



Circulation: Cardiovascular Genetics

Manuscript Submission and Peer Review System

Disclaimer: The manuscript and its contents are confidential, intended for journal review purposes only, and not to be further disclosed.

URL: <http://circgenetics-submit.aha-journals.org>

Title: New blood pressure associated loci identified in meta-analyses of 475,000 individuals

Manuscript number: CIRCCVG/2017/001778R2

Author(s): Aldi Kraja, Washington University in St. Louis School of Medicine

James Cook, THE UNIVERSITY OF LIVERPOOL

Helen Warren, Queen Mary University of London

Praveen Surendran, University of Cambridge

Chunyu Liu, National Heart, Lung, and Blood Institute

Evangelos Evangelou, Imperial College London

Alisa Manning, Massachusetts General Hospital

Niels Grarup, University of Copenhagen

Fotios Drenos, University of Bristol

Xueling Sim, National University of Singapore

Albert Smith, Icelandic Heart Association

Najaf Amin, Erasmus Medical Center

Alexandra Blakemore, Brunel University London

Jette Bork-Jensen, University of Copenhagen

Ivan Brandslund, Lillebaelt Hospital

Aliki-Eleni Farmaki, Harokopio University

Cristiano Fava, Lund University

Teresa Ferreira, University of Oxford

Karl-Heinz Herzig, University of Oulu

Ayush Giri, Vanderbilt University

Franco Giulianini, Brigham and Women's Hospital

Megan Grove, University of Texas Health Science Center

Xiuqing Guo, Los Angeles Biomedical Research Institute at Harbour-UCLA

Sarah Harris, University of Edinburgh

Christian Theil Have, Copenhagen University

Aki Havulinna, National Institute for Health and Welfare

He Zhang, University Of Michigan

Marit Jørgensen, Steno Diabetes Center

Annemari Käräjämäki, Vaasa Central Hospital

Charles Kooperberg, Fred Hutchinson Cancer Research Center

Allan Linneberg, Copenhagen University Hospital Glostrup

Louis Little, William Harvey Research Institute, Barts and The

London School of Medicine and Dentistry, Queen Mary University of

London, UK

Yongmei Liu, Wake Forest School of Medicine

Lori Bonnycastle, NIH

Yingchang Lu, The Charles Bronfman Institute for Personalized
Medicine, Icahn School of Medicine at Mount Sinai

Reedik Mägi, University of Tartu

Anubha Mahajan, University of Oxford

Giovanni Malerba, University of Verona

Riccardo Marioni, University of Edinburgh

Hao Mei, University of Mississippi Medical Center

Cristina Menni, King's College London

Alanna Morrison, University of Texas Health Science Center at Houston

Sandosh Padmanabhan, University of Glasgow

Walter Palmas, Columbia University

Alaitz Poveda, Lund University

Rainer Rauramaa, Kuopio Research Institute of Exercise Medicine

Kuopio, University of Eastern Finland,

Nigel Rayner, University of Oxford

Muhammad Riaz, University of Leicester

Ken Rice, University of Washington

Melissa Richard, The University of Texas Health Science Center at
Houston School of Public Health

Jennifer Smith, University of Michigan

Lorraine Southam, The Wellcome Trust Sanger Institute

Alena Stancáková, University of Eastern Finland

Kathleen Stirrups, University of Cambridge

Vinicius Tragante, University Medical Center Utrecht

Tiinamaija Tuomi, Helsinki University Hospital

Ioanna Tzoulaki, Imperial College London

Tibor Varga, Lund University

Stefan Weiss, University Medicine and Ernst-Moritz-Arndt University
Greifswald

Andrianos Yiorkas, Imperial College London

Robin Young, Department of Public Health and Primary Care,
University of Cambridge, UK

Weihua Zhang, Department of Epidemiology and Biostatistics, Imperial
College London

Michael Barnes, Queen Mary University of London

Claudia Cabrera, William Harvey Research Institute, Barts and The
London School of Medicine and Dentistry, Queen Mary University of London

He Gao, Imperial College London

Mike Boehnke, University of Michigan

Eric Boerwinkle, University of Texas Health Science Center at Houston

John Chambers, Imperial College London

John Connell, University of Dundee

Cramer Christensen, Lillebaelt Hospital

Rudolf de Boer, University of Groningen

Ian Deary, University of Edinburgh

George Dedoussis, Department of Dietetics-Nutrition, Harokopio
University, 70 El. Venizelou Str

Panos Deloukas, Queen Mary University of London

Anna Dominiczak, University of Glasgow

Marcus Dörr, University Medicine Greifswald

Roby Joehanes, Harvard Medical School

Todd Edwards, Vanderbilt university

Tõnu Esko, University of Tartu

Myriam Fornage, University of Texas Health Science Center at Houston

Nora Franceschini, University of North Carolina at Chapel Hill

Paul Franks, Lund University

Giovanni Gambaro, Università Cattolica del Sacro Cuore, Roma

Leif Groop, University of Lund

Göran Hallmans, Umeå University

Torben Hansen, The Novo Nordisk Foundation Center for Basic Metabolic Research, Section of Metabolic Genetics, Faculty of

Health and Medical Sciences, University of Copenhagen

Caroline Hayward, University of Edinburgh

Oksa Heikki, Tampere University Hospital

Erik Ingelsson, Stanford University School of Medicine

Jaakko Tuomilehto, National Institute for Health and Welfare

Marjo-Riitta Jarvelin, Imperial College London

Sharon Kardia, University of Michigan

Fredrik Karpe, University of Oxford

Jaspal Kooner, Imperial College London

Timo Lakka, University of Kuopio

Claudia Langenberg, Medical Research Council Epidemiology Unit

Lars Lind, Uppsala University

Ruth Loos, Mount Sinai School of Medicine

Markku Laakso, University of Kuopio

Mark McCarthy, The Wellcome Trust Centre for Human Genetics

Olle Melander, Skåne University Hospital and Lund University, Malmö, Sweden

Karen Mohlke, University of North Carolina

Andrew Morris, University of Liverpool

Colin Palmer, University of Dundee

Oluf Pedersen, University of Copenhagen

Ozren Polasek, University of Split

Neil Poulter, Imperial College London, School of Public Health

Michael Province, Washington University School of Medicine

Bruce Psaty, University of Washington & Group Health Research Inst,

Group Health Cooperative

Paul Ridker, Harvard Medical School

Jerome Rotter, Lo Angeles BioMedicalResearch Instiute

Igor Rudan, University of Edinburgh

Veikko Salomaa, National Institute for Health and Welfare

Nilesh Samani, University of Leicester

Peter Sever, Imperial College London

Tea Skaaby, Research Centre for Prevention and Health, The Capital Region

Jeanette Stafford, Wake Forest School of Medicine

John Starr, University of Edinburgh

Pim van der Harst, University Medical Center Groningen, University

of Groningen

Peter van der Meer, University Medical Centre Groningen

Cornelia van Duijn, Eramus Medical Center

Anne-Claire Vergnaud, Imperial College London

Vilmundur Gudnason, Icelandic Heart Association

Nicholas Wareham, University of Cambridge

James Wilson, University of Mississippi Medical Center

Cristen Willer, University of Michigan Medical School

Daniel Witte, Aarhus University

Eleftheria Zeggini, Wellcome Trust Sanger Institute

Danish Saleheen, University of Pennsylvania

Adam Butterworth, University of Cambridge

John Danesh, University of Cambridge

Folkert Asselbergs, University Medical Center Utrecht

Louise Wain, University of Leicester

Georg Ehret, Johns Hopkins Univ. School of Medicine

Daniel Chasman, Brigham and Women's Hospital

Mark Caulfield, Queen Mary University of London

Paul Elliott, Imperial College London

Cecilia Lindgren, University of Oxford

Daniel Levy, NHLBI

Christopher Newton-Cheh, Massachusetts General Hospital

Patricia Munroe, Queen Mary University of London

Joanna Howson, University of Cambridge

Disclaimer: This manuscript and its contents are confidential, intended for internal review purposes only, and not to be further disseminated.

New blood pressure associated loci identified in meta-analyses of 475,000 individuals

Running Title: Kraja *et al.* New blood pressure associated loci

Authors:

Aldi T Kraja^{1*}, DSc, PhD, James P Cook², PhD, Helen R Warren^{3,4}, PhD, Praveen Surendran⁵, PhD, Chunyu Liu^{6,7}, PhD, Evangelos Evangelou^{8,9}, PhD, Alisa K Manning^{10,11}, PhD, Niels Grarup¹², MD, PhD, Fotios Drenos^{13,14} PhD, Xueling Sim^{15,16}, PhD, Albert Vernon Smith^{17,18}, PhD, Najaf Amin¹⁹, DSc, PhD, Alexandra IF Blakemore^{20,21}, PhD, Jette Bork-Jensen¹², PhD, Ivan Brandslund^{22,23}, MD, Aliko-Eleni Farmaki²⁴, PhD, Cristiano Fava^{25,26}, MD, PhD, Teresa Ferreira²⁷, PhD, Karl-Heinz Herzig^{28,29,30}, MD, PhD, Ayush Giri³¹, PhD, Franco Giulianini³², PhD, Megan L Grove³³, MSc, Xiuqing Guo³⁴, PhD, Sarah E Harris^{35,36}, PhD, Christian T Have¹², PhD, Aki S Havulinna^{37,38}, DSc, He Zhang³⁹, PhD, Marit E Jørgensen⁴⁰, MD, PhD, AnneMari Käräjämäki^{41,42}, MD, Charles Kooperberg⁴³, PhD, Allan Linneberg^{44,45}, MD, PhD, Yongmei Liu⁴⁶, MD, PhD, Bonnycastle L Lori⁴⁷, PhD, Yingchang Lu^{48,49}, MD, PhD, Reedik Mägi⁵⁰, PhD, Anubha Mahajan²⁷, PhD, Giovanni Malerba⁵¹, PhD, Riccardo E Marioni^{35,36}, PhD, Hao Mei⁵², PhD, Cristina Menni⁵³, PhD, Alanna C Morrison³³, PhD, Sandosh Padmanabhan⁵⁴, MD, PhD, Walter Palmas⁵⁵, MD, Alaitz Poveda⁵⁶, PhD, Rainer Rauramaa^{57,58}, MD, PhD, N William Rayner^{27,59,60}, PhD, Muhammad Riaz^{61,62}, PhD, Kenneth Rice⁶³, PhD, Melissa A Richard³³, PhD, Jennifer A Smith⁶⁴, PhD, Lorraine Southam^{27,60}, MSc, Alena Stančáková⁶⁵, MD, PhD, Kathleen E Stirrups^{3,66}, PhD, Vinicius Tragante⁶⁷, PhD, Tiinamaija Tuomi^{68,69,90}, MD, PhD, Ioanna Tzoulaki^{8,9,70}, PhD, Tibor V Varga⁵⁷, PhD, Stefan Weiss^{71,72}, Dr., Andrianos M Yiorkas^{20,21}, MSc, Robin Young⁵, PhD, Weihua Zhang^{8,73}, Dr., Michael R Barnes^{3,4}, PhD, Claudia P Cabrera^{3,4}, PhD, He Gao^{8,70}, PhD, Michael Boehnke¹⁵, PhD, Eric Boerwinkle^{33,74}, PhD, John C Chambers^{8,73,75}, MD, PhD, John M Connell⁷⁶, MD, Cramer K Christensen⁷⁷, MD, DMsc, Rudolf A de Boer⁷⁸, MD, PhD, Ian J Deary^{35,79}, PhD, George Dedoussis²⁴, PhD, Panos Deloukas³, PhD, Anna F Dominiczak⁵⁴, MD, FRCP, Marcus Dörr^{71,80}, MD, Roby Joehanes^{6,81,82}, PhD, Todd L Edwards⁸³, PhD, Tõnu Esko⁵⁰, PhD, Myriam Fornage⁸⁴, PhD, Nora Franceschini⁸⁵, MD, Paul W Franks^{56,86,87}, PhD, Giovanni Gambaro⁸⁸, MD, PhD, Leif Groop^{89,90}, MD, PhD, Göran Hallmans⁹¹, MD, PhD, Torben Hansen¹², MD, PhD, Caroline Hayward⁹², Dr., Oksa Heikki⁹³, MD, PhD, Erik Ingelsson^{94,95}, MD, PhD, Jaakko Tuomilehto^{96,97,98,99}, MD, PhD, Marjo-Riitta Jarvelin^{8,70,100}, MD, PhD, Sharon LR Kardina⁶⁴, PhD, Fredrik Karpe^{59,101}, MD, PhD, Jaspal S

Kooner^{73,75,102}, MD, Timo A Lakka^{57,58,103}, MD, PhD, Claudia Langenberg¹⁰⁴, MD, PhD, Lars Lind⁹⁵, MD, PhD, Ruth JF Loos⁴⁸, PhD, Markku Laakso¹⁰⁵, MD, PhD, Mark I McCarthy^{27,59,101}, MD, Olle Melander²⁵, MD, PhD, Karen L Mohlke¹⁰⁶, PhD, Andrew P Morris², PhD, Colin Palmer¹⁰⁷, PhD, Oluf Pedersen¹², MD, DMSc, Ozren Polasek¹⁰⁸, Dr., Neil Poulter¹⁰⁹, FMedSci, Michael A Province¹, PhD, Bruce M Psaty^{110,111}, MD, PhD, Paul M Ridker^{32,112}, MD, Jerome I Rotter³⁴, MD, Igor Rudan¹¹³, PhD, Veikko Salomaa³⁷, MD, PhD, Nilesh J Samani^{61,62}, MD, Peter J Sever¹⁰⁹, MD, Tea Skaaby⁴⁴, MD, PhD, Jeanette M Stafford¹¹⁴, MSc, John M Starr^{35,115}, PhD, Pim van der Harst^{78,116}, MD, PhD, Peter van der Meer⁷⁸, MD, PhD, The Understanding Society Scientific Group, Cornelia M van Duijn¹⁹, PhD, Anne-Claire Vergnaud⁸, PhD, Vilmundur Gudnason^{17,18}, MD, PhD, Nicholas J Wareham¹⁰⁴, MD, PhD, James G Wilson¹¹⁷, MD, Cristen J Willer^{118,119,120}, PhD, Daniel R Witte^{121,122}, PhD, Eleftheria Zeggini⁶⁰, PhD, Danish Saleheen^{123,124,125}, PhD, Adam S Butterworth⁵, PhD, John Danesh^{5,60,126,127}, PhD, Folkert W Asselbergs^{67,128}, MD, PhD, Louise V Wain¹²⁹, PhD, Georg B. Ehret^{130,131}, MD, Daniel I Chasman^{32,112}, PhD, Mark J Caulfield^{3,4}, MD, Paul Elliott^{8,70}, PhD, Cecilia M Lindgren^{27,132,133}, PhD, Daniel Levy^{6,7}, MD, Christopher Newton-Cheh^{10,133,134†}, MD, Patricia B Munroe^{3,4†}, PhD, Joanna MM Howson^{5†}, PhD

on behalf of the CHARGE EXOME BP, CHD Exome+, Exome BP, GoT2D:T2DGenes consortia, The UK Biobank Cardio-Metabolic traits Consortium Blood Pressure Working Groups

Affiliations:

¹Division of Statistical Genomics, Department of Genetics and Center for Genome Sciences and Systems Biology, Washington University School of Medicine, St. Louis, MO, USA

²Department of Biostatistics, University of Liverpool, Liverpool, UK

³William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK

⁴National Institute for Health Research Barts Cardiovascular Biomedical Research Unit, Queen Mary University of London, London, UK

⁵MRC/BHF Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK

⁶The Framingham Heart Study, Framingham, MA, USA

⁷The Population Sciences Branch, Division of Intramural Research, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, USA

⁸Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, UK

⁹Department of Hygiene and Epidemiology, University of Ioannina Medical School, Ioannina, Greece

¹⁰Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA, USA

¹¹Department of Medicine, Harvard Medical School, Boston, MA, USA

¹²The Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

¹³Medical Research Council Integrative Epidemiology Unit, School of Social and Community Medicine, University of Bristol, Oakfield House, Oakfield Grove, Bristol, UK

¹⁴Centre for Cardiovascular Genetics, Institute of Cardiovascular Science, University College London, London, UK

¹⁵Department of Biostatistics and Center for Statistical Genetics, University of Michigan, Ann Arbor, MI, USA

¹⁶Saw Swee Hock School of Public Health, National University of Singapore, Singapore, Singapore

¹⁷Icelandic Heart Association, Kopavogur, Iceland

¹⁸Faculty of Medicine, University of Iceland, Reykjavik, Iceland

¹⁹Genetic Epidemiology Unit, Department of Epidemiology, Erasmus Medical Center, Rotterdam, Netherlands

²⁰Department of Life Sciences, Brunel University London, London, UK

²¹Section of Investigative Medicine, Department of Medicine, Imperial College London, London, UK

²²Department of Clinical Biochemistry, Lillebaelt Hospital, Vejle, Denmark

²³Institute of Regional Health Research, University of Southern Denmark, Odense, Denmark

²⁴Department of Nutrition and Dietetics, School of Health Science and Education, Harokopio University, Athens, Greece

²⁵University of Lund, Department of Clinical Sciences, Malmö, Sweden

²⁶Department of Medicine, University of Verona, Verona, Italy

²⁷Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK

²⁸Research Unit of Biomedicine, and Biocenter of Oulu, Oulu of University, 90014 Oulu, Finland

²⁹Medical Research Center (MRC) and Oulu University Hospital, Oulu, Finland

³⁰Department of Gastroenterology and Metabolism, Poznan University of Medical Sciences, Poznan, Poland

³¹Vanderbilt Epidemiology Center, Institute for Medicine and Public Health, Vanderbilt University Medical Center, Nashville, TN, USA

³²Division of Preventive Medicine, Brigham and Women's Hospital, Boston, MA, USA

³³Human Genetics Center, School of Public Health, The University of Texas Health Science Center at Houston, Houston, TX, USA

³⁴Institute for Translational Genomics and Population Sciences and Department of Pediatrics, Harbor-UCLA Medical Center, Torrance, CA, USA

³⁵Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK

³⁶Centre for Genomic and Experimental Medicine, University of Edinburgh, Edinburgh, UK

³⁷Department of Health, National Institute for Health and Welfare, Helsinki, Finland

³⁸Institute of Molecular Medicine Finland, Helsinki, Finland

³⁹Department of Internal Medicine, Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, MI, USA

⁴⁰Steno Diabetes Center, Copenhagen, Gentofte, Denmark

⁴¹Department of Primary Health Care, Vaasa Central Hospital, Vaasa, Finland

⁴²Diabetes Center, Vaasa Health Care Center, Vaasa, Finland.

⁴³Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA

⁴⁴Research Centre for Prevention and Health, The Capital Region of Denmark, Copenhagen, Denmark

⁴⁵Department of Clinical Experimental Research, Rigshospitalet, Glostrup, Denmark

⁴⁶Epidemiology & Prevention Center for Genomics and Personalized Medicine Research, Wake Forest Baptist Medical Center, Medical Center Boulevard, Winston-Salem, NC, USA

⁴⁷Medical Genomics and Metabolic Genetics Branch, National Human Genome Research Institute, NIH, Bethesda, MD, USA

⁴⁸Charles Bronfman Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA

⁴⁹Division of Epidemiology, Department of Medicine, Vanderbilt-Ingram Cancer Center, Vanderbilt Epidemiology Center, Vanderbilt University School of Medicine, Nashville, TN, USA

⁵⁰Estonian Genome Center, University of Tartu, Tartu, Estonia

⁵¹Section of Biology and Genetics, Department of Neuroscience, Biomedicine and Movement, University of Verona, Verona, Italy

⁵²Department of Data Science, University of Mississippi Medical Center, Jackson, MS, USA

⁵³Department of Twin Research & Genetic Epidemiology, King's College London, UK

⁵⁴British Heart Foundation Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, UK

⁵⁵Department of Medicine, Columbia University Medical Center, New York, NY, USA

⁵⁶Department of Clinical Sciences, Genetic and Molecular Epidemiology Unit, Lund University, Malmö, Sweden

⁵⁷Kuopio Research Institute of Exercise Medicine, Kuopio, Finland

⁵⁸Department of Clinical Physiology and Nuclear Medicine, Kuopio University Hospital, Kuopio, Finland

⁵⁹Oxford Centre for Diabetes, Endocrinology and Metabolism, Radcliffe Department of Medicine, University of Oxford, Oxford, UK

⁶⁰Wellcome Trust Sanger Institute, Hinxton, Cambridge, UK

⁶¹Department of Cardiovascular Sciences, University of Leicester, Leicester, UK

⁶²NIHR Leicester Biomedical Research Centre, Glenfield Hospital, Leicester, UK

⁶³Department of Biostatistics, University of Washington, Seattle, WA, USA

⁶⁴Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, MI, USA

⁶⁵University of Eastern Finland and Kuopio University Hospital, Kuopio, Finland

⁶⁶Department of Haematology, University of Cambridge, Cambridge, UK

- ⁶⁷Department of Cardiology, University Medical Center Utrecht, Utrecht, Netherlands
- ⁶⁸Folkhälsan Research Centre, Helsinki, Finland
- ⁶⁹Department of Endocrinology, Helsinki University Central Hospital, Helsinki, Finland.
- ⁷⁰MRC-PHE Centre for Environment and Health, Imperial College London, London, UK
- ⁷¹Interfaculty Institute for Genetics and Functional Genomics, University Medicine and Ernst-Moritz-Arndt-University Greifswald, Greifswald, Germany
- ⁷²DZHK (German Centre for Cardiovascular Research), Partner Site Greifswald, Greifswald, Germany
- ⁷³Department of Cardiology, Ealing Hospital, London North West Healthcare NHS Trust, London, UK
- ⁷⁴Human Genome Sequencing Center, Baylor College of Medicine, Houston, TX, USA
- ⁷⁵Imperial College Healthcare NHS Trust, London, UK
- ⁷⁶University of Dundee, Ninewells Hospital & Medical School, Dundee, UK
- ⁷⁷Medical Department, Lillebaelt Hospital, Vejle, Denmark
- ⁷⁸University of Groningen, University Medical Center Groningen, Department of Cardiology, Groningen, Netherlands
- ⁷⁹Psychology, University of Edinburgh, Edinburgh, UK
- ⁸⁰Department of Internal Medicine B - Cardiology, Pneumology, Infectious Diseases, Intensive Care Medicine, University Medicine Greifswald, Greifswald, Germany
- ⁸¹Mathematical and Statistical Computing Laboratory, Center for Information Technology, National Institutes of Health, Bethesda, MD, USA
- ⁸²Institute for Aging Research, Hebrew SeniorLife, Harvard Medical School, Boston, MA, USA
- ⁸³Vanderbilt Epidemiology Center, Institute for Medicine and Public Health, Vanderbilt University Medical Center, Nashville, TN, USA
- ⁸⁴Brown Foundation Institute of Molecular Medicine, McGovern Medical School, University of Texas Health Science Center at Houston, Texas, Houston, TX, USA
- ⁸⁵Department of Epidemiology, University of North Carolina, Chapel Hill, NC, USA
- ⁸⁶Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA
- ⁸⁷Department of Public Health & Clinical Medicine, Umeå University, Umeå, Sweden

- ⁸⁸Department of Nephrology and Dialysis, Università Cattolica del Sacro Cuore, Roma, Italy
- ⁸⁹Department of Clinical Sciences, Diabetes and Endocrinology, Lund University Diabetes Centre, Malmö, Sweden
- ⁹⁰Finnish Institute for Molecular Medicine (FIMM), Helsinki University, Helsinki, Finland
- ⁹¹Department of Biobank Research, Umeå University, Umeå, Sweden
- ⁹²Medical Research Council Human Genetics Unit, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK
- ⁹³Tampere University Hospital, Tampere, Finland
- ⁹⁴Department of Medicine, Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, California, USA
- ⁹⁵Department of Medical Sciences, Molecular Epidemiology and Science for Life Laboratory, Uppsala University, Uppsala, Sweden
- ⁹⁶Chronic Disease Prevention Unit, National Institute for Health and Welfare, Helsinki, Finland
- ⁹⁷Dasman Diabetes Institute, Dasman, Kuwait
- ⁹⁸Diabetes Research Group, King Abdulaziz University, Jeddah, Saudi Arabia
- ⁹⁹Department of Neurosciences and Preventive Medicine, Danube University Krems, Krems, Austria
- ¹⁰⁰Center for Life Course Health Research, Faculty of Medicine, University of Oulu, Oulu, Finland
- ¹⁰¹Oxford NIHR Biomedical Research Centre, Oxford University Hospitals Trust, Oxford, UK
- ¹⁰²National Heart and Lung Institute, Imperial College London, Hammersmith Hospital Campus, London, UK
- ¹⁰³Institute of Biomedicine/Physiology, University of Eastern Finland, Kuopio, Finland
- ¹⁰⁴MRC Epidemiology Unit, University of Cambridge School of Clinical Medicine, Institute of Metabolic Science, Cambridge Biomedical Campus, Cambridge, UK
- ¹⁰⁵Department of Medicine, University of Eastern Finland and Kuopio University Hospital, Kuopio, Finland
- ¹⁰⁶Department of Genetics, University of North Carolina, Chapel Hill, NC, USA
- ¹⁰⁷Medical Research Institute, University of Dundee, Ninewells Hospital and Medical School, Dundee, Scotland, UK
- ¹⁰⁸Faculty of Medicine, University of Split, Split, Croatia

¹⁰⁹International Centre for Circulatory Health, Imperial College London, UK

¹¹⁰Cardiovascular Health Research Unit, Departments of Medicine, Epidemiology and Health Services, University of Washington, Seattle, WA, USA

¹¹¹Kaiser Permanente Washington Health Research Institute, Seattle, WA, USA

¹¹²Harvard Medical School, Boston, MA, USA

¹¹³Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, UK

¹¹⁴Division of Public Health Sciences, Department of Biostatistical Sciences, Wake Forest School of Medicine, Winston-Salem, NC, USA

¹¹⁵Alzheimer Scotland Research Centre, University of Edinburgh, Edinburgh, UK

¹¹⁶University of Groningen, University Medical Center Groningen, Department of Genetics, Groningen, Netherlands

¹¹⁷Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, MS, USA

¹¹⁸Department of Internal Medicine, Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, MI, USA

¹¹⁹Department of Computational Medicine and Bioinformatics, University of Michigan, Ann Arbor, MI, USA

¹²⁰Department of Human Genetics, University of Michigan, Ann Arbor, MI, USA

¹²¹Department of Public Health, Aarhus University, Aarhus, Denmark

¹²²Danish Diabetes Academy, Odense, Denmark

¹²³Department of Biostatistics and Epidemiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

¹²⁴Centre for Non-Communicable Diseases, Karachi, Pakistan

¹²⁵Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK

¹²⁶NIHR Blood and Transplant Research Unit in Donor Health and Genomics, University of Cambridge, Cambridge, UK

¹²⁷British Heart Foundation, Cambridge Centre for Excellence, Department of Medicine, University of Cambridge, Cambridge, UK

¹²⁸Institute of Cardiovascular Science, Faculty of Population Health Sciences, University College London, London, UK

¹²⁹Department of Health Sciences, University of Leicester, Leicester, UK

¹³⁰Center for Complex Disease Genomics, McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA

¹³¹Cardiology, Department of Medicine, Geneva University Hospital, Geneva, Switzerland

¹³²Big Data Institute at the Li Ka Shing Centre for Health Information and Discovery, University of Oxford, Oxford, UK.

¹³³Program in Medical and Population Genetics, Broad Institute of Harvard and MIT, Cambridge, MA, USA

¹³⁴Cardiovascular Research Center, Massachusetts General Hospital, Boston, MA, USA.

†These coauthors jointly supervised the project

*Correspondence:

Aldi T Kraja, DSc, PhD
Division of Statistical Genomics,
Department of Genetics, Center for Genome Sciences and Systems Biology
Washington University School of Medicine, St. Louis, MO, USA
aldi@wustl.edu, Phone: (314) 362-2498, Fax: (314) 362-4227

Disclaimer: The manuscript and its contents are confidential, intended for journal review purposes only, and not to be further disclosed.

Abstract

Background: Genome-wide association studies have recently identified over 400 loci that harbor DNA sequence variants that influence blood pressure (BP). Our earlier work identified and validated 56 single nucleotide variants (SNVs) associated with BP from meta-analyses of Exome Chip genotype data. An additional 100 variants yielded suggestive evidence of association.

Methods and Results: Here, we augment the sample with 140,886 European individuals from the UK Biobank, in whom 77 of the 100 suggestive SNVs were available for association analysis with systolic or diastolic blood pressure (SBP, DBP) or pulse pressure (PP). We performed two meta-analyses, one in individuals of European, South Asian, African and Hispanic descent (pan-ancestry, ~475,000), and the other in the subset of individuals of European descent (~423,000).

Twenty-one SNVs were genome-wide significant ($P < 5 \times 10^{-8}$) for BP, of which four are new BP loci: rs9678851 (missense, *SLC4A1AP*), rs7437940 (*AFAP1*), rs13303 (missense, *STAB1*) and rs1055144 (*7p15.2*). In addition, we identified a potentially independent novel BP-associated SNV (rs3416322 (missense, *SYNPO2L*) at a known locus, uncorrelated with the previously reported SNVs. Two SNVs are associated with expression levels of nearby genes, and SNVs at three loci are associated with other traits. One SNV with a minor allele frequency < 0.01 , (rs3025380 at *DBH*) was genome-wide significant.

Conclusions: We report four novel loci associated with BP regulation, and one independent variant at an established BP locus. This analysis highlights several candidate genes with variation that alter protein function or gene expression for potential follow-up.

Key words from the journal subject terms and two additional in red color: “Blood Pressure”, “Genetics”, “Genetic, Association Studies”, “Gene Expression and Regulation”, “Exome chip”, “UK Biobank”.

High blood pressure (BP) is a major risk factor for coronary artery disease, heart failure, stroke, renal failure and premature mortality¹. High BP has been estimated to cause 10.7 million deaths worldwide in 2015^{2,3}. Pharmacologic interventional trials of BP-lowering therapies in patients with hypertension have demonstrated reductions in cardiovascular complications, including mortality⁴. While several anti-hypertensive drug classes exist, variability in treatment response by individual patients and ethnic/racial groups, and residual risks, suggest that identification of previously unrecognized BP regulatory pathways could identify novel targets and pave the way for new treatments for cardiovascular disease prevention.

Genetic association studies have identified over 400 loci at $P < 5 \times 10^{-8}$ that influence BP⁵⁻¹¹. Two recent reports independently performed discovery analyses, in sample sizes of up to ~146k (CHARGE Exome BP consortium) and ~192k individuals (the European-led Exome consortia [contributory consortia, CHD Exome+, ExomeBP, and GoT2D:T2DGenes])^{8,9}. All samples were genotyped on the Illumina Exome array that was designed to interrogate rare and low frequency non-synonymous and other putative functional variants, as well as non-coding variants for association with biomedical traits. They each identified ~80 promising single nucleotide variant (SNV) associations with systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP) or hypertension and took them forward for replication in the reciprocal consortium^{8,9} resulting in the identification of 56 novel BP-associated loci across the two reports, including associations with coding and rare SNVs. A total of 100 SNVs remained of interest, but did not achieve genome-wide significance. Increasing the sample size, is likely to identify additional BP-associated SNVs among these variants.

In the current report, we augmented the sample size of these studies with up to 140,886 European individuals from the UK Biobank, and analyzed 77 SNVs available in the UK Biobank for association with SBP, DBP and PP, in a total sample size of up to ~475,000 individuals (up to ~423,000 EUR).

Materials and Methods

Samples

These analyses consisted of a meta-analysis of results from three independent publications, the CHARGE Exome BP consortium⁸, European-led Exome consortia (contributory consortia, CHD Exome+, ExomeBP, and GoT2D:T2DGenes)⁹ and the BP analyses from the UK Biobank Cardiometabolic consortium¹¹.

The CHARGE Exome BP consortium included 120,473 individuals of EUR descent from 15 cohorts, 21,503 individuals of African (AFR) descent from 10 cohorts and 4,586 individuals of Hispanic (HIS) ancestry from 2 cohorts as previously described⁸. The European-led consortia included 165,276 individuals of EUR descent from 51 cohorts and 27,487 individuals of South Asian (SAS) descent from two cohorts⁹. The UK Biobank data included 140,886 unrelated individuals of EUR descent¹¹.

All samples from the CHARGE and European-led Exome consortia were genotyped on Exome arrays that includes ~242,000 markers > 90% of which are non-synonymous or splice variants, with enrichment for variants with MAF < 0.05. The UK Biobank used the Affymetrix UK Biobank Axiom Array (N~100,00), or the Affymetrix UK BiLEVE Axiom Array (N~50,000) to genotype ~800,000 SNVs with subsequent imputation based on UK10K sequencing and 1000 Genomes reference panels. SNVs with an imputation threshold INFO score of < 0.10 were filtered by the Warren *et al.* UK Biobank Nature Genetics 2017 manuscript, from which the SNV association statistics for UK Biobank were provided¹¹. Imputation scores in the UK Biobank samples for the variants presented in Table 1 had INFO > 0.6. SNVs that produced significant results are highlighted in green in Supplemental Tables 1 and 2, with a median INFO of 1. The studies by Surendran *et al.*, Liu *et al.* and Warren *et al.* examined genomic inflation factors in the contributing studies and the combined meta-analyses for each of the traits analysed. Genomic inflation ranged between 1.04 and 1.11 in these contributing studies and therefore did not suggest there were significant issues with population stratification^{8, 9, 11}. In the current analyses, 77 non-validated BP-associated SNVs were available for analysis across all three datasets.

Institutional Review Board (IRB) approval was obtained from each participating cohort and informed consent was obtained from all subjects^{8, 9}. The UK Biobank study has approval

from the North West Multi-Centre Research Ethics Committee and has Research Tissue Bank approval.

Phenotypes

Three BP traits were examined: systolic BP (SBP), diastolic BP (DBP) and pulse pressure (PP), where PP was calculated as the difference between SBP and DBP. For individuals taking anti-hypertensive therapies, 15 mm Hg and 10 mm Hg were added to the observed SBP and DBP, respectively, to estimate the BP that would be observed off anti-hypertensive therapy^{12, 13}. The traits were approximately normally distributed, and no transformations of the traits were performed.

Statistical analyses

In the CHARGE Exome BP consortium, in cohorts of unrelated individuals single SNV association tests were implemented via linear regression in R/PLINK/SNPTEST. For family-based cohorts linear mixed effects models in R was used to estimate kinship via R KINSHIP2 package and using the LMEKIN function, to account for familial correlations (<https://cran.r-project.org/web/packages/coxme/vignettes/lmekin.pdf>; Supplemental Table 21 of Liu *et al.*⁸). The component studies of the European-led consortia (CHD Exome+, ExomeBP and GoT2D:T2D genes) used linear regression as implemented in PLINK¹⁴ or linear mixed models as implemented in Genome-Wide Efficient Mixed Model Association (GEMMA)¹⁵ or EMMAX (the Efficient Mixed-Model Association eXpedited, EMMAX)¹⁶, to test variants for association with BP traits. The UK Biobank study used linear regression models as implemented in SNPTEST¹⁷. All studies assumed an additive allelic effects model.

All studies adjusted for age, age², sex, body mass index and additional cohort-specific covariates including (where appropriate) principal components of genetic ancestry, field centers, genotyping array, or case/control status for samples ascertained on case/control status for a non-BP trait. Both study-level QC and central QC was performed prior to the meta-analyses being performed. Full details are given in the reports from the component consortia^{8, 9, 11}.

At the consortium level, meta-analyses of cohort-level association results were performed independently within CHARGE-Exome and the European-led Exome consortia using inverse variance-weighted fixed effects meta-analysis. These meta-analyses results were combined with the UK Biobank association results using fixed effects inverse variance weighted meta-analysis as implemented in METAL¹⁸. Two meta-analyses were performed, one pan-ancestry (AA, EUR, HIS, SAS), and a second of EUR ancestry. Statistical significance was set at genome-wide significance, $P < 5 \times 10^{-8}$.

Functional annotation

Associated variants were annotated using HG38 dbSNP and Entrez Gene (NCBI). We interrogated publically available gene expression regulatory features from ENCODE and ROADMAP Epigenome projects using HaploReg¹⁹ and RegulomeDB²⁰. eQTLs were assessed using data from GTEx²¹ GRASP²², Westra *et al.*²³, Lappalainen *et al.*²⁴ and STARNET²⁵. In addition we used the FHS eQTL results from microarray-based gene and exon expression levels in whole blood from 5,257 individuals²⁶. We queried whether any of the five BP-associated SNVs were eQTLs for genes in the five BP-associated regions, or whether they were in LD ($r^2 > 0.8$) with any of the eQTLs for genes in these regions. Where putative eQTLs were identified, we verified the BP-associated SNVs were in LD ($r^2 > 0.8$) with the top eQTL for that gene.

We interrogated publically available GWAS databases through PhenoScanner²⁷, a curated database holding publicly available results from large-scale genome-wide association studies facilitating “phenome scans”. We report results for SNVs with P -value $\leq 5 \times 10^{-8}$.

Capture HiC interactions were accessed from the Capture HiC Plotter (www.CHiCP.org). Javierre *et al.*²⁸ used an interaction confidence score derived using CHiCAGO software²⁹. The interactions with a CHiCAGO score ≥ 5 in at least one cell type were considered as high-confidence interactions.

Results

Association results for the 77 SNVs with the three BP traits are shown in Supplemental Table 1 for the pan-ancestry (PA: European, South Asian, African and Hispanic descent) meta-analysis and in Supplemental Table 2 for the European (EUR) meta-analysis. Twenty-one of the

77 SNVs were associated with at least one BP trait with genome wide significance, $P < 5 \times 10^{-8}$ and concordant directions of effects across the results from all contributing datasets (Table 1). Sixteen SNVs (*PKN2*, *ARHGEF3*, *AFAP1*, *ANKDD1B*, *LOC105375508*, *ZFAT*, *RABGAP1*, *DBH*, *SYNPO2L*, *BDNF-AS*, *AGBL2*, *NOX4*, *CEP164*, *HOXC4*, *CFDP1* and *COMT*) were genome-wide significant in both PA- and EUR samples. Two SNVs at *SLC4A1AP* and 7p15.2, respectively, were significant only in the PA sample; and three SNVs at *STAB1/NT5DC2*, *KDM5A* and *LACTB* only in the EUR sample. All the significant SNVs were common (minor allele frequencies ≥ 0.19), except the SNV at the *DBH* locus (PA, MAF = 0.0043). While this report was in preparation, 17 of these loci were published elsewhere^{7, 10, 11}. Four loci remain novel: rs9678851 (*SLC4A1AP*, missense), rs7437940 (*AFAP1*, intron), rs13303 (*STAB1*, missense) and rs1055144 (7p15.2, non-coding transcript; Supplemental Figures 1a-d). The *SLC4A1AP* (rs9678851) was associated with SBP and *AFAP1* (rs7437940) and 7p15.2 (rs1055144) were associated with PP. We also observed a potentially new independent BP association ($r^2 \sim 0.001$ in 1000G EUR and PA samples) at a recently published locus rs34163229 (*SYNPO2L*, missense; Table 1; Supplemental Figure 1e). We used a conservative $r^2 < 0.1$ threshold to minimize the possibility of an association due to correlation with a strongly associated established BP variant. Furthermore, conditional analyses within the ~140,000 UK Biobank participants with comprehensive genomic coverage suggested that the association with SBP of rs34163229 was independent of the established SNV, rs4746172. Regional association plots in UK Biobank are provided in Supplemental Figures 2a-e. Conditional analyses within the full dataset was not possible given the targeted nature of the Exome array which makes claims of independence provisional. Twenty-two of the 77 SNVs had minor allele frequency (MAF) ≤ 0.01 , and one rs3025380, a missense variant in *DBH* was confirmed as a BP-associated locus.

Three of the five newly discovered BP-associated SNVs are missense variants, mapping to *SLC4A1AP*, *STAB1* and *SYNPO2L* (Table 1 and Supplemental Table 3). At *SLC4A1AP*, rs9678851 (C>A, Pro139Thr) has MAF=0.46 and the C allele is associated with an increase of 0.23 mmHg in SBP. This variant is correlated with two other missense variants in *C2orf16* (rs1919126 and rs1919125, $r^2 = 0.81$ (EUR) based on 1000G³⁰, for both). At *STAB1*, the C allele of rs13303 (T>C, Met2506Thr, with MAF=0.44) is associated with an increase of 0.15 mmHg in PP per minor allele in EUR. This residue is located in a conserved region of the protein³¹

(Supplemental Table 4). The T allele of rs34163229, the new association at the *SYNPO2L* locus, (G>T, Ser833Tyr, with MAF=0.15), is associated with an increase of 0.36 mmHg in SBP per allele. This variant is in LD with another missense variant in *SYNPO2L* (rs3812629 $r^2=1$, 1000G EUR)³⁰. Using Polyphen2 (<http://genetics.bwh.harvard.edu/pph2/index.shtml>), the SNVs rs9678851 in *SLC4A1AP*, and rs13303 in *STAB1* were predicted to be *benign*, while rs34163229 in *SYNPO2L* was predicted to have a *possible damaging* impact on the corresponding human proteins' structure and function.

We interrogated publicly available expression quantitative trait loci (eQTL) datasets through GTEx, ENCODE, RoadMap projects, PhenoScanner²⁷, STARNET²⁵ and Framingham Heart Study²⁶ to further highlight potential causal genes and mechanisms at each of the newly identified BP loci (Supplemental Table 3). The PP-associated SNV, rs13303, at *STAB1* is correlated ($r^2 > 0.8$ 1000G EUR) with the top eQTLs for *NT5DC2* in atherosclerotic-lesion free internal mammary artery, atherosclerotic aortic root, subcutaneous adipose, visceral abdominal fat and liver tissues (all $P < 1 \times 10^{-11}$)²⁵. The rs13303 was also associated with expression levels of *NT5DC2* in EBV-transformed lymphocytes, transformed fibroblasts²⁵ and thyroid cells (Supplemental Table 3)²¹. The SBP-associated SNV at *SYNPO2L* (rs34163229) is correlated ($r^2=0.86$ in 1000G EUR) with the top eQTL (rs2177843) for *MYOZ1* in heart atrial appendage tissue (Supplemental Table 3)²¹. The five new BP associated SNVs were not in LD with the top eQTLs for these gene regions in whole blood in the Framingham Heart Study eQTL data. We also took the opportunity to assess whether the additional fifteen recently established genome-wide significant BP-associated SNVs were eQTLs in the Framingham sample. Amongst the genome-wide significant BP SNVs, three, rs4680 at *COMT*, rs12680655 at *ZFAT* and rs10760260 at *RABGAP1*, were the top eQTL for the corresponding genes in whole blood (Supplemental Table 5). We also examined the five BP-associated SNVs in endothelial precursor cell Hi-C data (www.chicp.org;^{28,32}) to explore long-range chromatin interactions. rs13303 was found to contact *NISCH* (score 17.34) and rs34163229 contacts *USP54* (score 33.89)

Finally, we assessed the association of the new BP-associated variants and their close proxies ($r^2 > 0.8$) with cardiovascular disease risk factors, molecular metabolic traits and clinical phenotypes using PhenoScanner, the NHGRI-EBI GWAS catalog and GRASP²⁷. We observed

five of the newly discovered BP-associated SNVs to have genome wide significant associations with other traits, including height (7p15.2)³³, waist-to-hip ratio (*STAB1* and 7p15.2)^{34, 35}, triglycerides (*SLC4A1P*), adiponectin levels (*STAB1*)³⁶, and atrial fibrillation (rs7915134 which has $r^2=0.92$ in the EUR 1000G samples with rs34163229 in *SYNPO2L*)³⁷ (Supplemental Table 3).

Of the 77 analysed SNVs, from the original Exome array analyses, 56 SNVs were not genome-wide significant in the current analysis. With ~300 BP loci reported since the time of our analysis, we investigated whether any of the 56 SNVs that were not genome-wide significant in our meta-analysis have been reported as new BP-associated loci in any of the three recent publications^{7, 10, 11}. Twelve SNVs in our dataset were located within 1 Mb of a recently reported BP locus : *CACNA1S*, *TSC22D2*, *RPL26L1*, *EDN1*, *GPRC6A*, *ACHE*, *CAVI*, *NOX5*, *PGLYRP2*, *NAPB*, *EDEM2* and *KCNBI*; (Supplemental Tables 1 and 2), although none of the SNVs were in LD ($r^2 > 0.1$ in all 1000G populations) with the published variants at these loci.

Discussion

We identified genome-wide significant associations with BP for 21 additional SNVs from our original Exome array analyses^{8,9} by including UK Biobank participants to augment our sample size to ~475,000 individuals. Four of the twenty-one BP-related loci we identified were novel, of which two were missense variants, and one was a putative new independent signal at an established locus and was a missense variant.

A missense SNV in *SLC4A1AP* (rs9678851) marks the PP-associated locus on chromosome 2. *SLC4A1AP*, encodes a solute carrier also known as kidney anion exchanger adapter protein, although it is widely expressed in most GTEx tissues.

At the new locus on chromosome 3 (rs13303), three potential candidate genes are highlighted: *STAB1*, *NT5DC2* and *NISCH*. *STAB1* encodes stabilin1, a protein known to endocytose low density lipoprotein cholesterol, gram-positive and -negative bacteria, and advanced glycosylation end products^{38,39}. The gene product is also referred to as CLEVER-1, a common lymphatic endothelial and vascular endothelial receptor-1⁴⁰, which is expressed in macrophages⁴¹. *SNX17* interacts with *STAB1* and is a trafficking adaptor of *STAB1* in

endothelial cells^{38,42}. The rs13303 is located 500bp downstream of *NT5DC2*. This additional gene is highlighted through the association of rs13303 with expression of *NT5DC2* in multiple tissues (Supplemental Table 3). *NT5DC2* encodes the 5'-nucleotidase domain containing 2 protein. The gene is widely expressed, with higher levels observed in the heart and coronary artery, although its function is unknown. Lastly, exploration of long-range chromatin interaction identified contact of the SNV region with the genetic sequence including the gene *NISCH*, which encodes the nonadrenergic imidazoline-1 receptor protein localized to the cytosol and anchored to the inner layer of the plasma membrane. This protein binds to the adapter insulin receptor substrate 4 (*IRS4*) to mediate translocation of alpha-5 integrin from the cell membrane to endosomes. In human cardiac tissue, this protein has been found to affect cell growth and death⁴³.

The PP-associated variant, rs7437940 on chromosome 4 is intronic to *AFAP1*, and is located in promoter histone marks in right atrial tissue, based on regulatory chromatin states from DNase and histone ChIP-Seq in Roadmap Epigenomics Consortium (identified with HaploReg, Supplemental Table 4)⁴⁴. *AFAP1* encodes actin filament associated protein 1. This protein is thought to have a role in the regulation of actin filament integrity, and formation and maintenance of the actin network⁴⁵.

At the locus on chromosome 10 (rs34163229), two candidate genes were highlighted (*SYNPO2L* and *MYOZ1*). *SYNPO2L* encodes synaptopodin like 2, which is not well characterized, but may play a role in modulating actin-based shape. The lead SNV is also associated with expression levels of *MYOZ1* in heart appendage tissues. *MYOZ1* encodes myozenin 1, an alpha actinin and gamma filamin binding Z line protein predominantly expressed in skeletal muscle⁴⁶.

At two loci (*SLC4A1AP* and *SYNPO2L*) we observed more than one missense variant in high LD ($r^2 > 0.8$). Functional follow up of these variants may be challenging to disentangle the causal variants. At the *SLC4A1AP* locus, there are three missense variants, none of which are predicted to be damaging. Two of these are in *C2orf16*, which is predicted to encode an uncharacterized protein. Current evidence is at the transcriptional level. Cellular assays

comparing the function of *SLC4A1AP* with the missense variant may be developed or an animal model could be created and BP can be measured. In the first instance, a knockout model may be required, due to the predicted weak effects of the BP variants. At the *SYNPO2L* locus, the two missense variants are both in *SYNPO2L*, of which one is predicted damaging, cellular experiments testing functional effects of this variant alone or part of a haplotype maybe a good starting point.

In conclusion, we identified four new loci and one potential new SNV in a known locus, that influence BP variation and highlight specific genes and pathways that could potentially facilitate an improved understanding of BP regulation, and identify novel therapeutic targets to reduce the burden of cardiovascular disease.

Acknowledgments

A detailed list of acknowledgments is presented in the Online Appendix, together with the full list of members of the contributing consortia.

Conflict of Interest

DIC received funding for genotyping of the exome chip and collaborative scientific support from Amgen.

MJC is Chief Scientist for Genomics England, a UK government company.

EE is a scientific advisor for Precision Wellness, Cellink and Olink Proteomics for work unrelated to the present project.

NP has received financial support from several pharmaceutical companies which manufacture either blood pressure lowering or lipid lowering agents, or both, and consultancy fees. BMP serves on the DSMB of a clinical trial funded by the manufacturer (Zoll LifeCor) and on the Steering Committee of the Yale Open Data Access project funded by Johnson & Johnson.

PJS has received research awards from Pfizer Inc.

All other coauthors declare NONE.

References

1. Rapsomaniki E, Timmis A, George J, Pujades-Rodriguez M, Shah AD, Denaxas S, et al. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1.25 million people. *Lancet*. 2014;383:1899-911.
2. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380:2224-60.
3. Collaborators GBDRF. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388:1659-1724.
4. Rahman M, Pressel S, Davis BR, Nwachuku C, Wright JT, Jr., Whelton PK, et al. Renal outcomes in high-risk hypertensive patients treated with an angiotensin-converting enzyme inhibitor or a calcium channel blocker vs a diuretic: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med*. 2005;165:936-46.
5. International Consortium for Blood Pressure Genome-Wide Association S, Ehret GB, Munroe PB, Rice KM, Bochud M, Johnson AD, et al. Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. *Nature*. 2011;478:103-9.
6. Wain LV, Verwoert GC, O'Reilly PF, Shi G, Johnson T, Johnson AD, et al. Genome-wide association study identifies six new loci influencing pulse pressure and mean arterial pressure. *Nat Genet*. 2011;43:1005-11.
7. Ehret GB, Ferreira T, Chasman DI, Jackson AU, Schmidt EM, Johnson T, et al. The genetics of blood pressure regulation and its target organs from association studies in 342,415 individuals. *Nat Genet*. 2016;48:1171-84.
8. Liu C, Kraja AT, Smith JA, Brody JA, Franceschini N, Bis JC, et al. Meta-analysis identifies common and rare variants influencing blood pressure and overlapping with metabolic trait loci. *Nat Genet*. 2016;48:1162-70.
9. Surendran P, Drenos F, Young R, Warren H, Cook JP, Manning AK, et al. Trans-ancestry meta-analyses identify rare and common variants associated with blood pressure and hypertension. *Nat Genet*. 2016;48:1151-61.
10. Hoffmann TJ, Ehret GB, Nandakumar P, Ranatunga D, Schaefer C, Kwok PY, et al. Genome-wide association analyses using electronic health records identify new loci influencing blood pressure variation. *Nat Genet*. 2017;49:54-64.
11. Warren HR, Evangelou E, Cabrera CP, Gao H, Ren M, Mifsud B, et al. Genome-wide association analysis identifies novel blood pressure loci and offers biological insights into cardiovascular risk. *Nat Genet*. 2017.
12. Tobin MD, Sheehan NA, Scurrah KJ and Burton PR. Adjusting for treatment effects in studies of quantitative traits: antihypertensive therapy and systolic blood pressure. *Stat Med*. 2005;24:2911-35.
13. Wu J, Kraja AT, Oberman A, Lewis CE, Ellison RC, Arnett DK, et al. A summary of the effects of antihypertensive medications on measured blood pressure. *Am J Hypertens*. 2005;18:935-42.
14. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. *American journal of human genetics*. 2007;81:559-75.
15. Zhou N and Wang L. Effective selection of informative SNPs and classification on the HapMap genotype data. *BMC Bioinformatics*. 2007;8:484.

16. Kang HM, Sul JH, Service SK, Zaitlen NA, Kong SY, Freimer NB, et al. Variance component model to account for sample structure in genome-wide association studies. *Nat Genet.* 2010;42:348-54.
17. Marchini J, Howie B, Myers S, McVean G and Donnelly P. A new multipoint method for genome-wide association studies by imputation of genotypes. *Nat Genet.* 2007;39:906-13.
18. Willer CJ, Li Y and Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. *Bioinformatics.* 2010;26:2190-1.
19. Ward LD and Kellis M. HaploReg: a resource for exploring chromatin states, conservation, and regulatory motif alterations within sets of genetically linked variants. *Nucleic acids research.* 2012;40:D930-4.
20. Boyle AP, Hong EL, Hariharan M, Cheng Y, Schaub MA, Kasowski M, et al. Annotation of functional variation in personal genomes using RegulomeDB. *Genome Res.* 2012;22:1790-7.
21. GTEx Consortium. Human genomics. The Genotype-Tissue Expression (GTEx) pilot analysis: multitissue gene regulation in humans. *Science.* 2015;348:648-60.
22. Leslie R, O'Donnell CJ and Johnson AD. GRASP: analysis of genotype-phenotype results from 1390 genome-wide association studies and corresponding open access database. *Bioinformatics.* 2014;30:i185-94.
23. Westra HJ, Peters MJ, Esko T, Yaghootkar H, Schurmann C, Kettunen J, et al. Systematic identification of trans eQTLs as putative drivers of known disease associations. *Nat Genet.* 2013;45:1238-43.
24. Lappalainen T, Sammeth M, Friedlander MR, Hoen PA, Monlong J, Rivas MA, et al. Transcriptome and genome sequencing uncovers functional variation in humans. *Nature.* 2013;501:506-11.
25. Franzen O, Ermel R, Cohain A, Akers NK, Di Narzo A, Talukdar HA, et al. Cardiometabolic risk loci share downstream cis- and trans-gene regulation across tissues and diseases. *Science.* 2016;353:827-30.
26. Joehanes R, Zhang X, Huan T, Yao C, Ying SX, Nguyen QT, et al. Integrated genome-wide analysis of expression quantitative trait loci aids interpretation of genomic association studies. *Genome Biol.* 2017;18:16.
27. Staley JR, Blackshaw J, Kamat MA, Ellis S, Surendran P, Sun BB, et al. PhenoScanner: a database of human genotype-phenotype associations. *Bioinformatics.* 2016;32:3207-3209.
28. Javierre BM, Burren OS, Wilder SP, Kreuzhuber R, Hill SM, Sewitz S, et al. Lineage-Specific Genome Architecture Links Enhancers and Non-coding Disease Variants to Target Gene Promoters. *Cell.* 2016;167:1369-1384 e19.
29. Cairns J, Freire-Pritchett P, Wingett SW, Varnai C, Dimond A, Plagnol V, et al. CHiCAGO: robust detection of DNA looping interactions in Capture Hi-C data. *Genome Biol.* 2016;17:127.
30. Machiela MJ and Chanock SJ. LDlink: a web-based application for exploring population-specific haplotype structure and linking correlated alleles of possible functional variants. *Bioinformatics.* 2015;31:3555-7.
31. Garber M, Guttman M, Clamp M, Zody MC, Friedman N and Xie X. Identifying novel constrained elements by exploiting biased substitution patterns. *Bioinformatics.* 2009;25:i54-62.
32. Schofield EC, Carver T, Achuthan P, Freire-Pritchett P, Spivakov M, Todd JA, et al. CHiCP: a web-based tool for the integrative and interactive visualization of promoter capture Hi-C datasets. *Bioinformatics.* 2016;32:2511-3.
33. Wood AR, Esko T, Yang J, Vedantam S, Pers TH, Gustafsson S, et al. Defining the role of common variation in the genomic and biological architecture of adult human height. *Nat Genet.* 2014;46:1173-86.
34. Shungin D, Winkler TW, Croteau-Chonka DC, Ferreira T, Locke AE, Magi R, et al. New genetic loci link adipose and insulin biology to body fat distribution. *Nature.* 2015;518:187-96.

35. Heid IM, Jackson AU, Randall JC, Winkler TW, Qi L, Steinhorsdottir V, et al. Meta-analysis identifies 13 new loci associated with waist-hip ratio and reveals sexual dimorphism in the genetic basis of fat distribution. *Nat Genet.* 2010;42:949-60.
36. Dastani Z, Hivert MF, Timpson N, Perry JR, Yuan X, Scott RA, et al. Novel loci for adiponectin levels and their influence on type 2 diabetes and metabolic traits: a multi-ethnic meta-analysis of 45,891 individuals. *PLoS genetics.* 2012;8:e1002607.
37. Christophersen IE, Rienstra M, Roselli C, Yin X, Geelhoed B, Barnard J, et al. Large-scale analyses of common and rare variants identify 12 new loci associated with atrial fibrillation. *Nat Genet.* 2017;49:946-952.
38. Kzhyshkowska J, Gratchev A and Goerdt S. Stabilin-1, a homeostatic scavenger receptor with multiple functions. *J Cell Mol Med.* 2006;10:635-49.
39. Adachi H and Tsujimoto M. FEEL-1, a novel scavenger receptor with in vitro bacteria-binding and angiogenesis-modulating activities. *J Biol Chem.* 2002;277:34264-70.
40. Irjala H, Elima K, Johansson EL, Merinen M, Kontula K, Alanen K, et al. The same endothelial receptor controls lymphocyte traffic both in vascular and lymphatic vessels. *Eur J Immunol.* 2003;33:815-24.
41. Kzhyshkowska J. Multifunctional receptor stabilin-1 in homeostasis and disease. *ScientificWorldJournal.* 2010;10:2039-53.
42. Adachi H and Tsujimoto M. Adaptor protein sorting nexin 17 interacts with the scavenger receptor FEEL-1/stabilin-1 and modulates its expression on the cell surface. *Biochim Biophys Acta.* 2010;1803:553-63.
43. Sano H, Liu SC, Lane WS, Piletz JE and Lienhard GE. Insulin receptor substrate 4 associates with the protein IRAS. *J Biol Chem.* 2002;277:19439-47.
44. Ernst J, Kheradpour P, Mikkelsen TS, Shores N, Ward LD, Epstein CB, et al. Mapping and analysis of chromatin state dynamics in nine human cell types. *Nature.* 2011;473:43-9.
45. Xiao H, Han B, Lodyga M, Bai XH, Wang Y and Liu M. The actin-binding domain of actin filament-associated protein (AFAP) is involved in the regulation of cytoskeletal structure. *Cell Mol Life Sci.* 2012;69:1137-51.
46. Takada F, Vander Woude DL, Tong HQ, Thompson TG, Watkins SC, Kunkel LM, et al. Myozenin: an alpha-actinin- and gamma-filamin-binding protein of skeletal muscle Z lines. *Proc Natl Acad Sci U S A.* 2001;98:1595-600.

Table 1. Variants associated with SBP, DBP or PP in the Pan-ancestry or EUR-ancestry meta-analyses in up to ~475,000 individuals.

rsID	Gene	Annotation	chr-pos	Trait	Meta	a1/2	Freq1	b(S.E.)	P-value	Dir	HetP	N	UK-BioBank INFO
New loci													
rs9678851	<i>SLC4A1AP</i>	missense	2-27664167	S	PA	a/c	0.54	-0.23 (0.04)	1.07E-09	---	0.09	474,569	1.0000
rs13303*	<i>STAB1</i>	missense	3-52523992	P	EUR	t/c	0.44	-0.15 (0.03)	3.72E-08	---	0.11	418,405	1.0000
rs7437940	<i>AFAP1</i>	Intronic	4-7885773	P	EUR,PA	t/c	0.47	-0.15 (0.03)	2.88E-08	---	0.007	420,616	0.9974
rs1055144	7p15.2	nc-transcript	7-25831489	P	PA	a/g	0.19	0.19 (0.03)	3.47E-08	+++	0.18	453,880	1.0000
Recently reported loci													
rs786906	<i>PKN2</i>	synonymous	1-88805891	S,P	EUR,PA	t/c	0.44	0.19(0.03)	1.29E-12	+++	0.08	422,556	1.0000
rs3772219	<i>ARHGEF3</i>	missense	3-56737223	S,D	EUR,PA	a/c	0.68	0.25(0.04)	2.00E-10	+++	0.25	474,558	1.0000
rs40060	<i>ANKDD1B</i>	3'UTR	5-75671561	D	EUR,PA	t/c	0.65	-0.17(0.02)	3.47E-12	---	0.46	422,598	0.9938
rs972283	<i>LOC105375508</i>	intronic	7-130782095	S,D	EUR,PA	a/g	0.47	-0.23(0.04)	9.12E-10	---	0.1	474,569	1.0000
rs12680655	<i>ZFAT</i>	intronic	8-134625094	S,D	EUR,PA	c/g	0.6	-0.29(0.04)	1.62E-12	---	0.18	402,962	1.0000
rs10760260	<i>RABGAP1</i>	intronic	9-122951247	P	EUR,PA	t/g	0.14	-0.25(0.04)	2.88E-10	---	0.12	421,223	0.9975
rs3025380	<i>DBH</i>	missense	9-133636634	S,D	EUR,PA	c/g	0.004	-1.14(0.19)	1.23E-09	---	0.05	400,891	0.8763
rs34163229*	<i>SYNPO2L</i>	missense	10-73647154	S,P	EUR,PA	t/g	0.15	0.36(0.05)	1.15E-11	+++	0.32	448,759	1.0000
rs925946	<i>BDNF-AS</i>	intronic	11-27645655	D	EUR,PA	t/g	0.31	-0.16(0.02)	7.08E-12	---	0.25	474,564	1.0000
rs12286721	<i>AGBL2</i>	missense	11-47679976	S,D	EUR,PA	a/c	0.56	-0.17(0.02)	3.39E-13	---	0.05	422,593	1.0000
rs10765211	<i>NOX4</i>	intronic	11-89495257	P	EUR,PA	a/g	0.38	-0.19(0.03)	6.46E-12	---	0.05	474,550	0.9964
rs8258	<i>CEP164</i>	3'UTR	11-117412960	P	EUR,PA	a/g	0.37	0.22(0.03)	1.95E-15	+++	0.003	422,546	1.0000
rs11062385	<i>KDM5A</i>	missense	12-318409	P	EUR	a/g	0.73	-0.17(0.03)	2.69E-08	---	0.84	422,563	1.0000
rs7136889†	<i>HOXC4</i>	intronic	12-54043968	S,P	EUR,PA	t/g	0.69	0.36(0.05)	1.58E-13	+++	0.33	419,905	0.6070
rs2729835*	<i>LACTB</i>	missense	15-63141567	S	EUR	a/g	0.68	-0.24(0.04)	1.29E-08	---	0.25	394,656	1.0000
rs2865531	<i>CFDP1</i>	intronic	16-75356418	S,P	EUR,PA	a/t	0.6	0.42(0.06)	2.14E-13	+++	0.51	217,419	0.9998
rs4680	<i>COMT</i>	missense	22-19963748	P	EUR,PA	a/g	0.51	0.16(0.03)	2.24E-09	+++	0.005	418,385	1.0000

Note: rsID-SNV name, **Gene**-name of the closest gene or cytogenetic band based on Gene Entrez of NCBI; **Annotation**-SNV annotation based on dbSNP of NCBI; **Chr-pos**-chromosome-bp position in Human Genome build 38; **Trait**- the blood pressure trait

(**DBP**, **SBP** or **PP**) the variant is associated with; **Meta**- the meta-analysis the variant is associated in, **Pan-Ancestry** and/or **EUROpean**; **A1/2**-allele 1/allele 2; **Freq1**-allele frequency for allele 1; **β (SE)**-effect estimate, β and its standard error for allele 1 from the corresponding meta-analysis (highlighted in bold); **P-value** – P from meta-analysis (highlighted in bold); **Direction**- direction of effect in each of the contributing consortia in the following order: EUROPEAN led Exome Consortia, UK-BIOBANK and CHARGE-BP Consortium; **HetP**- P -value of heterogeneity across the three contributing consortia, **N**- Sample size for the trait and meta-analysis with the lowest P -value (bold). * indicates potential new signal at a recently reported locus (LD- $r^2 < 0.1$ with a published BP SNV), and † indicates first report of this variant as genome-wide significant. For more details, see Supplemental Tables 1 and 2. **UK-BIOBANK INFO**- a quality of imputation score in UK BIOBANK.

Disclaimer: The manuscript and its content are confidential, intended for journal review purposes only, and should not be further disclosed.