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

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

Authors:

Aldi T Kraja1\*, DSc, PhD, James P Cook2, PhD, Helen R Warren3,4,PhD, Praveen Surendran5, PhD, Chunyu Liu6,7, PhD, Evangelos Evangelou8,9, PhD, Alisa K Manning10,11, PhD, Niels Grarup12, MD, PhD, Fotios Drenos13,14 PhD, Xueling Sim15,16, PhD, Albert Vernon Smith17,18, PhD, Najaf Amin19, DSc, PhD, Alexandra IF Blakemore20,21, PhD, Jette Bork-Jensen12, PhD, Ivan Brandslund22,23, MD, Aliki-Eleni Farmaki24, PhD, Cristiano Fava25,26, MD, PhD, Teresa Ferreira27, PhD, Karl-Heinz Herzig28,29,30, MD, PhD, Ayush Giri31, PhD, Franco Giulianini32, PhD, Megan L Grove33, MSc, Xiuqing Guo34, PhD, Sarah E Harris35,36, PhD, Christian T Have12, PhD, Aki S Havulinna37,38, DSc, He Zhang39, PhD, Marit E Jørgensen40, MD, PhD, AnneMari Käräjämäki41,42, MD, Charles Kooperberg43, PhD, Allan Linneberg44,45, MD, PhD, Yongmei Liu46, MD, PhD, Bonnycastle L Lori47, PhD, Yingchang Lu48,49, MD, PhD, Reedik Mägi50, PhD, Anubha Mahajan27, PhD, Giovanni Malerba51, PhD, Riccardo E Marioni35,36, PhD, Hao Mei52, PhD, Cristina Menni53, PhD, Alanna C Morrison33, PhD, Sandosh Padmanabhan54, MD, PhD, Walter Palmas55, MD, Alaitz Poveda56, PhD, Rainer Rauramaa57,58, MD, PhD, N William Rayner27,59,60, PhD, Muhammad Riaz61,62, PhD, Kenneth Rice63, PhD, Melissa A Richard33, PhD, Jennifer A Smith64, PhD, Lorraine Southam27,60, MSc, Alena Stančáková65, MD, PhD, Kathleen E Stirrups3,66, PhD, Vinicius Tragante67, PhD, Tiinamaija Tuomi68,69.90, MD, PhD, Ioanna Tzoulaki8,9,70, PhD, Tibor V Varga57, PhD, Stefan Weiss71,72, Dr., Andrianos M Yiorkas20,21, MSc, Robin Young5, PhD, Weihua Zhang8,73, Dr., Michael R Barnes3,4, PhD, Claudia P Cabrera3,4, PhD, He Gao8,70, PhD, Michael Boehnke15, PhD, Eric Boerwinkle33,74, PhD, John C Chambers8,73,75, MD, PhD, John M Connell76, MD, Cramer K Christensen77, MD, DMsc, Rudolf A de Boer78, MD, PhD, Ian J Deary35,79, PhD, George Dedoussis24, PhD, Panos Deloukas3, PhD, Anna F Dominiczak54, MD, FRCP, Marcus Dörr71,80, MD, Roby Joehanes6,81,82, PhD, Todd L Edwards83, PhD, Tõnu Esko50, PhD, Myriam Fornage84, PhD, Nora Franceschini85, MD, Paul W Franks56,86,87, PhD, Giovanni Gambaro88, MD, PhD, Leif Groop89,90, MD, PhD, Göran Hallmans91, MD, PhD, Torben Hansen12, MD, PhD, Caroline Hayward92, Dr., Oksa Heikki93, MD, PhD, Erik Ingelsson94,95, MD, PhD, Jaakko Tuomilehto96,97,98,99, MD, PhD, Marjo-Riitta Jarvelin8,70,100, MD, PhD, Sharon LR Kardia64, PhD, Fredrik Karpe59,101, MD, PhD, Jaspal S Kooner73,75,102, MD, Timo A Lakka57,58,103, MD, PhD, Claudia Langenberg104, MD, PhD, Lars Lind95, MD, PhD, Ruth JF Loos48, PhD, Markku Laakso105, MD, PhD, Mark I McCarthy27,59,101, MD, Olle Melander25, MD, PhD, Karen L Mohlke106, PhD, Andrew P Morris2, PhD, Colin Palmer107, PhD, Oluf Pedersen12, MD, DMsc, Ozren Polasek108, Dr., Neil Poulter109, FMedSci, Michael A Province1, PhD, Bruce M Psaty110,111, MD, PhD, Paul M Ridker32,112, MD, Jerome I Rotter34, MD, Igor Rudan113, PhD, Veikko Salomaa37, MD, PhD, Nilesh J Samani61,62, MD, Peter J Sever109, MD, Tea Skaaby44, MD, PhD, Jeanette M Stafford114, MSc, John M Starr35,115, PhD, Pim van der Harst78,116, MD, PhD, Peter van der Meer78, MD, PhD, The Understanding Society Scientific Group, Cornelia M van Duijn19, PhD, Anne-Claire Vergnaud8, PhD, Vilmundur Gudnason17,18, MD, PhD, Nicholas J Wareham104, MD, PhD, James G Wilson117, MD, Cristen J Willer118,119,120, PhD, Daniel R Witte121,122, PhD, Eleftheria Zeggini60, PhD, Danish Saleheen123,124,125, PhD, Adam S Butterworth5, PhD, John Danesh5,60,126,127, PhD, Folkert W Asselbergs67,128, MD, PhD, Louise V Wain129, PhD, Georg B. Ehret130,131, MD, Daniel I Chasman32,112, PhD, Mark J Caulfield3,4, MD, Paul Elliott8,70, PhD, Cecilia M Lindgren27,132,133, PhD, Daniel Levy6,7, MD, Christopher Newton-Cheh10,133,134†, MD, Patricia B Munroe3,4†, PhD, Joanna MM Howson5†, PhD

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

Affiliations:

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

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

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

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

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

6The Framingham Heart Study, Framingham, MA, USA

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

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

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

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

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

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

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

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

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

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

17Icelandic Heart Association, Kopavogur, Iceland

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

38Institute of Molecular Medicine Finland, Helsinki, Finland

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

40Steno Diabetes Center, Copenhagen, Gentofte, Denmark

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

57Kuopio Research Institute of Exercise Medicine, Kuopio, Finland

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

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

60Wellcome Trust Sanger Institute, Hinxton, Cambridge, UK

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

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

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

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

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

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

67Department of Cardiology, University Medical Center Utrecht, Utrecht, Netherlands

68Folkhälsan Research Centre, Helsinki, Finland

69Department of Endocrinology, Helsinki University Central Hospital, Helsinki, Finland.

70MRC-PHE Centre for Environment and Health, Imperial College London, London, UK

71Interfaculty Institute for Genetics and Functional Genomics, University Medicine and Ernst-Moritz-Arndt-University Greifswald, Greifswald, Germany

72DZHK (German Centre for Cardiovascular Research), Partner Site Greifswald, Greifswald, Germany

73Department of Cardiology, Ealing Hospital, London North West Healthcare NHS Trust, London, UK

74Human Genome Sequencing Center, Baylor College of Medicine, Houston, TX, USA

75Imperial College Healthcare NHS Trust, London, UK

76University of Dundee, Ninewells Hospital & Medical School, Dundee, UK

77Medical Department, Lillebaelt Hospital, Vejle, Denmark

78University of Groningen, University Medical Center Groningen, Department of Cardiology, Groningen, Netherlands

79Psychology, University of Edinburgh, Edinburgh, UK

80Department of Internal Medicine B - Cardiology, Pneumology, Infectious Diseases, Intensive Care Medicine, University Medicine Greifswald, Greifswald, Germany

81Mathematical and Statistical Computing Laboratory, Center for Information Technology, National Institutes of Health, Bethesda, MD, USA

82Institute for Aging Research, Hebrew SeniorLife, Harvard Medical School, Boston, MA, USA

83Vanderbilt Epidemiology Center, Institute for Medicine and Public Health, Vanderbilt University Medical Center, Nashville, TN, USA

84Brown Foundation Institute of Molecular Medicine, McGovern Medical School, University of Texas Health Science Center at Houston, Texas, Houston, TX, USA

85Department of Epidemiology, University of North Carolina, Chapel Hill, NC, USA

86Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA

87Department of Public Health & Clinical Medicine, Umeå University, Umeå, Sweden

88Department of Nephrology and Dialysis, Università Cattolica del Sacro Cuore, Roma, Italy

89Department of Clinical Sciences, Diabetes and Endocrinology, Lund University Diabetes Centre, Malmö, Sweden

90Finnish Institute for Molecular Medicine (FIMM), Helsinki University, Helsinki, Finland

91Department of Biobank Research, Umeå University, Umeå, Sweden

92Medical Research Council Human Genetics Unit, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK

93Tampere University Hospital, Tampere, Finland

94Department of Medicine, Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, California, USA

95Department of Medical Sciences, Molecular Epidemiology and Science for Life Laboratory, Uppsala University, Uppsala, Sweden

96Chronic Disease Prevention Unit, National Institute for Health and Welfare, Helsinki, Finland

97Dasman Diabetes Institute, Dasman, Kuwait

98Diabetes Research Group, King Abdulaziz University, Jeddah, Saudi Arabia

99Department of Neurosciences and Preventive Medicine, Danube University Krems, Krems, Austria

100Center for Life Course Health Research, Faculty of Medicine, University of Oulu, Oulu, Finland

101Oxford NIHR Biomedical Research Centre, Oxford University Hospitals Trust, Oxford, UK

102National Heart and Lung Institute, Imperial College London, Hammersmith Hospital Campus, London, UK

103Institute of Biomedicine/Physiology, University of Eastern Finland, Kuopio, Finland

104MRC Epidemiology Unit, University of Cambridge School of Clinical Medicine, Institute of Metabolic Science, Cambridge Biomedical Campus, Cambridge, UK

105Department of Medicine, University of Eastern Finland and Kuopio University Hospital, Kuopio, Finland

106Department of Genetics, University of North Carolina, Chapel Hill, NC, USA

107Medical Research Institute, University of Dundee, Ninewells Hospital and Medical School, Dundee, Scotland, UK

108Faculty of Medicine, University of Split, Split, Croatia

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

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

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

112Harvard Medical School, Boston, MA, USA

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

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

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

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

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

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

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

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

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

122Danish Diabetes Academy, Odense, Denmark

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

124Centre for Non-Communicable Diseases, Karachi, Pakistan

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

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

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

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

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

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

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

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

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

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

†These coauthors jointly supervised the project

\*Correspondence:

Aldi T Kraja, DSc, PhD

Division of Statistical Genomics,

Department of Genetics, Center for Genome Sciences and Systems Biology

Washington University School of Medicine, St. Louis, MO, USA

[aldi@wustl.edu](mailto:aldi@wustl.edu), Phone: (314) 362-2498, Fax: (314) 362-4227

**Abstract**

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

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

Twenty-one SNVs were genome-wide significant (*P* < 5x10-8) for BP, of which four are new BP loci: rs9678851 (missense, *SLC4A1AP*), rs7437940 (*AFAP1*), rs13303 (missense, *STAB1*) and rs1055144 (*7p15.2*). In addition, we identified a potentially independent novel BP-associated SNV (rs3416322 (missense, *SYNPO2L*) at a known locus, uncorrelated with the previously reported SNVs. Two SNVs are associated with expression levels of nearby genes, and SNVs at three loci are associated with other traits. One SNV with a minor allele frequency < 0.01, (rs3025380 at *DBH*) was genome-wide significant.

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

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

High blood pressure (BP) is a major risk factor for coronary artery disease, heart failure, stroke, renal failure and premature mortality 1. High BP has been estimated to cause 10.7 million deaths worldwide in 2015 2, 3. Pharmacologic interventional trials of BP-lowering therapies in patients with hypertension have demonstrated reductions in cardiovascular complications, including mortality 4. While several anti-hypertensive drug classes exist, variability in treatment response by individual patients and ethnic/racial groups, and residual risks, suggest that identification of previously unrecognized BP regulatory pathways could identify novel targets and pave the way for new treatments for cardiovascular disease prevention.

Genetic association studies have identified over 400 loci at *P* < 5x10-8 that influence BP 5-11. Two recent reports independently performed discovery analyses, in sample sizes of up to ~146k (CHARGE Exome BP consortium) and ~192k individuals (the European-led Exome consortia [contributory consortia, CHD Exome+, ExomeBP, and GoT2D:T2DGenes]) 8, 9. All samples were genotyped on the Illumina Exome array that was designed to interrogate rare and low frequency non-synonymous and other putative functional variants, as well as non-coding variants for association with biomedical traits. They each identified ~80 promising single nucleotide variant (SNV) associations with systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP) or hypertension and took them forward for replication in the reciprocal consortium 8, 9 resulting in the identification of 56 novel BP-associated loci across the two reports, including associations with coding and rare SNVs. A total of 100 SNVs remained of interest, but did not achieve genome-wide significance. Increasing the sample size, is likely to identify additional BP-associated SNVs among these variants.

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

**Materials and Methods**

*Samples*

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

The CHARGE Exome BP consortium included 120,473 individuals of EUR descent from 15 cohorts, 21,503 individuals of African (AFR) descent from 10 cohorts and 4,586 individuals of Hispanic (HIS) ancestry from 2 cohorts as previously described8. The European-led consortia included 165,276 individuals of EUR descent from 51 cohorts and 27,487 individuals of South Asian (SAS) descent from two cohorts 9. The UK Biobank data included 140,886 unrelated individuals of EUR descent11.

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

Institutional Review Board (IRB) approval was obtained from each participating cohort and informed consent was obtained from all subjects 8, 9. The UK Biobank study has approval from the North West Multi-Centre Research Ethics Committee and has Research Tissue Bank approval.

*Phenotypes*

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

*Statistical analyses*

In the CHARGE Exome BP consortium, in cohorts of unrelated individuals single SNV association tests were implemented via linear regression in R/PLINK/SNPTEST. For family-based cohorts linear mixed effects models in R was used to estimate kinship via R KINSHIP2 package and using the LMEKIN function, to account for familial correlations (<https://cran.r-project.org/web/packages/coxme/vignettes/lmekin.pdf>; Supplemental Table 21 of Liu *et al*. 8). The component studies of the European-led consortia (CHD Exome+, ExomeBP and GoT2D:T2D genes) used linear regression as implemented in PLINK 14 or linear mixed models as implemented in Genome-Wide Efficient Mixed Model Association (GEMMA) 15 or EPACTS (the Efficient Mixed-Model Association eXpedited, EMMAX) 16, to test variants for association with BP traits. The UK Biobank study used linear regression models as implemented in SNPTEST 17. All studies assumed an additive allelic effects model.

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

At the consortium level, meta-analyses of cohort-level association results were performed independently within CHARGE-Exome and the European-led Exome consortia using invervse variance-weighted fixed effects meta-analysis. These meta-analyses results were combined with the UK Biobank association results using fixed effects inverse variance weighted meta-analysis as implemented in METAL 18. Two meta-analyses were performed, one pan-ancestry (AA, EUR, HIS, SAS), and a second of EUR ancestry. Statistical significance was set at genome-wide significance, *P* < 5x10-8.

*Functional annotation*

Associated variants were annotated using HG38 dbSNP and Entrez Gene (NCBI). We interrogated publically available gene expression regulatory features from ENCODE and ROADMAP Epigenome projects using HaploReg 19 and RegulomeDB 20. eQTLs were assessed using data from GTEx 21 GRASP 22, Westra *et al*. 23, Lappalainen *et al*. 24 and STARNET 25. In addition we used the FHS eQTL results from microarray-based gene and exon expression levels in whole blood from 5,257 individuals 26. We queried whether any of the five BP-associated SNVs were eQTLs for genes in the five BP-associated regions, or whether they were in LD (r2 > 0.8) with any of the eQTLs for genes in these regions. Where putative eQTLs were identified, we verified the BP-associated SNVs were in LD (r2 >0.8) with the top eQTL for that gene.

We interrogated publically available GWAS databases through PhenoScanner 27, a curated database holding publicly available results from large-scale genome-wide association studies facilitating “phenome scans”. We report results for SNVs with *P*-value ≤ 5x10-8.

Capture HiC interactions were accessed from the Capture HiC Plotter (www.CHiCP.org). Javierre *et al* 28 used an interaction confidence score derived using CHiCAGO software 29. The interactions with a CHiCAGO score ≥ 5 in at least one cell type were considered as high-confidence interactions.

**Results**

Association results for the 77 SNVs with the three BP traits are shown in Supplemental Table 1 for the pan-ancestry (PA: European, South Asian, African and Hispanic descent) meta-analysis and in Supplemental Table 2 for the European (EUR) meta-analysis. Twenty-one of the 77 SNVs were associated with at least one BP trait with genome wide significance, *P* < 5x10-8 and concordant directions of effects across the results from all contributing datasets (Table 1). Sixteen SNVs (*PKN2*, *ARHGEF3*, *AFAP1*, *ANKDD1B*, *LOC105375508*, *ZFAT*, *RABGAP1*, *DBH*, *SYNPO2L*, *BDNF-AS*, *AGBL2*, *NOX4*, *CEP164*, *HOXC4*, *CFDP1* and *COMT*) were genome-wide significant in both PA- and EUR samples. Two SNVs at *SLC4A1AP* and 7p15.2, respectively, were significant only in the PA sample; and three SNVs at *STAB1/NT5DC2*, *KDM5A* and *LACTB* only in the EUR sample. All the significant SNVs were common (minor allele frequencies ≥ 0.19), except the SNV at the *DBH* locus (PA, MAF = 0.0043). While this report was in preparation, 17 of these loci were published elsewhere 7, 10, 11. Four loci remain novel: rs9678851 (*SLC4A1AP*, missense), rs7437940 (*AFAP1*, intron), rs13303 (*STAB1*, missense) and rs1055144 (7p15.2, non-coding transcript; Supplemental Figures 1a-d). The *SLC4A1AP* (rs9678851) was associated with SBP and *AFAP1* (rs7437940) and 7p15.2 (rs1055144) were associated with PP. We also observed a potentially new independent BP association (r2 ~ 0.001 in 1000G EUR and PA samples) at a recently published locus rs34163229 (*SYNPO2L*, missense; Table 1; Supplemental Figure 1e). We used a conservative r2 < 0.1 threshold to minimize the possibility of an association due to corelation with a strongly associated established BP variant. Furthermore, conditional analyses within the ~140,000 UK Biobank participants with comprehensive genomic coverage suggested that the association with SBP of rs34163229 was independent of the established SNV, rs4746172. Regional association plots in UK Biobank are provided in Supplemental Figures 2a-e. Conditional analyses within the full dataset was not possible given the targeted nature of the Exome array which makes claims of independence provisional. Twenty-two of the 77 SNVs had minor allele frequency (MAF) ≤ 0.01, and one rs3025380, a missense variant in DBH was confirmed as a BP-associatd locus.

Three of the five newly discovered BP-associated SNVs are missense variants, mapping to *SLC4A1AP, STAB1* and *SYNPO2L* (Table 1 and Supplemental Table 3). At *SLC4A1AP*, rs9678851 (C>A, Pro139Thr) has MAF=0.46 and the C allele is associated with an increase of 0.23 mmHg in SBP. This variant is correlated with two other missense variants in *C2orf16* (rs1919126 and rs1919125, r2 = 0.81 (EUR) based on 1000G 30, for both). At *STAB1*, the C allele of rs13303 (T>C, Met2506Thr, with MAF=0.44) is associated with an increase of 0.15 mmHg in PP per minor allele in EUR. This residue is located in a conserved region of the protein 31 (Supplemental Table 4). The T allele of rs34163229, the new association at the *SYNPO2L* locus, (G>T, Ser833Tyr, with MAF=0.15), is associated with an increase of 0.36 mmHg in SBP per allele. This variant is in LD with another missense variant in *SYNPO2L* (rs3812629 r2=1, 1000G EUR) 30. Using Polyphen2 (http://genetics.bwh.harvard.edu/pph2/index.shtml), the SNVs rs9678851 in *SLC4A1AP*, and rs13303 in *STAB1* were predicted to be *benign*, while rs34163229 in *SYNPO2L* was predicted to have a *possible damaging* impact on the corresponding human proteins’ structure and function.

We interrogated publicly available expression quantitative trait loci (eQTL) datasets through GTEx, ENCODE, RoadMap projects, PhenoScanner 27, STARNET 25 and Framingham Heart Study 26 to further highlight potential causal genes and mechanisms at each of the newly identified BP loci (Supplemental Table 3). The PP-associated SNV, rs13303, at *STAB1* is correlated (r2 >0.8 1000G EUR) with the top eQTLs for *NT5DC2* in atherosclerotic-lesion free internal mammary artery, atherosclerotic aortic root, subcutaneous adipose, visceral abdominal fat and liver tissues (all *P* < 1x10-11) 25. The rs13303 was also associated with expression levels of *NT5DC2* in EBV-transformed lymphocytes, transformed fibroblasts 25 and thyroid cells (Supplemental Table 3) 21. The SBP-associated SNV at *SYNPO2L* (rs34163229) is correlated (r2=0.86 in 1000G EUR) with the top eQTL (rs2177843) for *MYOZ1* in heart atrial appendage tissue (Supplemental Table 3) 21. The five new BP associated SNVs were not in LD with the top eQTLs for these gene regions in whole blood in the Framingham Heart Study eQTL data. We also took the opportunity to assess whether the additional fifteen recently established genome-wide significant BP-associated SNVs were eQTLs in the Framingham sample. Amongst the genome-wide significant BP SNVs, three, rs4680 at *COMT*, rs12680655 at *ZFAT* and rs10760260 at *RABGAP1*, were the top eQTL for the corresponding genes in whole blood (Supplemental Table 5). We also examined the five BP-associated SNVs in endothelial precursor cell Hi-C data (www.chicp.org; 28, 32) to explore long-range chromatin interactions. rs13303 was found to contact *NISCH* (score 17.34) and rs34163229 contacts *USP54* (score 33.89)

Finally, we assessed the association of the new BP-associated variants and their close proxies (r2>0.8) with cardiovascular disease risk factors, molecular metabolic traits and clinical phenotypes using PhenoScanner, the NHGRI-EBI GWAS catalog and GRASP 27. We observed five of the newly discovered BP-associated SNVs to have genome wide significant associations with other traits, including height (7p15.2) 33, waist-to-hip ratio (*STAB1* and 7p15.2) 34, 35, triglycerides (*SLC4A1P*), adiponectin levels (*STAB1*) 36, and atrial fibrillation (rs7915134 which has r2=0.92 in the EUR 1000G samples with rs34163229 in *SYNPO2L*) 37 (Supplemental Table 3).

Of the 77 analysed SNVs, from the original Exome array analyses, 56 SNVs were not genome-wide significant in the current analysis. With ~300 BP loci reported since the time of our analysis, we investigated whether any of the 56 SNVs that were not genome-wide significant in our meta-analysis have been reported as new BP-associated loci in any of the three recent publications 7, 10, 11. Twelve SNVs in our dataset were located within 1 Mb of a recently reported BP locus : *CACNA1S, TSC22D2, RPL26L1, EDN1, GPRC6A, ACHE, CAV1, NOX5, PGLYRP2, NAPB, EDEM2* and *KCNB1*; (Supplemental Tables 1 and 2), although none of the SNVs were in LD (r2 >0.1 in all 1000G populations) with the published variants at these loci.

**Discussion**

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

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

At the new locus on chromosome 3 (rs13303), three potential candidate genes are highlighted: *STAB1*, *NT5DC2* and *NISCH*. *STAB1* encodes stabilin1, a protein known to endocytose low density lipoprotein cholesterol, gram-positive and -negative bacteria, and advanced glycosylation end products 38, 39. The gene product is also referred to as CLEVER-1, a common lymphatic endothelial and vascular endothelial receptor-1 40, which is expressed in macrophages 41. SNX17 interacts with STAB1 and is a trafficking adaptor of STAB1 in endothelial cells 38, 42. The rs13303 is located 500bp downstream of *NT5DC2*. This additional gene is highlighted through the association of rs13303 with expression of *NT5DC2* in multiple tissues (Supplemental Table 3). *NT5DC2* encodes the 5'-nucleotidase domain containing 2 protein. The gene is widely expressed, with higher levels observed in the heart and coronary artery, although its function is unknown. Lastly, exploration of long-range chromatin interaction identified contact of the SNV region with the genetic sequence including the gene *NISCH,* which encodes the nonadrenergic imidazoline-1 receptor protein localized to the cytosol and anchored to the inner layer of the plasma membrane. This protein binds to the adapter insulin receptor substrate 4 (*IRS4*) to mediate translocation of alpha-5 integrin from the cell membrane to endosomes. In human cardiac tissue, this protein has been found to affect cell growth and death 43.

The PP-associated variant, rs7437940 on chromosome 4 is intronic to *AFAP1*, and is located in promoter histone marks in right atrial tissue, based on regulatory chromatin states from DNAse and histone ChIP-Seq in Roadmap Epigenomics Consortium (identified with HaploReg, Supplemental Table 4) 44. *AFAP1* encodes actin filament associated protein 1. This protein is thought to have a role in the regulation of actin filament integrity, and formation and maintenance of the actin network 45.

At the locus on chromosome 10 (rs34163229), two candidate genes were highlighted (*SYNPO2L* and *MYOZ1*). *SYNPO2L* encodes synaptopodin like 2, which is not well characterized, but may play a role in modulating actin-based shape. The lead SNV is also associated with expression levels of *MYOZ1* in heart appendage tissues. *MYOZ1* encodes myozenin 1, an alpha actinin and gamma filamin binding Z line protein predominantly expressed in skeletal muscle 46.

At two loci (*SLC4A1AP* and *SYNPO2L*) we observed more than one missense variant in high LD (r2 > 0.8). Functional follow up of these variants may be challenging to disentangle the causal variants. At the *SLC4A1AP* locus, there are three misssense variants, none of which are predicted to be damaging. Two of these are in *C2orf16,* which is predicted to encode an uncharacterized protein. Current evidence is at the transcriptional level. Cellular assays comparing the function of *SLC4A1AP* with the missense variant may be developed or an animal model could be created and BP can be measured. In the first instance, a knockout model may be required, due to the predicted weak effects of the BP variants. At the *SYNPO2L* locus, the two missense variants are both in *SYNPO2L*, of which one is predicted damaging, cellular experiments testing functional effecs of this variant alone or part of a haplotype maybe a good starting point.

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

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

**Conflict of Interest**

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

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

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

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

PJS has received research awards from Pfizer Inc.

All other coauthors declare NONE.

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

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

**Note: rsID**-SNV name, **Gene**-name of the closest gene or cytogenetic band based on Gene Entrez of NCBI; **Annotation**-SNV annotation based on dbSNP of NCBI; **Chr-pos**-chromosome-bp position in Human Genome build 38; **Trait**- the blood pressure trait (**D**BP, **S**BP or **P**P) the variant is associated with; **Meta**- the meta-analysis the variant is associated in, **P**an-**A**ncestry and/or **EUR**opean; **A1/2**-allele 1/allele 2; **Freq1**-allele frequency for allele 1; **β (SE)**-effect estimate, β and its standard error for allele 1 from the corresponding meta-analysis (highlighted in bold); ***P*-value** – *P* from meta-analysis (highlighted in bold); **Dir**ection- direction of effect in each of the contributing consortia in the following order: EUROPEAN led Exome Consortia, UK-BIOBANK and CHARGE-BP Consortium; **HetP**- *P*-value of heterogeneity across the three contributing consortia, **N**- Sample size for the trait and meta-analysis with the lowest *P*-value (bold). \* indicates potential new signal at a recently reported locus (LD- r2 < 0.1 with a published BP SNV), and † indicates first report of this variant as genome-wide significant. For more details, see Supplemental Tables 1 and 2. **UK-BIOBANK INFO**- a quality of imputation score in UK BIOBANK.