

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. Wain¹, Ahmad Vaez^{2,3}, Rick Jansen⁴, Roby Joehanes^{5,6}, Peter J. van der Most², A. Mesut Erzurumluoglu¹, Paul O'Reilly⁷, Claudia P. Cabrera^{8,9}, Helen R. Warren^{8,9}, Lynda M. Rose¹⁰, Germaine C. Verwoert¹¹, Jouke-Jan Hottenga¹², Rona J. Strawbridge^{13,14}, Tonu Esko^{15,16,17}, Dan E. Arking¹⁸, Shih-Jen Hwang^{19,20}, Xiuqing Guo²¹, Zoltan Kutalik^{22,23}, Stella Trompet^{24,25}, Nick Shrine¹, Alexander Teumer^{26,27}, Janina S. Ried²⁸, Joshua C. Bis²⁹, Albert V. Smith^{30,31}, Najaf Amin³², Ilja M. Nolte², Leo-Pekka Lyytikäinen^{33,34}, Anubha Mahajan³⁵, Nicholas J. Wareham³⁶, Edith Hofer^{37,38}, Peter K. Joshi³⁹, Kati Kristiansson⁴⁰, Michela Traglia⁴¹, Aki S. Havulinna⁴⁰, Anuj Goel^{42,35}, Mike A. Nalls^{43,44}, Siim Söber⁴⁵, Dragana Vuckovic^{46,47}, Jian'an Luan³⁶, Fabiola Del Greco M.⁴⁸, Kristin L. Ayers⁴⁹, Jaume Marrugat⁵⁰, Daniela Ruggiero⁵¹, Lorna M. Lopez^{52,53,54}, Teemu Niiranen⁴⁰, Stefan Enroth⁵⁵, Anne U. Jackson⁵⁶, Christopher P. Nelson^{57,58}, Jennifer E. Huffman⁵⁹, Weihua Zhang^{60,61}, Jonathan Marten⁶², Ilaria Gandin⁴⁷, Sarah E Harris^{52,63}, Tatijana Zemunik⁶⁴, Yingchang Lu⁶⁵, Evangelos Evangelou^{60,66}, Nabi Shah^{67,68}, Martin H. de Borst⁶⁹, Massimo Mangino^{70,71}, Bram P. Prins⁷², Archie Campbell^{73,74}, Ruifang Li-Gao⁷⁵, Ganesh Chauhan^{76,77}, Christopher Oldmeadow⁷⁸, Gonçalo Abecasis⁷⁹, Maryam Abedi⁸⁰, Caterina M. Barbieri⁴¹, Michael R. Barnes^{8,9}, Chiara Batini¹, John Beilby^{81,82,83}, BIOS Consortium⁸⁴, Tineka Blake¹, Michael Boehnke⁵⁶, Erwin P. Bottinger⁶⁵, Peter S. Braund^{57,58}, Morris Brown^{8,9}, Marco Brumat⁴⁷, Harry Campbell³⁹, John C. Chambers^{60,61,85}, Massimiliano Cocca⁴⁷, Francis Collins⁸⁶, John Connell⁸⁷, Heather J. Cordell⁸⁸, Jeffrey J. Damman⁸⁹, Gail Davies^{52,90}, Eco J. de Geus¹², Renée de Mutsert⁷⁵, Joris Deelen⁹¹, Yusuf Demirkale⁹², Alex S.F. Doney⁶⁷, Marcus Dörr^{93,27}, Martin Farrall^{42,35}, Teresa Ferreira³⁵, Mattias Frånberg^{13,14,94}, He Gao⁶⁰, Vilmantas Giedraitis⁹⁵, Christian Gieger⁹⁶, Franco

Giulianini¹⁰, Alan J. Gow^{52,97}, Anders Hamsten^{13,14}, Tamara B. Harris⁹⁸, Albert Hofman^{11,99}, Elizabeth G. Holliday⁷⁸, Jennie Hui^{81,82,100,83}, Marjo-Riitta Jarvelin^{101,102,103,104}, Åsa Johansson⁵⁵, Andrew D. Johnson^{6,105}, Pekka Jousilahti⁴⁰, Antti Jula⁴⁰, Mika Kähönen^{106,107}, Sekar Kathiresan^{108,109,110}, Kay-Tee Khaw¹¹¹, Ivana Kolcic¹¹², Seppo Koskinen⁴⁰, Claudia Langenberg³⁶, Marty Larson⁶, Lenore J. Launer⁹⁸, Benjamin Lehne⁶⁰, David C.M. Liewald^{52,90}, Lifelines Cohort Study¹¹³, Li Lin¹¹⁴, Lars Lind¹¹⁵, François Mach¹¹⁴, Chrysovalanto Mamasoula¹¹⁶, Cristina Menni⁷⁰, Borbala Mifsud⁸, Yuri Milaneschi¹¹⁷, Anna Morgan⁴⁷, Andrew D. Morris¹¹⁸, Alanna C. Morrison¹¹⁹, Peter J. Munson⁹², Priyanka Nandakumar¹⁸, Quang Tri Nguyen⁹², Teresa Nutile⁵¹, Albertine J. Oldehinkel¹²⁰, Ben A. Oostra³², Elin Org¹⁵, Sandosh Padmanabhan^{121,74}, Aarno Palotie¹²², Guillaume Paré¹²³, Alison Pattie⁹⁰, Brenda W.J.H. Penninx¹¹⁷, Neil Poulter¹²⁴, Peter P. Pramstaller^{48,125,126}, Olli T. Raitakari^{127,128}, Meixia Ren^{8,129}, Kenneth Rice¹³⁰, Paul M. Ridker^{10,131}, Harriëtte Riese¹²⁰, Samuli Ripatti¹²², Antonietta Robino¹³², Jerome I. Rotter¹³³, Igor Rudan³⁹, Yasaman Saba¹³⁴, Aude Saint Pierre^{48,135}, Cinzia F. Sala⁴¹, Antti-Pekka Sarin¹²², Reinhold Schmidt³⁷, Rodney Scott^{78,136,137}, Marc A. Seelen⁶⁹, Denis C. Shields¹³⁸, David Siscovick¹³⁹, Rossella Sorice^{51,140}, Alice Stanton¹⁴¹, David J. Stott¹⁴², Johan Sundström¹¹⁵, Morris Swertz¹⁴³, Kent D. Taylor^{144,145}, Simon Thom¹⁴⁶, Ioanna Tzoulaki⁶⁰, Christophe Tzourio^{76,77,147}, André G. Uitterlinden^{11,148}, Understanding Society Scientific group⁸⁴, Uwe Völker^{149,27}, Peter Vollenweider¹⁵⁰, Sarah Wild³⁹, Gonneke Willemsen¹², Alan F. Wright⁶², Jie Yao²¹, Sébastien Thériault¹²³, David Conen¹⁵¹, Attia John^{78,136,137}, Peter Sever¹⁵², Stéphanie Debette^{76,77,153}, Dennis O. Mook-Kanamori^{75,154}, Eleftheria Zeggini⁷², Tim D. Spector⁷⁰, Pim van der Harst¹⁵⁵, Colin N.A. Palmer⁶⁷, Anne-Claire Vergnaud⁶⁰, Ruth J.F. Loos^{36,156,157}, Ozren Polasek¹¹², John M. Starr^{52,158}, Giorgia Grotto^{47,46}, Caroline Hayward^{159,74}, Jaspal S. Kooner^{160,61,85}, Cecila M. Lindgren^{17,35}, Veronique Vitart⁵⁹, Nilesh J. Samani^{57,58}, Jaakko Tuomilehto^{161,162,163,164}, Ulf Gyllensten⁵⁵, Paul Knekt⁴⁰, Ian J. Deary^{52,90}, Marina Ciullo^{51,140}, Roberto Elosua⁵⁰, Bernard D. Keavney¹⁶⁵, Andrew A. Hicks⁴⁸, Robert A. Scott³⁶, Paolo Gasparini^{46,47}, Maris Laan^{45,166}, YongMei Liu¹⁶⁷, Hugh Watkins^{42,35}, Catharina A. Hartman¹²⁰, Veikko Salomaa⁴⁰, Daniela Toniolo⁴¹, Markus Perola^{40,122,168}, James F. Wilson^{39,62}, Helena Schmidt^{134,169}, Jing Hua Zhao³⁶, Terho Lehtimäki^{33,34}, Cornelia M. van Duijn³², Vilmundur Gudnason^{30,31}, Bruce M. Psaty^{29,170,171,172}, Annette Peters²⁸, Rainer Rettig¹⁷³, Alan James^{174,175}, J Wouter Jukema²⁴, David P. Strachan¹⁷⁶, Walter Palmas¹⁷⁷, Andres Metspalu¹⁵, Erik Ingelsson^{178,179}, Dorret I. Boomsma¹², Oscar H. Franco¹¹, Murielle Bochud²², Christopher Newton-Cheh^{180,108,110,17}

Patricia B. Munroe^{8,9}, Paul Elliott¹⁰⁴, Daniel I. Chasman^{10,131}, Aravinda Chakravarti¹⁸, Joanne Knight¹⁸¹, Andrew P. Morris^{182,35}, Daniel Levy^{183,20}, Martin D. Tobin¹, 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 Association, 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, Icahn 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 University 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)

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 BP 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.

Keywords: blood pressure, hypertension, GWAS, eSNP, complex traits, cardiovascular risk

INTRODUCTION

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. A number of 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 blood pressure (SBP) and diastolic blood pressure (DBP), reflecting roughly the peak and trough of the BP curve, and pulse pressure (PP), the difference between SBP and DBP ²⁰ reflecting arterial stiffness. Using these three traits, we undertook a meta-analysis of 150,134 individuals from 54 genome-wide association studies 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=23049), 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 **Supplementary Table 1**.

Study-level genotyping and association testing

Three quantitative BP traits were analyzed: SBP, DBP, and PP (difference between SBP and DBP). Within each study, individuals known to be taking anti-hypertensive medication had 15 mmHg added to their raw SBP value and 10 mmHg added to their raw DBP values ²¹. A summary of BP phenotypes in each study is given in **Supplementary Table 2**. Association testing was undertaken according to a central analysis plan that specified the use of sex,

age, age², and body mass index (BMI) as covariates and optional inclusion of additional covariates to account for population stratification (**Supplementary Table 3**). Trait residuals were calculated for each trait using a normal linear regression of the medication-adjusted trait values (mmHg) onto all covariates. The genotyping array, pre-imputation quality control filters, imputation software and association testing software used by each study are listed in **Supplementary Table 4**. All studies imputed to the 1000 Genomes Project Phase 1 integrated release version 3 [March 2012] all ancestry reference panel²². Imputed genotype dosages were used to take into account uncertainty in the imputation. Association testing was carried out 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 (**Supplementary Table 3**). Results for all variants (SNPs and 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 (i.e. to highlight phenotype issues) and generation of quantile-quantile (QQ) plots and genomic inflation factor lambdas to check for over- or under-inflation 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 less than 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 \pm 500kb from the sentinel and re-ranking the remaining variants. This was undertaken iteratively until all sentinel variants representing 1Mb regions containing associations with $P < 10^{-6}$ had been identified. To identify additional signals represented by secondary sentinel variants within 500kb of each of the sentinel variants, GCTA²³ was used to run conditional analyses (conditioned on the first sentinel variant) on each of the 1Mb regions using GWAS summary statistics and LD information from ARIC. This was done both for putatively novel regions and for regions that had previously been reported. A chi-squared 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 $-\log_{10} P$ value was less than 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

(i.e. totaling 228,245 individuals). Stage 2 study details, including full study names, are given in **Supplementary Table 6** and included 3C-Dijon (n=4061), Airwave (n=14023), 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=13376), 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 utilized 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 linkage disequilibrium $r^2 > 0.6$ 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

Following meta-analysis of stage 1 and stage 2 results, signals with a $P > 5 \times 10^{-8}$ were excluded. Of the signals with a final $P < 5 \times 10^{-8}$, support for independent replication within the stage 2 studies only was sought. Any signals which had $P < 5 \times 10^{-8}$ and evidence for independent replication in stage 2 alone, indicated by $P < 8.2 \times 10^{-4}$ (Bonferroni correction for 61 tests) were reported as novel signals of association with BP. Any signals which 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 (**Supplementary Table 5**).

Genotype and gene expression

We searched for signals of association of genotype with gene expression for the 22 signals (including 8 novel) signals described in this study (**Supplementary Table 7**) and all signals reported prior to our study (**Supplementary Table 10**)^{3-16, 18, 24} in 3 whole-blood data sets, 1 kidney data set and the GTEx multiple tissue data resource, which included whole-blood²⁵. We selected cis signals of association which were significant after controlling for 5% False Discovery Rate (FDR). The 3 whole-blood eQTL data sets were the NHLBI Systems Approach to Biomarker Research in Cardiovascular Disease initiative whole-blood eQTL resource (SABRe) (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 donors²⁶. Full details of each data set can be found in the **Supporting Information**. The source transcriptomic renal data as described²⁶ 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 (Feb. 20th, 2015), using 503 subjects of European ancestry²². r^2 between the sentinel SNPs and all other bi-allelic SNPs within the corresponding 2 Mb area was calculated using the Tabix and PLINK software package (v1.07)^{27, 28}. Annotation was performed using the ANNOVAR software package²⁹.

Gene-based pathway analysis

All genes identified in 3 or 4 of the whole-blood eQTL resources above (**Table 2**), and genes containing a non-synonymous variant with $r^2 > 0.5$ with the sentinel variant (**Supplementary Table 13**), were tested for enrichment of biological pathways and gene ontology terms using ConsensusPathDB³⁰ using a FDR < 5% cut-off. 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 two prioritized candidate gene sets into a single query gene set as (i) genes mapping to the non-synonymous SNPs (nsSNPs) in high LD ($r^2 > 0.5$) with the corresponding sentinel BP associated SNP, and (ii) genes with eQTL evidence from 3 or 4 of the blood eQTL resources. Three sentinel SNPs (rs185819, rs926552 and rs805303) mapping to the HLA region on chromosome 6 were excluded from downstream analyses. The single query gene set was then used as input for the functional network analysis³¹. We used the Cytoscape³² software platform extended by the GeneMANIA³³ plugin (Data Version: 8/12/2014)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 Gene Ontology terms (GO terms)³⁵ to identify the most relevant GO terms using the same plugin³⁴.

DNase1 Hypersensitivity overlap enrichment across tissue and cell-types

The Functional element Overlap analysis of the Results of Genome Wide Association Study (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 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 gene ontology enrichment analyses were further investigated for potential druggable or drugged targets using the drug gene interaction database (DGIdb). 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 (**Online Methods; Supplementary Tables 1-4, Supplementary Figures 1 and 2**) and 7,994,604 variants with minor allele frequency (MAF) > 1% and an effective sample size of at least 60% of the total (**Online Methods**). We employed the widely used 2-stage design³⁷ and identified 61 signals in the discovery analysis that were candidates for novel BP signals ($P < 10^{-6}$ for any trait; **Supplementary Table 5**). 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 Biobank¹⁹ (**Supplementary Table 6 and Online Methods**). 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 ($P < 8.2 \times 10^{-4}$, Bonferroni correction for 61 tests) and genome-wide significance ($P < 5 \times 10^{-8}$) in a meta-analysis across all 378,376 individuals (**Online methods, Table 1, Supplementary Table 7**). Of these, 14 were subsequently published in two other studies^{17, 19} which presented genome-wide significant associations with evidence of replication. A further two were highlighted as putative novel signals in one of those studies¹⁷ 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 (**Supplementary Figure 3**) and one novel independent signal near a previously reported hit near *TNXB* (**Online Methods, Supplementary Table 8, Supplementary Figure 4**). The novel signals show both significant evidence of replication in the independent stage-2 studies ($P < 8.2 \times 10^{-4}$, Bonferroni correction for 61 tests) and

genome-wide significance ($P < 5 \times 10^{-8}$) in a meta-analysis across all 378,376 individuals. The sentinel variants at all 8 signals were common (MAF>5%) and the novel secondary signal at *TNXB* was in high linkage-disequilibrium ($r^2 > 0.8$) with a non-synonymous 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 **Supplementary Table 9**).

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 reported prior to these studies^{17, 19}, and 22 novel signals of association identified and confirmed in this study and two contemporaneous studies^{3-19, 24} (**Supplementary Table 10**), and searched for evidence of association with gene expression in whole-blood (four studies, total n=12,607; **Online Methods**) and in kidney tissue (n=134, the largest kidney eQTL resource currently available). Although of unclear direct relevance to BP, whole-blood was studied due to 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.³⁸ 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}. Expression quantitative trait loci (eQTL) signals were filtered by false

discovery rate (FDR < 5%) and we examined *cis* (within 1Mb) associations only (**Online methods and Supporting Information**).

The four blood eQTL data sets were NESDA-NTR^{39,40}, SABRe¹⁵, the BIOS resource⁴¹ and GTEx²⁵ (**Online Methods and Supporting Information**). The BIOS resource (n=2,116) has not previously been utilized in the analysis of BP associations, 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 one or more of the 4 blood datasets at experiment-wide significance (**Supplementary Table 11**). This included 14 genes for 6 of the 8 novel signals. For 110 genes, we found eQTL evidence in 2 out of 4 datasets (**Figure 1**), 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 linkage disequilibrium (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 function⁴².

For 48 genes, we found evidence in 3 out of the 4 resources (**Table 2**), suggesting robustness of the SNP-gene expression 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 dataset (TransplantLines)²⁶, there was association of gene expression and genotype for nine SNPs and 13 genes (**Table 2, Figure 1 and Supplementary Table 12**). Nine

of the SNP-gene expression associations were also observed in the whole-blood eQTL datasets, suggesting that those signals may not be unique to the kidney. We report three 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 anti-sense 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 co-expressed) with ENaC subunits which mediate trans-epithelial Na transport in the distal nephron of the kidney⁴³. The comparatively small number of signals using kidney tissue (**Table 2** and **Figure 1**) compared to whole-blood could be due to the small sample size. Complete GTEx results are in Supplementary Table 13.

For genes implicated by eQTL information from whole-blood, we tested for enrichment of biological pathways and gene ontologies (**Online Methods**). We noted enrichment of the 48 genes implicated by 3 or 4 blood eQTL resources, **Table 2**, and a further 53 genes containing a non-synonymous variant with $r^2 > 0.5$ with the top SNP (**Supplementary Table 14**), in pathways and ontology terms related to actin and striated muscle (**Supplementary Tables 15 and 16, Online Methods**). Network analysis using the same genes highlighted further GO terms relating to muscle function, particularly cardiac muscle (**Online Methods, Supplementary Table 17**). We tested the overlap of 161 non-HLA BP associated variants with DNase Hypersensitivity sites identified in the Roadmap and ENCODE cell lines (**Online Methods**) and identified an overall enrichment in multiple cell and tissue types including heart, kidney and smooth muscle (**Supplementary Figure 5**).

We next investigated these genes for potential suitability as drug targets (druggability), known tool compounds and clinically approved drugs using the drug gene interaction database (DGIdb) ⁴⁴ (**Supplementary Table 18**). Twelve genes had known drugs, including four genes with known antihypertensive drugs. We noted that drugs modulating all but one of the 12 drugged targets had a reported influence on blood pressure, either as a primary antihypertensive indication or as a reported side effect of raised blood pressure. 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/chembl/db/; 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 blood pressure 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 two signals we present, for the first time, stringent evidence of replication, confirming their relevance to blood pressure genetics.

The path from signal to genes is the essential next step towards 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 biologic 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 dataset and microarray-based expression levels for the kidney and other blood datasets), 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 three 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 blood pressure 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 a number of drugged targets in the pathways identified, including four existing hypertension targets. Other drugs identified are not suitable candidates for repositioning to hypertension, as most were reported in adverse events to raise blood pressure, however the targets would be valid for investigation using a reverse mechanism, e.g. agonism in place of inhibition. We also identified seven 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.

Amongst the genes implicated in our eQTL analyses were several for which there is already some evidence that they are relevant to blood pressure regulation. The intronic SNP rs10926988 was independently associated with expression of *SDCCAG8* in all four whole-blood resources. Rare mutations in *SDCCAG8* cause Bardet-Biedl syndrome, which features hypertension. Expression levels of *MYBPC3* were correlated with rs7103648¹⁵ in the 3 largest blood eQTL resources (i.e. 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 so far. 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.

DISCLOSURES

The authors declare competing financial interests (see corresponding section in the Supporting Information).

SOURCES OF FUNDING: See end of the manuscript.

NOTE: Online data supplements are available in the online version of the paper.

ACKNOWLEDGEMENTS

We thank all the study participants of this study for their contributions. Detailed acknowledgment of funding sources is provided in the **Supporting Information**.

REFERENCES

1. Nelson MR, Tipney H, Painter JL, Shen J, Nicoletti P, Shen Y, Floratos A, Sham PC, Li MJ, Wang J, Cardon LR, Whittaker JC, Sanseau P. The support of human genetic evidence for approved drug indications. *Nat Genet.* 2015;47:856-860.
2. Mancia G, Fagard R, Narkiewicz K, et al. 2013 esh/esc guidelines for the management of arterial hypertension: The task force for the management of arterial hypertension of the european society of hypertension (esh) and of the european society of cardiology (esc). *Eur Heart J.* 2013;34:2159-2219.
3. Ehret GB, Munroe PB, Rice KM, et al. Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. *Nature.* 2011;478:103-109.
4. Ganesh SK, Chasman DI, Larson MG, et al. Effects of long-term averaging of quantitative blood pressure traits on the detection of genetic associations. *American journal of human genetics.* 2014;95:49-65.
5. Johnson AD, Newton-Cheh C, Chasman DI, et al. Association of hypertension drug target genes with blood pressure and hypertension in 86,588 individuals. *Hypertension.* 2011;57:903-910.
6. Johnson T, Gaunt TR, Newhouse SJ, et al. Blood pressure loci identified with a gene-centric array. *The American Journal of Human Genetics.* 2011;89:1-13.
7. Kato N, Takeuchi F, Tabara Y, et al. Meta-analysis of genome-wide association studies identifies common variants associated with blood pressure variation in east asians. *Nat Genet.* 2011;43:531-538.
8. Levy D, Ehret GB, Rice K, et al. Genome-wide association study of blood pressure and hypertension. *Nat Genet.* 2009;41:677-687.

9. Newton-Cheh C, Johnson T, Gateva V, et al. Genome-wide association study identifies eight loci associated with blood pressure. *Nat Genet.* 2009;41:666-676.
10. Newton-Cheh C, Larson MG, Vasan RS, et al. Association of common variants in nppa and nppb with circulating natriuretic peptides and blood pressure. *Nat Genet.* 2009;41:348-353.
11. Padmanabhan S, Melander O, Johnson T, et al. Genome-wide association study of blood pressure extremes identifies variant near umod associated with hypertension. *PLoS Genet.* 2010;6:e1001177.
12. Simino J, Shi G, Bis JC, et al. Gene-age interactions in blood pressure regulation: A large-scale investigation with the charge, global bpgen, and icbp consortia. *American journal of human genetics.* 2014;95:24-38.
13. Tragante V, Barnes MR, Ganesh SK, et al. Gene-centric meta-analysis in 87,736 individuals of european ancestry identifies multiple blood-pressure-related loci. *American journal of human genetics.* 2014;94:349-360.
14. Wain LV, Verwoert GC, O'Reilly PF, et al. Genome-wide association study identifies six new loci influencing pulse pressure and mean arterial pressure. *Nat Genet.* 2011;43:1005-1011.
15. Ehret GB, Ferreira T, Chasman DI, et al. The genetics of blood pressure regulation and its target organs from association studies in 342,415 individuals. *Nat Genet.* 2016;48:1171-1184.
16. Liu C, Kraja AT, Smith JA, et al. Meta-analysis identifies common and rare variants influencing blood pressure and overlapping with metabolic trait loci. *Nat Genet.* 2016;48:1162-1170.

17. Hoffmann TJ, Ehret GB, Nandakumar P, Ranatunga D, Schaefer C, Kwok PY, Iribarren C, Chakravarti A, Risch N. Genome-wide association analyses using electronic health records identify new loci influencing blood pressure variation. *Nat Genet.* 2017;49:54-64.
18. Surendran P, Drenos F, Young R, et al. Trans-ancestry meta-analyses identify rare and common variants associated with blood pressure and hypertension. *Nat Genet.* 2016;48:1151-1161.
19. Warren HR, Evangelou E, Cabrera CP, et al. Genome-wide association analysis identifies novel blood pressure loci and offers biological insights into cardiovascular risk. *Nat Genet.* 2017;49:403-415.
20. Safar ME, Nilsson PM, Blacher J, Mimran A. Pulse pressure, arterial stiffness, and end-organ damage. *Curr Hypertens Rep.* 2012;14:339-344.
21. Tobin MD, Sheehan NA, Scurrah KJ, Burton PR. Adjusting for treatment effects in studies of quantitative traits: Antihypertensive therapy and systolic blood pressure. *Stat Med.* 2005;24:2911-2935.
22. Genomes Project C, Abecasis GR, Auton A, Brooks LD, DePristo MA, Durbin RM, Handsaker RE, Kang HM, Marth GT, McVean GA. An integrated map of genetic variation from 1,092 human genomes. *Nature.* 2012;491:56-65.
23. Yang J, Lee SH, Goddard ME, Visscher PM. Gcta: A tool for genome-wide complex trait analysis. *American journal of human genetics.* 2011;88:76-82.
24. Kato N, Loh M, Takeuchi F, et al. Trans-ancestry genome-wide association study identifies 12 genetic loci influencing blood pressure and implicates a role for DNA methylation. *Nat Genet.* 2015;47:1282-1293.

25. Consortium GT. Human genomics. The genotype-tissue expression (gtex) pilot analysis: Multitissue gene regulation in humans. *Science*. 2015;348:648-660.
26. Damman J, Bloks VW, Daha MR, van der Most PJ, Sanjabi B, van der Vlies P, Snieder H, Ploeg RJ, Krikke C, Leuvenink HG, Seelen MA. Hypoxia and complement-and-coagulation pathways in the deceased organ donor as the major target for intervention to improve renal allograft outcome. *Transplantation*. 2015;99:1293-1300.
27. Li H. Tabix: Fast retrieval of sequence features from generic tab-delimited files. *Bioinformatics*. 2011;27:718-719.
28. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, Maller J, Sklar P, de Bakker PI, Daly MJ, Sham PC. Plink: A tool set for whole-genome association and population-based linkage analyses. *American journal of human genetics*. 2007;81:559-575.
29. Wang K, Li M, Hakonarson H. Annovar: Functional annotation of genetic variants from high-throughput sequencing data. *Nucleic Acids Res*. 2010;38:e164.
30. Kamburov A, Stelzl U, Lehrach H, Herwig R. The consensuspathdb interaction database: 2013 update. *Nucleic Acids Res*. 2013;41:D793-800.
31. Vaez A, Jansen R, Prins BP, Hottenga JJ, de Geus EJ, Boomsma DI, Penninx BW, Nolte IM, Snieder H, Alizadeh BZ. In silico post genome-wide association studies analysis of c-reactive protein loci suggests an important role for interferons. *Circ Cardiovasc Genet*. 2015;8:487-497.
32. Saito R, Smoot ME, Ono K, Ruscheinski J, Wang PL, Lotia S, Pico AR, Bader GD, Ideker T. A travel guide to cytoscape plugins. *Nat Methods*. 2012;9:1069-1076.

33. Mostafavi S, Ray D, Warde-Farley D, Grouios C, Morris Q. Genemania: A real-time multiple association network integration algorithm for predicting gene function. *Genome Biol.* 2008;9 Suppl 1:S4.
34. Montojo J, Zuberi K, Rodriguez H, Kazi F, Wright G, Donaldson SL, Morris Q, Bader GD. Genemania cytoscape plugin: Fast gene function predictions on the desktop. *Bioinformatics.* 2010;26:2927-2928.
35. Ashburner M, Ball CA, Blake JA, et al. Gene ontology: Tool for the unification of biology. The gene ontology consortium. *Nat Genet.* 2000;25:25-29.
36. Dunham I, Kulesha E, Iotchkova V, Morganello S, Birney E. Forge : A tool to discover cell specific enrichments of gwas associated snps in regulatory regions. *BioRxiv.* 2014;10.1101/013045 .
37. Skol AD, Scott LJ, Abecasis GR, Boehnke M. Optimal designs for two-stage genome-wide association studies. *Genet Epidemiol.* 2007;31:776-788.
38. Trevisan M, Ostrow D, Cooper R, Liu K, Sparks S, Okonek A, Stevens E, Marquardt J, Stamler J. Abnormal red blood cell ion transport and hypertension. The people's gas company study. *Hypertension.* 1983;5:363-367.
39. Wright FA, Sullivan PF, Brooks AI, et al. Heritability and genomics of gene expression in peripheral blood. *Nat Genet.* 2014;46:430-437.
40. Jansen R, Batista S, Brooks AI, et al. Sex differences in the human peripheral blood transcriptome. *BMC Genomics.* 2014;15:33.
41. Zhernakova DV, Deelen P, Vermaat M, et al. Identification of context-dependent expression quantitative trait loci in whole blood. *Nat Genet.* 2017;49:139-145.

42. Marusugi K, Nakano K, Sasaki H, Kimura J, Yanobu-Takanashi R, Okamura T, Sasaki N. Functional validation of tensin2 sh2-ptb domain by crispr/cas9-mediated genome editing. *J Vet Med Sci.* 2016;78:1413-1420.
43. Jeggle P, Smith ES, Stewart AP, Haerteis S, Korbmacher C, Edwardson JM. Atomic force microscopy imaging reveals the formation of ASIC/ENAC cross-clade ion channels. *Biochem Biophys Res Commun.* 2015;464:38-44.
44. Wagner AH, Coffman AC, Ainscough BJ, Spies NC, Skidmore ZL, Campbell KM, Krysiak K, Pan D, McMichael JF, Eldred JM, Walker JR, Wilson RK, Mardis ER, Griffith M, Griffith OL. Dgidb 2.0: Mining clinically relevant drug-gene interactions. *Nucleic Acids Res.* 2016;44:D1036-1044.
45. Carrier L, Mearini G, Stathopoulou K, Cuello F. Cardiac myosin-binding protein c (mybpc3) in cardiac pathophysiology. *Gene.* 2015;573:188-197.

NOVELTY AND SIGNIFICANCE

What is New: The root origin of hypertension and hence blood pressure variability in the population remains unclear. This study adds data to explain the genetic basis of blood pressure variability and identifies genes likely active in blood pressure 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 blood pressure loci to the collection of loci currently known. Using these and previous data, 48 BP genes are identified for priority follow-up.

FIGURE LEGENDS

Figure 1: Overlap of eQTL evidence from four whole-blood and one kidney resource

The figure indicates overlap of evidence for eQTLs from four whole-blood studies (SABRe, NESDA-NTR, BIOS, and GTEx) and from one kidney resource (TransplantLines). Every colored line indicates that this gene was analysis-wide significant in a given resource (see **Online Methods**). Only genes identified by at least two resources are shown. The genes are sorted by genomic position on the y-axis.

Table 1. Novel genome-wide significant signals of association

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. Genome-wide significant *P* values ($P < 5 \times 10^{-8}$) are in bold. Abbreviations: CAF: coded allele frequency se: standard error, Neff: effective sample size. #Novel signal at previously reported locus. ¹For intragenic variants the nearest genes are listed, all other variants are intronic unless indicated otherwise; ns= non-synonymous, s=synonymous, UTR= Untranslated Region. 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.

Variant ID (noncoded/coded allele) chr:position, Nearest gene(s)(type ¹)	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				SBP	DBP	PP	
		Beta (se)	P value	Neff	Beta (se)	P value	Neff	Beta (se)	P value	Neff				
SBP														
rs1048238 (C/T) 1:16341649, <i>HSPB7</i> (3'UTR)	0.571	0.366 (0.074)	8.09E- 07	140299	NA	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	28721 7	7.07E- 12	1.07E- 10	5.48E- 06	
#rs185819 (T/C) 6:32,050,067, <i>TNXB</i> (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	36414 4	1.04E- 17	2.24E- 11	8.50E- 15	
rs6557876 (C/T) 8:25,900,675, <i>EBF2</i>	0.252	-0.411 (0.084)	8.50E- 07	143653	- 0.350	5.66E- 09	225803	-0.371 (0.049)	2.85E- 14	36945 7	2.85E- 14	2.50E- 10	1.51E- 08	

Variant ID (noncoded/coded allele) chr:position, Nearest gene(s)(type ¹)	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
					(0.060)								
rs35783704 (G/A) 8:105,966,258, <i>LRP12/ZFPM2</i>	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	34945 2	7.08E- 09	1.60E- 06	2.92E- 07
rs73099903 (C/T) 12:53,440,779, <i>LOC283335</i>	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	34331 8	1.95E- 10	4.53E- 06	5.46E- 08
rs8904 (G/A) 14:35,871,217, <i>NFKBIA</i> (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	36519 5	1.31E- 12	1.13E- 04	3.44E- 12
rs57927100 (C/G) 17:75,317,300, <i>SEPT9</i>	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	34718 8	4.04E- 10	1.16E- 10	1.81E- 05
DBP													
rs9710247 (A/G) 19:40,760,449, <i>AKT2</i>	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	30802 8	3.82E- 02	1.61E- 09	5.03E- 01

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. Signals of association of SNP genotype and gene expression in other non-blood tissues in GTEx and in kidney are also indicated. Blood dataset order: (i) SABRe, (ii) NESDA-NTR, (iii) BIOS, (iv) 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 one 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 **Supplementary Table 12**.

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	<i>CLCN6</i>	YYYY		Y		Y
rs2169137	1	204497913	<i>MDM4</i>	YYYY	Y	Y		Y
rs10926988	1	243483279	<i>SDCCA G8</i>	YYYY		Y		
rs319690	3	47927484	<i>MAP4</i>	YYYY	Y	Y		Y
rs12521868	5	131784393	<i>SLC22A 5</i>	YYYY		Y		
rs900145	11	13293905	<i>ARNTL</i>	YYYY		Y		Y
rs1060105	12	123806219	<i>CDK2A P1</i>	YYYY	Y	Y	Y	
rs1378942	15	75077367	<i>SCAMP 2</i>	YYYY				
rs1126464	16	89704365	<i>CHMP 1A</i>	YYYY		Y		Y
rs1126464	16	89704365	<i>FANCA</i>	YYYY				Y
rs12946454	17	43208121	<i>DCAKD</i>	YYYY		Y	Y	Y
Signal in 3 (out of 4) whole-blood eQTL resources								
rs17367504	1	11862778	<i>MTHFR</i>	YYYN		Y		Y
rs871524	1	38411445	<i>FHL3</i>	NYYY		Y		
rs871524	1	38411445	<i>SF3A3</i>	NYYY		Y		
rs4660293	1	40028180	<i>PABPC 4</i>	YYYN	Y	Y		Y
rs6749447	2	169041386	<i>STK39</i>	YYYN	Y			

rs347591	3	11290122	ATG7	YYYN		Y		
rs319690	3	47927484	ZNF58 9	YYNY		Y		
rs12521868	5	131784393	SLC22A 4	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	FAM16 7A	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	SWAP7 0	YYYN	Y	Y		?
rs7129220	11	10350538	ADM	YYYN				Y
rs7103648	11	47461783	MYBPC 3	YYYN				
rs3741378	11	65408937	CTSW	YYYN				
rs7302981	12	50537815	LIMA1	YYYN				Y
rs7302981	12	50537815	ATF1	YYNY		Y		
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	GATAD 2A	YYYN				
rs867186	20	33764554	EIF6	NYYY		Y		
rs6095241	20	47308798	PREX1	YYYN				
rs9306160	21	45107562	RRP1B	YNYY	Y	Y		

CONTRIBUTIONS / ACKNOWLEDGMENTS

AUTHOR CONTRIBUTIONS

Secondary analyses

Design of secondary analyses: L.V.W., G.B.E, M.J.C., H.Snieder, M.D.T , R.Joehanes, A.V., R.Jansen, A.V., J.K., P.O.R., A.P.M., C.P.C. Computation of secondary analysis: L.V.W., G.B.E., A.P.M., M.E., T.B., L.Lin, R.Joehanes, A.V., P.J.v.d.M., R.Jansen, C.P.C.

Discovery

WGHS : Study phenotyping: P.M.R. Genotyping or analysis: D.I.C., L.M.R. Study PI: D.I.C., P.M.R.

RS : Study phenotyping: G.C.V. Genotyping or analysis: G.C.V., A.G.U. Study PI: O.H.F., A.Hofman, A.G.U.

NTR : Study phenotyping: E.J.d.G., G.W. Genotyping or analysis: J.J.H., E.J.d.G., G.W. Study PI: D.I.B., E.J.d.G.

STR : Study phenotyping: E.I. Genotyping or analysis: R.J.S., M.Frånberg Study PI: E.I., A.Hamsten

EGCUT : Genotyping or analysis: T.E. Study PI: A.Metspalu

ARIC : Genotyping or analysis: D.E.A., A.C.M., P.N. Study PI: A.Chakravarti

FHS : Study phenotyping: D.L. Genotyping or analysis: S.J.H. Study PI: D.L.

MESA : Study phenotyping: J.I.R. Genotyping or analysis: W.P., X.G., J.I.R., J.Y. Study PI: W.P.

B58C : Study phenotyping: D.P.S. Genotyping or analysis: D.P.S. Study PI: D.P.S.

COLAUS : Study phenotyping: P.V. Genotyping or analysis: M.Bochud, Z.K. Study PI: P.V.

PROSPER : Study phenotyping: J.W.J., D.J.S. Genotyping or analysis: S.Trompet, J.D. Study PI: J.W.J.

BHS : Study phenotyping: A.James Genotyping or analysis: N.Shrine, J.H., J.B.

SHIP : Study phenotyping: M.D. Genotyping or analysis: A.T., M.D., U.V. Study PI: R.R.

KORA S4 : Genotyping or analysis: J.S.R. Study PI: A.Peters

CHS : Study phenotyping: B.M.P. Genotyping or analysis: J.C.B., K.R., K.D.T. Study PI: B.M.P.

AGES-Reykjavik : Genotyping or analysis: A.V.S. Study PI: V.Gudnason, T.B.H., L.J.L.

ERF : Study phenotyping: C.M.v.D., B.A.O. Genotyping or analysis: N.A. Study PI: C.M.v.D., B.A.O.

NESDA : Study phenotyping: B.W.J.H.P. Genotyping or analysis: I.M.N., Y.M. Study PI: H.Snieder, B.W.J.H.P.

YFS : Study phenotyping: T.L., M.K., O.T.R. Genotyping or analysis: T.L., L.P.L., M.K., O.T.R. Study PI: T.L., M.K., O.T.R.

EPIC : Genotyping or analysis: N.J.W. Study PI: J.H.Z.

ASPS : Study phenotyping: R.Schmidt Genotyping or analysis: H.Schmidt, E.H., Y.S., R.Schmidt Study PI: H.Schmidt, R.Schmidt

ORCADES : Study phenotyping: J.F.W., H.C., S.W. Genotyping or analysis: J.F.W., P.K.J., S.W. Study PI: J.F.W.

FINRISK (COROGENE_CTRL) : Study phenotyping: P.J. Genotyping or analysis: K.K., A.P.S. Study PI: M.P., P.J.

INGI-VB : Study phenotyping: C.F.S. Genotyping or analysis: M.T., C.M.B., C.F.S. Study PI: D.T.

FINRISK_PREDICT_CVD : Study phenotyping: V.S., A.S.H. Study PI: V.S., A.Palotie, S.R.

TRAILS : Study phenotyping: H.R. Genotyping or analysis: P.J.v.d.M. Study PI: C.A.H., A.J.O.

PROCARDIS : Study phenotyping: A.G. Genotyping or analysis: A.G. Study PI: H.W., M.Farrall

HABC : Study phenotyping: Y.Liu, T.B.H. Genotyping or analysis: M.A.N. Study PI: Y.Liu, T.B.H.

KORA S3 : Study phenotyping: C.G. Genotyping or analysis: S.S., C.G., E.O. Study PI: M.Laan

INGI-FVG : Genotyping or analysis: D.V., M.Brumat, M.Cocca Study PI: P.G.

Fenland : Study phenotyping: R.A.S., J.a.L., C.L., N.J.W. Genotyping or analysis: R.A.S., J.a.L., C.L., N.J.W. Study PI: R.A.S., C.L., N.J.W.

MICROS : Genotyping or analysis: A.A.H., F.D.G.M., A.S.P. Study PI: F.D.G.M., P.P.P.

HTO : Study phenotyping: B.D.K. Genotyping or analysis: B.D.K., K.L.A., C.Mamasoula Study PI: B.D.K., H.J.C.

MIGEN : Study phenotyping: R.E., J.Marrugat, S.Kathiresan, D.S. Genotyping or analysis: R.E., S.Kathiresan, D.S. Study PI: S.Kathiresan

ULSAM : Study phenotyping: V.Giedraitis, E.I. Genotyping or analysis: A.P.M., A.Mahajan Study PI: A.P.M., V.Giedraitis, E.I.

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

LBC1936 : Study phenotyping: I.J.D., A.J.G. Genotyping or analysis: L.M.L., G.D., A.J.G. Study PI: I.J.D.

H2000_CTRL : Study phenotyping: T.Niiranen Study PI: P.K., A.Jula, S.Koskinen

NSPHS : Genotyping or analysis: S.E., Å.J. Study PI: U.G.

FUSION : Genotyping or analysis: A.U.J. Study PI: J.T., M.Boehnke, F.C.

GRAPHIC : Study phenotyping: N.J.S., P.S.B., M.D.T. Genotyping or analysis: C.P.N., P.S.B., M.D.T. Study PI: N.J.S.

CROATIA_Vis : Study phenotyping: I.R. Genotyping or analysis: V.V., J.E.H. Study PI: V.V., I.R.

PIVUS : Study phenotyping: L.Lind, J.S. Genotyping or analysis: C.M.L., A.Mahajan Study PI: C.M.L., L.Lind, J.S.

LOLIPOP : Study phenotyping: J.S.K., J.C.C. Genotyping or analysis: J.S.K., W.Z., J.C.C., B.L. Study PI: J.S.K., J.C.C.

CROATIA_Korcula : Genotyping or analysis: C.H., J.Marten Study PI: C.H., A.F.W.

INGI-CARL : Study phenotyping: G.G. Genotyping or analysis: I.G., A.Morgan, A.R.

LBC1921 : Study phenotyping: J.M.S., A.Pattie Genotyping or analysis: J.M.S., S.E.H., D.C.M.L., A.Pattie Study PI: J.M.S.

CROATIA_SPLIT : Study phenotyping: O.P., I.K. Genotyping or analysis: O.P., T.Z. Study PI: O.P.

BioMe (formerly IPM) : Genotyping or analysis: Y.Lu Study PI: R.J.F.L., E.P.B.

Replication

UKB-BP : Genotyping or analysis: H.R.W., M.R.B., C.P.C., E.E., H.G., B.M., M.R., I.T. Study PI: P.E., M.J.C.

GoDARTS : Study phenotyping: C.N.A.P., A.S.F.D. Genotyping or analysis: C.N.A.P., N.Shah Study PI: C.N.A.P., A.D.M.

Lifelines : Study phenotyping: M.H.d.B. Genotyping or analysis: M.S. Study PI: P.v.d.H.

TwinsUK : Study phenotyping: C.Menni Genotyping or analysis: M.M., C.Menni Study PI: T.D.S.

Airwave Health Monitoring Study : Genotyping or analysis: A.C.V., E.E., H.G., I.T. Study PI: E.E.

The UK Household Longitudinal Study (UKHLS) : Genotyping or analysis: B.P.P. Study PI: E.Z.

Generation Scotland (GS:SFHS) : Study phenotyping: S.P. Genotyping or analysis: C.H., A.Campbell

JUPITER : Study phenotyping: P.M.R. Genotyping or analysis: D.I.C., L.M.R., F.G., P.M.R. Study PI: D.I.C., P.M.R.

NEO : Study phenotyping: R.d.M. Genotyping or analysis: D.O.M.K., R.L.G. Study PI: R.d.M.

Three City-Dijon : Study phenotyping: S.D., C.T. Genotyping or analysis: G.C. Study PI: S.D., C.T.

ASCOT-UK : Study phenotyping: P.S., N.P. Genotyping or analysis: P.B.M., H.R.W. Study PI: P.B.M., P.S., N.P., M.J.C.

ASCOT-SC : Study phenotyping: S.Thom, M.J.C. Genotyping or analysis: D.C.S., A.S., H.R.W., P.B.M. Study PI: S.Thom, M.J.C., P.B.M.

Hunter Community Study : Study phenotyping: R.Scott Genotyping or analysis: C.O., E.G.H. Study PI: A.John

GAPP : Study phenotyping: D.C. Genotyping or analysis: D.C., S.Thériault, G.P. Study PI: D.C.

BRIGHT : Study phenotyping: M.Brown, J.C. Genotyping or analysis: M.Farrall, P.B.M., H.R.W. Study PI: M.Brown, J.C., M.Farrall, P.B.M., M.J.C.

Resources for secondary analyses

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

eQTL kidney : Study phenotyping: J.J.D., M.A.S. Genotyping or analysis: P.J.v.d.M. 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.D., P.J.M., Q.T.N. Genotyping or analysis: R.Joehanes Design of secondary analysis: D.L. Study PI: D.L.

ICBP-Steering Committee

G.A., M.J.C., A.Chakravarti, D.I.C., G.B.E., P.E., T.F., M.R.J., A.D.J., M.Larson, D.L., A.P.M., P.B.M., C.N.C., P.O.R., W.P., B.M.P., K.R., A.V.S., H.Snieder, M.D.T., C.M.v.D., L.V.W., H.R.W.

ACKNOWLEDGMENTS

This research used the ALICE and SPECTRE High Performance Computing Facilities at the University of Leicester. G.B.E 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 Health Care NHS Trust and Imperial College Biomedical Research Centre.

ARIC: The Atherosclerosis Risk in Communities Study is carried out 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). The authors thank the staff and participants of the ARIC study for their important contributions. The authors thank the staff and participants of the ARIC study for their important contributions.

ASCOT: This work was supported by Pfizer, New York, NY, USA, 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. The authors thank the staff and the participants of the ASPS for their valuable contributions. The authors 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 utilized 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 NHLBI contracts HHSN268201200036C, HHSN268200800007C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086, 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 MC. 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, 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 would like to 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 carried out by the Genetics Core Laboratory at the Wellcome Trust Clinical Research Facility, WGH, Edinburgh, Scotland. SNP genotyping for CROATIA-Korcula was performed by Helmholtz Zentrum München, 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: JAL, CL, RAS and NJW 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, 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 NIH grants R01-DK062370 (to M.B.) and intramural project number ZIA-HG000024 (to F.S.C.). 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 carried out 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, 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 anonymised 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). CPN and NJS are supported by the British Heart Foundation and NJS is a 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 utilized 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 1,664 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 about 3,000 descendants from the original population, living in 7 villages along the valley and in the mountains. Participants were healthy people 18-102 years of age that 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 DT. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. We thank the inhabitants of the VB that 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 Paolo Gasparini, RC2008 to Paolo Gasparini

INGI-FVG: Italian Ministry of Health RF2010 to Paolo Gasparini, RC2008 to Paolo Gasparini

JUPITER: Genetic analysis in the JUPITER trial was funded by a grant from AstraZeneca (DIC and PMR, Co-Pis).

KORA S3: KORA S3 500K blood pressure project was supported by Estonian Research Council, grant IUT34-12 (for Maris Laan). The KORA Augsburg studies have been financed by the Helmholtz Zentrum München, 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 co-workers, 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. The authors wish to 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, 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 carried out 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, 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 Raffaella Stocker, Stefan Waldner, Toni Pizzocco, 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.

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. Dennis 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, lab 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, 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 (#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 would like to 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.F and H.W acknowledge the support of the Wellcome Trust core award (090532/Z/09/Z) and M.F, H.W, the BHF Centre of Research Excellence (RE/13/1/30181). A.G, H.W acknowledge European Union Seventh Framework Programme FP7/2007-2013 under grant agreement no. HEALTH-F2-2013-601456 (CVGenes@Target) & and A.G, the Wellcome Trust Institutional strategic support fund. 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.F and H.W acknowledge the support of the Wellcome Trust core award (090532/Z/09/Z) and M.F, H.W, the BHF Centre of Research Excellence (RE/13/1/30181). A.G, H.W acknowledge European Union Seventh Framework Programme FP7/2007-2013 under grant agreement no. HEALTH-F2-2013-601456 (CVGenes@Target) & and A.G, the Wellcome Trust Institutional strategic support fund.

PROSPER: The PROSPER study was supported by an investigator initiated grant obtained from Bristol-Myers Squibb. Prof. 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 datasets are supported by the Netherlands Organisation of Scientific Research NWO Investments (nr. 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 nr. 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. The authors 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'Éducation 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. Ganesh Chauhan, Christophe Tzourio and Stéphanie 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 analysed 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 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 carried out 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, USA, 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: This research has been conducted using the UK Biobank Resource under application number 236. H.R.W., C.P.C and M.R.B. 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 MR was funded by the National Institute for Health Research (NIHR) Biomedical Research Unit in Cardiovascular Disease at Barts. MR is recipient from China Scholarship Council (No. 2011632047). B.M. holds an MRC eMedLab Medical Bioinformatics Career Development Fellowship, funded from award MR/L016311/1. PE 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. Andrew 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.