Original Article

New Blood Pressure–Associated Loci Identified in Meta-Analyses of 475 000 Individuals

Aldi T. Kraja, DSc, PhD; James P. Cook, PhD; Helen R. Warren, PhD; Praveen Surendran, PhD; Chunyu Liu, PhD; Evangelos Evangelou, PhD; Alisa K. Manning, PhD; Niels Grarup, MD, PhD; Fotios Drenos, PhD; Xueling Sim, PhD; Albert Vernon Smith, PhD; Najaf Amin, DSc, PhD; Alexandra I.F. Blakemore, PhD; Jette Bork-Jensen, PhD; Ivan Brandslund, MD; Aliki-Eleni Farmaki, PhD; Cristiano Fava, MD, PhD; Teresa Ferreira, PhD; Karl-Heinz Herzig, MD, PhD; Ayush Giri, PhD; Franco Giulianini, PhD; Megan L. Grove, MSc; Xiuqing Guo, PhD; Sarah E. Harris, PhD; Christian T. Have, PhD; Aki S. Havulinna, DSc; He Zhang, PhD; Marit E. Jørgensen, MD, PhD; AnneMari Käräjämäki, MD; Charles Kooperberg, PhD; Allan Linneberg, MD, PhD; Louis Little;Yongmei Liu, MD, PhD; Lori L. Bonnycastle, PhD; Yingchang Lu, MD, PhD; Reedik Mägi, PhD; Anubha Mahajan, PhD; Giovanni Malerba, PhD; Riccardo E. Marioni, PhD; Hao Mei, PhD; Cristina Menni, PhD; Alanna C. Morrison, PhD; Sandosh Padmanabhan, MD, PhD; Walter Palmas, MD; Alaitz Poveda, PhD; Rainer Rauramaa, MD, PhD; Nigel William Rayner, PhD; Muhammad Riaz, PhD; Ken Rice, PhD; Melissa A. Richard, PhD; Jennifer A. Smith, PhD; Lorraine Southam, MSc; Alena Stančáková, MD, PhD; Kathleen E. Stirrups, PhD; Vinicius Tragante, PhD; Tiinamaija Tuomi, MD, PhD; Ioanna Tzoulaki, PhD; Tibor V. Varga, PhD; Stefan Weiss, PhD; Andrianos M. Yiorkas, MSc; Robin Young, PhD; Weihua Zhang, PhD; Michael R. Barnes, PhD; Claudia P. Cabrera, PhD; He Gao, PhD; Michael Boehnke, PhD; Eric Boerwinkle, PhD; John C. Chambers, MD, PhD; John M. Connell, MD; Cramer K. Christensen, MD, DMsc; Rudolf A. de Boer, MD, PhD; Ian J. Deary, PhD; George Dedoussis, PhD; Panos Deloukas, PhD; Anna F. Dominiczak, MD, FRCP; Marcus Dörr, MD; Roby Joehanes, PhD; Todd L. Edwards, PhD; Tõnu Esko, PhD; Myriam Fornage, PhD; Nora Franceschini, MD; Paul W. Franks, PhD; Giovanni Gambaro, MD, PhD; Leif Groop, MD, PhD; Göran Hallmans, MD, PhD; Torben Hansen, MD, PhD; Caroline Hayward, PhD; Oksa Heikki, MD, PhD; Erik Ingelsson, MD, PhD; Jaakko Tuomilehto, MD, PhD; Marjo-Riitta Jarvelin, MD, PhD; Sharon L.R. Kardia, PhD; Fredrik Karpe, MD, PhD; Jaspal S. Kooner, MD; Timo A. Lakka, MD, PhD; Claudia Langenberg, MD, PhD; Lars Lind, MD, PhD; Ruth J.F. Loos, PhD; Markku Laakso, MD, PhD; Mark I. McCarthy, MD; Olle Melander, MD, PhD; Karen L. Mohlke, PhD; Andrew P. Morris, PhD; Colin N.A. Palmer, PhD; Oluf Pedersen, MD, DMsc; Ozren Polasek, MD, MPH, PhD; Neil R. Poulter, FMedSci; Michael A. Province, PhD; Bruce M. Psaty, MD, PhD; Paul M. Ridker, MD; Jerome I. Rotter, MD; Igor Rudan, PhD; Veikko Salomaa, MD, PhD; Nilesh J. Samani, MD; Peter J. Sever, MD; Tea Skaaby, MD, PhD; Jeanette M. Stafford, MSc; John M. Starr, PhD; Pim van der Harst, MD, PhD; Peter van der Meer, MD, PhD; The Understanding Society Scientific Group, Cornelia M. van Duijn, PhD; Anne-Claire Vergnaud, PhD; Vilmundur Gudnason, MD, PhD; Nicholas J. Wareham, MD, PhD; James G. Wilson, MD; Cristen J. Willer, PhD; Daniel R. Witte, PhD; Eleftheria Zeggini, PhD; Danish Saleheen, PhD; Adam S. Butterworth, PhD; John Danesh, PhD; Folkert W. Asselbergs, MD, PhD; Louise V. Wain, PhD; Georg B. Ehret, MD; Daniel I. Chasman, PhD; Mark J. Caulfield, MD; Paul Elliott, PhD; Cecilia M. Lindgren, PhD; Daniel Levy, MD; Christopher Newton-Cheh, MD*; Patricia B. Munroe, PhD*; Joanna M.M. Howson, 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 Group†

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†A list of all study participants is given in the Data Supplement.

*Drs Newton-Cheh, Munroe, and Howson coauthors jointly supervised this project.

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***Background*—**Genome-wide association studies have recently identified >400 loci that harbor DNA sequence variants that influence blood pressure (BP). Our earlier studies 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 BP or diastolic BP or pulse pressure. We performed 2 meta-analyses, one in individuals of European, South Asian, African, and Hispanic descent (pan-ancestry, ≈475 000), and the other in the subset of individuals of European descent (≈423 000). Twenty-one SNVs were genome-wide significant ($P<5\times10^{-8}$) for BP, of which 4 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 3 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 4 novel loci associated with BP regulation, and 1 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. **(*Circ Cardiovasc Genet*. 2017;10:e. DOI: 10.1161/CIRCGENETICS.117.001778.)**

Key Words: blood pressure ■ exome ■ genetics ■ genotype ■ sample size

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] Pharmacological interventional trials of BP-lowering therapies in patients with hypertension have demonstrated reductions in cardiovascular complications, including mortality.[4] Although several antihypertensive drug classes exist, variability in treatment response by individual patients and ethnic/racial groups, and residual risks, suggests that identification of previously unrecognized BP regulatory pathways could identify novel targets and pave the way for new treatments for cardiovascular disease prevention.

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Genetic association studies have identified >400 loci at $P<5\times10^{-8}$ that influence BP.[5–11] Two recent reports independently performed discovery analyses, in sample sizes of up to ≈146 000 (CHARGE Exome BP consortium [The Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium]) and ≈192 000 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 nonsynonymous and other putative functional variants and noncoding 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 2 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 European [EUR]).

Materials and Methods

Samples

These analyses consisted of a meta-analysis of results from 3 independent publications, the CHARGE Exome BP consortium,[8] European-led Exome consortia (contributory consortia, CHD Exome+, ExomeBP, and GoT2D:T2DGenes),[9] and the BP analyses from the UK Biobank Cardiometabolic consortium.[11]

The CHARGE Exome BP consortium included 120 473 individuals of EUR descent from 15 cohorts, 21 503 individuals of African descent from 10 cohorts, and 4586 individuals of Hispanic ancestry from 2 cohorts as described previously.[8] The European-led consortia included 165 276 individuals of EUR descent from 51 cohorts and 27 487 individuals of South Asian descent from 2 cohorts.[9] The UK Biobank data included 140 886 unrelated individuals of EUR descent.[11]

All samples from the CHARGE and European-led Exome consortia were genotyped on Exome arrays that includes ≈242 000 markers >90% of which are nonsynonymous or splice variants, with enrichment for variants with minor allele frequency (MAF)<0.05. The UK Biobank used the Affymetrix UK Biobank Axiom Array (approximately 100 000) or the Affymetrix UK BiLEVE Axiom Array (approximately 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[11] UK Biobank Nature Genetics 2017 article, from which the SNV association statistics for UK Biobank were provided.[11] Imputation

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Correspondence to Aldi T. Kraja, DSc, PhD, Division of Statistical Genomics, Department of Genetics, Center for Genome Sciences and Systems Biology, Washington University in St. Louis School of Medicine, 4444 Forest Park Ave, 6th Floor, Room 6314, Campus Box 8506, St. Louis, MO 63108. E-mail aldi@wustl.edu

scores in the UK Biobank samples for the variants presented in the Table had INFO>0.6. SNVs that produced significant results are highlighted in green in Tables I and II in the Data Supplement, with a median INFO of 1. The studies by Surendran et al,[9] Liu et al,[8] and Warren et al[11] examined genomic inflation factors in the contributing studies and the combined meta-analyses for each of the traits analyzed. Genomic inflation ranged between 1.04 and 1.11 in these contributing studies and therefore did not suggest that there were significant issues with population stratification. In the current analyses, 77 nonvalidated BP-associated SNVs were available for analysis across all 3 data sets.

Institutional review board 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: SBP, DBP, and PP, where PP was calculated as the difference between SBP and DBP. For individuals taking antihypertensive 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 antihypertensive 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[15] or EPACTS (the Efficient Mixed-Model Association eXpedited,[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, age^2, 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 were performed before the meta-analyses being performed. Full details are given in the reports from the component consortia.[8,9,11]

At the consortium level, meta-analyses of cohort-level association results were performed independently within CHARGE-Exome and the European-led Exome consortia using inverse variance-weighted fixed effects meta-analysis. These meta-analyses results were combined with the UK Biobank association results using fixed-effects inverse variance-weighted meta-analysis as implemented in METAL.[18] Two meta-analyses were performed, one pan-ancestry (PA; AA, European ancestry [EUR], Hispanic, South Asian) and the other of EUR ancestry. Statistical significance was set at genome-wide significance, $P<5\times10^{-8}$.

Functional Annotation

Associated variants were annotated using Human Genome Build 38 dbSNP and Entrez Gene (The National Center for Biotechnology Information). We interrogated publically available gene expression regulatory features from the Encyclopedia of DNA Elements consortium and ROADMAP Epigenome projects using HaploReg[19] and RegulomeDB.[20] Expression quantitative trait loci (eQTLs) were assessed using data from Genotype-Tissue Expression consortium,[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 5257 individuals.[26] We queried whether any of the 5 BP-associated SNVs were eQTLs for genes in the 5 BP-associated regions or whether they were in LD (r^2>0.8) with any of the eQTLs for genes in these regions. Where putative eQTLs were identified, we verified the BP-associated SNVs were in LD (r^2>0.8) with the top eQTL for that gene.

We interrogated publicly 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$\leq5\times10^{-8}$.

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 1 cell type were considered as high-confidence interactions.

Results

Association results for the 77 SNVs with the 3 BP traits are shown in Table I in the Data Supplement for the PA (European, South Asian, African, and Hispanic descent) meta-analysis and in Table II in the Data Supplement for the EUR meta-analysis. Twenty-one of the 77 SNVs were associated with at least 1 BP trait with genome-wide significance, $P<5\times10^{-8}$ and concordant directions of effects across the results from all contributing data sets (Table). 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 3 SNVs at *STAB1/NT5DC2*, *KDM5A,* and *LACTB* only in the EUR sample. All the significant SNVs were common (MAFs≥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, noncoding transcript; Figure IA through ID in the Data Supplement). The *SLC4A1AP* (rs9678851) was associated with SBP, and *AFAP1* (rs7437940) and 7p15.2 (rs1055144) were associated with PP. We also observed a potentially new independent BP association (r^2=0.001 in 1000G EUR and PA samples) at a recently published locus rs34163229 (*SYNPO2L*, missense; Table; Figure IE in the Data Supplement). We used a conservative r^2<0.1 threshold to minimize the possibility of an association because of correlation with a strongly associated established BP variant. Furthermore, conditional analyses within the ≈140 000 UK Biobank participants with comprehensive genomic coverage suggested that the association with SBP of rs34163229 was independent of the established SNV, rs4746172. Regional association plots in UK Biobank are provided in Figure IIA through IIE in the Data Supplement. Conditional analyses within the full data set was not possible given the targeted nature of the Exome array that makes claims of independence provisional. Twenty-two of the 77 SNVs had MAF≤0.01, and 1 rs3025380, a missense variant in DBH, was confirmed as a BP-associated locus.

Three of the five newly discovered BP-associated SNVs are missense variants, mapping to *SLC4A1AP, STAB1,* and *SYNPO2L* (Table and Table III in the Data Supplement). At

SLC4A1AP, rs9678851 (C>A, Pro139Thr) has MAF=0.46 and the C allele is associated with an increase of 0.23 mm Hg in SBP. This variant is correlated with 2 other missense variants in *C2orf16* (rs1919126 and rs1919125, r^2=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 mm Hg in PP per minor allele in EUR. This residue is located in a conserved region of the protein[31] (Table IV in the Data Supplement). 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 mm Hg in SBP per allele. This variant is in LD with another missense variant in *SYNPO2L* (rs3812629 r^2=1, 1000G EUR).[30] Using Polyphen2 (http://genetics.bwh.harvard.edu/pph2/index.shtml), the SNVs rs9678851 in *SLC4A1AP* and rs13303 in *STAB1* were predicted to be benign, whereas rs34163229 in *SYNPO2L* was predicted to have a possible damaging impact on the corresponding human proteins' structure and function.

We interrogated publicly available eQTL data sets through Genotype-Tissue Expression consortium, the Encyclopedia of DNA Elements consortium, 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 (Table III in the Data Supplement). The PP-associated SNV, rs13303, at *STAB1* is correlated (r^2>0.8 1000G EUR) with the top eQTLs for *NT5DC2* in atherosclerotic lesion-free internal mammary artery, atherosclerotic aortic root, subcutaneous adipose, visceral abdominal fat, and liver tissues (all $P<1\times10^{-11}$).[25] The rs13303 was also associated with expression levels of *NT5DC2* in EBV-transformed lymphocytes, transformed fibroblasts,[25] and thyroid cells (Table III in the Data Supplement).[21] The SBP-associated SNV at *SYNPO2L* (rs34163229) is correlated (r^2=0.86 in 1000G EUR) with the top eQTL (rs2177843) for *MYOZ1* in heart atrial appendage tissue (Table III in the Data Supplement).[21] The 5 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 15 recently established genome-wide significant BP-associated SNVs were eQTLs in the Framingham sample. Among the genome-wide significant BP SNVs, 3, rs4680 at *COMT*, rs12680655 at *ZFAT,* and rs10760260 at *RABGAP1*, were the top eQTL for the corresponding genes in whole blood (Table V in the Data Supplement). We also examined the 5 BP-associated SNVs in endothelial precursor cell Hi-C data (www.chicp.org) [28,32] to explore long-range chromatin interactions. rs13303 was found to contact *NISCH* (score 17.34) and rs34163229 contacts *USP54* (score 33.89)

Finally, we assessed the association of the new BP-associated variants and their close proxies (r^2>0.8) with cardiovascular disease risk factors, molecular metabolic traits, and clinical phenotypes using PhenoScanner, the NHGRI-EBI GWAS catalog and GRASP.[27] We observed 5 of the newly discovered BP-associated SNVs to have genome-wide significant associations with other traits, including height (7p15.2),[33] waist-to-hip ratio (*STAB1* and 7p15.2),[34,35] triglycerides (*SLC4A1P*), adiponectin levels (*STAB1*),[36] and atrial fibrillation (rs7915134 which has r^2=0.92 in the EUR 1000G samples with rs34163229 in *SYNPO2L*[37]; Table III in the Data Supplement).

Of the 77 analyzed 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 3 recent publications.[7,10,11] Twelve SNVs in our data set were located within 1 Mb of a recently reported BP locus: *CACNA1S, TSC22D2, RPL26L1, EDN1, GPRC6A, ACHE, CAV1, NOX5, PGLYRP2, NAPB, EDEM2,* and *KCNB1* (Tables I and II in the Data Supplement) although none of the SNVs were in LD (r^2>0.1 in all 1000G populations) with the published variants at these loci.

Discussion

We identified genome-wide significant associations with BP for 21 additional SNVs from our original Exome array analyses[8,9] by including UK Biobank participants to augment our sample size to ≈475 000 individuals. Four of the 21 BP-related loci we identified were novel, of which 2 were missense variants and 1 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 Genotype-Tissue Expression consortium tissues.

At the new locus on chromosome 3 (rs13303), 3 potential candidate genes are highlighted: *STAB1*, *NT5DC2,* and *NISCH*. *STAB1* encodes stabilin1, a protein known to endocytose low-density lipoprotein cholesterol, Gram-positive bacteria and Gram-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 500-bp downstream of *NT5DC2*. This additional gene is highlighted through the association of rs13303 with expression of *NT5DC2* in multiple tissues (Table III in the Data Supplement). *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. Finally, 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 α5 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

Table. Variants Associated With Systolic Blood Pressure, Diastolic Blood Pressure, or Pulse Pressure in the Pan-Ancestry or European-Ancestry Meta-Analyses in up to ≈475 000 Individuals

rsID	Gene	Annotation	chr-pos	Trait	Meta	a1/2	Freq1	β (SE)	*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

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 (diastolic blood pressure, systolic blood pressure, or pulse pressure) the variant is associated with; meta, the meta-analysis the variant is associated in, Pan-Ancestry or EURopean; A1/2, allele 1/allele 2; freq1, allele frequency for allele 1; β (SE), effect estimate, β and its SE for allele 1 from the corresponding meta-analysis; *P* value, *P* from meta-analysis; dir, 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 3 contributing consortia; N, sample size for the trait and meta-analysis with the lowest *P* value; UK-BIOBANK INFO, a quality of imputation score in UK BIOBANK. For more details, see Tables I and II in the Data Supplement. D indicates diastolic blood pressure; P, pulse pressure; S, systolic blood pressure; and SNV indicates single nucleotide variant.

*Potential new signal at a recently reported locus (LD, r^2<0.1 with a published BP SNV).

†First report of this variant as genome-wide significant.

in right atrial tissue, based on regulatory chromatin states from DNAse and histone ChIP-Seq in Roadmap Epigenomics Consortium (identified with HaploReg, Table IV in the Data Supplement).[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), 2 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 α-actinin and gamma filamin binding Z line protein predominantly expressed in skeletal muscle.[46]

At 2 loci (*SLC4A1AP* and *SYNPO2L*), we observed >1 missense variant in high LD (r^2>0.8). Functional follow-up of these variants are needed to disentangle the causal variants. At the *SLC4A1AP* locus, there are 3 misssense variants, none of which are predicted to be damaging. Two of these are in *C2orf16* that 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, because of the predicted weak effects of the BP variants. At the *SYNPO2L* locus, the 2 missense variants are both in *SYNPO2L*, of which 1 is predicted damaging, cellular experiments testing functional effects of this variant alone or part of a haplotype maybe a good starting point.

In conclusion, we identified 4 new loci and 1 potential new SNV in a known locus, which 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.

Appendix

From the Division of Statistical Genomics, Department of Genetics and Center for Genome Sciences and Systems Biology, Washington University School of Medicine, St. Louis, MO (A.T.K., M.A.P.); Department of Biostatistics, University of Liverpool, United Kingdom (J.P.C., A.P.M.); Department of Clinical Pharmacology, William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, United Kingdom (H.R.W., L.L., K.E.S., C.P.C., M.R.B., P.D., M.J.C., P.B.M.); National Institute for Health Research Barts Cardiovascular Biomedical Research Unit, Queen Mary University of London, United Kingdom (H.R.W., M.R.B., C.P.C., P.D., M.J.C., P.B.M.); MRC/BHF Cardiovascular Epidemiology Centre, Department of Public Health and Primary Care (P.S., R.Y., A.S.B., J.D., J.M.M.H.), Department of Haematology (K.E.S.), Department of Public Health and Primary Care (D.S.), NIHR Blood and Transplant Research Unit in Donor Health and Genomics (J.D.) and British Heart Foundation, Cambridge Centre for Excellence, Department of Medicine (A.S.B., J.D.), University of Cambridge, United Kingdom; The Framingham Heart Study, MA (C.L., R.J., D.L.); The Population Sciences Branch, Division of Intramural Research, National Heart, Lung, and Blood Institute (C.L., D.L.), Mathematical and Statistical Computing Laboratory, Center for Information Technology (R.J.), National Institutes of Health, Bethesda, MD; Department of Epidemiology and Biostatistics, School of Public Health (E.E., I.T., W.Z., H.G., J.C.C., M.-R.J., A.-C.V., P.E.), Section of Investigative Medicine, Department of Medicine (A.I.F.B., A.M.Y.), MRC-PHE Centre for Environment and Health (I.T., H.G., M.-R.J., P.E.), International Centre for Circulatory Health (N.R.P., P.J.S.), National Institute for Health Research Imperial College Healthcare NHS Trust Biomedical Research Unit (P.E.), Imperial College London, United Kingdom; Department of Hygiene and Epidemiology, University of Ioannina Medical School, Greece (E.E., I.T.); Center for Genomic Medicine (A.K.M., C.N.-C.), Cardiovascular Research Center, Massachusetts General Hospital (C.N.-C.); Department of Medicine (A.K.M., P.M.R., D.I.C.), Institute for Aging Research, Hebrew SeniorLife (R.J.), Harvard Medical School (P.M.R., D.I.C.), Boston, MA; The Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark (N.G., J.B.-J., C.T.H., T.H., O.P.); Medical Research Council Integrative Epidemiology Unit, School of Social and Community Medicine, University of Bristol, United Kingdom (F.D.); Centre for Cardiovascular Genetics, Institute of Cardiovascular Science (F.D.) and Faculty of Population Health Sciences (F.W.A.), University College London, United Kingdom; Department of Biostatistics and Center for Statistical Genetics (X.S., M.B.), Department of Internal Medicine, Division of Cardiovascular Medicine (H.Z., C.J.W.), Department of Epidemiology, School of Public Health (J.A.S., S.L.R.K.), Department of Computational Medicine and Bioinformatics (C.J.W.) and Department of Human Genetics (C.J.W.), University of Michigan, Ann Arbor; Saw Swee Hock School of Public Health, National University of Singapore (X.S.); Icelandic Heart Association, Kopavogur (A.V.S., V.G.); Faculty of Medicine, University of Iceland, Reykjavik (A.V.S., V.G.); Genetic Epidemiology Unit, Department of Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands (N.A., C.M.v.D.); Department of Life Sciences, Brunel University London, United Kingdom (A.I.F.B., A.M.Y.); Department of Clinical Biochemistry (I.B.), Medical Department (C.K.C.), Lillebaelt Hospital, Vejle, Denmark; Institute of Regional Health Research, University of Southern Denmark, Odense (I.B.); Department of Nutrition and Dietetics, School of Health Science and Education, Harokopio University, Athens, Greece (A.-E.F., G.D.); Department of Clinical Sciences, University of Lund, Malmö, Sweden (C.F., O.M.); Department of Medicine (C.F.) and Department of Neuroscience, Biomedicine and Movement, Section of Biology and Genetics (G.M.), University of Verona, Italy; Wellcome Trust Centre for Human Genetics (T.F., A.M., N.W.R., L.S., M.I.M., C.M.L.), Oxford Centre for Diabetes, Endocrinology and Metabolism, Radcliffe Department of Medicine (N.W.R., F.K., M.I.M.), and Big Data Institute at the Li Ka Shing Centre for Health Information and Discovery, University of Oxford, United Kingdom (C.M.L.); Research Unit of Biomedicine and Biocenter of Oulu, University of

Oulu, Finland (K.-H.H.); Medical Research Center (MRC) & Oulu University Hospital, Finland (K.-H.H.); Department of Gastroenterology and Metabolism, Poznan University of Medical Sciences, Poland (K.-H.H.); Vanderbilt Epidemiology Center, Institute for Medicine and Public Health, Vanderbilt University Medical Center, Nashville, TN (A.G., T.L.E.); Division of Preventive Medicine, Brigham and Women's Hospital, Boston, MA (F.G., P.M.R., D.I.C.); Human Genetics Center, School of Public Health (M.L.G., A.C.M., M.A.R., E.B.) and Brown Foundation Institute of Molecular Medicine, McGovern Medical School (M.A.R., M.F.), The University of Texas Health Science Center at Houston (M.L.G, A.C.M., E.B.); Institute for Translational Genomics and Population Sciences and Department of Pediatrics, Harbor-UCLA Medical Center, Torrance, CA (X.G., J.I.R.); Centre for Cognitive Ageing and Cognitive Epidemiology (S.E.H., R.E.M., I.J.D., J.M.S.), Centre for Genomic and Experimental Medicine (S.E.H., R.E.M.), Psychology (I.J.D.), Medical Research Council Human Genetics Unit, Institute of Genetics and Molecular Medicine (C.H.), Usher Institute of Population Health Sciences and Informatics (I.R.), and Alzheimer Scotland Research Centre (J.M.S.), University of Edinburgh, United Kingdom; Department of Health (A.S.H., V.S.), Chronic Disease Prevention Unit, National Institute for Health and Welfare (J.T.), and Institute of Molecular Medicine Finland (A.S.H.), Helsinki, Finland; Dasman Diabetes Institute, Kuwait (J.T.); Diabetes Research Group, King Abdulaziz University, Jeddah, Saudi Arabia (J.T.); Department of Neurosciences and Preventive Medicine, Danube University Krems, Austria (J.T.); Steno Diabetes Center, Copenhagen, Gentofte, Denmark (M.E.J.); Department of Primary Health Care, Vaasa Central Hospital, Finland (A.K.); Diabetes Center, Vaasa Health Care Center, Finland (A.K.); Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA (C.K.); Research Centre for Prevention and Health, The Capital Region of Denmark, Copenhagen (A.L., T.S.); Department of Clinical Experimental Research, Rigshospitalet, Glostrup, Denmark (A.L.); Epidemiology & Prevention Center for Genomics and Personalized Medicine Research, Wake Forest Baptist Medical Center, Medical Center Boulevard, Winston-Salem, NC (Y.Liu); Medical Genomics and Metabolic Genetics Branch, National Human Genome Research Institute, NIH, Bethesda, MD (L.L.B.); Charles Bronfman Institute for Personalized Medicine, Icahn Shool of Medicine at Mount Sinai, NY (Y.Lu, R.J.F.L.); Division of Epidemiology, Department of Medicine, Vanderbilt-Ingram Cancer Center, Vanderbilt Epidemiology Center, Vanderbilt University School of Medicine, Nashville, TN (Y.Lu); Estonian Genome Center, University of Tartu, Estonia (R.M., T.E.); Department of Data Science (H.M.) and Department of Physiology and Biophysics (J.G.W.), University of Mississippi Medical Center, Jackson; Department of Twin Research & Genetic Epidemiology, King's College London (C.M.); British Heart Foundation Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, College of Medical, Veterinary and Life Sciences, University of Glasgow, United Kingdom (S.P., A.F.D.); Department of Medicine, Columbia University Medical Center, New York, NY (W.P.); Department of Clinical Sciences, Genetic and Molecular Epidemiology Unit, Lund University, Malmö, Sweden (A.P., P.W.F.); Kuopio Research Institute of Exercise Medicine (R.R., T.V.V., T.A.L.), Department of Clinical Physiology and Nuclear Medicine (R.R., T.A.L.), University of Eastern Finland (A.S.), and Department of Medicine, University of Eastern Finland & Kuopio University Hospital (M.L.); Wellcome Trust Sanger Institute, Hinxton, United Kingdom (N.W.R., L.S., E.Z., J.D.); Department of Cardiovascular Sciences (M.R., N.J.S.) and Department of Health Sciences (L.V.W.), University of Leicester, United Kingdom; NIHR Leicester Biomedical Research Centre, Glenfield Hospital, United Kingdom (M.R., N.J.S.); Department of Biostatistics (K.R.), Cardiovascular Health Research Unit, Departments of Medicine, Epidemiology and Health Services, University of Washington, Seattle (B.M.P.); Department of Cardiology, University Medical Center Utrecht, The Netherlands (V.T., F.W.A.); Folkhälsan Research Centre (T.T.) and Department of Endocrinology (T.T.), Helsinki University Central Hospital, Finland; Interfaculty Institute for Genetics and Functional Genomics, University Medicine and Ernst-Moritz-Arndt-University Greifswald, Germany (S.W., M.D.); DZHK (German Centre for Cardiovascular Research), Partner Site Greifswald, Germany (S.W.); Department of Cardiology, Ealing Hospital, London North West Healthcare NHS Trust, United Kingdom (W.Z., J.C.C., J.S.K.); Human Genome Sequencing Center, Baylor College of Medicine, Houston, TX (E.B.); Imperial College Healthcare NHS Trust, London, United Kingdom (J.C.C., J.S.K.); University of Dundee, Ninewells Hospital & Medical School, United Kingdom (J.M.C.); Department of Cardiology (R.A.d.B., P.v.d.H., P.v.d.M.) and Department of Genetics (P.v.d.H.), University of Groningen, University Medical Center Groningen, The Netherlands; Department of Internal Medicine B-Cardiology, Pneumology, Infectious Diseases, Intensive Care Medicine, University Medicine Greifswald, Germany (M.D.); Department of Epidemiology (N.F.) and Department of Genetics (K.L.M.), University of North Carolina, Chapel Hill; Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA (P.W.F.); Department of Public Health & Clinical Medicine (P.W.F.) and Department of Biobank Research (T.T., G.H.), Umeå University, Sweden; Department of Nephrology and Dialysis, Università Cattolica del Sacro Cuore, Roma, Italy (G.G.); Department of Clinical Sciences, Diabetes and Endocrinology, Lund University Diabetes Centre, Malmö, Sweden (L.G.); Finnish Institute for Molecular Medicine (FIMM) (T.T., L.G.), Helsinki University, Finland; Tampere University Hospital, Finland (O.H.); Department of Medicine, Division of Cardiovascular Medicine, Stanford University School of Medicine, CA (E.I.); Department of Medical Sciences, Molecular Epidemiology and Science for Life Laboratory, Uppsala University, Sweden (E.I., L.L.); Center for Life Course Health Research, Faculty of Medicine, University of Oulu, Finland (M.-R.J.); Oxford NIHR Biomedical Research Centre, Oxford University Hospitals Trust, United Kingdom (F.K., M.I.M.); National Heart and Lung Institute, Imperial College London, Hammersmith Hospital Campus, United Kingdom (J.S.K.); Institute of Biomedicine/Physiology, University of Eastern Finland, Kuopio (T.A.L.); MRC Epidemiology Unit, University of Cambridge School of Clinical Medicine, Institute of Metabolic Science, Cambridge Biomedical Campus, United Kingdom (C.L., N.J.W.); Medical Research Institute, University of Dundee, Ninewells Hospital and Medical School, Scotland, United Kingdom (C.N.A.P.); Faculty of Medicine, University of Split, Croatia (O.P.); Kaiser Permanente Washington Health Research Institute, Seattle, (B.M.P.); Division of Public Health Sciences, Department of Biostatistical Sciences, Wake Forest School of Medicine, Winston-Salem, NC (J.M.S.); Department of Public Health, Aarhus University, Denmark (D.R.W.); Danish Diabetes Academy, Odense, Denmark (D.R.W.); Department of Biostatistics and Epidemiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia (D.S.); Centre for Non-Communicable Diseases, Karachi, Pakistan (D.S.); Center for Complex Disease Genomics, McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD (G.B.E.); Cardiology, Department of Medicine, Geneva University Hospital, Switzerland (G.B.E.); and Program in Medical and Population Genetics, Broad Institute of Harvard and MIT, Cambridge (C.M.L., C.N.-C.).

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CLINICAL PERSPECTIVE

We analyzed 77 single nucleotide variants that remained of interest, but did not achieve genome-wide significance with blood pressure (BP) traits from a prior analysis of Exome chip genotypes. A meta-analysis of results from the CHARGE Exome BP and European led consortia in combination with association results from UK Biobank samples (pan-ancestry sample of ≈475 000 and European only sample of ≈423 000) indicated 21 genome-wide significant loci. Four of these are novel BP loci: rs9678851 (missense, *SLC4A1AP*), rs7437940 (*AFAP1*), rs13303 (missense, *STAB1*), and rs1055144 (7p15.2). We also identified a potentially independent novel BP-associated single nucleotide variant, rs3416322 (missense, *SYNPO2L*) at a known locus. Two of the BP-associated single nucleotide variants influence expression levels of nearby genes. These new findings add to the growing number of BP loci and could potentially facilitate an improved understanding of BP regulation, and identify novel therapeutic targets to reduce the burden of cardiovascular disease.

Circulation
Cardiovascular Genetics

New Blood Pressure–Associated Loci Identified in Meta-Analyses of 475 000 Individuals

Aldi T. Kraja, James P. Cook, Helen R. Warren, Praveen Surendran, Chunyu Liu, Evangelos Evangelou, Alisa K. Manning, Niels Grarup, Fotios Drenos, Xueling Sim, Albert Vernon Smith, Najaf Amin, Alexandra I.F. Blakemore, Jette Bork-Jensen, Ivan Brandslund, Aliki-Eleni Farmaki, Cristiano Fava, Teresa Ferreira, Karl-Heinz Herzig, Ayush Giri, Franco Giulianini, Megan L. Grove, Xiuqing Guo, Sarah E. Harris, Christian T. Have, Aki S. Havulinna, He Zhang, Marit E. Jørgensen, AnneMari Käräjämäki, Charles Kooperberg, Allan Linneberg, Louis Little, Yongmei Liu, Lori L. Bonnycastle, Yingchang Lu, Reedik Mägi, Anubha Mahajan, Giovanni Malerba, Riccardo E. Marioni, Hao Mei, Cristina Menni, Alanna C. Morrison, Sandosh Padmanabhan, Walter Palmas, Alaitz Poveda, Rainer Rauramaa, Nigel William Rayner, Muhammad Riaz, Ken Rice, Melissa A. Richard, Jennifer A. Smith, Lorraine Southam, Alena Stancáková, Kathleen E. Stirrups, Vinicius Tragante, Tiinamaija Tuomi, Ioanna Tzoulaki, Tibor V. Varga, Stefan Weiss, Andrianos M. Yiorkas, Robin Young, Weihua Zhang, Michael R. Barnes, Claudia P. Cabrera, He Gao, Michael Boehnke, Eric Boerwinkle, John C. Chambers, John M. Connell, Cramer K. Christensen, Rudolf A. de Boer, Ian J. Deary, George Dedoussis, Panos Deloukas, Anna F. Dominiczak, Marcus Dörr, Roby Joehanes, Todd L. Edwards, Tõnu Esko, Myriam Fornage, Nora Franceschini, Paul W. Franks, Giovanni Gambaro, Leif Groop, Göran Hallmans, Torben Hansen, Caroline Hayward, Oksa Heikki, Erik Ingelsson, Jaakko Tuomilehto, Marjo-Riitta Jarvelin, Sharon L.R. Kardia, Fredrik Karpe, Jaspal S. Kooner, Timo A. Lakka, Claudia Langenberg, Lars Lind, Ruth J.F. Loos, Markku Laakso, Mark I. McCarthy, Olle Melander, Karen L. Mohlke, Andrew P. Morris, Colin N.A. Palmer, Oluf Pedersen, Ozren Polasek, Neil R. Poulter, Michael A. Province, Bruce M. Psaty, Paul M. Ridker, Jerome I. Rotter, Igor Rudan, Veikko Salomaa, Nilesh J. Samani, Peter J. Sever, Tea Skaaby, Jeanette M. Stafford, John M. Starr, Pim van der Harst, Peter van der Meer, The Understanding Society Scientific Group, Cornelia M. van Duijn, Anne-Claire Vergnaud, Vilmundur Gudnason, Nicholas J. Wareham, James G. Wilson, Cristen J. Willer, Daniel R. Witte, Eleftheria Zeggini, Danish Saleheen, Adam S. Butterworth, John Danesh, Folkert W. Asselbergs, Louise V. Wain, Georg B. Ehret, Daniel I. Chasman, Mark J. Caulfield, Paul Elliott, Cecilia M. Lindgren, Daniel Levy, Christopher Newton-Cheh, Patricia B. Munroe and Joanna M.M. Howson
on behalf of the CHARGE EXOME BP, CHD Exome+, Exome BP, GoT2D:T2DGenes Consortia, The UK Biobank Cardio-Metabolic Traits Consortium Blood Pressure Working Group

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Supplemental Material

Supplemental Table 1. Association of the 77 SNVs with BP in the pan-ancestry meta-analysis. Highlighted in green are SNVs with $P \leq 5x10^{-8}$ (equivalent to $-\log_{10}P = 7.3$). In yellow are highlighted the 21 BP findings. (See Excel Table)

Note: **No**-order number, table is ordered by chromosome and HG38 position; **rsID**-SNV name, **Gene Name**-gene name from the Entrez Gene of NCBI; **Variant role**-SNVs' role as defined by the NCBI dbSNP database; **Chrom-** chromosome; position HG38 and position HG19- positions based on NCBI builds batch 138 (HG19) and batch 147 (HG38); **diffposneargene-** position distance of a SNV from the closest gene's SNV in the NCBI dbSNP, if within the gene we assigned a 0 value; **Closest gene-** a gene name the same as Gene Name, when the SNV is within gene boundaries, in parenthesis when within 500KB of the closest gene, and in parenthesis with *()_beyond* when further intergenic; **Allele 1**-allele 1; **Allele 2**-allele 2; **Freq1**-allele frequency for Allele 1; **SBP beta** and its Standard Error as **SBP s.e.** followed by DBP and PP; **SBP direction-** direction of beta sign for contributing results in the following order: BP-EUROPEAN led Consortium, UK-BIOBANK and CHARGE-BP Consortium, similar for DBP and PP; followed by the same traits' order for **loghetp**-log10p of heterogeneity; **N**-meta-sample; and SBP-**meta -Log$_{10}$p** for SBP, DBP and PP.

Supplemental Table 2. Association of the 77 SNVs for BP in the European ancestry meta-analysis. Highlighted in green are SNVs with $P \leq 5x10^{-8}$ (equivalent to $-\log_{10}P = 7.3$). In yellow are highlighted the 21 BP findings. (See separate Excel Table).

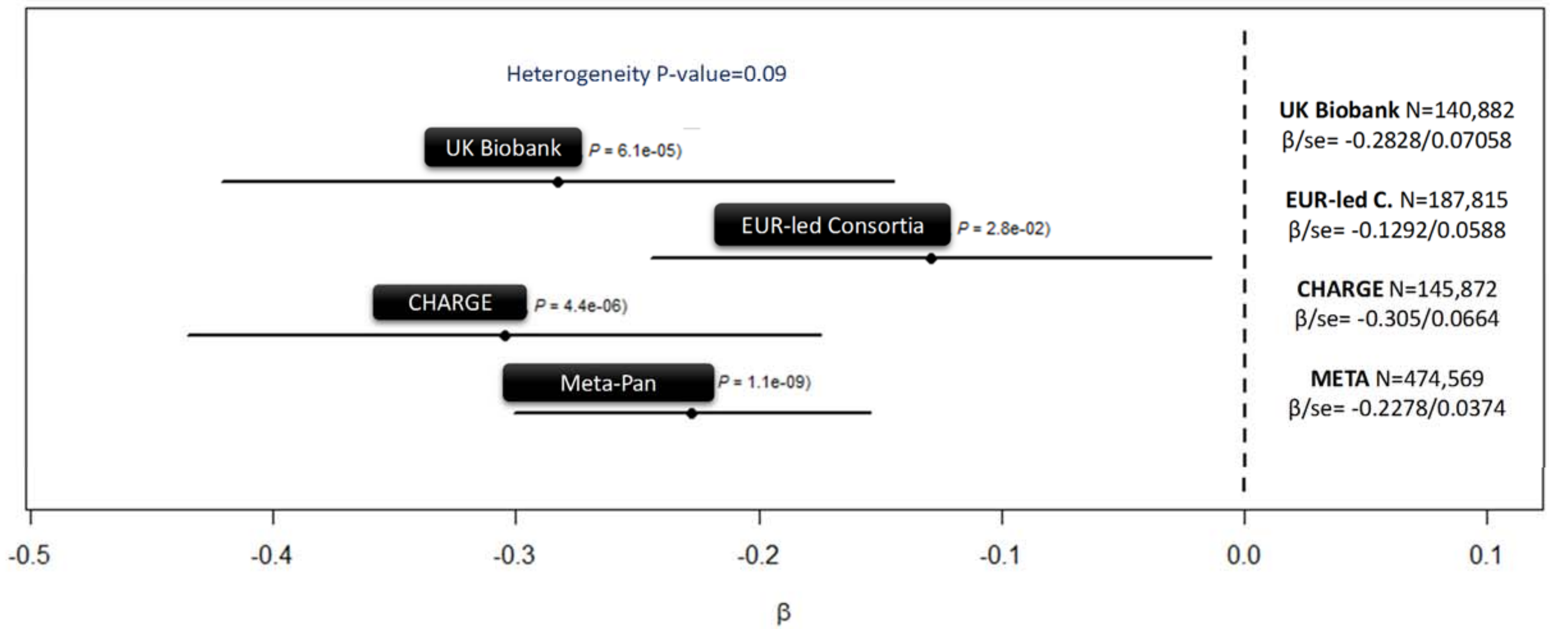
See Note above for Supplemental Table 1.

Supplemental Table 3. Association findings for new BP SNVs, including any associations with other traits and top ranked eQTLs with $P < 5 \times 10^{-8}$. For the eQTL results we only report tissues and genes where the BP-associated SNV and the expression SNV are in high LD ($r^2 > 0.8$). Sources of information were GWAS Catalog access on 1.12.2017, PhenoScanner [27] and GTex [46] (See separate Excel Table for referenced PMIDs).

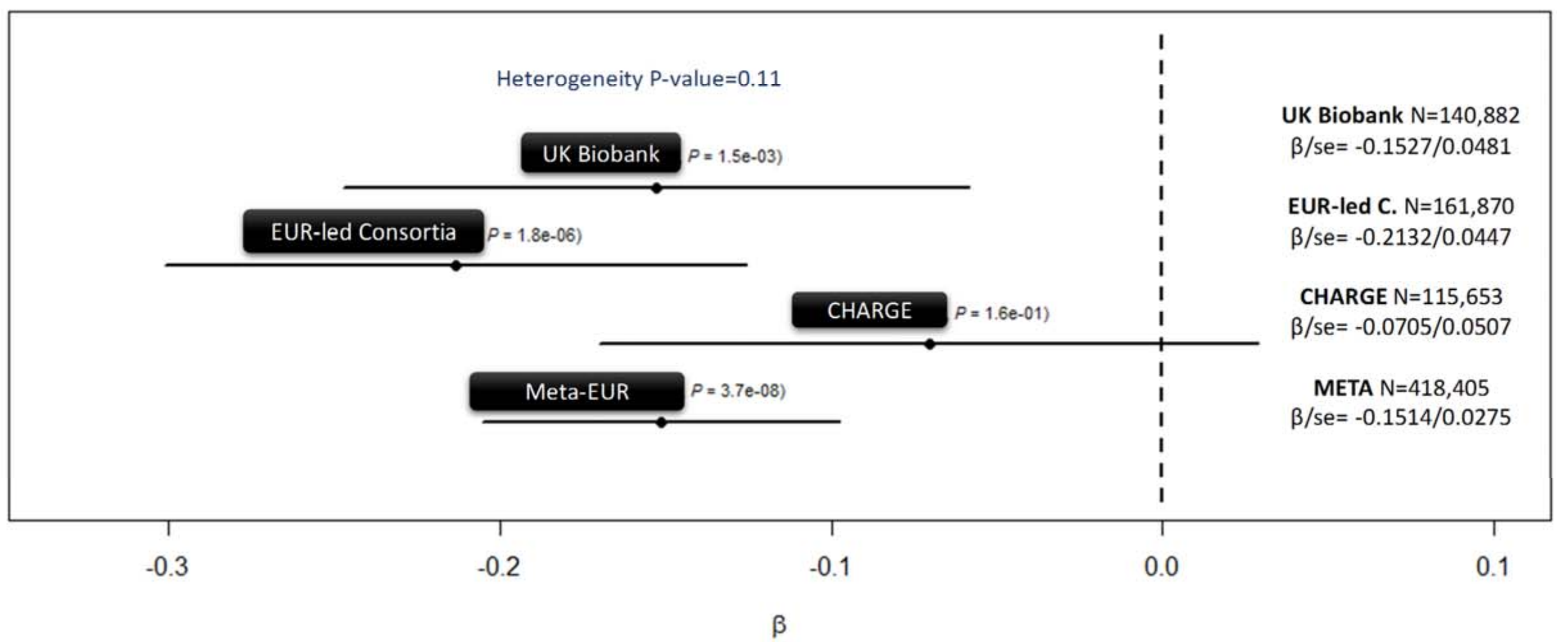
Supplemental Table 4. Cis- regulatory features of new BP SNVs based on HaploReg, which is using among others information from epigenome of ENCODE and RoadMap projects. (See separate Excel Table).

Supplemental Table 5. cis-eQTL identified in the Framingham heart study generation 3 whole blood expression data (See separate Excel Table).

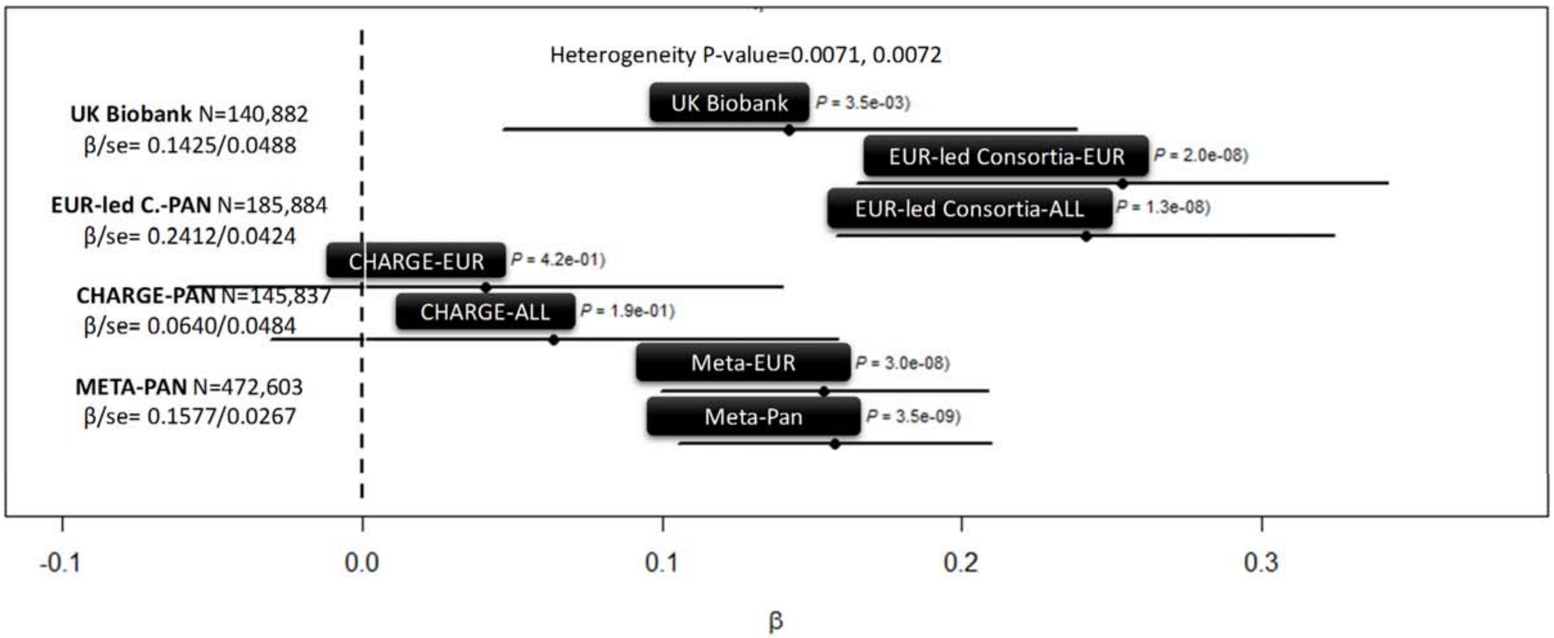
Supplemental Figures 1. Forest plots of 5 novel selected SNVs in association with BP. Depicted are the beta, 95% confidence interval around the beta for the overall meta-analysis and for each contributing consortium. The heterogeneity p-value is estimated from the overall meta-analysis. **(a)** The rs9678851 (missense) *SLC4A1AP* (SBP-Pan-ancestry, A=0.55)



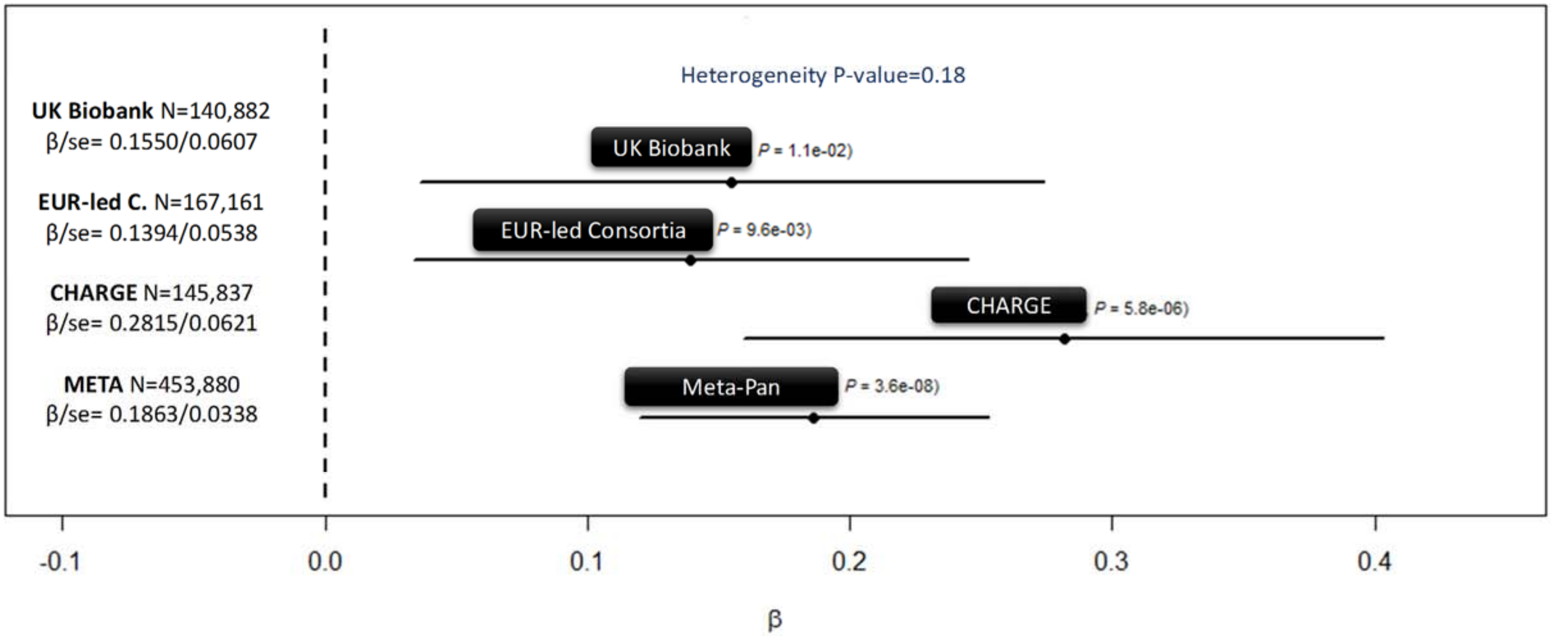
(b) The rs13303 (missense) *STAB1* (PP-EUR-ancestry, T=0.44)



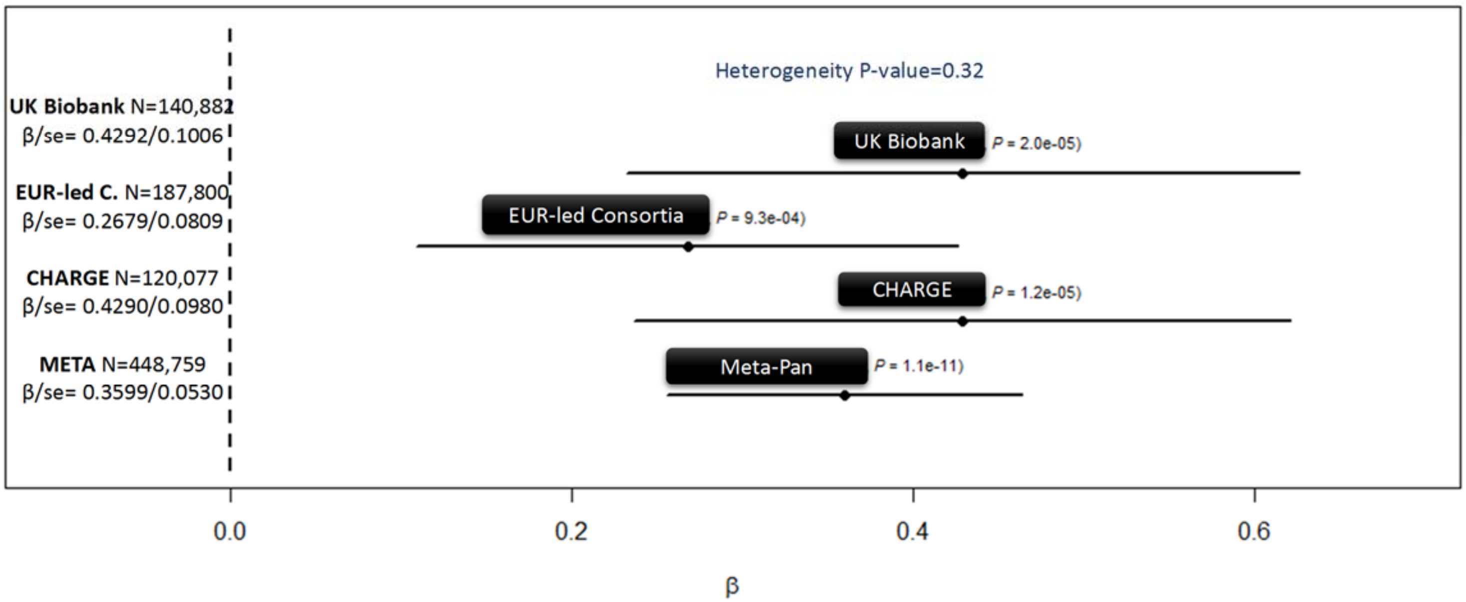
(c) The rs7437940 (intronic) *AFAP1* (PP-EUR & Pan-ancestry, T=0.47)



(d) The rs1055144 (nc-transcript) *7p15.2* (PP-Pan-ancestry, T=0.19)



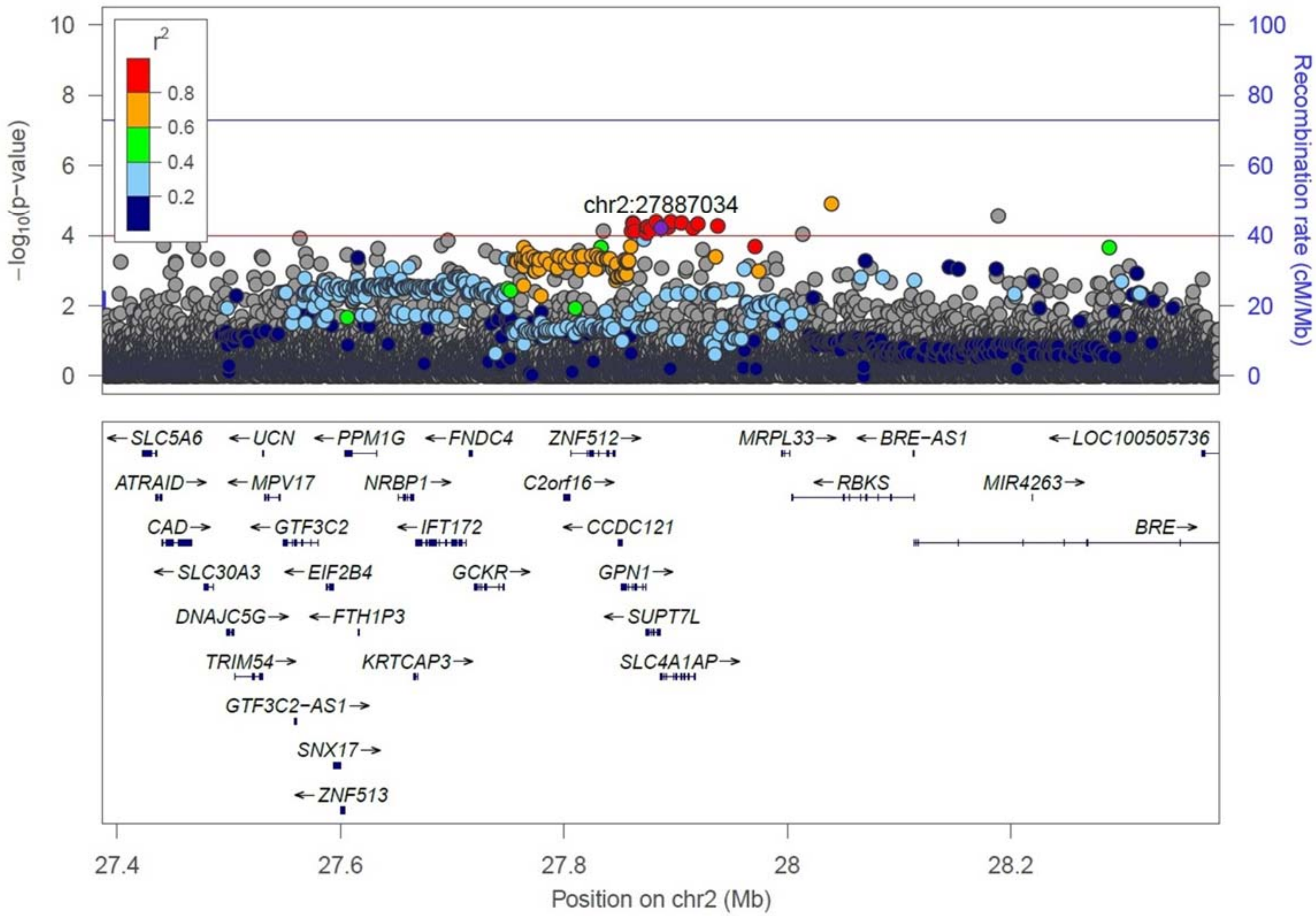
(e) The rs34163229 (missense) *SYNPO2L* (SBP-Pan-ancestry, T=0.15)



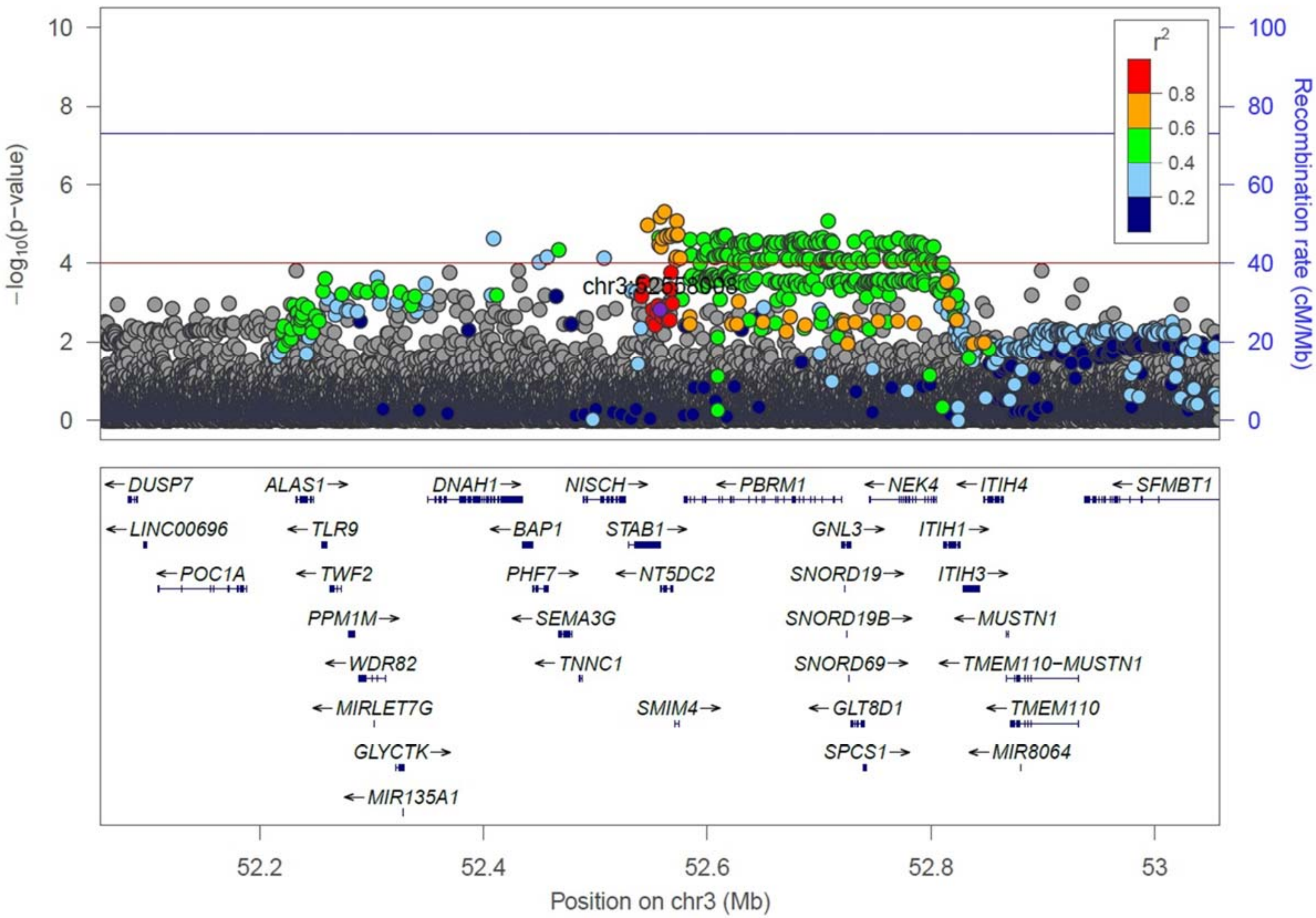
Notes for LocusZoom plots:

- Locus Zoom plots of region ±500kb from the reference SNV
- Showing results for the primary trait from the Mega-Exome analysis
- Association p-value results according to full UKB-EUR BP GWAS data
- LD calculated from UKB-EUR data for all UKB variants
- Grey points if LD has $r^2 < 0.1$
- All plots on same y-axis scale limits for equivalent comparison
- Significance threshold reference lines at 1×10^{-4} and 5×10^{-8}

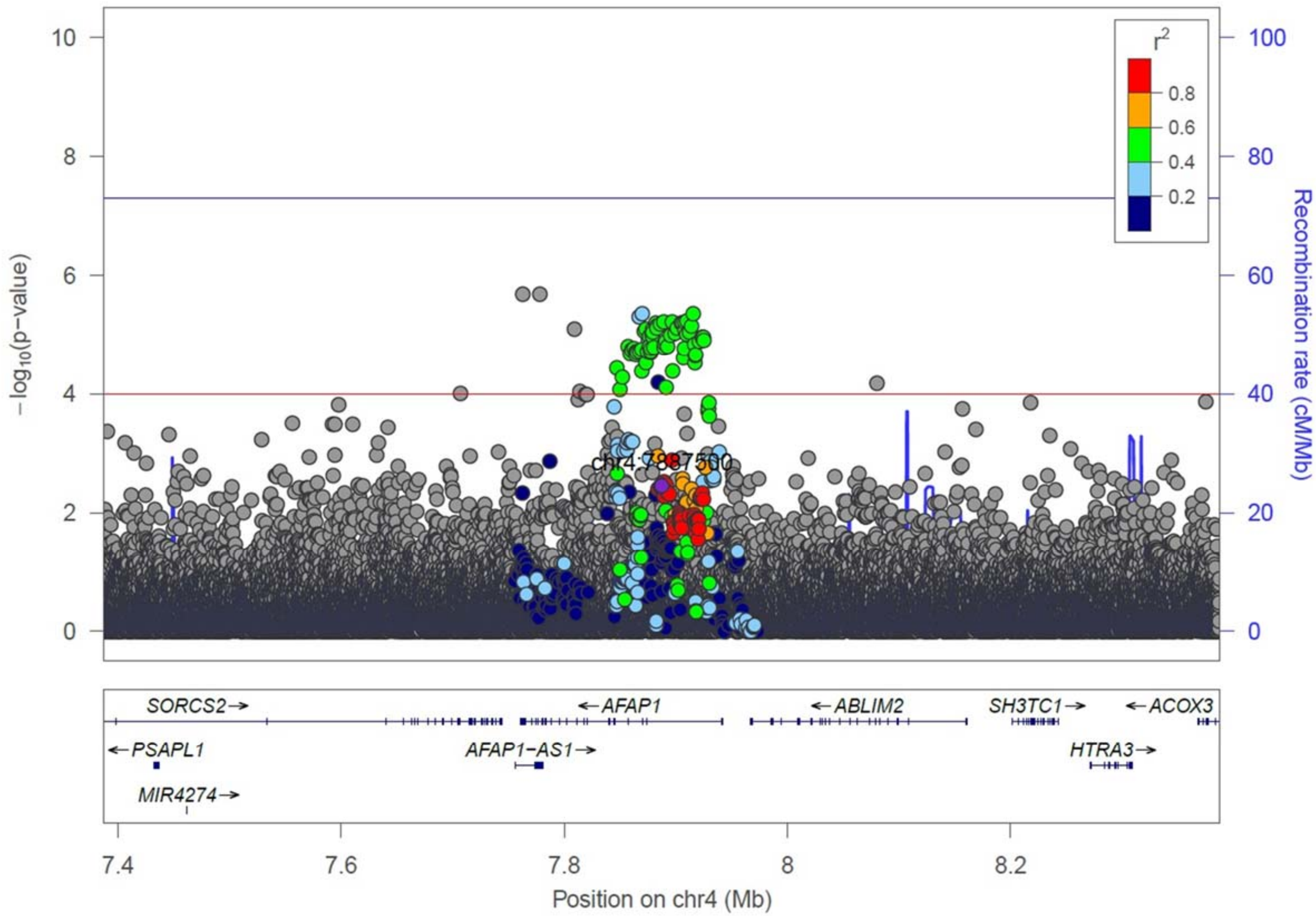
Supplemental Figures 2a-e. LocusZoom plots of 5 novel selected SNVs in association with BP. They represent regional association plots based on only UK Biobank results. (**a)** The *SLC4A1AP* (rs9678851) for SBP (novel locus)



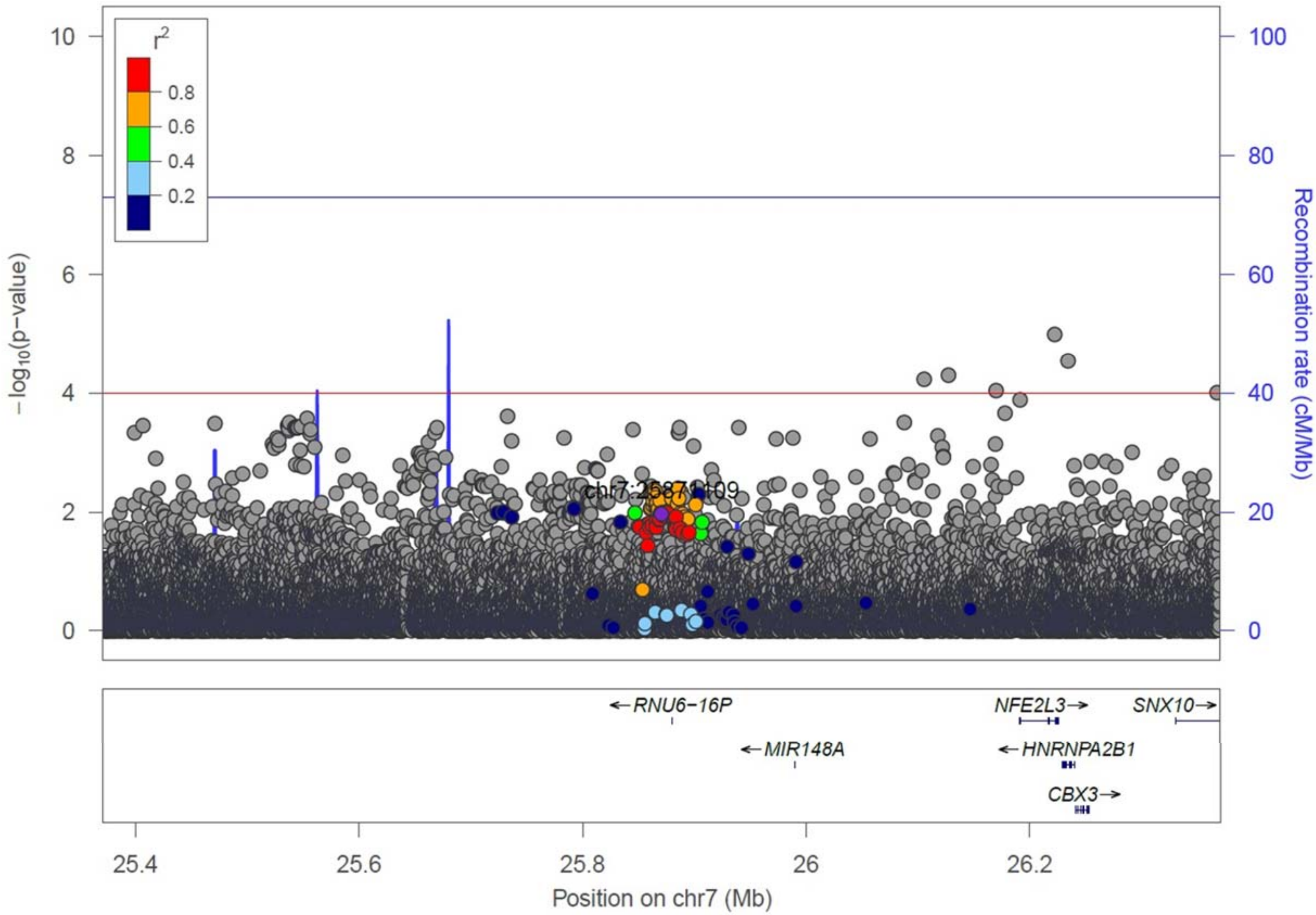
(b) The *STAB1* (rs13303) for PP (novel locus)



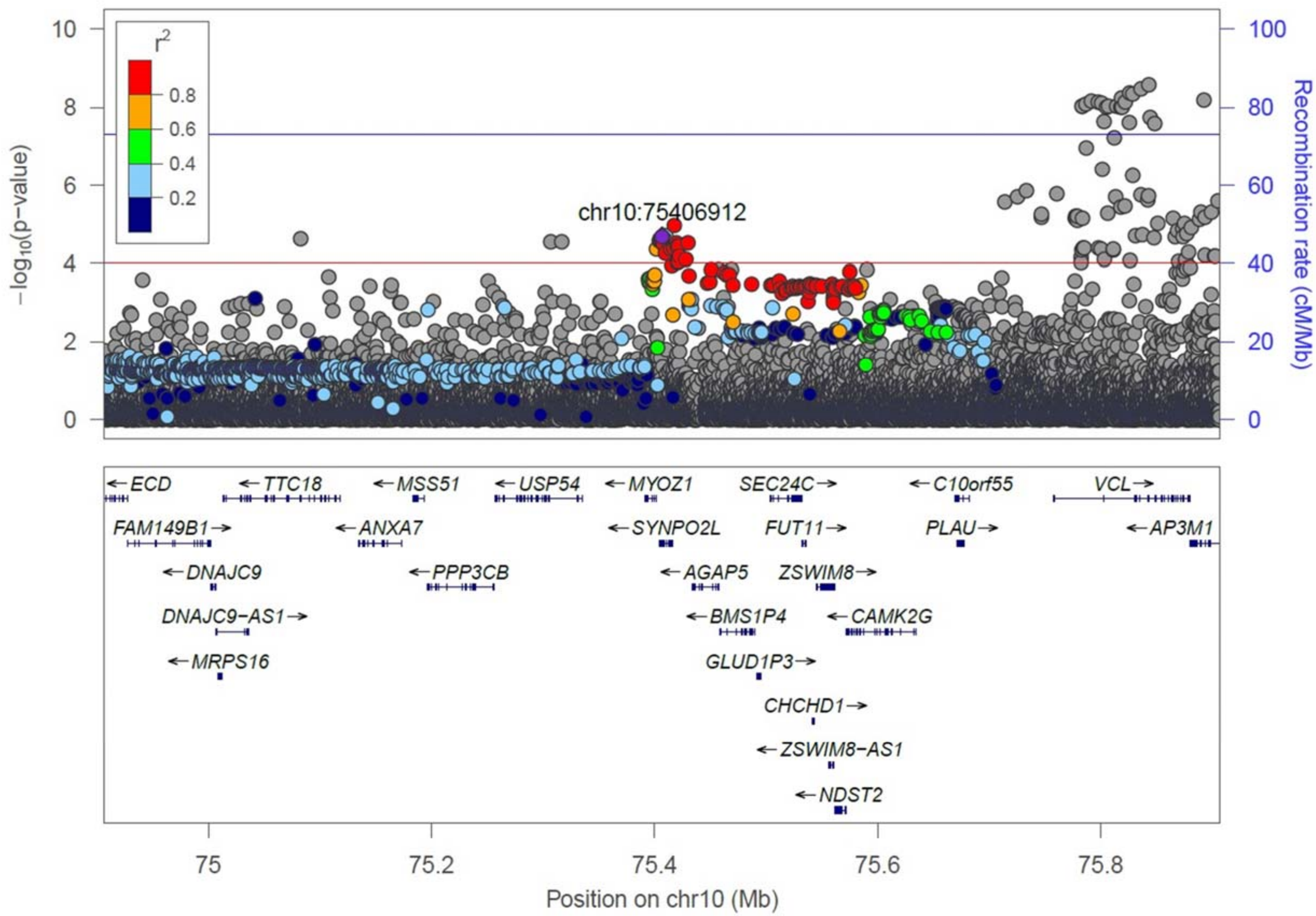
(c) The *AFAP1* (rs7437940) for PP (novel locus)



(d) The *7p15.2* (rs1055144) for PP (novel locus)



(e) The *SYNOPL2* (rs34163229) for SBP (secondary signal)



CHARGE EXOME BP

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CHD Exome+ Consortium

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UK-Exome BP Consortium

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GoT2D Consortium

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CHARGE+ Exome Chip Blood Pressure Consortium

Chunyu Liu[1,2,3,*], Aldi T. Kraja[4*], Jennifer A. Smith[5*], Jennifer A. Brody[6*], Nora Franceschini[7*], Joshua C. Bis[6], Kenneth Rice[8], Alanna C. Morrison[9], Yingchang Lu[10], Stefan Weiss[11,12], Xiuqing Guo[13], Walter Palmas[14], Lisa W. Martin[15], Yii-Der Ida Chen[13], Praveen Surendran[16], Fotios Drenos [17,18], James P. Cook[19,20], Paul L. Auer[21], Audrey Y. Chu[1,3,22], Ayush Giri[23], Wei Zhao[5] , Johanna Jakobsdottir[24], Li-An Lin[25], Jeanette M. Stafford[26] , Najaf Amin[27], Hao Mei[28], Jie Yao[13], Arend Voorman[29], CHD Exome Plus Consortium†, ExomeBP Consortium†, GoT2D Consortium/GoT2DGenes consortium†, Martin G. Larson[1,2,30] , Megan L. Grove[9], Albert V. Smith[24,31], Shih-Jen Hwang[1,3], Han Chen[32] , Tianxiao Huan[1,3], Gulum Kosova[33,34], Nathan O. Stitziel[35], Sekar Kathiresan[34,36], Nilesh Samani[37,38], Heribert Schunkert[39,40], Panos Deloukas[41,42], Myocardial Infarction Genetics and CARDIoGRAM Exome Consortia Investigators†, Man Li [43], Christian Fuchsberger[44], Cristian Pattaro[44], Mathias Gorski[45], CKDGen Consortium†, Charles Kooperberg[46], George J. Papanicolaou[47], Jacques E. Rossouw[47], Jessica D. Faul[48], Sharon L.R. Kardia[5], Claude Bouchard[49], Leslie J. Raffel[50], André G. Uitterlinden[51,52], Oscar H. Franco[51], Ramachandran S. Vasan[1,53], Christopher J. O'Donnell[1,54,55,56], Kent D. Taylor[13], Kiang Liu[57], Erwin P. Bottinger[10], Omri Gottesman[10], E. Warwick Daw[4], Franco Giulianini[22], Santhi Ganesh[58,59], Elias Salfati[60], Tamara B. Harris[61], Lenore J. Launer[62], Marcus Dörr[11,63], Stephan B. Felix[11,63], Rainer Rettig[11,64], Henry Völzke[11,65,66], Eric Kim[13], Wen-Jane Lee[67], I-Te Lee[68,69,70], Wayne H-H Sheu[68,69,71,72], Krystal S. Tsosie[23], Digna R. Velez Edwards[23,73], Yongmei Liu[74], Adolfo Correa[75], David R. Weir[48], Uwe Völker[11,12], Paul M. Ridker[22,76], Eric Boerwinkle[9], Vilmundur Gudnason[24,31], Alexander P. Reiner[77], Cornelia M. van Duijn[27], Ingrid B. Borecki[4], Todd L. Edwards[23,78], Aravinda Chakravarti[60], Jerome I. Rotter[79], Bruce M. Psaty[6,77,80,81], Ruth J.F. Loos[10,82], Myriam Fornage[25], Georg Ehret[60,83#], Christopher Newton-Cheh[33,34,84#], Daniel Levy[1,3#@], Daniel I. Chasman[22,76#@]

Affiliations

[1]Framingham Heart Study, National Heart, Lung, and Blood Institue, Framingham, MA, USA.
[2]Department of Biostatistics, School of Public Health, Boston University, Boston, MA, USA.
[3]The Population Sciences Branch, National Heart, Lung, and Blood Institute, Bethesda, MD, USA.
[4]Division of Statistical Genomics, Department of Genetics & Center for Genome Sciences and Systems Biology, Washington University School of Medicine, St. Louis, MO, USA.
[5]Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, MI, USA.
[6]Cardiovascular Health Research Unit, Department of Medicine, University of Washington, Seattle, WA, USA.
[7]Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA.
[8]Department of Biostatistics, University of Washington, Seattle, WA, USA.
[9]Human Genetics Center, School of Public Health, University of Texas Health Science Center at Houston, Houston TX, USA.
[10]The Charles Bronfman Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA.
[11]DZHK (German Center for Cardiovascular Research), partner site Greifswald, Greifswald, Germany.
[12]Interfaculty Institute for Genetics and Functional Genomics, University Medicine and Ernst-Moritz-Arndt University Greifswald, Greifswald, Germany.
[13]Institute for Translational Genomics and Population Sciences, Los Angeles Biomedical Research Institute and Department of Pediatrics, Harbor-UCLA Medical Center, Torrance, CA, USA.
[14]Columbia University Medical Center, 622 West 168th Street, PH 9 East, 107, New York, NY, USA.
[15]George Washington University School of Medicine and Health Sciences, Washington DC, USA.
[16]Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK.
[17]Centre for Cardiovascular Genetics, Institute of Cardiovascular Science, Rayne Building University College London, London, WC1E 6JF, UK.

[18]MRC Integrative Epidemiology Unit, School of Social and Community Medicine, University of Bristol, Oakfield House, Oakfield Grove, Bristol BS8 2BN, UK.
[19]Department of Biostatistics, University of Liverpool, Liverpool, L69 3GA, UK.
[20]Department of Health Sciences, University of Leicester, Leicester, LE1 7RH, UK.
[21]Joseph J. Zilber School of Public Health, University of Wisconsin, Milwaukee, WI, USA.
[22]Division of Preventive Medicine, Brigham and Women's Hospital, Boston, MA, USA.
[23]Vanderbilt Epidemiology Center, Vanderbilt Genetics Institute, Institute for Medicine and Public Health, Vanderbilt University Medical Center, Nashville, TN, USA.
[24]Icelandic Heart Association, Kopavogur, Iceland.
[25]Institute of Molecular Medicine, University of Texas Health Science Center at Houston, Houston, TX, USA.
[26]Division of Public Health Sciences, Department of Biostatistical Sciences, Wake Forest School of Medicine, Winston-Salem, NC, USA.
[27]Genetic Epidemiology Unit, Department of Epidemiology, Erasmus Medical Center, 3015 CN Rotterdam, the Netherlands.
[28]Center of Biostatistics and Bioinformatics, University of Mississippi Medical Center, Jackson, MS, USA.
[29]The Bill and Melinda Gates Foundation, 500 Fifth Avenue North, Seattle, WA, USA.
[30]Department of Mathematics and Statistics, Boston University, MA, USA.
[31]Faculty of Medicine, University of Iceland, Reykjavik, Iceland.
[32]Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA, USA.
[33]Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA, USA.
[34]Program in Medical and Population Genetics, Broad Institute of Harvard and MIT, Boston, MA, USA.
[35]Division of Cardiology, Department of Medicine & Department of Genetics, Washington University School of Medicine, Saint Louis, MO, USA.
[36] Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA, USA.
[37]Department of Cardiovascular Sciences, University of Leicester, Leicester, LE3 9QP, UK.
[38]NIHR Leicester Cardiovascular Biomedical Research Unit, Glenfield Hospital, Leicester, LE3 9QP, UK.
[39]Deutsches Herzzentrum MŸnchen and Technische UniversitŠt Mÿnchen, München, Germany.
[40]Deutsches Zentrum fŸr Herz- und Kreislaufforschung (DZHK), Munich Heart Alliance; Lazarettstra§e 36, München, Germany.
[41]Princess Al-Jawhara Al-Brahim Centre of Excellence in Research of Hereditary Disorders (PACER-HD), King Abdulaziz University, Jeddah 21589, Saudi Arabia.
[42]William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK.
[43]Department of Epidemiology, Johns Hopkins University, Baltimore, MD, USA.
[44]Center for Biomedicine, European Academy of Bozen/Bolzano (EURAC), affiliated to the University of LŸbeck, Bolzano, Italy.
[45]Department of Genetic Epidemiology, Institute of Epidemiology and Preventive Medicine, University of Regensburg, Regensburg, Germany.
[46]Fred Hutchinson Cancer Research Center, Division of Public Health Sciences, Seattle, Washington, USA.
[47]Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute, Bethesda, MD, USA.
[48]Survey Research Center, Institute for Social Research, University of Michigan, Ann Arbor, MI, USA.
[49]Pennington Biomedical Research Center, Louisiana State University System, Baton Rouge, LA, USA.
[50]Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA.
[51]Department of Epidemiology, Erasmus MC, Rotterdam, the Netherlands.
[52]Department of Internal Medicine, Erasmus MC, Rotterdam, the Netherlands.
[53]Department of Preventive Medicine, Boston University School of Medicine, Boston, MA, USA.
[54]Cardiology Section, Department of Medicine, Boston Veteran's Administration Healthcare, Boston, MA, USA.
[55]Cardiovascular Division, Brigham and Women's Hospital, Boston, MA, USA.

[56]Department of Medicine, Harvard Medical School, Boston, MA, USA.
[57]Northwestern University School of Medicine, Chicago, IL, USA.
[58]Departments of Human Genetics, University of Michigan, Ann Arbor MI, USA.
[59]Departments of Internal Medicine, University of Michigan, Ann Arbor MI, USA.
[60]Center for Complex Disease Genomics, McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA.
[61]Laboratory of Epidemiology, Demography, and Biometry, National Institute on Aging, National Institutes of Health, Bethesda, MD, USA.
[62]Neuroepidemiology Section, National Institute on Aging, National Institutes of Health, Bethesda, MD, USA.
[63]Department of Internal Medicine B, University Medicine Greifswald, Greifswald, Germany.
[64]Institute of Physiology, University of Greifswald, Greifswald-Karlsburg, Germany.
[65]DZD (German Center for Diabetes Research), Site Greifswald, Germany.
[66]Institute for Community Medicine, University Medicine Greifswald, Site Greifswald, Germany.
[67]Department of Medical Research, Taichung Veterans General Hospital, Taichung, Taiwan.
[68]Division of Endocrinology and Metabolism, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan.
[69]School of Medicine, National Yang-Ming University, Taipei, Taiwan.
[70]School of Medicine, Chung Shan Medical University, Taichung, Taiwan.
[71]Institute of Medical Technology, National Chung-Hsing University, Taichung, Taiwan.
[72]School of Medicine, National Defense Medical Center, Taipei, Taiwan.
[73]Department of Obstetrics and Gynecology, Vanderbilt University Medical Center, Nashville, TN, USA.
[74]Epidemiology & Prevention Center for Genomics and Personalized Medicine Research, Wake Forest Baptist Medical Center, Medical Center Boulevard, Winston-Salem, NC, USA.
[75]Department of Medicine, University of Mississippi Medical Center, Jackson, MS, USA.
[76]Harvard Medical School, Boston MA, USA
[77]Department of Epidemiology, University of Washington, Seattle, WA, USA.
[78]Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA.
[79]Institute for Translational Genomics and Population Sciences, Los Angeles Biomedical Research Institute and Departments of Pediatrics and Medicine, Harbor-UCLA Medical Center, Torrance, CA, USA.
[80]Department of Health Services, University of Washington, Seattle, WA, USA.
[81]Group Health Research Institute, Group Health Cooperative, Seattle, WA, USA.
[82]The Mindich Child Health and Development Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA.
[83]Cardiology, Geneva University Hospitals, Rue Gabrielle-Perret-Gentil, 4,1211 Genève 14 Switzerland.
[84]Cardiovascular Research Center, Massachusetts General Hospital, Boston, MA, USA.

CHD Exome+ Consortium

Praveen Surendran[1], Robin Young[1], Daniel R. Barnes[1], James R. Staley[1], Daniel F. Freitag[1], Sune Fallgaard Nielsen[2], Asif Rasheed[3], Maria Samuel[3], Wei Zhao[4], Jukka Kontto[5], Markus Perola[5,6,7], Muriel Caslake[8], Anton JM. de Craen[9], Stella Trompet[9,10], Maria Uria-Nickelsen[11], Anders Malarstig[12], Dermot F. Reily[13], Maarten Hoek[14], Thomas Vogt[14,15], J Wouter. Jukema[11,16], Naveed Sattar[17], Ian Ford[8], Chris J. Packard[8], Dewan S. Alam[18], Abdulla al Shafi. Majumder[19], Emanuele Di Angelantonio[1,20], Rajiv Chowdhury[1], Philippe Amouyel[21,22,23,24], Dominique Arveiler[25], Stefan Blankenberg[26,27], Jean Ferrières[28], Frank Kee[29], Kari Kuulasmaa[5], Martina Müller-Nurasyid[30,31,32], Giovanni Veronesi[33], Jarmo Virtamo[5], EPIC-CVD Consortium, Philippe Frossard[3], Børge Grønne Nordestgaard[2], Danish Saleheen[4,3,1], John Danesh[1,35,20], Adam S. Butterworth[1,20], Joanna MM. Howson[1]

Affiliations

1. Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK
2. Department of Clinical Biochemistry Herlev Hospital, Copenhagen University Hospital, Herlev, Denmark
3. Centre for Non-Communicable Diseases, Karachi, Pakistan
4. Department of Biostatistics and Epidemiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA
5. Department of Health, National Institute for Health and Welfare, Helsinki, Finland
6. Institute of Molecular Medicine FIMM, University of Helsinki, Finland
7. Estonian Genome Center, University of Tartu, Tartu, Estonia
8. University of Glasgow, Glasgow, UK
9. Department of Gerontology and Geriatrics, Leiden University Medical Center, Leiden, The Netherlands
10. Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands
11. Development Management and Planning, Pfizer Worldwide Research and Development
12. Pfizer Worldwide Research and Development, Stockholm, Sweden
13. Genetics and Pharmacogenomics, Merck Research Laboratories, Boston, Massachusetts, USA.
14. Merck Research Laboratories, Kenilworth, New Jersey, USA
15. CHDI Management/CHDI Foundation, Princeton, New Jersey, USA
16. The Interuniversity Cardiology Institute of the Netherlands, Utrecht, The Netherlands
17. Institute of Cardiovascular and Medical Sciences, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, UK
18. ICDDR, B; Mohakhali, Dhaka, Bangladesh
19. National Institute of Cardiovascular Diseases, Sher-e-Bangla Nagar, Dhaka, Bangladesh
20. The National Institute for Health Research Blood and Transplant Research Unit in Donor Health and Genomics, University of Cambridge, Cambridge, UK
21. University of Lille, Risk Factors and Molecular Determinants of aging-related diseases, Lille, France
22. Inserm, Lille, France
23. Centre Hospitalier Universitaire Lille, Public Health, Lille, France
24. Institute Pasteur de Lille, Lille, France
25. Department of Epidemiology and Public Health, EA 3430, University of Strasbourg, Strasbourg, France
26. Department of General and Interventional Cardiology, University Heart Center Hamburg, Germany

27. University Medical Center Hamburg-Eppendorf, Hamburg, Germany
28. Department of Epidemiology, UMR 1027- INSERM, Toulouse University-CHU Toulouse, Toulouse, France
29. Director, UKCRC Centre of Excellence for Public Health, Queens University, Belfast, Northern Ireland
30. Institute of Genetic Epidemiology, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany
31. Department of Medicine I, University Hospital Grosshadern, Ludwig-Maximilians-Universität, Munich, Germany
32. DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany
33. Research Center in Epidemiology and Preventive Medicine, Department of Clinical and Experimental Medicine, University of Insubria, Varese, Italy
34. A full list of members and affiliations appears in the Supplementary Note
35. Wellcome Trust Sanger Institute, Hinxton, UK

Exome BP Consortium

Fotios Drenos [1,2], Helen Warren [3,4], James P Cook [5,6], Kate Witkowska [3,4], Vinicius Tragante [7], Hanieh Yaghootkar [8], Nicholas Masca [9,10], Teresa Ferreira [11], Olga Giannakopoulou [12], Andrew Tinker [12,4], Magdalena Harakalova [7], Evelin Mihailov [13], Lorraine Southam [11,14], Jonathan Marten [15], Cristiano Fava [16,17], Therese Ohlsson [16], Angela Matchan [14], Kathleen E Stirrups [12,18], Susan Shaw-Hawkins [3], Aki S Havulinna [19], He Zhang [20], Louise A Donnelly [21], Christopher J Groves [22], N William Rayner [22,11,14], Matt J Neville [22,23], Neil R Robertson [11,22], Andrianos M Yiorkas [24,25], Karl-Heinz Herzig [26,27], Eero Kajantie [19,28,29], Weihua Zhang [30,31], Lars Lannfelt [32], Giovanni Malerba [33], Nicole Soranzo [34,18,35], Elisabetta Trabetti [33], Niek Verweij [36,38,37], Evangelos Evangelou [30,39], Alireza Moayyeri [30,40], Anne-Claire Vergnaud [30], Christopher P Nelson [9,10], Alaitz Poveda [41,42], Tibor V Varga [41], Jian'an Luan [43], Robert A Scott [43], Sarah E Harris [44,45], David CM Liewald [44,46], Riccardo Marioni [44,45,47], Cristina Menni [48], Aliki-Eleni Farmaki [49], Göran Hallmans [50], Frida Renström [41,50], Jennifer E Huffman [15,23], Ozren Polasek [51,52], Igor Rudan [51], Paul W Franks [41,53,54], George Dedoussis [49], Timothy D Spector [48], Ian J Deary [44,46], John M Starr [44,55], Nick J Wareham [43], Morris J Brown [12], Anna F Dominiczak [56], John M Connell [21], Tõnu Esko [13,57, 38], Reedik Mägi [13], Andres Metspalu [13,58], Rudolf A de Boer [59], Peter van der Meer [59], Pim van der Harst [59,60,61], Giovanni Gambaro [62], Erik Ingelsson [63,64], Lars Lind [63], Paul IW de Bakker [65,66], Mattijs E Numans [67,66], John C Chambers [30,31,68], Jaspal S Kooner [31,68,69] Alexandra IF Blakemore [24,25], Steve Franks [70], Marjo-Riitta Jarvelin [71,72,73,74], Fredrik Karpe [22,23], Jaakko Tuomilehto [19,75,76,77], Alex SF Doney [21], Andrew D Morris [78], Colin Palmer [21], Oddgeir Lingaas Holmen [79,80], Kristian Hveem [79,81], Cristen J Willer [20,82,83], Aarno Palotie [38,84,85], Samuli Ripatti [84,86,14], Veikko Salomaa [19], Mark I McCarthy [22,23,11], Neil Poulter [87], Alice V Stanton [88], Peter Sever [87], Panos Deloukas [12,89], Paul Elliott [71], Eleftheria Zeggini [14], Sekar Kathiresan [37,91,90,38], Olle Melander [16], Sandosh Padmanabhan [56], David Porteous [45], Caroline Hayward [15], Martin D Tobin [5], Mark J Caulfield [3,4], Anubha Mahajan [11], Andrew P Morris [11,6], Maciej Tomaszewski [9,10,92], Nilesh J Samani [9,10], Folkert W Asselbergs [7,61,93], Cecilia M Lindgren [94,38,11], Louise V Wain [5], Patricia B Munroe [3,4]

Affiliations

1. Medical Research Council Integrative Epidemiology Unit, School of Social and Community Medicine, University of Bristol, Oakfield House, Oakfield Grove, Bristol, UK
2. Centre for Cardiovascular Genetics, Institute of Cardiovascular Science, Rayne Building University College London, London, UK
3. Clinical Pharmacology, William Harvey Research Institute, Queen Mary University of London, London, UK
4. National Institute for Health Research Barts Cardiovascular Biomedical Research Unit, Queen Mary University of London, London, UK
5. Department of Health Sciences, University of Leicester, Leicester, UK
6. Department of Biostatistics, University of Liverpool, Liverpool, UK
and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
7. Department of Cardiology, University Medical Center Utrecht, Utrecht, The Netherlands
8. Genetics of Complex Traits, Institute of Biomedical and Clinical Science, University of Exeter Medical School, Exeter, UK
9. Department of Cardiovascular Sciences, University of Leicester, Leicester, UK
10. National Institute for Health Research Leicester Biomedical Research Unit in Cardiovascular Disease, Leicester, UK
11. Wellcome Trust Centre for Human Genetics, Nuffield Department of Medicine, University of Oxford, Oxford, UK
12. Heart Centre, William Harvey Research Institute, Barts and The London School of Medicine and

Dentistry, Queen Mary University of London, London, UK
13. Estonian Genome Center, University of Tartu, Tartu, Estonia
14. Wellcome Trust Sanger Institute, Genome Campus, Hinxton, UK
15. Medical Research Council Human Genetics Unit, Medical Research Council Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK
16. University of Lund, Department of Clinical Sciences, Malmö, Sweden
17. University of Verona, Department of Medicine, Verona, Italy
18. Department of Haematology, University of Cambridge, Cambridge, UK
19. Department of Health, National Institute for Health and Welfare, Helsinki, Finland
20. Department of Internal Medicine, Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, Michigan, USA
21. Medical Research Institute, University of Dundee, Ninewells Hospital and Medical School, Dundee, UK
22. Oxford Centre for Diabetes, Endocrinology, and Metabolism, Radcliffe Department of Medicine, University of Oxford, Oxford, UK
23. National Institute for Health Research Oxford Biomedical Research Centre, Oxford University Hospital Trusts, Oxford, UK
24. Section of Investigative Medicine, Imperial College London, London, UK
25. Department of Life Sciences, Brunel University London, London, UK
26. Institute of Biomedicine, Biocenter Oulu, University of Oulu, Oulu, Finland
27. Department of Gastroenterology and Metabolism, Poznan University of Medical Sciences, Poznan, Poland
28. Hospital for Children and Adolescents, Helsinki University Central Hospital and University of Helsinki, Helsinki, Finland
29. Department of Obstetrics and Gynaecology, Oulu University Hospital and University of Oulu, Oulu, Finland
30. Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, UK
31. Department of Cardiology, Ealing Hospital, Middlesex, UK
32. Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden
33. Section of Biology and Genetics, Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Italy
34. Human Genetics, Wellcome Trust Sanger Institute, Hinxton, UK
35. The National Institute for Health Research Blood and Transplant Research Unit in Donor Health and Genomics, University of Cambridge, Cambridge, UK
36. University Medical Center Groningen, University of Groningen, Department of Cardiology, The Netherlands
37. Center for Human Genetic Research, Massachusetts General Hospital, Boston, Massachusetts, USA
38. Program in Medical and Population Genetics, Broad Institute, 7 Cambridge Center, Cambridge, Massachusetts, USA
39. Department of Hygiene and Epidemiology, University of Ioannina Medical School, Ioannina, Greece
40. Farr Institute of Health Informatics Research, Institute of Health Informatics, University College London, London, UK
41. Department of Clinical Sciences, Genetic and Molecular Epidemiology Unit, Lund University, Malmö, Sweden
42. Department of Genetics, Physical Anthropology and Animal Physiology, Faculty of Science and

Technology, University of the Basque Country (UPV/EHU), Bilbao, Spain
43. Medical Research Council Epidemiology Unit, University of Cambridge School of Clinical Medicine, Box 285 Institute of Metabolic Science, Cambridge Biomedical Campus, Cambridge, UK
44. Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK
45. Centre for Genomic and Experimental Medicine, Medical Research Council Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK
46. Department of Psychology, University of Edinburgh, Edinburgh, UK
47. Queensland Brain Institute, The University of Queensland, Brisbane, Queensland, Australia
48. Department of Twin Research and Genetic Epidemiology, King's College London, UK
49. Department of Nutrition and Dietetics, School of Health Science and Education, Harokopio University, Athens, Greece
50. Department of Biobank Research, Umeå University, Umeå, Sweden
51. Centre for Global Health Research, Usher Institute for Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, UK
52. Faculty of Medicine, University of Split, Croatia
53. Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden
54. Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts, USA
55. Alzheimer Scotland Research Centre, University of Edinburgh, Edinburgh, UK
56. Institute of Cardiovascular and Medical Sciences, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, UK
57. Division of Endocrinology, Boston Children's Hospital, Boston, Massachusetts, USA
58. Institute of Molecular and Cell Biology, Tartu, Estonia
59. Department of Cardiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
60. Department of Genetics, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
61. Durrer Center for Cardiogenetic Research, ICIN-Netherlands Heart Institute, Utrecht, The Netherlands
62. Division of Nephrology, Department of Internal Medicine and Medical Specialties, Columbus - Gemelli University Hospital, Catholic University, Rome, Italy
63. Department of Medical Sciences, Molecular Epidemiology and Science for Life Laboratory, Uppsala University, Uppsala, Sweden
64. Department of Medicine, Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, California, USA
65. Department of Medical Genetics, Center for Molecular Medicine, University Medical Center Utrecht, Utrecht, The Netherlands
66. Department of Epidemiology, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands
67. Department of Public Health and Primary Care, Leiden University Medical Center, Leiden, The Netherlands
68. Imperial College Healthcare NHS Trust, London, UK
69. National Heart and Lung Institute, Imperial College London, London, UK
70. Institute of Reproductive and Developmental Biology, Imperial College London, London, UK
71. Department of Epidemiology and Biostatistics, Medical Research Council Public Health England Centre for Environment and Health, School of Public Health, Faculty of Medicine, Imperial College London, St. Mary's Campus, London, UK

72. Centre for Life Course Epidemiology, Faculty of Medicine, University of Oulu, Oulu, Finland
73. Biocenter Oulu, University of Oulu, Oulu, Finland
74. Unit of Primary Care, Oulu University Hospital, Oulu, Finland
75. Dasman Diabetes Institute, Dasman, Kuwait
76. Centre for Vascular Prevention, Danube-University Krems, Krems, Austria
77. King Abdulaziz University, Jeddah, Saudi Arabia
78. School of Molecular, Genetic and Population Health Sciences, University of Edinburgh, Medical School, Teviot Place, Edinburgh, UK
79. HUNT Research Centre, Department of Public Health and General Practice, Norwegian University of Science and Technology, Levanger, Norway
80. St. Olav Hospital, Trondheim University Hospital, Trondheim, Norway
81. Department of Medicine, Levanger Hospital, Nord- Trøndelag Health Trust, Levanger, Norway
82. Department of Computational Medicine and Bioinformatics, University of Michigan, Ann Arbor, Michigan, USA
83. Department of Human Genetics, University of Michigan, Ann Arbor, Michigan, USA
84. Institute for Molecular Medicine Finland University of Helsinki, Helsinki, Finland
85. Psychiatric and Neurodevelopmental Genetics Unit, Department of Psychiatry, Massachusetts General Hospital, Boston, Massachusetts, USA
86. Department of Public Health, University of Helsinki, Finland
87. International Centre for Circulatory Health, Imperial College London, UK
88. Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland, Dublin, Ireland
89. Princess Al-Jawhara Al-Brahim Centre of Excellence in Research of Hereditary Disorders (PACER-HD), King Abdulaziz University, Jeddah, Saudi Arabia
90. Cardiovascular Research Center, Massachusetts General Hospital, Boston, Massachusetts, USA
91. Department of Medicine, Harvard Medical School, Boston, Massachusetts, USA
92. Institute of Cardiovascular Sciences, University of Manchester, Manchester, UK
93. Faculty of Population Health Sciences, Institute of Cardiovascular Science, University College London, London, UK
94. The Big Data Institute at the Li Ka Shing Centre for Health Information and Discovery, University of Oxford, Oxford, UK

The Genetics of Type 2 Diabetes (GoT2D) and Type 2 Diabetes Genetic Exploration by Next-generation sequencing in multi-Ethnic Samples

(T2D-GENES) Consortia (http://type2diabetesgenetics.org)

Christian Fuchsberger[1], Jason Flannick[2,3], Tanya M Teslovich[1], Anubha Mahajan[4], Vineeta Agarwala[2,5], Kyle J Gaulton[4], Clement Ma[1], Pierre Fontanillas[2], Loukas Moutsianas[4], Davis J McCarthy[4,6], Manuel A Rivas[4], John R B Perry[4,7,8,9], Xueling Sim[1], Thomas W Blackwell[1], Neil R Robertson[4,10], N William Rayner[4,10,11], Pablo Cingolani[12,13], Adam E Locke[1], Juan Fernandez Tajes[4], Heather M Highland[14], Josee Dupuis[15,16], Peter S Chines[17], Cecilia M Lindgren[2,4], Christopher Hartl[2], Anne U Jackson[1], Han Chen[15,18], Jeroen R Huyghe[1], Martijn van de Bunt[4,10], Richard D Pearson[4], Ashish Kumar[4,19], Martina Müller-Nurasyid[20,21,22,23], Niels Grarup[24], Heather M Stringham[1], Eric R Gamazon[25], Jaehoon Lee[26], Yuhui Chen[4], Robert A Scott[8], Jennifer E Below[27], Peng Chen[28], Jinyan Huang[29], Min Jin Go[30], Michael L Stitzel[31], Dorota Pasko[7], Stephen C J Parker[32], Tibor V Varga[33], Todd Green[2], Nicola L Beer[10], Aaron G Day-Williams[11], Teresa Ferreira[4], Tasha Fingerlin[34], Momoko Horikoshi[4,10], Cheng Hu[35], Iksoo Huh[26], Mohammad Kamran Ikram[36,37,38], Bong-Jo Kim[30], Yongkang Kim[26], Young Jin Kim[30], Min-Seok Kwon[39], Juyoung Lee[30], Selyeong Lee[26], Keng-Han Lin[1], Taylor J Maxwell[27], Yoshihiko Nagai[13,40,41], Xu Wang[28], Ryan P Welch[1], Joon Yoon[39], Weihua Zhang[42,43], Nir Barzilai[44], Benjamin F Voight[45,46], Bok-Ghee Han[30], Christopher P Jenkinson[47,48], Teemu Kuulasmaa[49], Johanna Kuusisto[49,50], Alisa Manning[2], Maggie C Y Ng[51,52], Nicholette D Palmer[51,52,53], Beverley Balkau[54], Alena Stančáková[49], Hanna E Abboud[47]‡, Heiner Boeing[55], Vilmantas Giedraitis[56], Dorairaj Prabhakaran[57], Omri Gottesman[58], James Scott[59], Jason Carey[2], Phoenix Kwan[1], George Grant[2], Joshua D Smith[60], Benjamin M Neale[2,61,62], Shaun Purcell[2,62,63], Adam S Butterworth[64], Joanna M M Howson[64], Heung Man Lee[65], Yingchang Lu[58], Soo-Heon Kwak[66], Wei Zhao[67], John Danesh[11,64,68], Vincent K L Lam[65], Kyong Soo Park[66,69], Danish Saleheen[70,71], Wing Yee So[65], Claudia H T Tam[65], Uzma Afzal[42], David Aguilar[72], Rector Arya[73], Tin Aung[36,37,38], Edmund Chan[74], Carmen Navarro[75,76,77], Ching-Yu Cheng[28,36,37,38], Domenico Palli[78], Adolfo Correa[79], Joanne E Curran[80], Denis Rybin[15], Vidya S Farook[81], Sharon P Fowler[47], Barry I Freedman[82], Michael Griswold[83], Daniel Esten Hale[73], Pamela J Hicks[51,52,53], Chiea-Chuen Khor[28,36,37,84,85], Satish Kumar[80], Benjamin Lehne[42], Dorothée Thuillier[86], Wei Yen Lim[28], Jianjun Liu[28,85], Yvonne T van der Schouw[87], Marie Loh[42,88,89], Solomon K Musani[90], Sobha Puppala[81], William R Scott[42], Loïc Yengo[86], Sian-Tsung Tan[43,59], Herman A Taylor Jr[79], Farook Thameem[47], Gregory Wilson Sr[91], Tien Yin Wong[36,37,38], Pål Rasmus Njølstad[92,93], Jonathan C Levy[10], Massimo Mangino[9], Lori L Bonnycastle[17], Thomas Schwarzmayr[94], João Fadista[95], Gabriela L Surdulescu[9], Christian Herder[96,97], Christopher J Groves[10], Thomas Wieland[94], Jette Bork-Jensen[24], Ivan Brandslund[98,99], Cramer Christensen[100], Heikki A Koistinen[101,102,103,104], Alex S F Doney[105], Leena Kinnunen[101], Tõnu Esko[2,106,107,108], Andrew J Farmer[109], Liisa Hakaste[102,110,111], Dylan Hodgkiss[9], Jasmina Kravic[95], Valeriya Lyssenko[95], Mette Hollensted[24], Marit E Jørgensen[112], Torben Jørgensen[113,114,115], Claes Ladenvall[95], Johanne Marie Justesen[24], Annemari Käräjämäki[116,117], Jennifer Kriebel[97,118,119], Wolfgang Rathmann[120], Lars Lannfelt[56], Torsten Lauritzen[121], Narisu Narisu[17], Allan Linneberg[113,122,123], Olle Melander[124], Lili Milani[106], Matt Neville[10,125], Marju Orho-Melander[126], Lu Qi[127,128], Qibin Qi[127,129], Michael Roden[96,97,130], Olov Rolandsson[131], Amy Swift[17], Anders H Rosengren[95], Kathleen Stirrups[11], Andrew R Wood[7], Evelin Mihailov[106], Christine Blancher[132], Mauricio O Carneiro[2], Jared Maguire[2], Ryan Poplin[2], Khalid Shakir[2], Timothy Fennell[2], Mark DePristo[2], Martin Hrabé de Angelis[97,133,134], Panos Deloukas[135,136], Anette P Gjesing[24], Goo Jun[1,27], Peter Nilsson[137], Jacquelyn Murphy[2], Robert Onofrio[2], Barbara Thorand[97,118], Torben Hansen[24,138], Christa Meisinger[97,118], Frank B Hu[29,127], Bo Isomaa[110,139], Fredrik Karpe[10,125], Liming Liang[18,29], Annette Peters[23,97,118], Cornelia Huth[97,118], Stephen P O'Rahilly[140], Colin N A Palmer[141], Oluf

Pedersen[24], Rainer Rauramaa[142], Jaakko Tuomilehto[101,143,144,145,146], Veikko Salomaa[146], Richard M Watanabe[147,148,149], Ann-Christine Syvänen[150], Richard N Bergman[151], Dwaipayan Bharadwaj[152], Erwin P Bottinger[58], Yoon Shin Cho[153], Giriraj R Chandak[154], Juliana C N Chan[65,155,156], Kee Seng Chia[28], Mark J Daly[61], Shah B Ebrahim[57], Claudia Langenberg[8], Paul Elliott[42,157], Kathleen A Jablonski[158], Donna M Lehman[47], Weiping Jia[35], Ronald C W Ma[65,155,156], Toni I Pollin[159], Manjinder Sandhu[11,64], Nikhil Tandon[160], Philippe Froguel[86,161], Inês Barroso[11,140], Yik Ying Teo[28,162,163], Eleftheria Zeggini[11], Ruth J F Loos[58], Kerrin S Small[9], Janina S Ried[20], Ralph A DeFronzo[47], Harald Grallert[97,118,119], Benjamin Glaser[164], Andres Metspalu[106], Nicholas J Wareham[8], Mark Walker[165], Eric Banks[2], Christian Gieger[20,118,119], Erik Ingelsson[4,166], Hae Kyung Im[25], Thomas Illig[119,167,168], Paul W Franks[33,127,131], Gemma Buck[132], Joseph Trakalo[132], David Buck[132], Inga Prokopenko[4,10,161], Reedik Mägi[106], Lars Lind[169], Yossi Farjoun[170], Katharine R Owen[10,125], Anna L Gloyn[4,10,125], Konstantin Strauch[20,22], Tiinamaija Tuomi[102,110,111,171], Jaspal Singh Kooner[43,59,172], Jong-Young Lee[30], Taesung Park[26,39], Peter Donnelly[4,6], Andrew D Morris[173,174], Andrew T Hattersley[175], Donald W Bowden[51,52,53], Francis S Collins[17], Gil Atzmon[44,176], John C Chambers[42,43,172], Timothy D Spector[9], Markku Laakso[49,50], Tim M Strom[94,177], Graeme I Bell[178], John Blangero[80], Ravindranath Duggirala[81], E Shyong Tai[28,74,179], Gilean McVean[4,180], Craig L Hanis[27], James G Wilson[181], Mark Seielstad[182,183], Timothy M Frayling[7], James B Meigs[184], Nancy J Cox[25], Rob Sladek[13,40,185], Eric S Lander[186], Stacey Gabriel[2], Noël P Burtt[2], Karen L Mohlke[187], Thomas Meitinger[94,177], Leif Groop[95,171], Goncalo Abecasis[1], Jose C Florez[2,62,188,189], Laura J Scott[1], Andrew P Morris[4,106,190], Hyun Min Kang[1], Michael Boehnke[1], David Altshuler[2,3,107,188,189,191], Mark I McCarthy[4,10,125]

Affiliations

1. Department of Biostatistics and Center for Statistical Genetics, University of Michigan, Ann Arbor, Michigan, USA.
2. Program in Medical and Population Genetics, Broad Institute, Cambridge, Massachusetts, USA.
3. Department of Molecular Biology, Massachusetts General Hospital, Boston, Massachusetts, USA.
4. Wellcome Trust Centre for Human Genetics, Nuffield Department of Medicine, University of Oxford, Oxford, UK.
5. Harvard-MIT Division of Health Sciences and Technology, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA.
6. Department of Statistics, University of Oxford, Oxford, UK.
7. Genetics of Complex Traits, University of Exeter Medical School, University of Exeter, Exeter, UK.
8. MRC Epidemiology Unit, Institute of Metabolic Science, University of Cambridge, Cambridge, UK.
9. Department of Twin Research and Genetic Epidemiology, King's College London, London, UK.
10. Oxford Centre for Diabetes, Endocrinology and Metabolism, Radcliffe Department of Medicine, University of Oxford, Oxford, UK.
11. Department of Human Genetics, Wellcome Trust Sanger Institute, Hinxton, Cambridgeshire, UK.
12. School of Computer Science, McGill University, Montreal, Quebec, Canada.
13. McGill University and Génome Québec Innovation Centre, Montreal, Quebec, Canada.
14. Human Genetics Center, The University of Texas Graduate School of Biomedical Sciences at Houston, The University of Texas Health Science Center at Houston, Houston, Texas, USA.
15. Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts, USA.
16. National Heart, Lung, and Blood Institute's Framingham Heart Study, Framingham, Massachusetts, USA.

17. Medical Genomics and Metabolic Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland, USA.
18. Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts, USA.
19. Chronic Disease Epidemiology, Swiss Tropical and Public Health Institute, University of Basel, Basel, Switzerland.
20. Institute of Genetic Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany.
21. Department of Medicine I, University Hospital Grosshadern, Ludwig-Maximilians-Universität, Munich, Germany.
22. Institute of Medical Informatics, Biometry and Epidemiology, Chair of Genetic Epidemiology, Ludwig-Maximilians-Universität, Munich, Germany.
23. DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany.
24. The Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.
25. Department of Medicine, Section of Genetic Medicine, The University of Chicago, Chicago, Illinois, USA.
26. Department of Statistics, Seoul National University, Seoul, Republic of Korea.
27. Human Genetics Center, School of Public Health, The University of Texas Health Science Center at Houston, Houston, Texas, USA.
28. Saw Swee Hock School of Public Health, National University of Singapore, National University Health System, Singapore.
29. Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts, USA.
30. Center for Genome Science, Korea National Institute of Health, Chungcheongbuk-do, Republic of Korea.
31. The Jackson Laboratory for Genomic Medicine, Farmington, Connecticut, USA.
32. Departments of Computational Medicine & Bioinformatics and Human Genetics, University of Michigan, Ann Arbor, Michigan, USA.
33. Department of Clinical Sciences, Lund University Diabetes Centre, Genetic and Molecular Epidemiology Unit, Lund University, Malmö, Sweden.
34. Department of Epidemiology, Colorado School of Public Health, University of Colorado, Aurora, Colorado, USA.
35. Department of Endocrinology and Metabolism, Shanghai Diabetes Institute, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China.
36. Singapore Eye Research Institute, Singapore National Eye Centre, Singapore.
37. Department of Ophthalmology, Yong Loo Lin School of Medicine, National University of Singapore, National University Health System, Singapore.
38. The Eye Academic Clinical Programme, Duke-NUS Graduate Medical School, Singapore.
39. Interdisciplinary Program in Bioinformatics, Seoul National University, Seoul, Republic of Korea.
40. Department of Human Genetics, McGill University, Montreal, Quebec, Canada.
41. Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada.
42. Department of Epidemiology and Biostatistics, Imperial College London, London, UK.
43. Department of Cardiology, Ealing Hospital NHS Trust, Southall, Middlesex, UK.
44. Departments of Medicine and Genetics, Albert Einstein College of Medicine, New York, USA.
45. Department of Systems Pharmacology and Translational Therapeutics, University of Pennsylvania - Perelman School of Medicine, Philadelphia, Pennsylvania, USA.

46. Department of Genetics, University of Pennsylvania - Perelman School of Medicine, Philadelphia, Pennsylvania, USA.
47. Department of Medicine, University of Texas Health Science Center, San Antonio, Texas, USA.
48. Research, South Texas Veterans Health Care System, San Antonio, Texas, USA.
49. Faculty of Health Sciences, Institute of Clinical Medicine, Internal Medicine, University of Eastern Finland, Kuopio, Finland.
50. Kuopio University Hospital, Kuopio, Finland.
51. Center for Genomics and Personalized Medicine Research, Wake Forest School of Medicine, Winston-Salem, North Carolina, USA.
52. Center for Diabetes Research, Wake Forest School of Medicine, Winston-Salem, North Carolina, USA.
53. Department of Biochemistry, Wake Forest School of Medicine, Winston-Salem, North Carolina, USA.
54. Centre for Research in Epidemiology and Population Health, Inserm U1018, Villejuif, France.
55. German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany.
56. Department of Public Health and Caring Sciences, Geriatrics, Uppsala University, Uppsala, Sweden.
57. Centre for Chronic Disease Control, New Delhi, India.
58. The Charles Bronfman Institute for Personalized Medicine, The Icahn School of Medicine at Mount Sinai, New York, USA.
59. National Heart and Lung Institute, Cardiovascular Sciences, Hammersmith Campus, Imperial College London, London, UK.
60. Department of Genome Sciences, University of Washington School of Medicine, Seattle, Washington, USA.
61. Analytic and Translational Genetics Unit, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA.
62. Center for Human Genetic Research, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA.
63. Department of Psychiatry, Icahn Institute for Genomics and Multiscale Biology, Icahn School of Medicine at Mount Sinai, New York, USA.
64. Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK.
65. Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong, China.
66. Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea.
67. Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA.
68. NIHR Blood and Transplant Research Unit in Donor Health and Genomics, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK.
69. Department of Molecular Medicine and Biopharmaceutical Sciences, Graduate School of Convergence Science and Technology, and College of Medicine, Seoul National University, Seoul, Republic of Korea.
70. Department of Biostatistics and Epidemiology, University of Pennsylvania, Philadelphia, Pennsylvania, USA.
71. Center for Non-Communicable Diseases, Karachi, Pakistan.
72. Cardiovascular Division, Baylor College of Medicine, Houston, Texas, USA.
73. Department of Pediatrics, University of Texas Health Science Center, San Antonio, Texas, USA.

74. Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, National University Health System, Singapore.
75. Department of Epidemiology, Murcia Regional Health Council, IMIB-Arrixaca, Murcia, Spain.
76. CIBER Epidemiología y Salud Pública (CIBERESP), Spain.
77. Unit of Preventive Medicine and Public Health, School of Medicine, University of Murcia, Spain.
78. Cancer Research and Prevention Institute (ISPO), Florence, Italy.
79. Department of Medicine, University of Mississippi Medical Center, Jackson, Mississippi, USA.
80. South Texas Diabetes and Obesity Institute, Regional Academic Health Center, University of Texas Rio Grande Valley, Brownsville, Texas, USA.
81. Department of Genetics, Texas Biomedical Research Institute, San Antonio, Texas, USA.
82. Department of Internal Medicine, Section on Nephrology, Wake Forest School of Medicine, Winston-Salem, North Carolina, USA.
83. Center of Biostatistics and Bioinformatics, University of Mississippi Medical Center, Jackson, Mississippi, USA.
84. Department of Pediatrics, Yong Loo Lin School of Medicine, National University of Singapore, National University Health System, Singapore.
85. Division of Human Genetics, Genome Institute of Singapore, A*STAR, Singapore.
86. CNRS-UMR8199, Lille University, Lille Pasteur Institute, Lille, France.
87. Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands.
88. Institute of Health Sciences, University of Oulu, Oulu, Finland.
89. Translational Laboratory in Genetic Medicine (TLGM), Agency for Science, Technology and Research (A*STAR), Singapore, Singapore.
90. Jackson Heart Study, University of Mississippi Medical Center, Jackson, Mississippi, USA.
91. College of Public Services, Jackson State University, Jackson, Mississippi, USA.
92. KG Jebsen Center for Diabetes Research, Department of Clinical Science, University of Bergen, Bergen, Norway.
93. Department of Pediatrics, Haukeland University Hospital, Bergen, Norway.
94. Institute of Human Genetics, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany.
95. Department of Clinical Sciences, Diabetes and Endocrinology, Lund University Diabetes Centre, Malmö, Sweden.
96. Institute of Clinical Diabetology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University, Düsseldorf, Germany.
97. German Center for Diabetes Research (DZD), Neuherberg, Germany.
98. Institute of Regional Health Research, University of Southern Denmark, Odense, Denmark.
99. Department of Clinical Biochemistry, Vejle Hospital, Vejle, Denmark.
100. Department of Internal Medicine and Endocrinology, Vejle Hospital, Vejle, Denmark.
101. Department of Health, National Institute for Health and Welfare, Helsinki, Finland.
102. Abdominal Center: Endocrinology, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland.
103. Minerva Foundation Institute for Medical Research, Helsinki, Finland.
104. Department of Medicine, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland.
105. Division of Cardiovascular and Diabetes Medicine, Medical Research Institute, Ninewells Hospital and Medical School, Dundee, UK.

106. Estonian Genome Center, University of Tartu, Tartu, Estonia.
107. Department of Genetics, Harvard Medical School, Boston, Massachusetts, USA.
108. Division of Endocrinology, Boston Children's Hospital, Boston, Massachusetts, USA.
109. Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK.
110. Folkhälsan Research Centre, Helsinki, Finland.
111. Research Programs Unit, Diabetes and Obesity, University of Helsinki, Helsinki, Finland.
112. Steno Diabetes Center, Gentofte, Denmark.
113. Research Centre for Prevention and Health, Capital Region of Denmark, Glostrup, Denmark.
114. Department of Public Health, Institute of Health Sciences, University of Copenhagen, Copenhagen, Denmark.
115. Faculty of Medicine, Aalborg University, Aalborg, Denmark.
116. Department of Primary Health Care, Vaasa Central Hospital, Vaasa, Finland.
117. Diabetes Center, Vaasa Health Care Center, Vaasa, Finland.
118. Institute of Epidemiology II, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany.
119. Research Unit of Molecular Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany.
120. Institute for Biometrics and Epidemiology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University, Düsseldorf, Germany.
121. Department of Public Health, Section of General Practice, Aarhus University, Aarhus, Denmark.
122. Department of Clinical Experimental Research, Rigshospitalet, Glostrup, Denmark.
123. Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.
124. Department of Clinical Sciences, Hypertension and Cardiovascular Disease, Lund University, Malmö, Sweden.
125. Oxford NIHR Biomedical Research Centre, Oxford University Hospitals Trust, Oxford, UK.
126. Department of Clinical Sciences, Diabetes and Cardiovascular Disease, Genetic Epidemiology, Lund University, Malmö, Sweden.
127. Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts, USA.
128. Channing Division of Network Medicine, Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston, Massachusetts, USA.
129. Department of Epidemiology and Population Health, Albert Einstein College of Medicine, New York, USA.
130. Department of Endocrinology and Diabetology, Medical Faculty, Heinrich-Heine University, Düsseldorf, Germany.
131. Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden.
132. High Throughput Genomics, Oxford Genomics Centre, Wellcome Trust Centre for Human Genetics, Nuffield Department of Medicine, University of Oxford, Oxford, UK.
133. Institute of Experimental Genetics, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany.
134. Center of Life and Food Sciences Weihenstephan, Technische Universität München, Freising-Weihenstephan, Germany.
135. William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK.
136. Princess Al-Jawhara Al-Brahim Centre of Excellence in Research of Hereditary Disorders (PACER-HD), King Abdulaziz University, Jeddah, Saudi Arabia.

137. Department of Clinical Sciences, Medicine, Lund University, Malmö, Sweden.
138. Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark.
139. Department of Social Services and Health Care, Jakobstad, Finland.
140. Metabolic Research Laboratories, Institute of Metabolic Science, University of Cambridge, Cambridge, UK.
141. Pat Macpherson Centre for Pharmacogenetics and Pharmacogenomics, Ninewells Hospital and Medical School, University of Dundee, Dundee, UK.
142. Foundation for Research in Health, Exercise and Nutrition, Kuopio Research Institute of Exercise Medicine, Kuopio, Finland.
143. Center for Vascular Prevention, Danube University Krems, Krems, Austria.
144. Diabetes Research Group, King Abdulaziz University, Jeddah, Saudi Arabia.
145. Instituto de Investigacion Sanitaria del Hospital Universario LaPaz (IdiPAZ), University Hospital LaPaz, Autonomous University of Madrid, Madrid, Spain.
146. National Institute for Health and Welfare, Helsinki, Finland.
147. Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California, USA.
148. Department of Physiology & Biophysics, Keck School of Medicine, University of Southern California, Los Angeles, California, USA.
149. Diabetes and Obesity Research Institute, Keck School of Medicine, University of Southern California, Los Angeles, California, USA.
150. Department of Medical Sciences, Molecular Medicine and Science for Life Laboratory, Uppsala University, Uppsala, Sweden.
151. Cedars-Sinai Diabetes and Obesity Research Institute, Los Angeles, California, USA.
152. Functional Genomics Unit, CSIR-Institute of Genomics & Integrative Biology (CSIR-IGIB), New Delhi, India.
153. Department of Biomedical Science, Hallym University, Chuncheon, Republic of Korea.
154. CSIR-Centre for Cellular and Molecular Biology, Hyderabad, Telangana, India.
155. Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong, Hong Kong, China.
156. Hong Kong Institute of Diabetes and Obesity, The Chinese University of Hong Kong, Hong Kong, China.
157. MRC-PHE Centre for Environment and Health, Imperial College London, London, UK.
158. The Biostatistics Center, The George Washington University, Rockville, Maryland, USA.
159. Department of Medicine, Division of Endocrinology, Diabetes and Nutrition, and Program in Personalized and Genomic Medicine, University of Maryland School of Medicine, Baltimore, Maryland, USA.
160. Department of Endocrinology and Metabolism, All India Institute of Medical Sciences, New Delhi, India.
161. Department of Genomics of Common Disease, School of Public Health, Imperial College London, London, UK.
162. Life Sciences Institute, National University of Singapore, Singapore.
163. Department of Statistics and Applied Probability, National University of Singapore, Singapore.
164. Endocrinology and Metabolism Service, Hadassah-Hebrew University Medical Center, Jerusalem, Israel.
165. The Medical School, Institute of Cellular Medicine, Newcastle University, Newcastle, UK.
166. Department of Medical Sciences, Molecular Epidemiology and Science for Life Laboratory, Uppsala University, Uppsala, Sweden.

167. Hannover Unified Biobank, Hannover Medical School, Hanover, Germany.
168. Institute for Human Genetics, Hannover Medical School, Hanover, Germany.
169. Department of Medical Sciences, Uppsala University, Uppsala, Sweden.
170. Data Sciences and Data Engineering, Broad Institute, Cambridge, Massachusetts, USA.
171. Institute for Molecular Medicine Finland (FIMM), University of Helsinki, Helsinki, Finland.
172. Imperial College Healthcare NHS Trust, Imperial College London, London, UK.
173. Clinical Research Centre, Centre for Molecular Medicine, Ninewells Hospital and Medical School, Dundee, UK.
174. The Usher Institute to the Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, UK.
175. University of Exeter Medical School, University of Exeter, Exeter, UK.
176. Department of Natural Science, University of Haifa, Haifa, Israel.
177. Institute of Human Genetics, Technische Universität München, Munich, Germany.
178. Departments of Medicine and Human Genetics, The University of Chicago, Chicago, Illinois, USA.
179. Cardiovascular & Metabolic Disorders Program, Duke-NUS Medical School Singapore, Singapore.
180. Li Ka Shing Centre for Health Information and Discovery, University of Oxford, Oxford, UK.
181. Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, Mississippi, USA.
182. Department of Laboratory Medicine & Institute for Human Genetics, University of California, San Francisco, San Francisco, California, USA.
183. Blood Systems Research Institute, San Francisco, California, USA.
184. General Medicine Division, Massachusetts General Hospital and Department of Medicine, Harvard Medical School, Boston, Massachusetts, USA.
185. Division of Endocrinology and Metabolism, Department of Medicine, McGill University, Montreal, Quebec, Canada.
186. Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA.
187. Department of Genetics, University of North Carolina, Chapel Hill, North Carolina, USA.
188. Department of Medicine, Harvard Medical School, Boston, Massachusetts, USA.
189. Diabetes Research Center (Diabetes Unit), Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA.
190. Department of Biostatistics, University of Liverpool, Liverpool, UK.
191. Department of Biology, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA.

‡ Deceased.

UK Biobank CardioMetabolic Consortium BP working group

Helen R Warren[1,2], Evangelos Evangelou[3,4], Claudia P Cabrera[1,2], He Gao[3,5], Ioanna Ntalla[1], Praveen Surendran [6], Jaspal S Kooner[7-9], Bernard Keavney [10 11], Maciej Tomaszewski [10 11], Nilesh J Samani [12 11], Joanna M M Howson [6] , Martin D Tobin [13], Patricia B Munroe[1,2], Louise V Wain [13], Michael R Barnes[1,2], Ioanna Tzoulaki[3-5], Mark J Caulfield[1,2], Paul Elliott[3,5]

Affiliations

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

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

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

4 Department of Hygiene and Epidemiology, University of Ioannina Medical School, Ioannina, Greece.

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

6 Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK.

7 Department of Cardiology, Ealing Hospital NHS Trust, Southall, Middlesex, UK.

8 National Heart and Lung Institute, Cardiovascular Sciences, Hammersmith Campus, Imperial College London, London, UK.

9 Imperial College Healthcare NHS Trust, London, UK.

10 Division of Medicine, Central Manchester NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK.

11 Department of Cardiovascular Sciences, University of Leicester, BHF Cardiovascular Research Centre, Glenfield Hospital, Leicester, UK.

12 NIHR Leicester Cardiovascular Biomedical Research Unit, Glenfield Hospital, Leicester, UK.

13 Department of Health Sciences, University of Leicester, Leicester, UK.

Supplemental Table 1. Lead 77 SNVs for BP meta-analysis from the pan-ancestry sample.

No	rsID	Gene Name	Variant Role	Chrom	position HG38	position HG19	diffPosNearGene	Closest Gene	Allele1	Allele2	Freq1	SBP beta	DBP beta	PP beta	SBP s.e.	DBP s.e.	PP s.e.	SBP direction	DBP direction	PP direction	SBP logHetP	DBP logHetP	PP logHetP	SBP N	DBP N	PP N	SBP P-value	DBP P-value	PP P-value	UK-BIOBANK INFO
1	rs2782643	SZT2	missense	1	43420823	43,886,494.00	0	SZT2	t	c	0.3969	0.15	0.11	0.04	0.0385	0.0228	0.027	-++	-++	-++	-3.23	-3.11	-1.62	466023	466051	466005	9.12E-05	3.31E-06	9.77E-02	1
2	rs786906	PKN2	reference	1	88805891	89,271,574.00	0	PKN2	t	c	0.4473	0.26	0.08	0.19	0.0372	0.0221	0.0261	+++	+++	+++	-1.59	-0.30	-1.38	474564	474588	474541	7.08E-12	4.17E-04	1.29E-12	1
3	rs150035005	PALMD	missense	1	99689087	100,154,643.00	0	PALMD	t	c	0.002	-1.91	-0.50	-1.23	0.5717	0.3361	0.4003	-+-	++-	-+-	-3.58	-2.48	-2.11	332771	332769	332737	8.51E-04	1.35E-01	2.09E-03	0.95850003
4	rs61757359	NPR1	missense	1	153685821	153,658,297.00	0	NPR1	a	g	0.0033	-1.67	-1.07	-0.53	0.3499	0.2086	0.2435	---	---	---	-0.08	-0.64	-0.08	461732	461755	461710	1.95E-06	2.69E-07	3.09E-02	0.91715002
5	rs35856559	CACNA1S	missense	1	201089263	201,058,391.00	0	CACNA1S	a	g	0.996	-1.64	0.00	-1.96	0.543	0.3522	0.4199	-++	-++	-++	-0.51	-0.85	-0.15	309389	309373	309341	2.51E-03	1.00E+00	3.09E-06	0.42379099
6	rs1260326	GCKR	downstream-variant-500	2	27508073	27,730,940.00	0	GCKR	t	c	0.3742	0.18	0.06	0.11	0.0385	0.0228	0.0269	+++	+++	+++	-0.98	-0.85	-0.21	474557	474581	474534	3.31E-06	4.37E-03	7.41E-05	1
7	rs9678851	SLC4A1AP	missense	2	27664167	27,887,034.00	0	SLC4A1AP	a	c	0.5391	-0.23	-0.09	-0.14	0.0374	0.0221	0.0261	---	---	---	-1.04	-0.29	-1.05	474569	474593	474546	1.07E-09	1.17E-04	1.48E-07	1
8	rs289872			2	151209343	152,065,857.00	-38492	(RBM43)_beyond	a	g	0.0525	-0.38	-0.25	-0.14	0.1107	0.0672	0.0797	---	---	---	-1.19	-1.19	-0.35	467256	467269	467233	6.61E-04	2.40E-04	7.94E-02	0.97172397
9	rs56391938	TTN	missense	2	178568916	179,433,643.00	0	TTN	c	g	0.001	-1.47	-0.70	-0.68	0.6546	0.3912	0.4513	-++	-++	-+-	-3.31	-1.31	-2.48	387649	387639	387603	2.45E-02	7.41E-02	1.32E-01	0.899414
10	rs2727943			3	1856289	1,897,973.00	-240590	(CNTN4)_beyond	t	c	0.1787	0.00	0.00	-0.02	0.0508	0.0301	0.0357	+-+	+-+	--+	-0.17	-0.19	-0.12	464716	464740	464693	9.33E-01	9.12E-01	6.17E-01	1
11	rs13081389			3	12248301	12,289,800.00	-37558	(PPARG)_beyond	a	g	0.9356	0.22	-0.02	0.24	0.0781	0.0464	0.0545	-++	--+	+++	-0.86	-0.11	-0.90	441201	441225	441180	5.50E-03	7.24E-01	8.13E-06	1
12	rs13303	STAB1,NT5DC2	missense,downstream-v	3	52523992	52,558,008.00	0	STAB1,NT5DC2	t	c	0.4405	-0.15	0.00	-0.14	0.0376	0.0223	0.0263	---	++-	---	-2.15	-2.58	-1.07	469618	469647	469601	7.41E-05	9.33E-01	2.14E-07	1
13	rs3617	ITIH3	missense	3	52799789	52,833,805.00	0	ITIH3	a	c	0.4637	0.16	0.02	0.14	0.0374	0.0222	0.0262	+++	+-+	+++	-1.27	-1.17	-0.45	474513	474537	474490	2.34E-05	4.47E-01	2.00E-07	1
14	rs3772219	ARHGEF3	missense	3	56737223	56,771,251.00	0	ARHGEF3	a	c	0.6773	0.25	0.15	0.11	0.0396	0.0235	0.0278	+++	+++	+++	-0.60	-1.52	-0.04	474558	474582	474535	2.00E-10	3.31E-10	1.12E-04	1
15	rs6438013	PHLDB2	intron-variant	3	111794873	111,513,720.00	0	PHLDB2	t	g	0.3411	-0.14	-0.12	-0.04	0.0395	0.0234	0.0277	---	---	-+-	-0.67	-0.40	-0.64	474555	474579	474532	3.63E-04	5.01E-07	1.95E-01	0.99534798
16	rs879634	TSC22D2	missense	3	150410605	150,128,392.00	0	TSC22D2	a	g	0.2678	0.23	0.11	0.12	0.0505	0.0296	0.0349	+++	+++	+++	-1.29	-1.97	-0.21	331631	331660	331650	3.80E-06	1.45E-04	4.57E-04	1
17	rs1464510	LPP	intron-variant	3	188394766	188,112,554.00	0	LPP	t	g	0.4549	0.09	0.08	0.00	0.0402	0.0237	0.0282	+-+	+-+	--+	-1.55	-2.51	-0.16	409474	409459	409435	2.88E-02	1.48E-03	9.55E-01	1
18	rs7437940	AFAP1	intron-variant	4	7885773	7,887,500.00	0	AFAP1	t	c	0.4607	-0.17	0.00	-0.16	0.0381	0.0226	0.0267	---	+-+	---	-0.77	-0.03	-1.68	472626	472650	472603	1.17E-05	8.71E-01	3.47E-09	0.99741602
19	rs4371677	HOPX	intron-variant	4	56650730	57,516,896.00	0	HOPX	a	g	0.4661	-0.18	-0.09	-0.09	0.0372	0.022	0.0261	---	---	---	-1.26	-1.34	-0.79	474571	474595	474548	1.00E-06	6.61E-05	3.55E-04	1
20	rs138882001	HPSE	intron-variant	4	83306300	84,227,453.00	0	HPSE	t	c	0.0017	-0.04	-0.48	0.29	0.5574	0.3364	0.3916	++-	-+-	++-	-0.76	-0.69	-0.53	439295	439279	439232	9.55E-01	1.51E-01	4.57E-01	0.436883
21	rs2303986	ROPN1L	missense	5	10450034	10,450,146.00	0	ROPN1L	t	c	0.0011	2.52	1.42	1.08	0.7039	0.4246	0.488	++-	+++	++-	-3.14	-1.31	-3.22	411635	411662	411618	3.47E-04	8.32E-04	2.75E-02	0.683074
22	rs40060	ANKDD1B	utr-variant-3-prime	5	75671561	74,967,386.00	0	ANKDD1B	t	c	0.6317	-0.06	-0.16	0.09	0.0386	0.0229	0.027	++-	---	++-	-1.32	-0.76	-2.22	474571	474595	474548	1.51E-01	9.12E-12	1.26E-03	0.993765
23	rs757647	KDM3B	intron-variant	5	138371626	137,707,315.00	0	KDM3B	t	c	0.2287	0.14	0.04	0.10	0.0442	0.0263	0.0311	+++	+++	+++	-0.74	-0.13	-2.62	474566	474590	474543	1.15E-03	1.00E-01	1.12E-03	1
24	rs139433211	ARAP3	missense	5	141680003	141,059,570.00	0	ARAP3	t	c	0.0015	2.50	2.02	0.61	0.7077	0.4492	0.5336	+-+	+-+	+++	-0.41	-0.94	-0.02	400877	400899	400863	4.07E-04	7.08E-06	2.57E-01	0.871499
25	rs139271401	RPL26L1	missense	5	172968579	172,395,582.00	0	RPL26L1	a	g	0.0004	2.75	1.15	1.41	1.2753	0.7732	0.8869	+-+	--+	+-+	-3.45	-0.96	-3.12	372482	372478	372435	3.09E-02	1.35E-01	1.10E-01	0.79832202
26	rs5370	EDN1	missense	6	12296022	12,296,255.00	0	EDN1	t	g	0.2288	0.16	0.04	0.11	0.0443	0.0263	0.031	+++	+++	+++	-2.03	-0.16	-2.33	474564	474588	474541	2.88E-04	1.00E-01	2.75E-04	1
27	rs200658579	ARMC12	missense	6	35738101	35,705,878.00	0	ARMC12	a	g	0.9997	-2.37	-1.21	-0.96	1.707	1.0275	1.1913	--+	--+	--+	-2.58	-2.88	-0.86	405732	405750	405715	1.66E-01	2.40E-01	4.27E-01	0.34262899
28	rs2274911	GPRC6A	missense	6	116809541	117,130,704.00	0	GPRC6A	a	g	0.7262	-0.11	-0.12	0.01	0.0415	0.0245	0.029	+--	---	+--	-1.52	-1.10	-0.68	474567	474591	474544	8.71E-03	7.08E-07	6.92E-01	1
29	rs1055144	LOC100506236 (7p15.2)	nc-transcript-variant	7	25831489	25,871,109.00	0	LOC100506236	a	g	0.1932	0.17	-0.03	0.19	0.0483	0.0286	0.0338	+++	+--	+++	-1.37	-1.55	-0.73	453890	453924	453880	5.50E-04	3.55E-01	3.47E-08	1
30	rs7636	ACHE	intron-variant	7	100892456	100,490,077.00	0	ACHE	t	c	0.056	-0.45	-0.19	-0.25	0.0874	0.0524	0.062	---	---	---	-0.70	-0.52	-0.96	474555	474579	474532	2.40E-07	2.29E-04	7.59E-05	1
31	rs3807989	CAV1	intron-variant	7	116546187	116,186,241.00	0	CAV1	a	g	0.4214	0.11	-0.01	0.12	0.0375	0.0222	0.0263	+++	--+	+++	-1.01	-0.19	-1.53	474570	474594	474547	2.45E-03	7.59E-01	6.76E-06	1
32	rs187187121	PTPRZ1	intron-variant	7	122034099	121,674,153.00	0	PTPRZ1	t	c	0.9961	2.82	2.49	0.50	1.0749	0.6297	0.7919	+-+	+-+	-++	-0.10	-0.35	-0.01	349564	349595	349567	8.71E-03	7.76E-05	5.25E-01	0.89377803
33	rs4731112	ASB15	missense	7	123629064	123,269,118.00	0	ASB15	c	g	0.697	-0.20	-0.11	-0.09	0.0411	0.0244	0.0287	---	---	---	-1.27	-1.23	-1.49	457596	457581	457532	8.91E-07	2.82E-06	2.34E-03	1
34	rs972283	LOC105375508	intron-variant	7	130782095	130,466,854.00	0	LOC105375508	a	g	0.4653	-0.23	-0.13	-0.09	0.0372	0.022	0.026	---	---	---	-0.99	-0.21	-1.23	474569	474593	474546	9.12E-10	1.38E-09	3.63E-04	1
35	rs137894236	SLC13A4	missense	7	135681676	135,366,424.00	0	SLC13A4	t	c	0.0006	2.48	2.31	0.24	0.9222	0.5572	0.642	+++	+++	-++	-1.03	-0.97	-0.39	406883	406863	406825	7.24E-03	3.31E-05	7.08E-01	0.79188597
36	rs201109912	KIAA1549	reference	7	138917445	138,602,191.00	0	KIAA1549	a	g	0.0006	-1.15	-0.84	-0.29	1.0027	0.595	0.7107	---	---	-+-	-1.18	-3.11	-0.03	352258	352247	352213	2.51E-01	1.58E-01	6.76E-01	0.75553203
37	rs12680655	ZFAT	intron-variant	8	134625094	135,637,337.00	0	ZFAT	c	g	0.5958	-0.27	-0.13	-0.14	0.0386	0.0229	0.027	---	---	---	-0.64	-0.40	-0.58	454963	454948	454901	2.75E-12	6.31E-09	4.07E-07	1
38	rs41298151	FREM1	missense	9	14842660	14,842,658.00	0	FREM1	c	g	0.9813	0.71	0.28	0.41	0.1917	0.1134	0.1332	+-+	+-+	+++	-1.95	-1.44	-1.06	407793	407773	407736	2.29E-04	1.35E-02	2.14E-03	0.97621202
39	rs55789327	DDX58	missense	9	32492531	32,492,529.00	0	DDX58	a	g	0.0192	0.52	-0.02	0.57	0.2477	0.1518	0.1814	+++	---	+++	-1.03	0.00	-2.28	405535	405515	405478	3.47E-02	8.71E-01	1.58E-03	0.81488901
40	rs113084619	MORN5	intron-variant	9	122169705	124,931,984.00	0	MORN5	a	g	0.0072	0.56	0.02	0.52	0.2382	0.1413	0.1673	+-+	--+	+-+	-1.70	-0.38	-2.42	473618	473642	473595	2.00E-02	8.71E-01	1.91E-03	0.86303002
41	rs10760260	RABGAP1	intron-variant	9	122951247	125,713,526.00	0	RABGAP1	t	g	0.1718	-0.20	0.00	-0.21	0.0531	0.0314	0.0372	+--	+--	---	-1.91	-0.79	-1.58	467253	467266	467230	1.45E-04	9.33E-01	1.26E-08	0.99754298
42	rs146657712	GTF3C4	missense	9	132678319	135,553,706.00	0	GTF3C4	a	g	0.0084	-0.49	-0.09	-0.45	0.2187	0.1298	0.1527	-+-	-+-	-+-	-1.22	-0.14	-2.29	474158	474182	474135	2.63E-02	5.01E-01	3.47E-03	0.832295
43	rs77273740	DBH	missense	9	133636634	136,501,728.00	0	DBH	t	c	0.0294	-1.02	-0.73	-0.38	0.2772	0.1628	0.2001	+--	---	---	-0.63	-0.86	-0.17	433058	433052	433007	2.40E-04	7.08E-06	5.62E-02	0.67842501
44	rs3025380	DBH	missense	9	133636634	136,501,756.00	0	DBH	c	g	0.0043	-1.54	-1.06	-0.48	0.3069	0.183	0.2139	---	---	--+	-2.13	-1.83	-1.08	452903	452888	452841	4.90E-07	6.76E-09	2.51E-02	0.87633699
45	rs141194244	ANKRD30A	missense	10	37219328	37,508,256.00	0	ANKRD30A	c	g	0.0079	-0.29	0.00	-0.30	0.2334	0.1405	0.1632	+--	++-	+--	-4.02	-1.88	-2.19	456536	456521	456472	2.14E-01	9.77E-01	6.92E-02	0.635167
46	rs146887444	C10orf54	missense	10	71773367	73,533,124.00	0	C10orf54	t	c	0.0018	-1.15	-1.29	-0.01	0.988	0.5875	0.6959	+--	+--	+--	-2.35	-2.76	-0.72	410950	410934	410895	2.40E-01	2.82E-02	9.77E-01	0.870233
47	rs34163229	SYNPO2L	missense	10	73647154	75,406,912.00	0	SYNPO2L	t	g	0.1508	0.36	0.15	0.21	0.053	0.0315	0.0371	+++	+++	+++	-0.49	-1.02	-0.28	448759	448783	448736	1.15E-11	3.55E-06	1.66E-08	1
48	rs925946	BDNF-AS	intron-variant	11	27645655	27,667,202.00	0	BDNF-AS	t	g	0.311	-0.19	-0.16	-0.04	0.04	0.0237	0.028	---	---	-+-	-0.03	-0.61	-0.36	474540	474564	474517	1.86E-06	7.08E-12	1.95E-01	1
49	rs10458896	KIF18A	missense	11	28036410	28,057,957.00	0	KIF18A	t	c	0.6926	-0.17	-0.13	-0.04	0.0405	0.024	0.0284	---	---	---	-0.75	-1.51	-0.06	474535	474559	474512	3.63E-05	1.15E-07	1.23E-01	1
50	rs12286721	AGBL2	missense	11	47679976	47,701,528.00	0	AGBL2	a	c	0.5625	-0.23	-0.16	-0.08	0.0381	0.0226	0.0267	---	---	---	-1.52	-1.46	-0.69	453878	453912	453868	1.02E-09	5.01E-13	2.51E-01	1
51	rs503341	C11orf84	intron-variant	11	63819841	63,587,313.00	0	C11orf84	t	c	0.4602	0.15	0.05	0.09	0.0371	0.022	0.026	+-+	+-+	+++	-2.03	-2.01	-0.95	474563	474587	474540	7.41E-05	1.45E-02	5.62E-04	1
52	rs10765211	NOX4	intron-variant	11	89495257	89,228,425.00	0	NOX4	a	g	0.3811	-0.18	0.02	-0.19	0.0392	0.0232	0.0274	---	+++	---	-0.64	-0.05	-1.30	474573	474597	474550	3.39E-06	5.13E-01	6.46E-12	0.99641299
53	rs8258	CEP164	utr-variant-3-prime	11	117412960	117,283,676.00	0	CEP164	a	g	0.38	0.16	-0.06	0.21	0.0381	0.0226	0.0267	+++	---	+++	-1.55	-0.05	-3.34	474556	474580	474533	3.16E-05	4.27E-03	1.95E-15	1
54	rs61735123	OR8D2	missense	11	124320140	124,190,036.00	0	OR8D2	a	g	0.0136	-1.19	-0.25	-1.08	0.2963	0.1882	0.2252	---	---	---	-0.53	-2.23	-0.13	411888	411868	411831	5.89E-05	1.91E-01	1.51E-06	0.90992999
55	rs11062385	KDM5A	missense	12	318409	427,575.00	0	KDM5A	a	g	0.7223	-0.18	-0.04	-0.14	0.0412	0.0245	0.0289	---	-+-	---	-0.01	-0.29	-0.29	474571	474595	474548	2.00E-05	9.77E-02	9.55E-07	1
56	rs12368599	GPRC5A	missense	12	12908793	13,061,727.00	0	GPRC5A	a	g	0.9908	-0.26	-0.06	-0.14	0.1962	0.116	0.1371	++-	++-	++-	-3.59	-2.74	-1.54	472680	472704	472657	1.95E-01	6.17E-01	3.02E-01	0.99027401
57	rs141146368	KRT82	splice-donor-variant	12	52396011	52,789,795.00	0	KRT82	t	c	0.0029	1.78	1.16	0.70	1.2151	0.695	0.8678	--+	--+	--+	-1.59	-1.87	-0.71	342500	342482	342449	1.41E-01	9.33E-02	4.17E-01	0.50189602
58	rs7136889	HOXC4	intron-variant	12	54043968	54,437,752.00	0	HOXC4	t	g	0.6861	0.33	0.13	0.19	0.0452	0.0273	0.0319	+++	+++	+++	-0.51	-0.44	-0.40	471911	471935	471890	5.13E-13	8.51E-07	1.66E-09	0.606978
59	rs4899260	LOC105370548	intron-variant	14	68811487	69,278,204.00	0	LOC105370548	t	c	0.2532	0.21	0.13	0.07	0.0426	0.0253	0.0299	+++	+++	+++	-0.90	-0.54	-0.61	472675	472699	472652	6.92E-07	1.38E-07	2.24E-02	1
60	rs8014204	LOC105370568	upstream-variant-2KB	14	74856091	75,322,794.00	0	LOC105370568	a	g	0.5621	-0.20	-0.10	-0.10	0.0382	0.0226	0.0267	---	---	--+	-2.00	-0.31	-2.81	461383	461412	461366	1.78E-07	5.89E-06	3.63E-04	1
61	rs2076746	ATP10A	missense	15	25680896	25,926,043.00	0	ATP10A	t	c	0.0028	0.01	0.60	-0.51	0.758	0.499	0.586	++-	+++	-+-	-1.49	-0.85	-2.51	305313	305294	305261	1.00E+00	2.24E-01	3.80E-01	0.59459901
62	rs200238968	DUOX2	missense	15	45101859	45,394,057.00	0	DUOX2	a	g	0.0002	4.42	0.42	4.16	1.9782	1.1739	1.3958	+++	-++	++-	-0.41	-0.12	-1.50	355626	355608	355572	2.51E-02	7.24E-01	2.88E-03	0.30108199
63	rs2729835	LACTB	downstream-variant-500	15	63141567	63,433,766.00	0	LACTB	a	g	0.677	-0.20	-0.08	-0.13	0.0409	0.0242	0.0286	---	---	---	-1.03	-0.21	-0.89	443166	443190	443143	1.32E-06	1.86E-03	4.68E-06	1
64	rs148060387	NOX5	missense	15	69037050	69,329,390.00	0	NOX5	t	c	0.0004	5.89	3.37	2.24	1.4299	0.8866	1.0039	+-+	+-+	+++	-0.69	-1.52	-0.36	378077	378067	378032	3.80E-05	1.41E-04	2.57E-02	0.21792901
65	rs183355078	WDR90	missense	16	657113	707,113.00	0	WDR90	a	g	0.0048	0.94	0.23	0.62	0.312	0.185	0.2169	+++	+-+	+++	-0.59	-0.47	-0.23	453015	453048	453006	2.45E-03	2.24E-01	4.17E-03	0.703574
66	rs2865531	CFDP1	intron-variant	16	75356418	75,390,316.00	0	CFDP1	a	t	0.595	0.42	0.14	0.27	0.0569	0.0324	0.0399	+++	+++	+++	-0.29	-0.18	-0.15	217419	217420	215466	2.14E-13	8.51E-06	7.08E-12	0.99979597
67	rs187500530	GEMIN4	missense	17	747574	650,814.00	0	GEMIN4	t	c	0.0029	0.29	0.23	0.09	0.7421	0.4178	0.5078	++-	-+-	++-	-3.50	-1.22	-3.01	357498	357520	357488	6.92E-01	5.75E-01	8.71E-01	0.65881598
68	rs12949907	DHRS13	utr-variant-3-prime	17	28897781	27,224,799.00	0	DHRS13	t	c	0.8199	-0.01	-0.08	0.09	0.0483	0.0285	0.0337	-+-	---	+++	-0.19	-0.15	-0.01	474564	474588	474541	8.13E-01	4.68E-03	9.12E-03	1
69	rs12941884	SEZ6	missense	17	28957425	27,284,443.00	0	SEZ6	a	g	0.8576	-0.11	-0.11	0.03	0.0536	0.0318	0.0376	-+-	---	-++	-1.03	-1.44	-0.12	474568	474592	474545	4.07E-02	3.72E-04	4.79E-01	1
70	rs143262370	MC5R	missense	18	13826679	13,826,678.00	0	MC5R	t	c	0.0062	-0.98	-0.42	-0.44	0.2459	0.1464	0.1724	---	-+-	+--	-1.09	-1.06	-1.60	462926	462955	462909	7.08E-05	3.89E-03	1.05E-02	0.98301798
71	rs144764696	PGLYRP2	missense	19	15475808	15,586,619.00	0	PGLYRP2	a	g	0.0007	1.69	0.79	0.86	0.8577	0.5069	0.5915	+-+	+++	+-+	-3.36	-0.29	-5.25	401585	401614	401582	4.90E-02	1.17E-01	1.45E-01	0.761307
72	rs139045449	ZNF607	missense	19	37698726	38,189,627.00	0	ZNF607	t	c	0.9985	-1.71	-0.33	-1.26	0.557	0.3315	0.3856	-+-	-+-	-+-	-1.75	-0.37	-1.85	392318	392351	392311	2.14E-03	3.16E-01	1.10E-03	0.97834998
73	rs2303729	LTBP4	missense	19	40605163	41,111,069.00	0	LTBP4	a	g	0.4597	0.17	0.09	0.07	0.0373	0.0221	0.0261	+++	+++	+++	-0.42	-0.41	-0.28	471872	471896	471851	8.13E-06	3.47E-05	4.17E-03	1
74	rs117825139	NAPB	downstream-variant-500	20	23394987	23,375,624.00	0	NAPB	t	c	0.998	0.68	0.82	-0.02	0.4487	0.2672	0.3113	+++	+++	++-	-0.07	-1.75	-1.71	466374	466397	466352	1.29E-01	2.04E-03	9.33E-01	0.94418103
75	rs3746429	EDEM2	missense	20	35115804	33,703,607.00	0	EDEM2	t	c	0.1645	0.17	0.00	0.17	0.05	0.0296	0.0349	+++	+--	+++	-1.23	-0.36	-1.32	474567	474591	474544	5.37E-04	9.77E-01	1.82E-06	1
76	rs756529	KCNB1	intron-variant	20	49394471	48,011,008.00	0	KCNB1	a	g	0.4269	0.02	0.09	-0.06	0.0373	0.0221	0.0262	--+	+++	--+	-3.18	-3.71	-1.12	474373	474398	474351	5.62E-01	2.45E-05	1.95E-02	0.99444902
77	rs4680	COMT	missense	22	19963748	19,951,271.00	0	COMT	a	g	0.5103	0.19	0.05	0.15	0.0371	0.022	0.026	+++	+++	+++	-2.35	-0.37	-2.41	469599	469628	469582	2.40E-07	3.89E-02	7.76E-09	1

Notes: **In yellow are highlighted closest genes for significant results**

In light-green are highlighted p-values that pass the signifificance threshold per specific traits