China Scholarship Council (No. 2011632047). B. Mifsud holds an MRC eMedLab Medical Bioinformatics Career Development Fellowship, funded from award MR/L016311/1. P. Elliott was funded by the National Institutes for Health Research (NIHR) Imperial College Health Care NHS Trust and Imperial College London Biomedical Research Centre, the UK Medical Research Council and Public Health England as Director of the MRC-PHE Centre for Environment and Health, and the NIHR Health Protection Research Unit on the Health Effects of Environmental Hazards. Some of this work used computing resources provided by the Medical Research Council–funded UK MEDical Bioinformatics partnership programme (UK MED-BIO) (MR/L01632X/1).

ULSAM: This project was supported by Knut and Alice Wallenberg Foundation (Wallenberg Academy Fellow), European Research Council (ERC Starting Grant), Swedish Diabetes Foundation (grant no. 2013–024), Swedish Research Council (grant no. 2012-1397), and Swedish Heart-Lung Foundation (20120197). The computations were performed on resources provided by SNIC through Uppsala Multidisciplinary Center for Advanced Computational Science (UPPMAX) under Project b2011036. Genotyping was funded by the Wellcome Trust under award WT064890. Analysis of genetic data was funded by the Wellcome Trust under awards WT098017 and WT090532. A.P. Morris is a Wellcome Trust Senior Research Fellow in Basic Biomedical Science (WT098017). We thank the SNP&SEQ Technology Platform in Uppsala (www.genotyping.se) for excellent genotyping.

WGHS: The WGHS is supported by the National Heart, Lung, and Blood Institute (HL043851, HL080467, HL09935) and the National Cancer Institute (CA047988 and UM1CA182913) with collaborative scientific support and funding for genotyping provided by Amgen.

YFS: The Young Finns Study has been financially supported by the Academy of Finland: grants 286284, 134309 (Eye), 126925, 121584, 124282, 129378 (Salve), 117787 (Gendi), and 41071 (Skidi); the Social Insurance Institution of Finland; Kuopio, Tampere, and Turku University Hospital Medical Funds (grant X51001); Juho Vainio Foundation; Paavo Nurmi Foundation; Finnish Foundation for Cardiovascular Research; Finnish Cultural Foundation; Tampere Tuberculosis Foundation; Emil Aaltonen Foundation; Yrjö Jahnsson Foundation; Signe and Ane Gyllenberg Foundation; and Diabetes Research Foundation of Finnish Diabetes Association. The expert technical assistance in the statistical analyses by Irina Lisinen is gratefully acknowledged.

Disclosures

We declare competing financial interests (see corresponding section in the online-only Data Supplement).

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Novelty and Significance

What Is New?

- The root origin of hypertension and, hence, blood pressure (BP) variability in the population remains unclear.
- This study adds data to explain the genetic basis of BP variability and identifies genes likely active in BP-regulating pathways.

What Is Relevant?

- The results are of relevance for scientists, clinicians, and pharmacologists interested in hypertension.
- The BP loci and the BP genes identified constitute new leads for the understanding of BP pathogenesis and possibly therapeutic innovation.

Summary

Using 1000 Genomes Project–based imputation in 150 134 European ancestry and independent replication in a further 228 245 individuals, we contribute 8 replicated BP loci to the collection of loci currently known. Using these and previous data, 48 BP genes are identified for priority follow-up.

Online supplement

Novel blood pressure locus and gene discovery using GWAS and expression datasets from blood and the kidney

Running title: Novel blood pressure locus and gene discovery

Louise V. Wain[1], Ahmad Vaez[2,3], Rick Jansen[4], Roby Joehanes[5,6], Peter J. van der Most[2], A. Mesut Erzurumluoglu[1], Paul O'Reilly[7], Claudia P. Cabrera[8,9], Helen R. Warren[8,9], Lynda M. Rose[10], Germaine C. Verwoert[11], Jouke-Jan Hottenga[12], Rona J. Strawbridge[13,14], Tonu Esko[15,16,17], Dan E. Arking[18], Shih-Jen Hwang[19,20], Xiuqing Guo[21], Zoltan Kutalik[22,23], Stella Trompet[24,25], Nick Shrine[1], Alexander Teumer[26,27], Janina S. Ried[28], Joshua C. Bis[29], Albert V. Smith[30,31], Najaf Amin[32], Ilja M. Nolte[2], Leo-Pekka Lyytikäinen[33,34], Anubha Mahajan[35], Nicholas J. Wareham[36], Edith Hofer[37,38], Peter K. Joshi[39], Kati Kristiansson[40], Michela Traglia[41], Aki S. Havulinna[40], Anuj Goel[42,35], Mike A. Nalls[43,44], Siim Sõber[45], Dragana Vuckovic[46,47], Jian'an Luan[36], Fabiola Del Greco M.[48], Kristin L. Ayers[49], Jaume Marrugat[50], Daniela Ruggiero[51], Lorna M. Lopez[52,53,54], Teemu Niiranen[40], Stefan Enroth[55], Anne U. Jackson[56], Christopher P. Nelson[57,58], Jennifer E. Huffman[59], Weihua Zhang[60,61], Jonathan Marten[62], Ilaria Gandin[47], Sarah E Harris[52,63], Tatijana Zemunik[64], Yingchang Lu[65], Evangelos Evangelou[60,66], Nabi Shah[67,68], Martin H. de Borst[69], Massimo Mangino[70,71], Bram P. Prins[72], Archie Campbell[73,74], Ruifang Li-Gao[75], Ganesh Chauhan[76,77], Christopher Oldmeadow[78], Gonçalo Abecasis[79], Maryam Abedi[80], Caterina M. Barbieri[41], Michael R. Barnes[8,9], Chiara Batini[1], John Beilby[81,82,83], BIOS Consortium[84], Tineka Blake[1], Michael Boehnke[56], Erwin P. Bottinger[65], Peter S. Braund[57,58], Morris Brown[8,9], Marco Brumat[47], Harry Campbell[39], John C. Chambers[60,61,85], Massimiliano Cocca[47], Francis Collins[86], John Connell[87], Heather J. Cordell[88], Jeffrey J. Damman[89], Gail Davies[52,90], Eco J. de Geus[12], Renée de Mutsert[75], Joris Deelen[91], Yusuf Demirkale[92], Alex S.F. Doney[67], Marcus Dörr[93,27], Martin Farrall[42,35], Teresa Ferreira[35], Mattias Frånberg[13,14,94], He Gao[60], Vilmantas Giedraitis[95], Christian Gieger[96], Franco Giulianini[10], Alan J. Gow[52,97], Anders Hamsten[13,14], Tamara B. Harris[98], Albert Hofman[11,99], Elizabeth G. Holliday[78], Jennie Hui[81,82,100,83], Marjo-Riitta Jarvelin[101,102,103,104], Åsa Johansson[55], Andrew D. Johnson[6,105], Pekka Jousilahti[40], Antti Jula[40], Mika Kähönen[106,107], Sekar Kathiresan[108,109,110], Kay-Tee Khaw[111], Ivana Kolcic[112], Seppo Koskinen[40], Claudia Langenberg[36], Marty Larson[6], Lenore J. Launer[98], Benjamin Lehne[60], David C.M. Liewald[52,90], Lifelines Cohort Study[113], Li Lin[114], Lars Lind[115], François Mach[114], Chrysovalanto Mamasoula[116], Cristina Menni[70], Borbala Mifsud[8], Yuri Milaneschi[117], Anna Morgan[47], Andrew D. Morris[118], Alanna C. Morrison[119], Peter J. Munson[92], Priyanka Nandakumar[18],

Quang Tri Nguyen[92], Teresa Nutile[51], Albertine J. Oldehinkel[120], Ben A. Oostra[32], Elin Org[15], Sandosh Padmanabhan[121,74], Aarno Palotie[122], Guillaume Paré[123], Alison Pattie[90], Brenda W.J.H. Penninx[117], Neil Poulter[124], Peter P. Pramstaller[48,125,126], Olli T. Raitakari[127,128], Meixia Ren[8,129], Kenneth Rice[130], Paul M. Ridker[10,131], Harriëtte Riese[120], Samuli Ripatti[122], Antonietta Robino[132], Jerome I. Rotter[133], Igor Rudan[39], Yasaman Saba[134], Aude Saint Pierre[48,135], Cinzia F. Sala[41], Antti-Pekka Sarin[122], Reinhold Schmidt[37], Rodney Scott[78,136,137], Marc A. Seelen[69], Denis C. Shields[138], David Siscovick[139], Rossella Sorice[51,140], Alice Stanton[141], David J. Stott[142], Johan Sundström[115], Morris Swertz[143], Kent D. Taylor[144,145], Simon Thom[146], Ioanna Tzoulaki[60], Christophe Tzourio[76,77,147], André G. Uitterlinden[11,148], Understanding Society Scientific group[84], Uwe Völker[149,27], Peter Vollenweider[150], Sarah Wild[39], Gonneke Willemsen[12], Alan F. Wright[62], Jie Yao[21], Sébastien Thériault[123], David Conen[151], Attia John[78,136,137], Peter Sever[152], Stéphanie Debette[76,77,153], Dennis O. Mook-Kanamori[75,154], Eleftheria Zeggini[72], Tim D. Spector[70], Pim van der Harst[155], Colin N.A. Palmer[67], Anne-Claire Vergnaud[60], Ruth J.F. Loos[36,156,157], Ozren Polasek[112], John M. Starr[52,158], Giorgia Girotto[47,46], Caroline Hayward[159,74], Jaspal S. Kooner[160,61,85], Cecila M. Lindgren[17,35], Veronique Vitart[59], Nilesh J. Samani[57,58], Jaakko Tuomilehto[161,162,163,164], Ulf Gyllensten[55], Paul Knekt[40], Ian J. Deary[52,90], Marina Ciullo[51,140], Roberto Elosua[50], Bernard D. Keavney[165], Andrew A. Hicks[48], Robert A. Scott[36], Paolo Gasparini[46,47], Maris Laan[45,166], YongMei Liu[167], Hugh Watkins[42,35], Catharina A. Hartman[120], Veikko Salomaa[40], Daniela Toniolo[41], Markus Perola[40,122,168], James F. Wilson[39,62], Helena Schmidt[134,169], Jing Hua Zhao[36], Terho Lehtimäki[33,34], Cornelia M. van Duijn[32], Vilmundur Gudnason[30,31], Bruce M. Psaty[29,170,171,172], Annette Peters[28], Rainer Rettig[173], Alan James[174,175], J Wouter Jukema[24], David P. Strachan[176], Walter Palmas[177], Andres Metspalu[15], Erik Ingelsson[178,179], Dorret I. Boomsma[12], Oscar H. Franco[11], Murielle Bochud[22], Christopher Newton-Cheh[180,108,110,17], Patricia B. Munroe[8,9], Paul Elliott[104], Daniel I. Chasman[10,131], Aravinda Chakravarti[18], Joanne Knight[181], Andrew P. Morris[182,35], Daniel Levy[183,20], Martin D. Tobin[1], Harold Snieder[2*], Mark J. Caulfield[8,9*], Georg B. Ehret[18,114*]

*: contributing equally

Corresponding authors: Georg B. Ehret (georg@rhone.ch), tel. +41 22 3727200, fax +41 22 - 372 72 29, Louise V. Wain (louisewain@le.ac.uk), tel. +44 116 229 7252, fax +44 116 229 7250

AFFILIATIONS

1. Department of Health Sciences, University of Leicester, Leicester LE1 7RH, UK
2. Department of Epidemiology, University of Groningen, University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands
3. Research Institute for Primordial Prevention of Non-communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran
4. Department of Psychiatry, VU University Medical Center, Neuroscience Campus Amsterdam, Amsterdam, The Netherlands
5. Hebrew SeniorLife, Harvard Medical School, 1200 Centre Street Room #609, Boston, MA 02131, USA

6. National Heart, Lung and Blood Institute's Framingham Heart Study, Framingham, MA 01702, USA
7. Institute of Psychiatry, Psychology and Neuroscience, King's College London, London SE5 8AF, UK
8. Clinical Pharmacology, William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, EC1M 6BQ, UK
9. NIHR Barts Cardiovascular Biomedical Research Unit, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, EC1M 6BQ, UK
10. Division of Preventive Medicine, Brigham and Women's Hospital, Boston MA 02215, USA
11. Department of Epidemiology, Erasmus MC, Rotterdam, 3000CA, The Netherlands
12. Department of Biological Psychology, Vrije Universiteit, Amsterdam, EMGO+ institute, VU University medical center, Amsterdam, The Netherlands
13. Cardiovascular Medicine Unit, Department of Medicine Solna, Karolinska Institutet, Stockholm, 17176, Sweden
14. Centre for Molecular Medicine, Karolinska Universitetsjukhuset, Solna, 171 76, Sweden
15. Estonian Genome Center, University of Tartu, Tartu, 51010, Estonia
16. Divisions of Endocrinology/Children's Hospital, Boston, MA 02115, USA
17. Broad Institute of Harvard and MIT, Cambridge, MA 02139 USA
18. Center for Complex Disease Genomics, McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA
19. The Population Science Branch, Division of Intramural Research, National Heart Lung and Blood Institute national Institute of Health, Bethesda, MD 20892, USA
20. The Framingham Heart Study, Framingham MA 01702, USA
21. The Institute for Translational Genomics and Population Sciences, Department of Pediatrics, LABioMed at Harbor-UCLA Medical Center, 1124 W. Carson Street, Torrance, CA 90502, USA
22. Institute of Social and Preventive Medicine, Lausanne University Hospital, Route de la Corniche 10, 1010 Lausanne, Switzerland
23. Swiss Institute of Bioinformatics, Lausanne, Switzerland
24. Department of Cardiology, Leiden University Medical Center, Leiden, 2300RC, The Netherlands
25. Department of Gerontology and Geriatrics, Leiden University Medical Center, Leiden, 2300RC, The Netherlands
26. Institute for Community Medicine, University Medicine Greifswald, Greifswald, 17475, Germany
27. DZHK (German Centre for Cardiovascular Research), partner site Greifswald, Greifswald, 17475, Germany
28. Institute of Epidemiology II, Helmholtz Zentrum München, Neuherberg 85764, Germany
29. Cardiovascular Health Research Unit, Department of Medicine, University of Washington, Seattle, WA 98101, USA
30. Icelandic Heart Assoication, Kopavogur, Iceland
31. Faculty of Medicine, University of Iceland, Reykjavik, Iceland
32. Genetic Epidemiology Unit, Department of Epidemiology, Erasmus MC, Rotterdam, 3000CA, The Netherlands
33. Department of Clinical Chemistry, Fimlab Laboratories, Tampere 33520, Finland

34. Department of Clinical Chemistry, Faculty of Medicine and Life Sciences, University of Tampere, Tampere 33014, Finland
35. Wellcome Trust Centre for Human Genetics, University of Oxford, Roosevelt Drive, Oxford OX3 7BN, UK
36. MRC Epidemiology Unit, University of Cambridge School of Clinical Medicine, Institute of Metabolic Science, Cambridge Biomedical Campus, Cambridge, CB2 0QQ, UK
37. Clinical Division of Neurogeriatrics, Department of Neurology, Medical University Graz, Auenbruggerplatz 22, 8036 Graz, Austria
38. Institute of Medical Informatics, Statistics and Documentation, Medical University Graz, Auenbruggerplatz 2, 8036 Graz, Austria
39. Centre for Global Health Research, Usher Institute of Population Health Sciences and Informatics, University of Edinburgh EH89AG, Scotland, UK
40. Department of Health, National Institute for Health and Welfare (THL), Helsinki, Finland
41. Division of Genetics and Cell Biology, San Raffaele Scientific Institute, 20132 Milano, Italy
42. Division of Cardiovascular Medicine, Radcliffe Department of Medicine, University of Oxford, Oxford, OX3 9DU, UK
43. Laboratory of Neurogenetics, National Institute on Aging, NIH, Bethesda, 20892, USA
44. Data Tecnica International, Glen Echo, MD, USA
45. Human Molecular Genetics Research Group, Institute of Molecular and Cell Biology, University of Tartu, Riia St.23, 51010 Tartu, Estonia
46. Medical Genetics, IRCCS-Burlo Garofolo Children Hospital, Via dell'Istria 65, Trieste, Italy
47. Department of Medical, Surgical and Health Sciences, University of Trieste, Strada di Fiume 447, Trieste, 34100, Italy
48. Institute for Biomedicine, Eurac Research, Affiliated Institute of the University of Lübeck, Bolzano, Italy
49. Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA
50. Cardiovascular Epidemiology and Genetics, IMIM. Dr Aiguader 88, Barcelona, 08003, Spain
51. Institute of Genetics and Biophysics A. Buzzati-Traverso, CNR, via P. Castellino 111, 80131 Napoli, Italy
52. Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, 7 George Square, Edinburgh EH8 9JZ, UK
53. Department of Psychiatry, Royal College of Surgeons in Ireland, Education and Research Centre, Beaumont Hospital, Dublin, Ireland
54. University College Dublin, UCD Conway Institute, Centre for Proteome Research, UCD, Belfield, Dublin, Ireland
55. Department of Immunology, Genetics and Pathology, Uppsala Universitet, Science for Life Laboratory, Husargatan 3, Uppsala, SE-75108, Sweden
56. Department of Biostatistics and Center for Statistical Genetics, University of Michigan, Ann Arbor, MI 48109, USA
57. Department of Cardiovascular Sciences, University of Leicester, Leicester LE3 9QP, UK
58. NIHR Leicester Cardiovascular Biomedical Research Unit, Glenfield Hospital, Leicester LE3 9QP, UK

59. MRC Human Genetics Unit, IGMM, University of Edinburgh, Western General Hospital, Edinburgh, EH4 2XU Scotland, UK
60. Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London W2 1PG, United Kingdom
61. Department of Cardiology, Ealing Hospital, London North West Healthcare NHS Trust, Uxbridge Rd, Southall UB1 3HW, UK
62. MRC Human Genetics Unit, Institute of Genetics and Molecular Medicine, University of Edinburgh, Western General Hospital, Crewe Road, Edinburgh, EH4 2XU, UK
63. Medical Genetics Section, University of Edinburgh Centre for Genomic and Experimental Medicine and MRC Institute of Genetics and Molecular Medicine, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, UK
64. Department of Medical Biology, Faculty of Medicine, University of Split, Croatia
65. The Charles Bronfman Institute for Personalized Medicine, Icachn School of Medicine at Mount Sinai, New York, NY 10029, USA
66. Department of Hygiene and Epidemiology, University of Ioannina Medical School, Ioannina, 45110, Greece
67. Medical Research Institute, University of Dundee, Ninewells Hospital and Medical School, Dundee, DD1 9SY, Scotland, UK
68. Department of Pharmacy, COMSATS Institute of Information Technology, Abbottabad, 22060, Pakistan
69. Department of Internal Medicine, Division of Nephrology, University of Groningen, University Medical Center Groningen, PO Box 30001, 9700 RB Groningen, The Netherlands
70. Department of Twin Research and Genetic Epidemiology, King's College London, Lambeth Palace Rd, London, SE1 7EH, UK
71. National Institute for Health Research Biomedical Research Centre, London SE1 9RT, UK
72. Department of Human Genetics, Wellcome Trust Sanger Institute, CB10 1HH, United Kingdom
73. Medical Genetics Section, Centre for Genomic and Experimental Medicine, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh EH4 2XU, UK
74. Generation Scotland, Centre for Genomic and Experimental Medicine, University of Edinburgh, Edinburgh, EH4 2XU, UK
75. Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands
76. INSERM U 1219, Bordeaux Population Health center, Bordeaux, France
77. Bordeaux University, Bordeaux, France
78. Hunter Medical Research Institute, New Lambton, NSW 2305, Australia
79. Center for Statistical Genetics, Dept. of Biostatistics, SPH II, 1420 Washington Heights, Ann Arbor, MI 48109-2029, USA
80. Department of Genetics and Molecular Biology, Isfahan University of Medical Sciences, Isfahan, Iran
81. Busselton Population Medical Research Institute, Western Australia
82. PathWest Laboratory Medicine of Western Australia, NEDLANDS, Western Australia
83. School of Pathology and Laboratory Medicine, The University of Western Australia, NEDLANDS, Western Australia
84. For a complete list of contributing authors, please see Supporting Information.
85. Imperial College Healthcare NHS Trust, London, UK

86. Medical Genomics and Metabolic Genetics Branch, National Human Genome Research Institute, NIH, Bethesda, MD 20892, USA
87. University of Dundee, Ninewells Hospital & Medical School, Dundee, DD1 9SY, UK
88. Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, UK
89. Department of Pathology, Amsterdam Medical Center, Meibergdreef 9, 1105 AZ, Amsterdam, The Netherlands
90. Department of Psychology, University of Edinburgh, 7 George Square, Edinburgh, EH8 9JZ, UK
91. Department of Molecular Epidemiology, Leiden University Medical Center, Leiden, 2300RC, The Netherlands
92. Center for Information Technology, NIH, USA
93. Department of Internal Medicine B, University Medicine Greifswald, Greifswald, 17475, Germany
94. Department of Numerical Analysis and Computer Science, Stockholm University, Lindstedtsvägen 3, Stockholm, 100 44, Sweden
95. Department of Public Health and Caring Sciences, Geriatrics, Uppsala 752 37, Sweden
96. Helmholtz Zentrum Muenchen, Deutsches Forschungszentrum fuer Gesundheit und Umwelt (GmbH), Ingolstaedter Landstr. 1, 85764 Neuherberg, München, Germany
97. Department of Psychology, School of Social Sciences, Heriot-Watt University, Edinburgh, EH14 4AS, UK
98. Intramural Research Program, Laboratory of Epidemiology, Demography, and Biometry, National Institute on Aging, USA
99. Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA 02115, USA
100. School of Population and Global Health, The University of Western Australia, NEDLANDS, Western Australia
101. Center For Life-course Health Research, P.O. Box 5000, FI-90014 University of Oulu, Finland
102. Biocenter Oulu, P.O. Box 5000, Aapistie 5A, FI-90014 University of Oulu, Finland
103. Unit of Primary Care, Oulu University Hospital, Kajaanintie 50, P.O. Box 20, FI-90220 Oulu, 90029 OYS, Finland
104. MRC-PHE Centre for Environment and Health, Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, Norfolk Place, W2 1PG London, UK
105. National Heart, Lung and Blood Institute, Cardiovascular Epidemiology and Human Genomics Branch, Bethesda, MD 20814, USA
106. Department of Clinical Physiology, Tampere University Hospital, Tampere 33521, Finland
107. Department of Clinical Physiology, Faculty of Medicine and Life Sciences, University of Tampere, Tampere 33014, Finland
108. Cardiovascular Research Center, Massachusetts General Hospital, Boston, MA 02114, USA
109. Center for Human Genetics, Massachusetts General Hospital, 185 Cambridge Street, Boston, MA 02114, USA
110. Program in Medical and Population Genetics, Broad Institute, 7 Cambridge Center, Cambridge, MA 02142, USA

111. Department of Public Health and Primary Care, Institute of Public Health, University of Cambridge, Cambridge CB2 2SR, UK
112. Department of Public Health, Faculty of Medicine, University of Split, Croatia
113. See complete listing of contributors in the Supporting Information.
114. Cardiology, Department of Medicine, Geneva University Hospital, Rue Gabrielle-Perret-Gentil 4, 1211 Geneva 14, Switzerland
115. Department of Medical Sciences, Cardiovascular Epidemiology, Uppsala University, Uppsala 751 85, Sweden
116. Institute of Health and Society, Newcastle University, Newcastle upon Tyne, UK
117. Department of Psychiatry, EMGO Institute for Health and Care Research, VU University Medical Center, A.J. Ernststraat 1187, 1081 HL Amsterdam, The Netherlands
118. School of Molecular, Genetic and Population Health Sciences, University of Edinburgh, Medical School,Teviot Place, Edinburgh, EH8 9AG, Scotland, UK
119. Department of Epidemiology, Human Genetics and Environmental Sciences, School of Public Health, University of Texas Health Science Center at Houston, 1200 Pressler St., Suite 453E, Houston, TX 77030, USA
120. Interdisciplinary Center Psychopathology and Emotion Regulation (IPCE), University of Groningen, University Medical Center Groningen, Hanzeplein 1, PO Box 30001, 9700 RB Groningen, The Netherlands
121. British Heart Foundation Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow G12 8TA, UK
122. Institute for Molecular Medicine Finland (FIMM), University of Helsinki, Helsinki, Finland
123. Department of Pathology and Molecular Medicine, McMaster University, 1280 Main St W, Hamilton, L8S 4L8, Canada
124. School of Public Health, Imperial College London, W2 1PG, UK
125. Department of Neurology, General Central Hospital, Bolzano, Italy
126. Department of Neurology, University of Lübeck, Lübeck, Germany
127. Department of Clinical Physiology and Nuclear Medicine, Turku University Hospital, Turku 20521, Finland
128. Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku, Turku 20014, Finland
129. Department of Cardiology, Fujian Provincial Hospital, Fujian Medical University, Fuzhou 350001, China
130. Department of Biostatistics University of Washington, Seattle, WA 98101, USA
131. Harvard Medical School, Boston MA, USA
132. Institute for Maternal and Child Health IRCCS Burlo Garofolo, Via dell'Istria 65, Trieste, 34200, Italy
133. The Institute for Translational Genomics and Population Sciences, Departments of Pediatrics and Medicine, LABioMed at Harbor-UCLA Medical Center, 1124 W. Carson Street, Torrance, CA 90502, USA
134. Institute of Molecular Biology and Biochemistry, Centre for Molecular Medicine, Medical University of Graz, Harrachgasse 21, 8010 Graz, Austria
135. INSERM U1078, Etablissement Français du Sang, 46 rue Félix Le Dantec, CS 51819, Brest Cedex 2 29218, France
136. Faculty of Health, University of Newcastle, Callaghan NSW 2308, Australia

137. John Hunter Hospital, New Lambton NSW 2305, Australia
138. School of Medicine, Conway Institute, University College Dublin, Ireland
139. The New York Academy of Medicine. 1216 5th Ave, New York, NY 10029, USA
140. IRCCS Neuromed, Pozzilli, Isernia, Italy
141. Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland, Dublin 2, Ireland
142. Institute of Cardiovascular and Medical Sciences, Faculty of Medicine, University of Glasgow, United Kingdom
143. Department of Genetics, University of Groningen, University Medical Center Groningen, PO Box 30001, 9700 RB Groningen, The Netherlands
144. Institute for Translational Genomics and Population Sciences. Los Angeles BioMedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA, 90502, USA
145. Division of Genetic Outcomes, Department of Pediatrics, Harbor-UCLA Medical Center, Torrance, CA, 90502, USA
146. International Centre for Circulatory Health, Imperial College London, W2 1PG, UK
147. Department of Public Health, Bordeaux University Hospital, Bordeaux, France
148. Department of Internal Medicine, Erasmus MC, Rotterdam, 3000CA, The Netherlands
149. Interfaculty Institute for Genetics and Functional Genomics, University Medicine Greifswald, Greifswald, 17475, Germany
150. Department of Internal Medicine, Lausanne Universiyt Hospital, CHUV, 1011 Lausanne, Switzerland
151. Population Health Research Institute, McMaster University, Hamilton Ontario, Canada
152. National Heart and Lung Institute, Imperial College London, W2 1PG, UK
153. Department of Neurology, Bordeaux University Hospital, Bordeaux, France
154. Department of Public Health and Primary Care, Leiden University Medical Center, Leiden, The Netherlands
155. Department of Cardiology, University of Groningen, University Medical Center Groningen, PO Box 30001, 9700 RB Groningen, The Netherlands
156. The Charles Bronfman Institute for Personalized Medicine, The Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA
157. Mindich Child health Development Institute, The Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA
158. Alzheimer Scotland Dementia Research Centre, University of Edinburgh, 7 George Square, Edinburgh, EH8 9JZ, UK
159. Medical Research Council Human Genetics Unit, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh EH4 2XU, UK
160. National Heart and Lung Institute, Imperial College London, Hammersmith Hospital Campus, Du Cane Road, London W12 0NN, UK
161. Diabetes Prevention Unit, National Institute for Health and Welfare, 00271 Helsinki, Finland
162. South Ostrobothnia Central Hospital, 60220 Seinäjoki, Finland
163. Red RECAVA Grupo RD06/0014/0015, Hospital Universitario La Paz, 28046 Madrid, Spain
164. Centre for Vascular Prevention, Danube-University Krems, 3500 Krems, Austria
165. Division of Cardiovascular Sciences, The University of Manchester, Manchester, UK and Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK

166. Institute of Biomedicine and Translational Medicine, University of Tartu, Ravila Str. 19, 50412 Tartu, Estonia
167. Division of Public Health Sciences, Wake Forest School of Medicine, Winston-Salem, 27106, USA
168. University of Tartu, Tartu, Estonia
169. Department of Neurology, Medical University Graz, Auenbruggerplatz 22, 8036 Graz, Austria
170. Department of Epidemiology University of Washington, Seattle, WA 98101, USA
171. Department of Health Services, University of Washington, Seattle, WA 98101, USA
172. Group Health Research Institute, Group Health, Seattle, WA, 98101, USA
173. Institute of Physiology, University Medicine Greifswald, Karlsburg, 17495, Germany
174. Department of Pulmonary Physiology and Sleep, Sir Charles Gairdner Hospital, Hospital Avenue, Nedlands 6009,H57, Western Australia
175. School of Medicine and Pharmacology, University of Western Australia, Australia
176. Population Health Research Institute, St George's, University of London, London SW17 0RE, UK
177. Department of Medicine, Columbia University Medical Center, 622 West 168th Street, PH 9, East, 107, New York, NY 10032, USA
178. Department of Medical Sciences, Molecular Epidemiology and Science for Life Laboratory, Uppsala University, Uppsala 752 37, Sweden
179. Department of Medicine, Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, CA 94305, USA
180. Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA 02114, USA
181. Data Science Institute and Lancaster Medical School, Lancaster University, LA1 4YG, UK
182. Department of Biostatistics, University of Liverpool, Block F, Waterhouse Building, 1-5 Brownlow Street, Liverpool L69 3GL, UK
183. The population Science Branch, Division of Intramural Research, National Heart Lung and Blood Institute national Institute of Health, Bethesda MD 20892, USA

Corresponding authors: Louise V. Wain (louisewain@le.ac.uk) and Georg B. Ehret (georg@jhmi.edu)

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Studies contributing to discovery (Stage 1) of signals of association with systolic (SBP) and diastolic blood pressure (DBP), and Pulse Pressure (PP)

All studies contributing genome-wide association results for SBP, DBP and PP to the discovery meta-analysis undertook genome-wide imputation to the 1000 Genomes Project reference panel. Study details are given in **Supplementary Table 1 (S1)** (including study design, ethnicity and key references), **Supplementary Table 2 (S2)** (overall descriptive statistics of SBP, DBP, PP, hypertension, age, sex and BMI, and blood pressure measurement details), **Supplementary Table 3 (S3)** (quality control, association testing method and adjustments for ancestry and relatedness) and **Supplementary Table 4 (S4)** (genotyping and imputation details).

Studies contributing association results for variants selected for replication/follow-up (Stage 2)

Details of all studies contributing data for the 61 variants followed-up to stage 2 are given in **Supplementary Table 5 (S5)**.

Studies contributing eQTL data

SABRe

The expression quantitative trait locus (eQTL) analysis was performed in 5,257 whole blood samples of Framingham Heart Study (FHS) Offspring and Generation 3 cohort participants having both genotypic and expression datasets. The genotypic data came from Affymetrix 500K and 50K MIPS platforms, imputed to the 1000-Genomes "Cosmopolitan" panel. Only 8,510,936 variants having minimum allele frequency (MAF) ≥ 0.01 and imputation R^2≥0.3 were chosen. The expression data came from Affymetrix Human Exon Array ST v1.0, processed using robust multi-chip average (RMA) algorithm under Affymetrix Power Tools (APT), yielding a total of 17,873 transcripts in log base 2 values. The association was performed on the expression values as the dependent variable, additive genetic dosage as an independent variable, adjusted for sex, age, imputed blood cell fractions, 20 factors of Bayesian confounding factors (PEER[1]), and familial correlations. The full details of eQTL analysis can be found in Joehanes, et al. Integrated Genome-wide Analysis of Expression Quantitative Trait Loci Identifies Putative Disease-Related Genes and Pathways.

The linkage disequilibrium (LD) database for the FHS was computed from 8,481 genotypic samples from individuals of FHS cohorts (Original, Offspring, and Generation 3), using the squared Pearson correlation of the imputed additive genotypic dosage, as defined by Hill and Robertson 1968[2]. All pairwise LDs of at least 0.1 were stored in the database and were used in this analysis.

NESDA/NTR

Subjects for eQTL analysis: The two parent projects that supplied data for the eQTL analysis are large-scale longitudinal studies: the Netherlands Study of Depression and Anxiety (NESDA)[3] and the Netherlands Twin Registry (NTR)[4]. NESDA and NTR studies were approved by the Central Ethics Committee on Research Involving Human Subjects of the VU University Medical Center, Amsterdam (institutional review board [IRB] number IRB-2991 under Federal wide Assurance 3703; IRB/institute codes: NESDA 03-183 and NTR 03-180). All participants provided written informed consent. The sample used for eQTL analysis consisted of 4,896 subjects with European ancestry (1,880 unrelated subjects from NESDA, 559 MZ twin pairs, 102 siblings of MZ twins (one per MZ twin pair), 594 DZ

twin pairs, 111 siblings of DZ twins (one per DZ twin pair), 51 parent-sibling trios and 344 unrelated subjects from NTR). The age of the participants ranged from 17 to 88 years (mean=38, *SD*=13); 65% of the sample was female.

Blood sampling, RNA extraction, and RNA expression measurement: Study protocols and biological sample collection methods were harmonized between NTR and NESDA. RNA processing and measurements have been described in detail previously[5, 6]. Venous blood samples were drawn in the morning after an overnight fast. Heparinized whole blood samples were transferred within 20 minutes of sampling into PAXgene Blood RNA tubes (Qiagen, Valencia, California, USA) and stored at −20°C. Gene expression assays were conducted at the Rutgers University Cell and DNA Repository. Samples were hybridized to Affymetrix U219 arrays (Affymetrix, Santa Clara, CA) containing 530,467 probes summarized in 49,293 probe sets. Array hybridization, washing, staining, and scanning were carried out in an Affymetrix GeneTitan System per the manufacturer's protocol. Gene expression data were required to pass standard Affymetrix QC metrics (Affymetrix expression console) before further analysis. We excluded from further analysis probes that did not map uniquely to the hg19 (Genome Reference Consortium Human Build 37) reference genome sequence, as well as probes targeting a messenger RNA (mRNA) molecule resulting from transcription of a DNA sequence containing a single nucleotide polymorphism (based on the dbSNP137 common database). After this filtering step, data for analysis remained for 423,201 probes, which could be summarized into 44,241 probe sets targeting 18,238 genes. Normalized probe set expression values were obtained using Robust Multi-array Average (RMA) normalization as implemented in the Affymetrix Power Tools software (APT, version 1.12.0, Affymetrix). Data for samples that displayed a low average Pearson correlation with the probe set expression values of other samples, and samples with incorrect sex-chromosome expression were removed, leaving 4,896 subjects for analysis.

Gene expression normalization: Inverse quantile normal transformation was applied for each expression probe set to obtain normal distributions. The transformed probeset data were then residualized by multiple linear regression with respect to the covariates sex, age, body mass index (kg/m^2), blood hemoglobin level, smoking status, several technical covariates (plate, well, hour of blood sampling, lab, days between blood sampling and RNA extraction and average correlation with other samples) and the scores on three principal components (PCs) as estimated from the imputed SNP genotype data[7] using the EIGENSOFT package. The residuals resulting from the linear regression analysis of the probe set intensity values onto the covariates listed above were subjected to a principal component analysis, with the aim to further filter out environmental variation from the data[8]. For each principal component a genome-wide association study was performed, and the first 50 principal components without genome-wide significant SNP associations were removed from the residualized probeset data before eQTL analysis.

DNA extraction and SNP genotyping and imputation: DNA was extracted from peripheral blood or buccal swabs as has described previously[9]. SNP genotype pre-imputation quality control, haplotype phasing and 1000 Genomes imputation were performed as described previously[10]. Imputed SNP genotypes were coded into reference allele dosage format, and filtered at MAF>0.01 and HW *P*>1E−04 resulting in 8,158,830 remaining SNPs for eQTL analysis.

eQTL analysis and FDR based on permutations accounting for relatedness: eQTL effects were detected with a linear model approach using MatrixeQTL[11] with expression level as dependent variable and SNP genotype values as independent variable. To account for relatedness of the NTR subjects, permutations were performed where in each permutation the relatedness was preserved (i.e, in each permutation the genotypes of the MZ twin pairs were assigned the expression of a random MZ twin pair, the genotypes of the DZ twin pairs were assigned the expression of a random DZ twin pair, the genotypes of the MZ twin pairs with sibling were assigned the expression of a random MZ twin pair with sibling, the genotypes of the parent-sibling trios were assigned the expression of a random parent-sibling trios and the genotypes of the unrelated subjects were

assigned the expression of a random subject from the group of unrelated subjects). For each permutation the complete *cis* or trans eQTL analysis was repeated, and after each permutation the *P*-value threshold for rejecting at FDR<0.05 was computed. This can be done in 2 ways: 1) divide the total number of significant eQTLs in the permuted data by the total number of significant eQTLs in the unpermuted data (=false positives/true positives) or 2) divide the total number of probesets with a significant eQTL in the permuted data by the total number of probesets with a significant eQTLs in the unpermuted data. We used the the second method which is more conservative and was proposed by[8] to account for large LD blocks with strong eQTL effects that inflate the FDR when using the first method. Similar as what was observed previously[8] only 10 permutations were needed to have the *P*-value threshold corresponding to FDR<5% converging. Of note, the eQTL P-values reported in this manuscript are based on the complete sample with related subject and thus are too liberal: however the FDR takes into account the family structure and should be used to draw conclusions. The reported betas from the linear models can be correctly estimated from samples containing related subjects.

eQTL effects were defined as *cis* when probe set–SNP pairs were at distance < 1M base pairs (Mb), and as *trans* when the SNP and the probe set were separated by more than 1 Mb on the genome according to hg19. For each probe set that displayed a statistically significant association with at least one SNP in the *cis* region, we identified the most significantly associated SNP (top eQTL). Conditional eQTL analysis was carried out by first residualizing probeset expression using the corresponding top eQTL and then repeating the eQTL analysis using the residualized data.

For this analysis, of the 164 SNPs requested, 12 were not available in the NESDA/NTR dataset leaving 152 for further analysis.

BIOS

eQTL analyses performed by the BIOS consortium have been described previously[12]. The method described in these papers are summarized below. Genotype data were harmonized towards the Genome of the Netherlands (GoNL)[13] using Genotype Hamonizer and subsequently imputed per cohort using Impute2 using the GoNL reference panel (v5). We removed SNPs with an imputation info-score below 0.5, a HWE *P*-value smaller than 10^{-4}, a call rate below 95% or a minor allele frequency smaller than 0.05. Total RNA from whole blood was deprived of globin using Ambions GLOBINclear kit and subsequently processed for sequencing using Illumina's Truseq version 2 library preparation kit. Paired-end sequencing of 2x50bp was performed using Illumina's Hiseq2000, pooling samples at 10 per lane, and aiming for >15M read pairs per sample. Finally, read sets per sample were generated using CASAVA, retaining only reads passing Illumina's Chastity Filter for further processing. The quality of the raw reads was checked using FastQC. The adaptors identified by FastQC (v0.10.1) were clipped using cutadapt (v1.1) applying default settings (min overlap 3, min length). Sickle (v1.200) (https://github.com/najoshi/sickle) used to trim low quality ends of the reads (min length 25, min quality 20). Read alignment was performed using STAR 2.3.0e. To avoid reference mapping bias all GoNL SNPs with MAF > 0.01 in the reference genome were masked. Read pairs with at most 8 mismatches, mapping to at most 5 positions were used. Mapping statistics from the BAM files were acquired through Samtools flagstat (v0.1.19-44428cd). The 5' and 3' coverage bias, duplication rate and insert sizes were assessed using Picard tools (v1.86). We estimated expression on the gene, exon, exon ratio and polyA ratio levels using Ensembl v.71 annotation (which corresponds to Gencode v.16). Overlapping exons (on either of the two strands) were merged into meta-exons and expression was quantified for the whole meta-exon. For that, custom scripts were developed which uses coverage per base from coverageBed and intersectBed from the Bedtools suite (v2.17.0) and R (v2.15.1). This resulted in base counts per exon or meta-exon. Expression data was first normalized using Trimmed Mean of M-values (TMM). Then expression values were log2 transformed, probe and sample means were centred to zero. To correct for batch effects, principal component analysis (PCA) was run on the sample correlation matrix and the first 25

PCs were removed. We saw that removing these PCs resulted in highest number of eQTLs detected. To ascertain that none of these 25 PCs are under genetic control, we ran separate QTL mapping on each principal component and ensured that there were no SNPs associated with them. After QC, data was available from 2,116 samples. Data was available for 123 of the 164 blood pressure associated SNPs. For each of the 123 SNPs, local (*cis*, genes < 1 MB from the SNP) effects were identified by computing Spearman rank correlations between SNPs and local gene expression. FDR was computed based on permutations[12]. For each of the significant associations, the genes were selected, the strongest eQTLs were identified for these genes sites, and LD between these strongest eQTLs and the corresponding SNP identified in the GWAS were computed. LD was computed using the European 1000G reference set.

TransplantLines eQTL data (kidney)

We performed an expression quantitative trait locus (eQTL) analysis in order to identify regulatory variants associated with the ICBP SNPs, using a gene-expression database from kidney biopsy specimens. The TransplantLines eQTL cohort used for the kidney analysis is part of a donor cohort for which gene expression results have been described previously[14]. The dataset includes kidneys from living donors, donated after brain death and donated after cardiac death (non-heart-beating). Time of biopsy (that is, before transplantation (T1), before reperfusion (T2) and after reperfusion (T3)) was recorded as well. For some donors multiple biopsies from different time points were taken. In addition, for some donors biopsies from both kidneys were available.

Samples were genotyped on the Illumina CytoSNP 12 v2 array and imputed using the 1000Genomes Phase 1 ALL reference panel[15] using Impute2[16]. Expression and genotype data were available for 236 kidney biopsies of 134 donors. Of the 164 SNPs identified by the ICBP consortium, two were not present in our dataset (chr 6: rs200999181; chr 9: rs9710247) and three were removed because of their proximity to the HLA region, leaving 159 SNPs available for eQTL analysis. In this study we only tested *cis* effects meaning that the probe was at a distance < 1Mb from the SNP on the genome according to GRCh37/hg19. Mixed model analyses were carried out in R[17] to account for multiple samples from a donor (package lme3 version 1.1.12[18]). SNP, sex, age, donor type, time of biopsy, and the first three principal components from the genotype data were included in the model as fixed effects; and sample ID was included as a random effect. Residuals of gene expression values after adjusting for the first 50 expression principal components to filter out environmental variation[8] were used as dependent variable. Probes with a false discovery rate <5% were considered statistically significant.

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Supplementary Table legends

Supplementary Table 1 (Table S1): Study design summary information for each of the studies contributing to Stage 1.
Details include study acronym, full study name, epidemiological study design, and total study sample size, information about ascertainment, ethnicity and origin and references (as PubMed ID [PMID]).

Supplementary Table 2 (Table S2): Summaries of blood pressure phenotypes and covariates for all studies contributing to Stage 1.
Mean, median, standard deviation (SD), minimum (min) and maximum (max) values for the blood pressure phenotypes being analysed (SBP, DBP and PP) and covariates (age, Body Mass Index [BMI]) in all stage 1 studies separately. Individuals were assigned as hypertension cases if they had SBP ≥140, or DBP ≥90, or used antihypertensive or blood pressure lowering medication. Method of blood pressure measurement is included.

Supplementary Table 3 (Table S3): Summaries of methods used to adjust for population stratification and kinship for all studies contributing to Stage 1.
PCA: Principal Components Analysis, PC: Principal Component. IBS: Identity By State.

Supplementary Table 4 (Table S4): Summary of genotyping and imputation strategy for all studies contributing to Stage 1.
HWE; Hardy-Weinberg Equilibrium P value threshold used for exclusion. MAF; Minor Allele Frequency.

Supplementary Table 5 (Table S5): Results for all 61 variants followed up in stage 2
Stage 2 results are shown separately for UK Biobank_CMC and all other replication studies separately and meta-analysed. The final column (Conclusion) includes an explanation as to why each signal was either classed as a novel signal or otherwise. Top_trait: trait for which the variant was found to be most strongly associated in Stage 1 and for which it was followed up in Stage 2. Se: standard error. gc: Genomic control correction applied. Neff: N effective (sum of the products of imputation quality and sample size for each contributing study). Results for rs1048238 and chr1:243458005:I were not available from UK Biobank_CMC and so proxy SNPs rs848309 and rs10926988 were selected as they had the next most significant P value, were in LD (r^2> 0.6) with the original sentinel variants and were measured in UK Biobank_CMC.

Supplementary Table 6 (Table S6): Stage 2 study details.
Details include study acronym, full study name, epidemiological study design, and total study sample size, information about ascertainment, ethnicity and origin and references (as PubMed ID [PMID]). Mean, median, standard deviation (SD), minimum (min) and maximum (max) values for the blood pressure phenotypes being analysed (SBP, DBP and PP) and covariates (age, Body Mass Index [BMI]) in all stage 1 studies separately. Individuals were assigned as hypertension cases if they had SBP ≥140, or DBP ≥90, or used antihypertensive or blood pressure lowering medication. Method of blood pressure measurement is included. PCA: Principal Components Analysis, PC: Principal Component. IBS: Identity By State. HWE; Hardy-Weinberg Equilibrium P value threshold used for exclusion. MAF; Minor Allele Frequency. *For UK Biobank_CMC, an additional 52 individuals were included in the HTN analysis as they used antihypertensive or blood pressure lowering medication (but did not have full data for SBP, DBP or PP and so were not included in the SBP, DBP and PP analyses).

Supplementary Table 7 (Table S7): a) Stage 1 and Stage 2 results separately and combined for all 22 novel signals of association with blood pressure b) Stage 1 and Stage 2 results separately and combined for a further 14 signals of association with blood pressure that were initially confirmed as putatively novel signals in this study but were subsequently reported in Hoffman et al 2016 and Warren et al 2017.

Results are shown separately for Stage 1, for the UK Biobank_CMC component of Stage 2 and for the other replication studies component of Stage 2 (see **Supplementary Figure 1** for list of other replication studies). Results are ordered by chromosome and position. Se: standard error. gc: Genomic control correction applied. Neff: N effective (sum of the products of imputation quality and sample size for each contributing study). Top_trait: trait for which the variant was found to be most strongly associated in Stage 1 and for which it was followed up in Stage 2.

Supplementary Table 8 (Table S8): Evidence for independence of secondary signals at previously reported loci
Summaries of conditional analyses establishing independence of novel secondary signals at previously reported loci. For each novel variant, association testing was repeated conditioning on the previously reported SNP. The conditional P value and the fold change in –log10 P value following conditioning are reported here. Linkage Disequilibrium (LD) r^2 and D' are from 1000 Genomes Project Phase 1. Se: standard error. gc: Genomic control correction applied. Neff: N effective (sum of the products of imputation quality and sample size for each contributing study).

Supplementary Table 9 (Table S9): Stage 1 association results for all 8 signals for all 3 blood pressure traits (SBP, DBP and PP)
Results from Stage 1 and from a meta-analysis of Stage 1 and Stage 2 are shown for all 3 blood pressure traits for all 8 signals. Genome-wide significant ($P < 5x10^{-8}$) signals are highlighted in green and results are ordered by chromosome and position. Se: standard error. gc: Genomic control correction applied. Neff: N effective (sum of the products of imputation quality and sample size for each contributing study).

Supplementary Table 10 (Table S10): Look-up of results in stage 1 for previously reported genome-wide significant signals of association with quantitative blood pressure traits.
Association results for SBP, DBP and PP from Stage 1 are shown for all previously reported signals of association. P values which are significant after Bonferroni adjustment for 141 tests are shown in green. Se: standard error. gc: Genomic control correction applied. Neff: N effective (sum of the products of imputation quality and sample size for each contributing study).[19-34]

Supplementary Table 11 (Table S11): Genes with levels of expression associated with novel or previously reported signals of association with blood pressure.
Each row represents a correlation of SNP genotype and gene expression. The 4 whole-blood data sets (BIOS, SABRe, NESDA/NTR, GTEx whole blood) are presented first in columns 6 to 9 followed by the all-tissue results from GTEx and from kidney. The number of blood data sets for which an eQTL signal was significant (FDR<5%) is indicated in column 5.

Supplementary Table 12 (Table S12): Kidney eQTL results
Variants in the TransplantLines eQTL analysis (see Supplementary Note) with a FDR < 0.05. FDR: False Discovery Rate.

Supplementary Table 13 (Table S13): Complete GTEx results.
The complete lookup results for each ICBP sentinel SNP are presented. If a proxy SNP was used for the GTEx lookup, it is indicated in this table.

Supplementary Table 14 (Table S14): LD lookup of sentinel SNPs in 1000G.
Variants with r^2>0.5 with novel and previously reported BP associated variants. LD: linkage disequilibrium, AF_EUR: Allele Frequency in 1000 Genomes Project EUR samples. Annotation also includes GWAScatalog results.

Supplementary Table 15 (Table S15): Gene-based pathway enrichment analysis of blood pressure genes

Summary of overrepresented known biological pathways for the 49 genes with evidence from 3 or 4 blood eQTL resources. FDR: False Discovery Rate.

Supplementary Table 16 (Table S16): Gene-based Gene Ontology enrichment analysis of blood pressure genes

Summary of overrepresented Gene Ontology (GO) for the 49 genes with evidence from 3 or 4 blood eQTL resources. FDR: False Discovery Rate. GO term categories (m= molecular function, b= biological process, c= cellular component) and levels (1 to 5, with highest level GO terms assigned to level 1) are indicated.

Supplementary Table 17 (Table S17): Network analysis

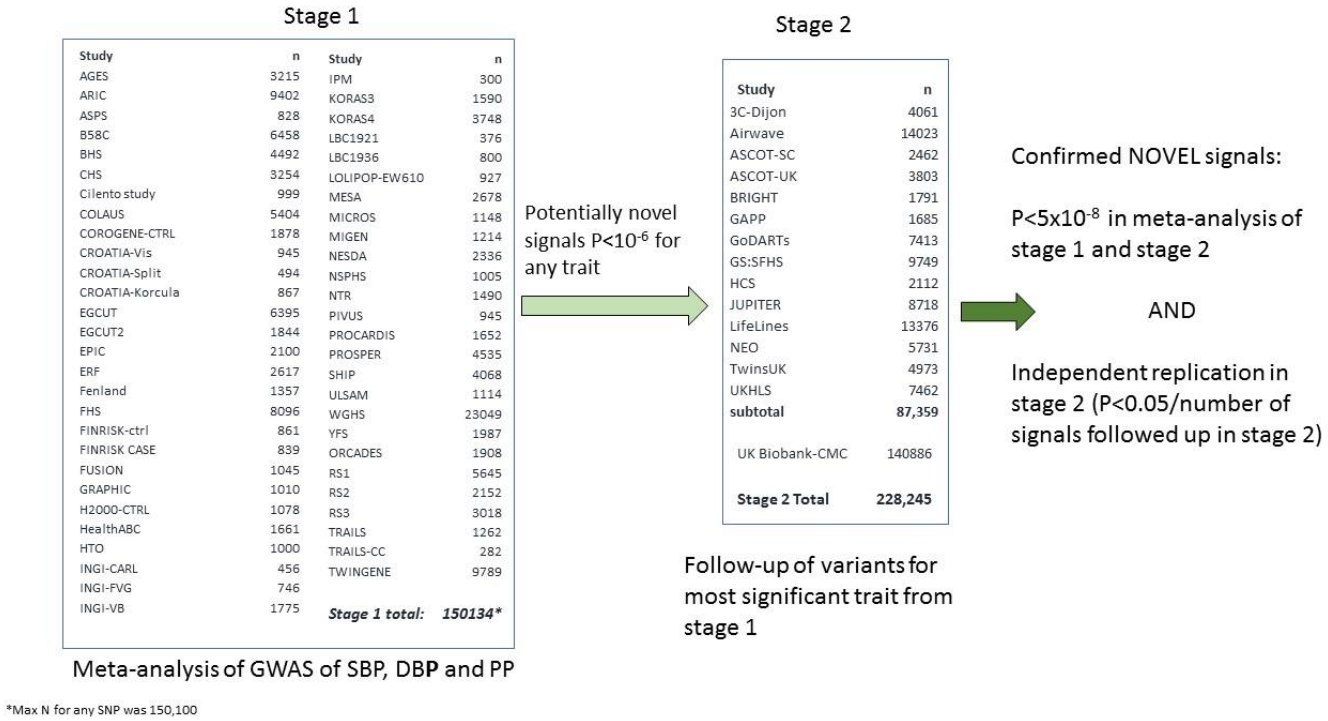
Results of GO term enrichment analysis following functional network construction. FDR: False Discovery Rate. An FDR cutoff of <0.01 was used.

Supplementary Table 18 (Table S18): Drug Target Analysis

Known drug-gene interactions and genes druggability prediction, investigating only expert curated data for the 48 genes with evidence from 3 or 4 blood eQTL resources and the non-synonymous SNPs in high LD (r2>0.50) with the sentinel BP associated SNPs (**Supplementary Table 13 (S13)**).

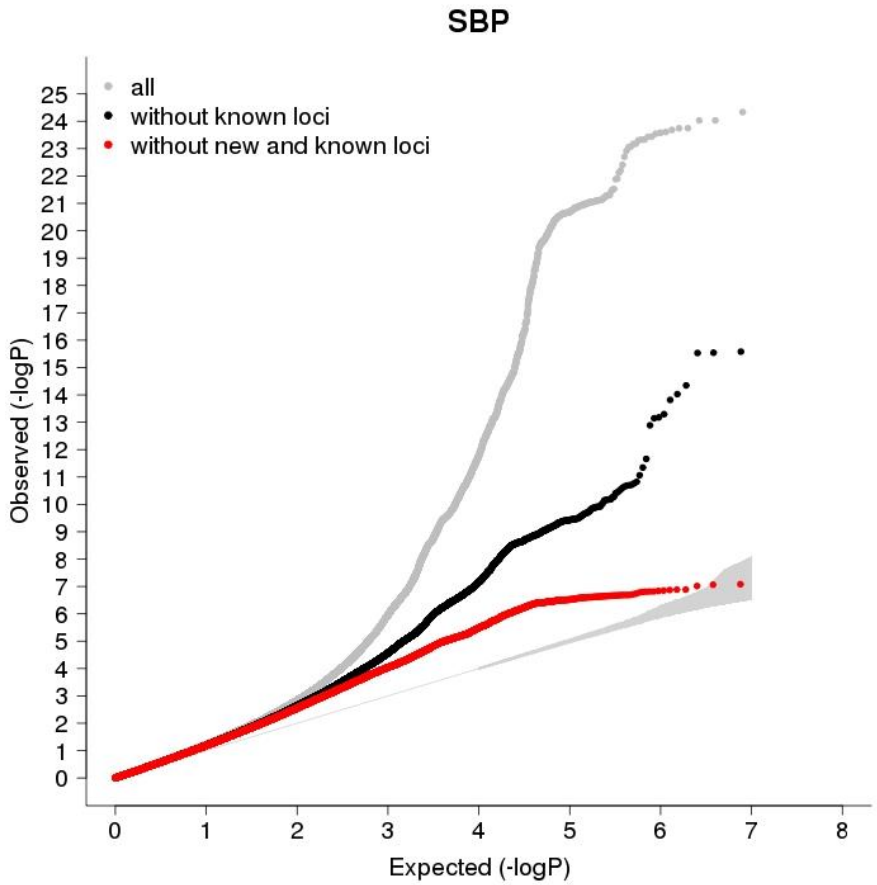
Supplementary Figures

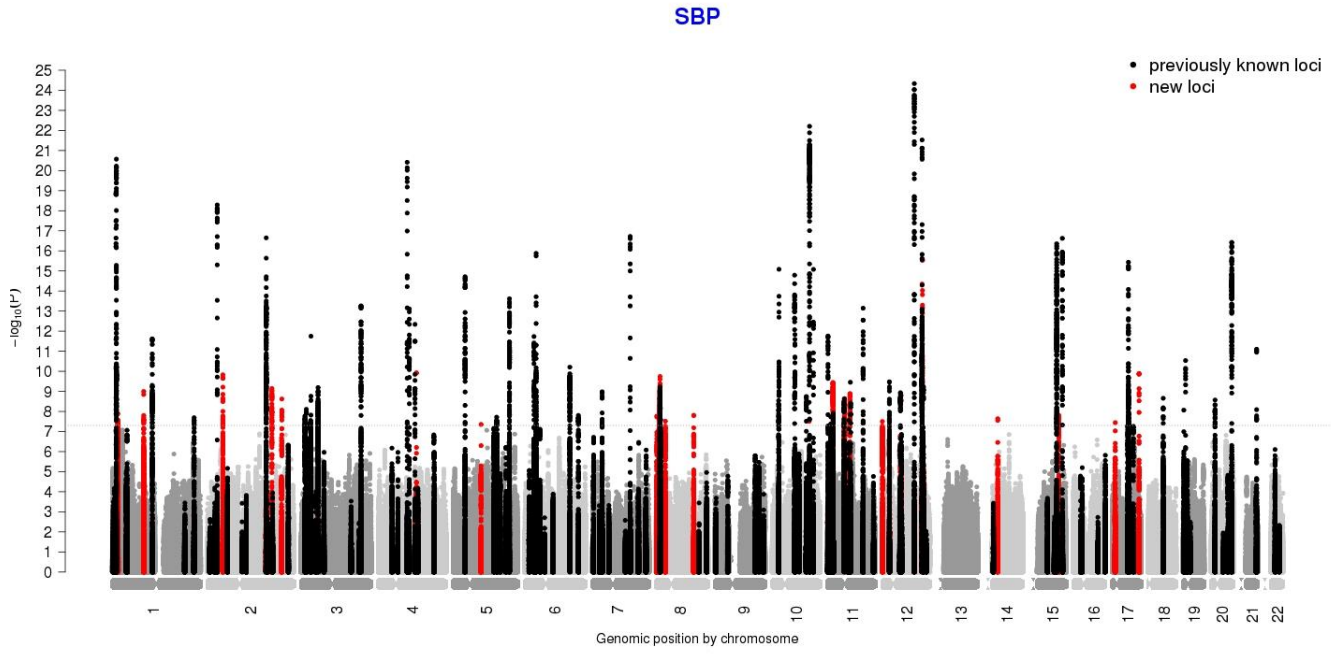
Supplementary Figure 1 (Figure S1): Study design.

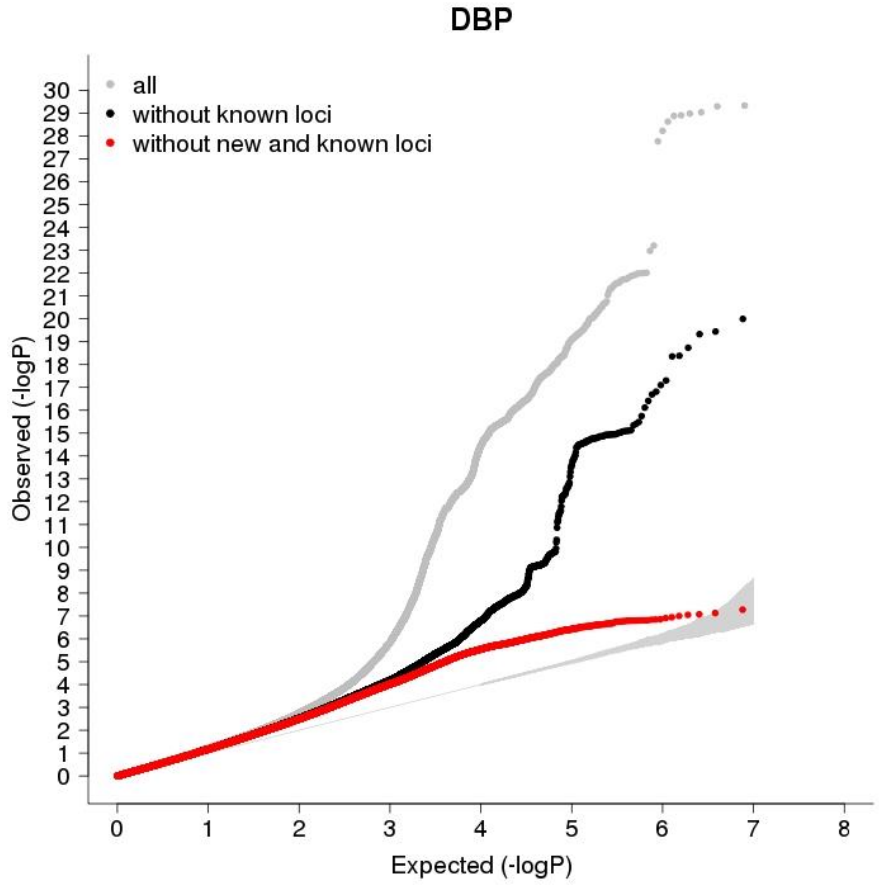


Overview of study design showing studies contributing to stage 1 (discovery) and studies contributing to stage 2 (replication/follow-up). Full study names are given in **Supplementary Table 1 (S1)** (Stage 1) and **Supplementary Table 6 (S6)** (Stage 2).

Supplementary Figure 2 (Figure S2): Manhattan and QQ plots



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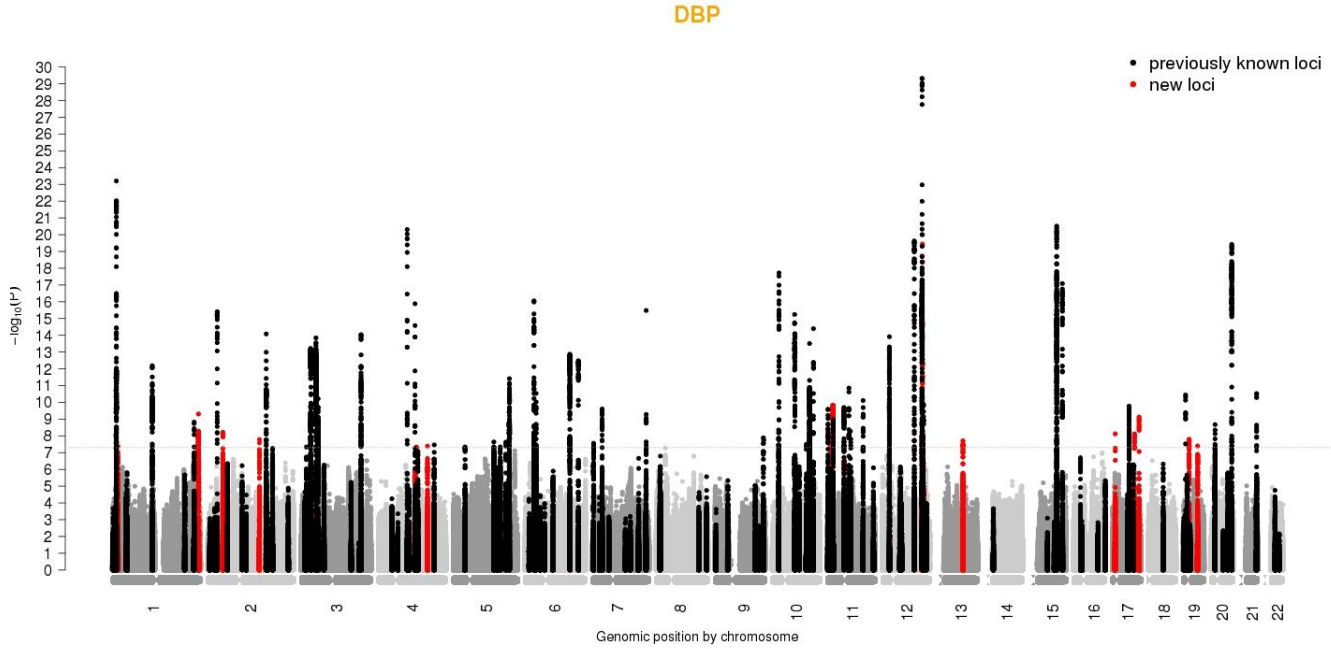
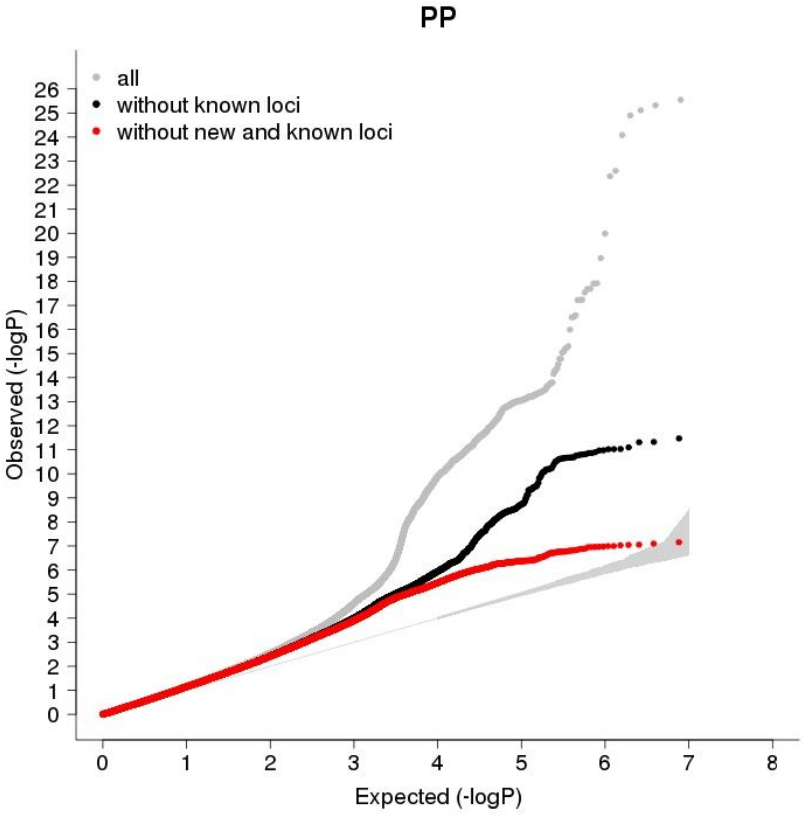
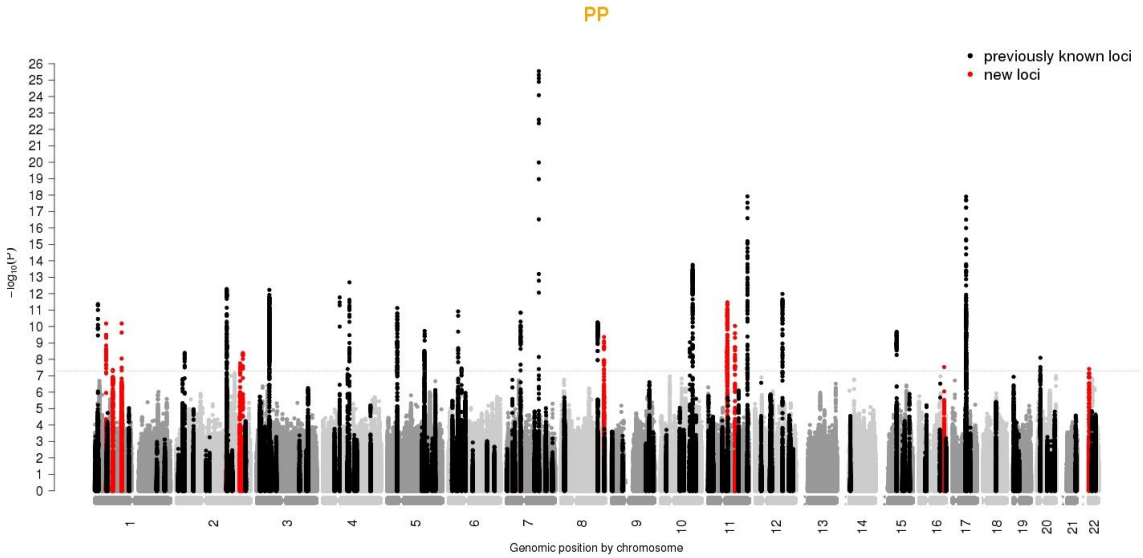
without known loci
without new and known loci
Observed (-logP)
Expected (-logP)


DBP
previously known loci
new loci
Genomic position by chromosome

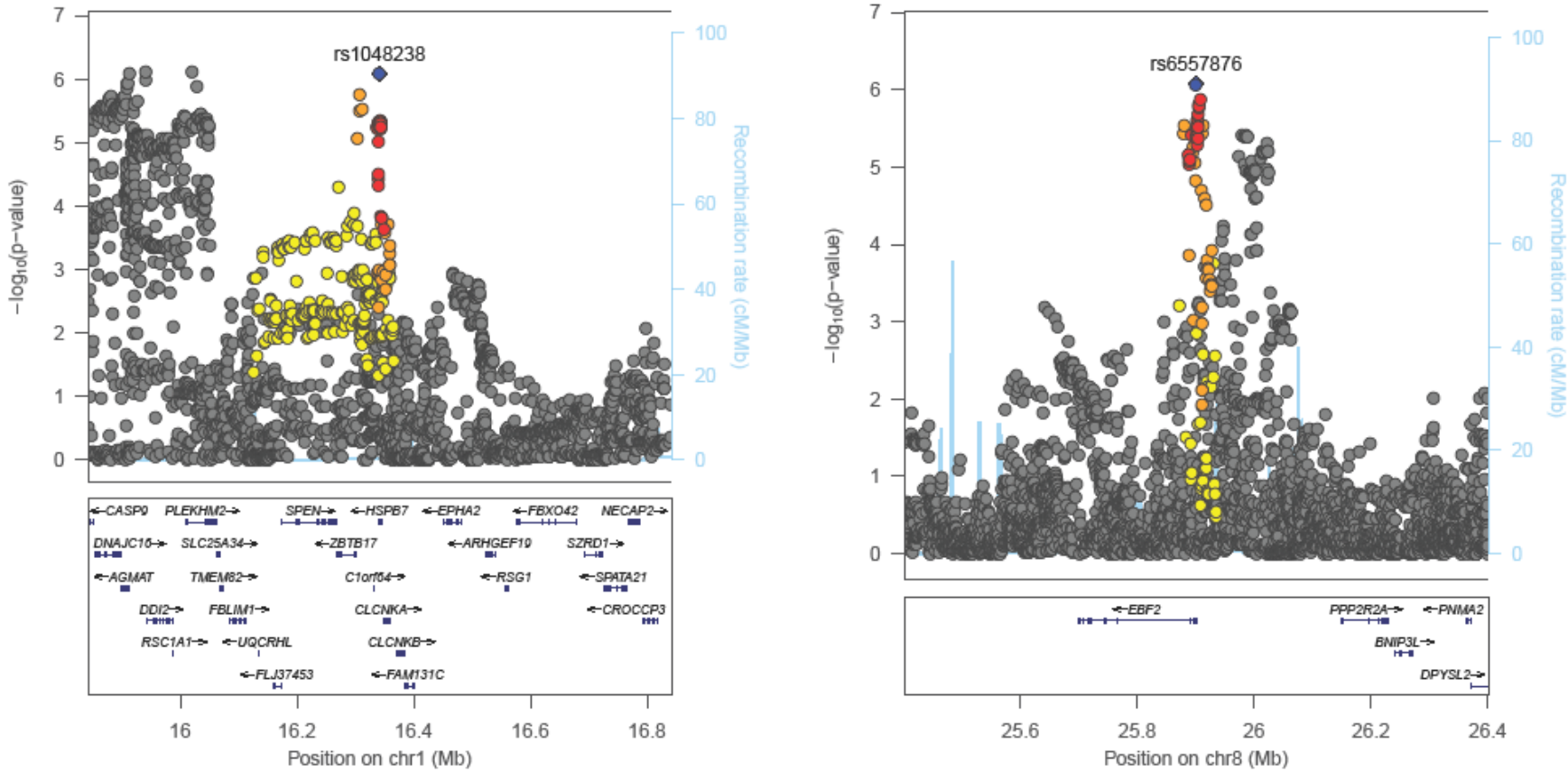


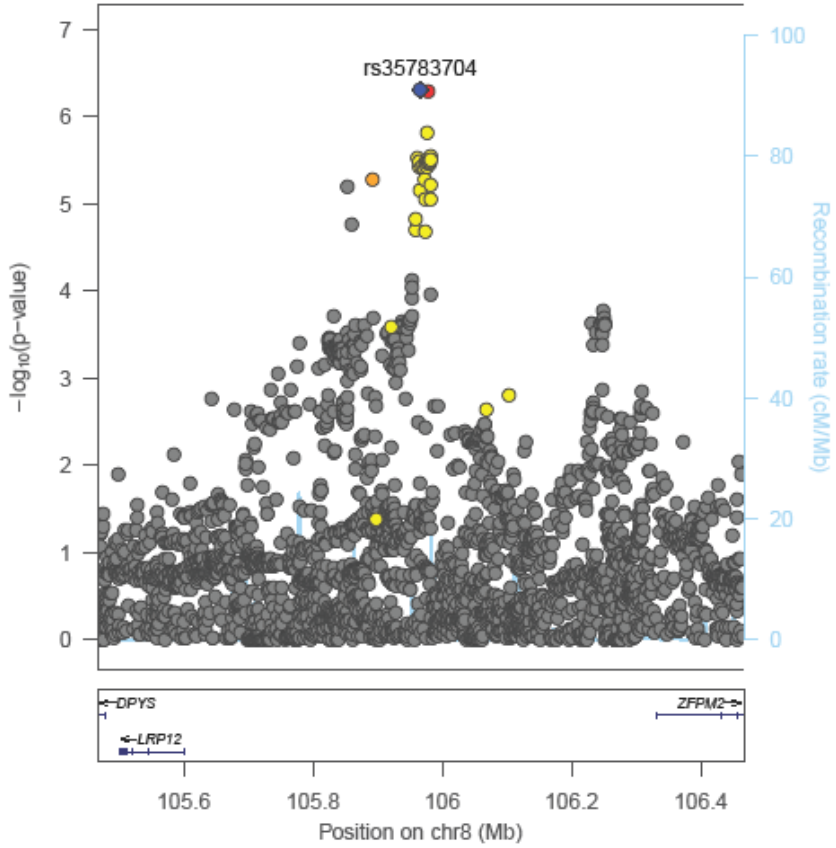


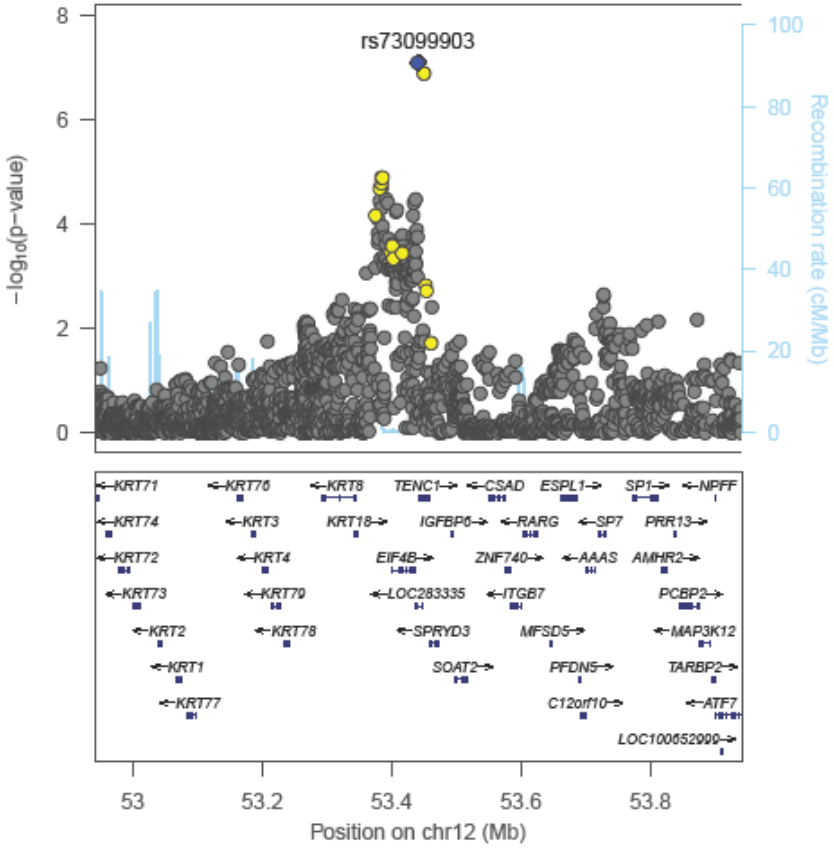
Known loci refers to signals published prior to this study. New includes signals that were initially identified as novel in this study but were subsequently reported in Warren et al 2017 and Hoffman et al 2016.

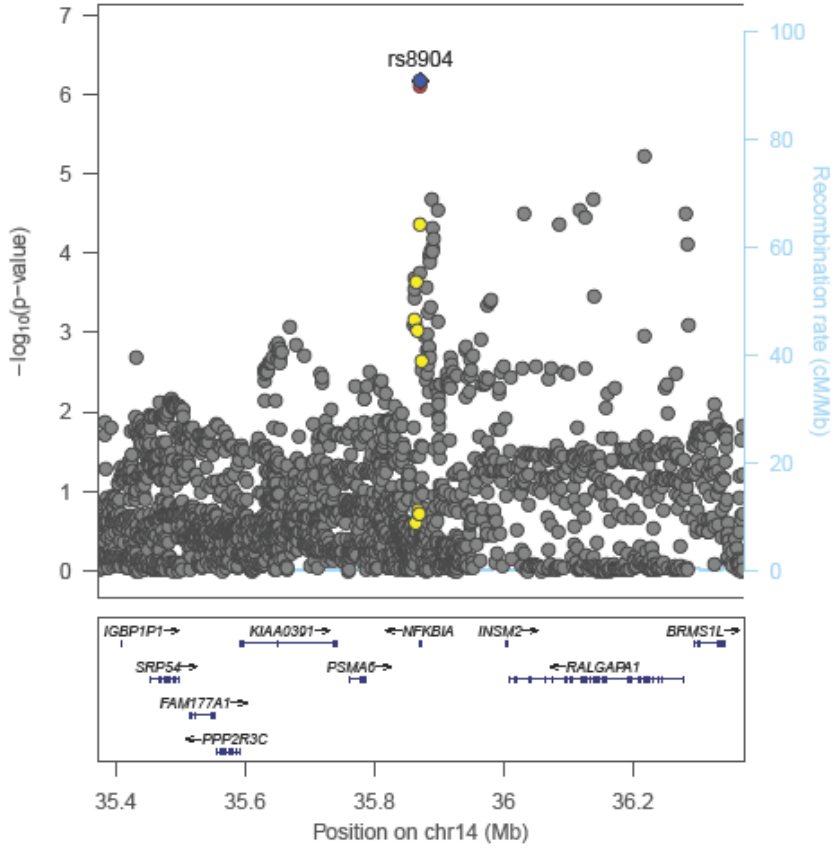
Supplementary Figure 3 (Figure S3): Region plots for 8 novel signals representing 7 novel regions of association for SBP (A), DBP (B) and PP (C).

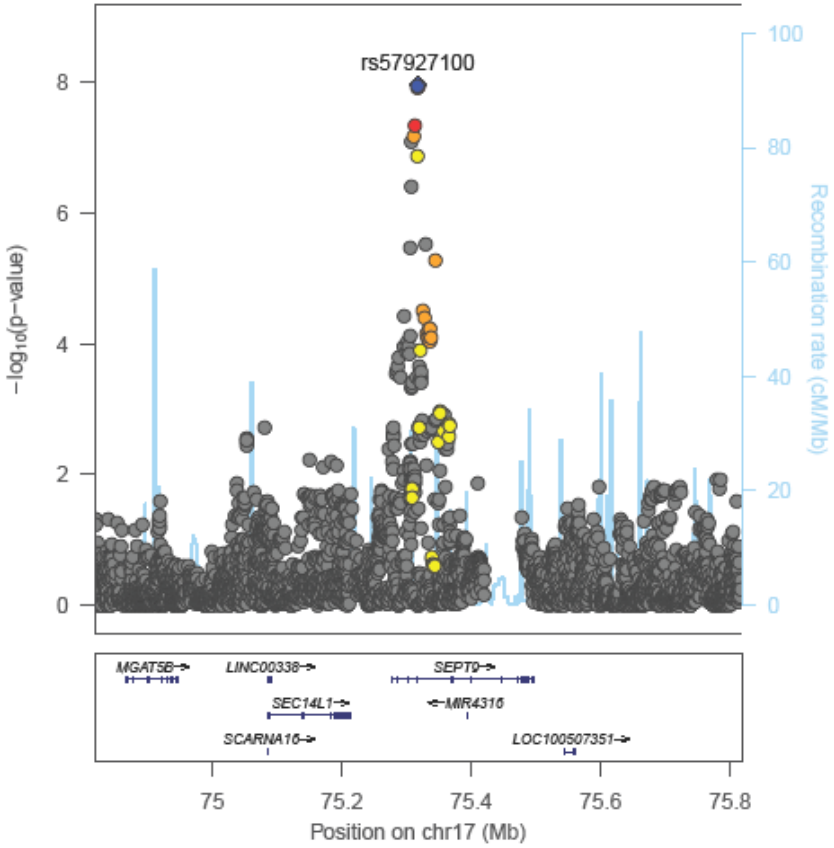
A) SBP



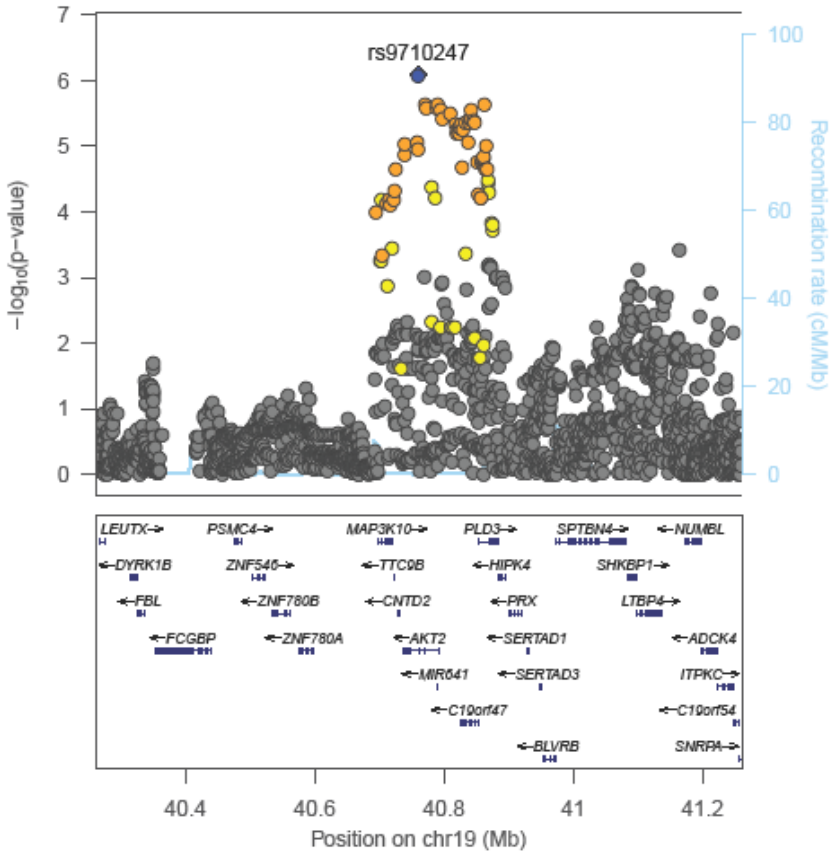

rs35783704
−log10(p−value)
Recombination rate (cM/Mb)
DPYS
ZFPM2
LRP12
105.6
105.8
106
106.2
106.4
Position on chr8 (Mb)


rs73099903
−log10(p−value)
Recombination rate (cM/Mb)
KRT71
KRT76
KRT8
TENC1
CSAD
ESPL1
SP1
NPFF
KRT74
KRT3
KRT18
IGFBP6
RARG
SP7
PRR13
KRT72
KRT4
EIF4B
ZNF740
AAAS
AMHR2
KRT73
KRT79
LOC283335
ITGB7
PCBP2
KRT2
KRT78
SPRYD3
MFSD5
MAP3K12
KRT1
SOAT2
PFDN5
TARBP2
KRT77
C12orf10
ATF7
LOC100652999
53
53.2
53.4
53.6
53.8
Position on chr12 (Mb)


rs8904
−log10(p−value)
Recombination rate (cM/Mb)
IGBP1P1
KIAA0391
NFKBIA
INSM2
BRMS1L
SRP54
PSMA6
RALGAPA1
FAM177A1
PPP2R3C
35.4
35.6
35.8
36
36.2
Position on chr14 (Mb)

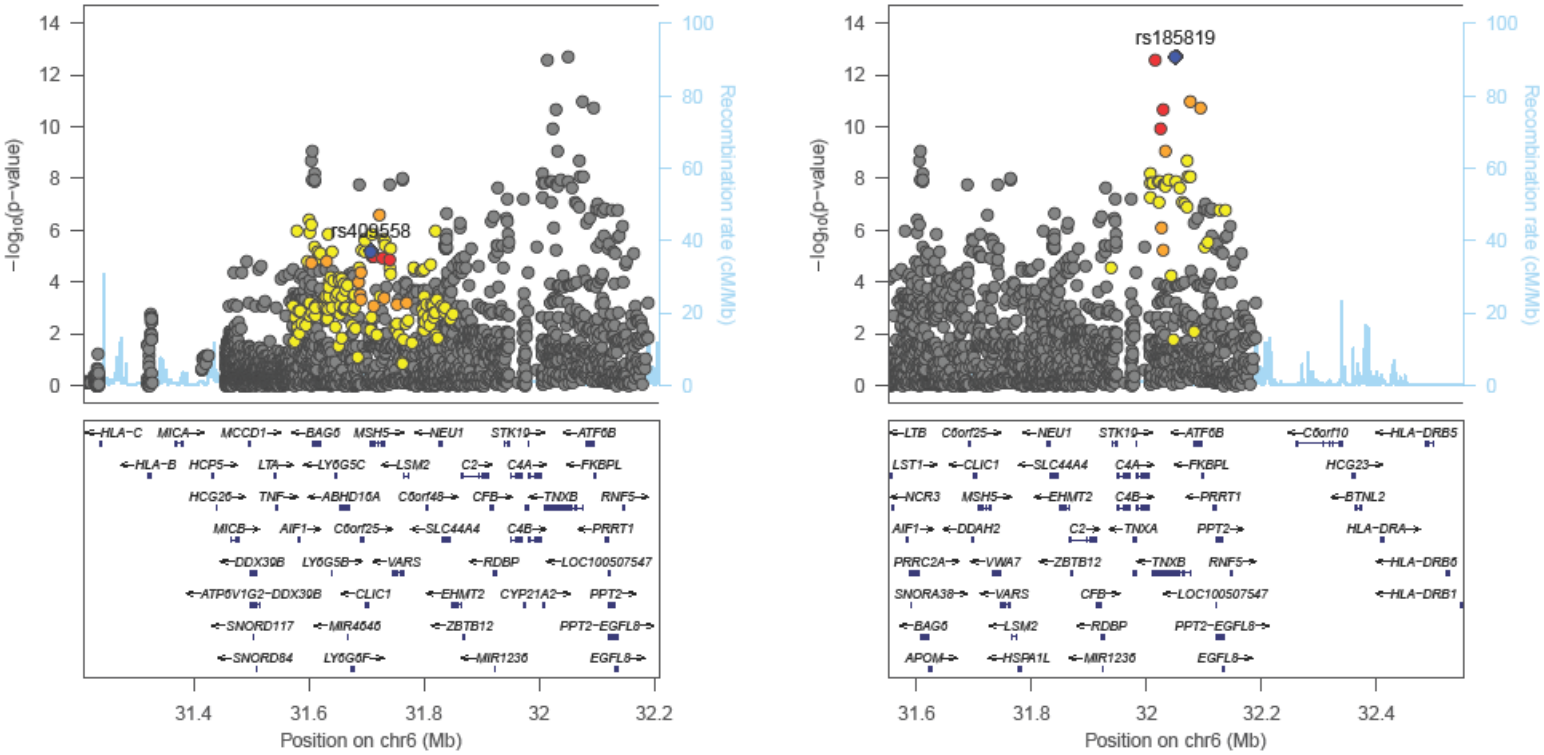

rs57927100
−log10(p−value)
Recombination rate (cM/Mb)
MGAT5B
LINC00338
SEPT9
SEC14L1
MIR4316
SCARNA16
LOC100507351
75
75.2
75.4
75.6
75.8
Position on chr17 (Mb)

B) DBP


rs9710247
−log10(p−value)
Recombination rate (cM/Mb)
LEUTX
PSMC4
MAP3K10
PLD3
SPTBN4
NUMBL
DYRK1B
ZNF546
TTC9B
HIPK4
SHKBP1
FBL
ZNF780B
CNTD2
PRX
LTBP4
FCGBP
ZNF780A
AKT2
SERTAD1
ADCK4
MIR641
SERTAD3
ITPKC
C19orf47
C19orf54
BLVRB
SNRPA
40.4
40.6
40.8
41
41.2
Position on chr19 (Mb)

Supplementary Figure 4 (Figure S4): Region plots for a novel signal at a previously reported region of association.

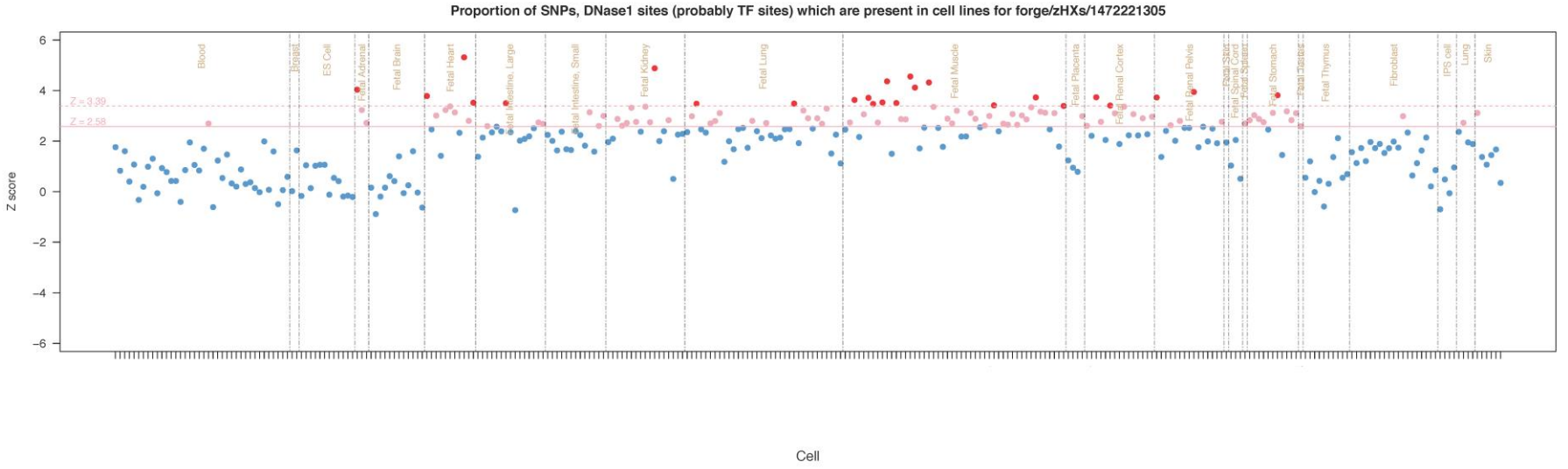
SBP: rs185819 (novel signal reported in this study)



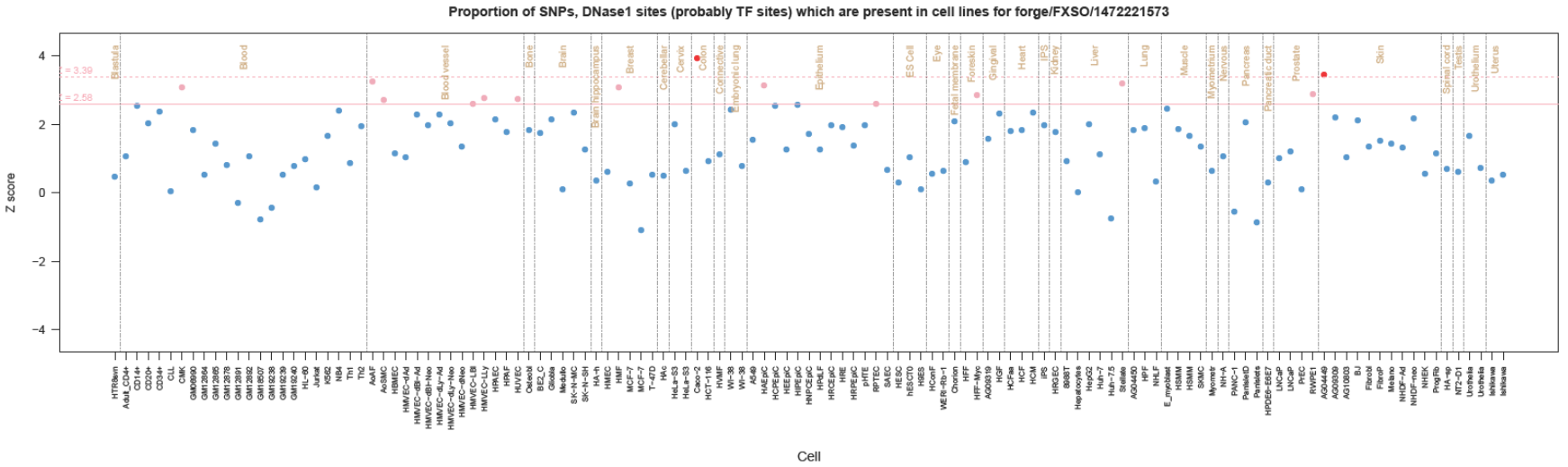
The region plot for the previously reported signal is shown (left) alongside the region plot for the novel signal. Results for association of the novel signal after conditioning on the previously reported signal are shown in **Supplementary Table 8 (S8)**.

Supplementary Figure 5 (Figure S5): Enrichment of overlap of DNase1 site in Roadmap (a) and ENCODE (b) tissues and cell lines.

a)



b)


Proportion of SNPs, DNase1 sites (probably TF sites) which are present in cell lines for forge/FXSO/1472221573
Z score
Cell
= 3.39
= 2.58
Blastula
Blood
Blood vessel
Bone
Brain
Brain hippocampus
Breast
Cerebellar
Cervix
Colon
Connective
Embryonic lung
Epithelium
ES Cell
Eye
Fetal membrane
Foreskin
Gingival
Heart
IPS
Kidney
Liver
Lung
Muscle
Myometrium
Nervous
Pancreas
Pancreatic duct
Prostate
Skin
Spinal cord
Testis
Urothelium
Uterus

Competing financial interests

Mike A. Nalls' participation is supported by a consulting contract between Data Tecnica International and the National Institute on Aging, NIH, Bethesda, MD, USA, as a possible conflict of interest Dr. Nalls also consults for Illumina Inc, the Michael J. Fox Foundation and University of California Healthcare among others.

Consortium membership

BIOS Consortium

(Biobank-based Integrative Omics Study)

Management Team Bastiaan T. Heijmans (chair)[1], Peter A.C. 't Hoen[2], Joyce van Meurs[3], Aaron Isaacs[4], Rick Jansen[5], Lude Franke[6].

Cohort collection Dorret I. Boomsma[7], René Pool[7], Jenny van Dongen[7], Jouke J. Hottenga[7] (Netherlands Twin Register); Marleen MJ van Greevenbroek[8], Coen D.A. Stehouwer[8], Carla J.H. van der Kallen[8], Casper G. Schalkwijk[8] (Cohort study on Diabetes and Atherosclerosis Maastricht); Cisca Wijmenga[6], Lude Franke[6], Sasha Zhernakova[6], Ettje F. Tigchelaar[6] (LifeLines Deep); P. Eline Slagboom[1], Marian Beekman[1], Joris Deelen[1], Diana van Heemst[9] (Leiden Longevity Study); Jan H. Veldink[10], Leonard H. van den Berg[10] (Prospective ALS Study Netherlands); Cornelia M. van Duijn[4], Bert A. Hofman[11], Aaron Isaacs[4], André G. Uitterlinden[3] (Rotterdam Study).

Data Generation Joyce van Meurs (Chair)[3], P. Mila Jhamai[3], Michael Verbiest[3], H. Eka D. Suchiman[1], Marijn Verkerk[3], Ruud van der Breggen[1], Jeroen van Rooij[3], Nico Lakenberg[1].

Data management and computational infrastructure Hailiang Mei (Chair)[12], Maarten van Iterson[1], Michiel van Galen[2], Jan Bot[13], Dasha V. Zhernakova[6], Rick Jansen[5], Peter van 't Hof[12], Patrick Deelen[6], Irene Nooren[13], Peter A.C. 't Hoen[2], Bastiaan T. Heijmans[1], Matthijs Moed[1].

Data Analysis Group Lude Franke (Co-Chair)[6], Martijn Vermaat[2], Dasha V. Zhernakova[6], René Luijk[1], Marc Jan Bonder[6], Maarten van Iterson[1], Patrick Deelen[6], Freerk van Dijk[14], Michiel van Galen[2], Wibowo Arindrarto[12], Szymon M. Kielbasa[15], Morris A. Swertz[14], Erik. W van Zwet[15], Rick Jansen[5], Peter-Bram 't Hoen (Co-Chair)[2], Bastiaan T. Heijmans (Co-Chair)[1].

1. Molecular Epidemiology Section, Department of Medical Statistics and Bioinformatics, Leiden University Medical Center, Leiden, The Netherlands
2. Department of Human Genetics, Leiden University Medical Center, Leiden, The Netherlands
3. Department of Internal Medicine, ErasmusMC, Rotterdam, The Netherlands
4. Department of Genetic Epidemiology, ErasmusMC, Rotterdam, The Netherlands
5. Department of Psychiatry, VU University Medical Center, Neuroscience Campus Amsterdam, Amsterdam, The Netherlands
6. Department of Genetics, University of Groningen, University Medical Centre Groningen, Groningen, The Netherlands
7. Department of Biological Psychology, VU University Amsterdam, Neuroscience Campus Amsterdam, Amsterdam, The Netherlands
8. Department of Internal Medicine and School for Cardiovascular Diseases (CARIM), Maastricht University Medical Center, Maastricht, The Netherlands
9. Department of Gerontology and Geriatrics, Leiden University Medical Center, Leiden, The Netherlands
10. Department of Neurology, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, The Netherlands
11. Department of Epidemiology, ErasmusMC, Rotterdam, The Netherlands
12. Sequence Analysis Support Core, Leiden University Medical Center, Leiden, The Netherlands
13. SURFsara, Amsterdam, the Netherlands
14. Genomics Coordination Center, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands
15. Medical Statistics Section, Department of Medical Statistics and Bioinformatics, Leiden University Medical Center, Leiden, The Netherlands

LifeLines Cohort Study

Behrooz Z Alizadeh (*Department of Epidemiology, University of Groningen, University Medical Center Groningen, The Netherlands*), H Marike Boezen (*Department of Epidemiology, University of Groningen, University Medical Center Groningen, The Netherlands)*, Lude Franke (*Department of*

Genetics, University of Groningen, University Medical Center Groningen, The Netherlands), Pim van der Harst (*Department of Cardiology, University of Groningen, University Medical Center Groningen, The Netherlands*), Gerjan Navis (*Department of Internal Medicine, Division of Nephrology, University of Groningen, University Medical Center Groningen, The Netherlands*), Marianne Rots (*Department of Medical Biology, University of Groningen, University Medical Center Groningen, The Netherlands*), Harold Snieder (*Department of Epidemiology, University of Groningen, University Medical Center Groningen, The Netherlands*), Morris Swertz (*Department of Genetics, University of Groningen, University Medical Center Groningen, The Netherlands*), Bruce HR Wolffenbuttel (*Department of Endocrinology, University of Groningen, University Medical Center Groningen, The Netherlands*), Cisca Wijmenga (*Department of Genetics, University of Groningen, University Medical Center Groningen, The Netherlands*)

UKHLS

Michaela Benzeval(1), Jonathan Burton(1), Nicholas Buck(1), Annette Jäckle(1), Meena Kumari(1), Heather Laurie(1), Peter Lynn(1), Stephen Pudney(1), Birgitta Rabe(1), Dieter Wolke(2)
1) Institute for Social and Economic Research
2) University of Warwick