

Discovery and validation of 107 blood pressure loci from UK Biobank offers novel biological insights into cardiovascular risk

SUPPLEMENTARY INFORMATION

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Supplementary Figure 1: Functional analyses schematic for the functional annotation and prioritisation of GWAS associated variants and genes. SNVs: single nucleotide variants; LD: Linkage Disequilibrium; eQTL: expression Quantitative Trait Loci; UCSC: University of California Santa Cruz (UCSC) genome browser; IPA: Ingenuity Pathway Analysis (IPA) software (IPA®, QIAGEN Redwood City, www.qiagen.com/ingenuity); DEPICT: Data-driven Expression Prioritized Integration for Complex Traits; GREAT: Genomic Regions Enrichment of Annotations Tool.

Supplementary Figure 2: UK Biobank GWAS discovery circos Manhattan plots (A), (B) and (C) for systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse pressure (PP) respectively. *P*-value results are plotted on a $-\log_{10}$ scale (see legend) for all ~9.8 million variants with Minor Allele Frequency (MAF) $\geq 1\%$ and imputation quality INFO > 0.1 analysed within the GWAS discovery. Associations are plotted in red for all variants within validated novel loci, in black for variants within novel loci which were looked-up ($P < 1 \times 10^{-6}$) in replication data but did not replicate, in blue for all variants within previously reported blood pressure loci, and grey otherwise. Loci names labelled around the edge are specific to each blood pressure trait, with red labels corresponding to novel loci validated for the given trait (102 validated novel loci from Table 1a in total across all three plots from GWAS), and blue labels corresponding to previously reported loci within which new independent secondary variants were identified (20 GWAS variants in total from Table 2b).

Supplementary Figure 3: Locus zoom plots of (A) 102 validated novel sentinel variants from UK Biobank GWAS discovery and (B) 5 validated novel sentinel variants from UK Biobank exome discovery. Linkage Disequilibrium is calculated within UK Biobank, with grey corresponding to $r^2 < 0.1$. SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; MAF: Minor Allele Frequency; INFO: Imputation quality score from SNPTEST.

Supplementary Figure 4: Heat map of blood pressure associations using $-\log_{10}(P\text{-values})$ from the combined meta-analysis. The rows of the heat map are the 107 sentinel validated novel SNVs from Table 1 from both GWAS and exome discovery, ordered by trait, then by chromosome and genomic position base pairs. Red shows genomewide significance ($P < 5 \times 10^{-8}$), orange shows moderate significance ($5 \times 10^{-8} \leq P < 0.01$) and yellow shows no significant association ($P \geq 0.01$). SBP: systolic BP; DBP: diastolic BP; PP: pulse pressure.

Supplementary Figure 5: Results of previously reported variants: comparison of UK Biobank (UKB) and originally published results. Plot (A) compares the Minor Allele Frequency (MAF) values in UK Biobank with those from the originally published studies, for all 163 previously reported blood pressure (BP) variants. The plotted points are colour-coded according to the type of genetic association study that each variant was identified from. For example, “GWAS” refers to standard Genome-Wide Association Studies in Europeans, whereas “Other Ancestries” refers to analyses in non-Europeans; “Bespoke chips” refers to e.g. studies using the CardioChip or MetaboChip; “New Methods” refers to analyses using other methodological strategies which were not main-effect associations, e.g. interaction analyses or multivariate analyses. Plot (B) compares the effect sizes for a subset of the previously reported variants, restricted to non-rare variants (1 variant excluded from “Exome-chip” with MAF $< 1\%$ in UKB) from main effect analyses (excluding “New Methods” category) of people of European ancestry (“Other Ancestries” category excluded). Three separate plots are provided for systolic (SBP), diastolic (DBP) and pulse pressure (PP) traits (hence any variants identified for hypertension or Mean Arterial Pressure are excluded), with effect sizes given in mmHg units. Each variant is plotted only once, for the primary BP trait that was originally reported. In each plot, the dotted line represents the

Y=X line, and the r^2 values report the statistical correlation between the UK Biobank and the published effect sizes.

Supplementary Figure 6: Validated novel loci eQTLs across all tissues. The figure represents the number of validated novel loci (n=107) which contain at least one variant (in LD of $r^2 \geq 0.8$ with the sentinel SNV) with an eQTL association observed for each tissue type, according to the GTEx database. eQTL: expression quantitative trait loci ; LD linkage disequilibrium; SNV: single nucleotide variant; GTEx The Genotype-Tissue Expression project.

Supplementary Figure 7: In silico evidence supporting an eQTL in the *SF3A3* gene. (A) UCSC (University of California Santa Cruz) Genome Browser view of the 3' region of *SF3A3*. ENCODE (Encyclopedia of DNA Elements) Transcription factor Chip-Seq data shows widespread binding in the region of rs4360494, including the transcription Factor AP-2 Alpha/Gamma B) GTEx Tibial Artery eQTL demonstrating decreased expression of *SF3A3* in homozygous minor allele carriers. (C) G>C transversion removes predicted AP-2 binding. (eQTL: expression Quantitative Trait Locus)

Supplementary Figure 8: DEPICT tissue enrichment across validated novel and previously reported blood pressure associations. We find enrichment of expression across 31 tissues and cells, with highest enrichment found in arteries ($P = 1.9 \times 10^{-6}$; FDR < 0.01). Enrichment association passing false discovery testing is indicated in red. Figures: (a) Physiological systems tissue enrichment; (b) Tissue enrichment; (c) Cardiovascular system enrichment; (d) Endocrine system enrichment. Figures (c) and (d) are detailed subsections for tissues of interest taken from figure (a). DEPICT: Data-driven Expression Prioritized Integration for Complex Traits; FDR: False discovery rate.

Supplementary Figure 9: FORGE results. Sentinel variants for association with blood pressure are investigated for enrichment in ENCODE (Encyclopedia of DNA Elements) DNase I regulatory regions using FORGE. (A) FORGE DNase I sensitive region enrichment for validated novel and previously reported sentinel variants. Strongest enrichment is seen in vasculature (MVEC, Microvascular Endothelium) and highly vascularised tissues. Tissues in red are significant after correction for false discovery. (B) To further investigate the regulatory basis of the associated loci, candidate regulatory variants are selected for (B) 107 validated novel loci and (C) validated novel and previously reported loci. Again enrichment is seen for vascular tissue especially vascular smooth muscle and endothelial cell types.

Supplementary Figure 10: Genome-wide enrichment of histone methylation marks among validated novel and previously reported sentinel variants for association with blood pressure. Histone mark enrichment is investigated using GenomeRunner.

Supplementary Figure 11: The expression of genes contained within the 107 validated novel loci is investigated using K-means clustering in the fantom5 gene expression reference data set, focusing on cardiovascular relevant tissues that show evidence of enrichment in DEPICT (Data-driven Expression Prioritized Integration for Complex Traits) and FORGE analysis. With K-means set to 5 clusters, tissue specific clusters are apparent, including vascular smooth muscle cells (VSMC) and fibroblasts, endothelial cells (including probable endothelial cells in highly vascularised tissues), and a combined vascular cell cluster. Clusters are also apparent for cardiopulmonary genes. A further 65 genes do not cluster within tissue groups (not shown) and 71 genes are not detected in the fantom5 data. Yellow indicates down-regulation, purple indicates up-regulation.

Supplementary Figure 12: Gene expression in human vascular smooth muscle cells (VSMCs) and endothelial cells (ECs) detected by quantitative Polymerase Chain Reaction (qPCR) with standardization to internal control of 18S. Dots represent individual samples from each genotype with

numbers indicated. Data are analysed using the $2^{-\Delta\Delta Ct}$ method, log transformed and shown as mean with error bars, Standard Error of the Mean (SEM) on left (VSMCs) and right (ECs) of each panel. Differences are determined by one-way Analysis of Variance (ANOVA) with Bonferroni correction for multiple comparisons. In (a): the sentinel variant rs4360494 at the *SF3A3* locus is significantly associated with expression of *SF3A3* in cell type-specific manner, with the major C allele associated with increased expression of *SF3A3* in human VSMCs, but no genetic difference in ECs. In (b): A similar cell-type specificity is shown for genetic effect of sentinel variant rs62012628 on *ADAMTS7* expression, with a significantly lower expression level for the minor T allele in human VSMCs. In (c) the minor A allele of sentinel variant rs2289125 at *NOX4* gene locus is significantly related with a lower *NOX4* expression level in human ECs.

Supplementary Figure 13: Relationship between allele frequency and effect size of blood pressure associated variants, comparing validated novel and previously reported variants. The MAF values and effect sizes, all taken from UK Biobank discovery results, are plotted according to the most significant trait in the UK Biobank discovery data for previously reported variants, and for the validated trait for all other variants. Variants are colour coded according to the type of variant (see legend). Note that the “validated secondary SNVs” are validated SNVs at novel loci which were not independent of the sentinel SNV after conditional analysis. SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; MAF: Minor Allele Frequency; SNV: single nucleotide variant.

Supplementary Figure 14: Ethnicity clustering performed using PCA. PC1 is plotted against PC2 for all N~150,000 UK Biobank participants, colour-coded according to the five ethnic clusters created from our K-means PCA clustering, from which only “White” Caucasians are selected for analysis of individuals of European ancestry. PCA: Principal Component Analysis; QC: Quality Control; PCs: Principal Components.

Supplementary Figure 15: Quantile-Quantile plots of results for (A) systolic blood pressure (SBP) from UK Biobank GWAS, (B) diastolic blood pressure (DBP) from GWAS, (C) pulse pressure (PP) from GWAS, (D) SBP from UK Biobank exome, (E) DBP from exome and (F) PP from exome. The black curves are based on all the variants in the corresponding analysis, with ~9.8 million variants with Minor Allele Frequency $\geq 1\%$ and imputation quality INFO > 0.1 for GWAS for plots (A-C) and ~150,000 exome variants for plots (D-F). The green curves are results after excluding previously reported blood pressure variants and all variants in Linkage Disequilibrium with them ($r^2 \geq 0.2$). The genomic inflation factor, λ , is reported (NB: LD Score regression analysis yields $\lambda \sim 1.05$ for each BP-GWAS, confirming that any inflation in the GWAS findings reflects polygenic influence on blood pressure).

Supplementary Methods

1. UK Biobank data

The UK Biobank cohort includes ~500,000 volunteers aged 40-69 years of age ascertained through NHS registers¹. Following informed consent participants completed a standardised questionnaire on life course exposures, medical history and treatments and underwent a standardised portfolio of phenotypic tests including two blood pressure measurements taken seated after two minutes rest using an appropriate cuff and an Omron HEM-7015IT digital blood pressure monitor. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m²) with weight measured using an electronic weighing scales (Tanita BC-418). The participants undergo longitudinal life course linkage to electronic health data including Hospital Episode Statistics and Office for National Statistics cause of death data.

The UK Biobank and UK BiLEVE genotyping arrays overlap with over 95% of SNVs content in common. These customised chips were designed to give genome-wide coverage of SNVs, including some insertion deletion polymorphisms (indels) and include validated exome content from the first 55K participants in the UK exome chip study. With approved access to the full genetic data, a total of ~73 million autosomal genetic variants were available for analysis, of which ~9.8 million SNVs with minor allele frequency (MAF) >1% and imputation quality INFO > 0.1 are analysed here for GWAS.

2. Quality Control

All SNVs had passed central Quality Control (QC) checks, such as tests of Hardy-Weinberg Equilibrium, batch and plate effects, multi-allelic SNVs and poorly called SNVs. The SNVs which failed QC were set to missing for all individuals in the corresponding batch within the final genetic data files provided. Likewise, the QC performed centrally for each sample tested for heterozygosity and missing rates. Samples were further investigated for relatedness and Principal Components Analysis (PCA) was performed. Full details of the QC of the genetic data performed centrally by UK Biobank are available².

We performed additional QC of the genetic data, using QC files provided by UK Biobank. Variants were excluded according to two lists provided by UK Biobank: (i) 417 SNVs with discordant results between the two 1000 Genomes control samples added to each plate; (ii) 65 SNVs which were later found by UK Biobank to be discordant. Samples were excluded after application of basic QC filters following the central QC tests: (i) N=480 individuals indicated in the data, which were recommended for exclusion due to high missingness or heterozygosity rates; (ii) N=459 individuals flagged as QC failures from UK BiLEVE; (iii) N=191 individuals whose phenotypic sex differs from the genetically inferred sex.

We restricted our data to a subset of unrelated European ancestry individuals for analysis. First, we selected European ancestry individuals using the Principal Component (PC) results from the centrally generated PCA, which included the first 15 PCs for all ~150k samples. We performed a 4-means clustering according to each of PC1 and PC2 separately using the *kmeans* algorithm in R statistical software, corresponding to four ethnic groups (White, Black, Asian, Chinese) and created an intersection of these two clusterings, to create five final clusters (White, Black, Asian, Chinese, Mixed/Other) (**Supplementary Fig. 14**). We selected individuals corresponding to the White cluster, and further removed any remaining individuals with self-reported mixed ethnicity. A total of N=145,315 Europeans remained in the data for further QC. We note that this is larger than the subset of 120,286 individuals which UK Biobank classified as being “probable Caucasians amongst people who self-identified as British” and used as a homogeneous European ancestry sample for variant QC², as stricter homogeneity is required for QC than for analysis.

Furthermore, we used the results of the central UK Biobank kinship analyses, which provided kinship coefficients and IBS0 estimates. We identified pairs of related samples and restricted the data to a set of unrelated individuals, by removing the individual with highest missingness rate within any pair of twins, 1st or 2nd degree relatives. Overall a total of N=141,647 unrelated European ancestry individuals remained post-QC.

3. Phenotypic data

In parallel, the phenotypic data were also considered for QC. In order to calculate the mean of the two blood pressure (BP) measurements, we restricted the data to individuals with both measurements available. From the full original dataset, this led to the exclusion of N=142 individuals with missing data for both 1st and 2nd BP readings, and N=139 / N=135 with only 1 of the 2 measurements available for systolic BP (SBP) / diastolic BP (DBP) respectively, as well as the exclusion of N=95 individuals who only had BP measurements from a manual sphygmomanometer. Individuals with missing covariates were removed from the data, hence excluding N=324 individuals with missing BMI. Furthermore we excluded N=35 pregnant women. These phenotypic sample exclusions were applied to all individuals who had passed the above genetic QC. Following both genetic and phenotypic data QC, the sample size for analysis therefore included N=140,882 and N=140,886 unrelated European ancestry individuals for SBP and DBP, respectively.

Analysis of the summary descriptive statistics of the UK Biobank sample (**Supplementary Table 1**) shows there were small but significant differences when comparing the UK Biobank vs UK BiLEVE participants, for age and BMI, due to large sample sizes. UK BiLEVE participants were slightly older and heavier compared to the UK Biobank participants. Moreover males and females were equally represented in the UK BiLEVE sample whereas more females (54.3%) were included in UK Biobank data.

4. Linkage Disequilibrium calculations

Linkage Disequilibrium (LD) was calculated between sets of variants within the full genetic dataset using PLINK software³. In order to do this, all genetic data were converted from BGEN format to PLINK binary format. For any given SNV for which LD calculations were performed, the LD was estimated for all variants within a 500kb window downstream and upstream of this reference SNV. All variants in LD with the reference SNV reaching an $r^2 \geq 0.2$ threshold were identified.

5. Exome variants

Considering all 247,870 SNVs from the exome chip (Illumina HumanExome BeadChip arrays) annotation file, we searched for all 241,561 autosomal SNVs from the polymorphic SNVs within our data. There were 149,325 SNVs covered directly, and a further 486 exome chip SNVs were covered by proxies ($r^2 > 0.7$) according to LD from the 1000G reference data set (phase3 v5a.20130502 and phase1 v3.20101123), giving a total of 149,811 SNVs to consider. All SNVs are directly genotyped on the exome chip within the two exome replication datasets.

6. Post-results Quality Control (QC)

We undertook further QC checks for any potential outliers. The additional QC included plots comparing trends between Minor Allele Frequency (MAF), Standard Error (SE), betas and *P*-values, Quantile-Quantile plots (**Supplementary Fig. 15**) with and without exclusion of known-LD variants, and the corresponding lambda values for genomic inflation were also calculated. After inspection of

our QQ-plots, we applied the LD score regression approach⁴ to determine whether any inflation was due to polygenicity or underlying population stratification. In particular, inspection and comparison of such plots enabled the selection of the optimal threshold for MAF and INFO filters, where INFO is the imputation quality score output from SNPTEST. We applied a post-analysis filter using an INFO threshold of 0.1, to exclude SNVs with low imputation quality from our results. Inspection of the plots from UKB documentation⁵ shows that imputation quality is high for SNVs with $MAF \geq 1\%$, and any SNVs with $INFO \leq 0.1$ are mostly rare SNVs. Note that an INFO threshold of 0.1 is lower than previously used in smaller GWAS, but appears suitable due to the much larger sample size and high statistical power in UK Biobank⁵. Furthermore, our validated findings all have good imputation quality.

For the UK Biobank exome discovery, there were 149,026 Exome SNVs which were polymorphic with $INFO > 0.1$. Inspection of QC diagnostic plots specifically for these SNVs alone suggested an optimal MAF filter of 0.01%, thus excluding rare variant outliers with large beta and SE values. This gave 114,641 remaining SNVs. In keeping with other exome-based studies of rare variants, we chose a less stringent P -value threshold for these analyses to account for the lower statistical power to detect effects of rare variants. We considered for follow-up all SNVs with $MAF \geq 0.01\%$, $INFO > 0.1$ and $P < 1 \times 10^{-5}$ for any of the three BP traits.

7. Loci assignment and classification

SNVs achieving the lookup threshold from both the UK Biobank GWAS and exome discovery efforts were combined with the previously reported BP associated SNVs to identify all variants in LD, referred to as the LD-lookup SNVs. We define a locus according to both an LD threshold of $r^2 \geq 0.2$ and a 1Mb interval region. Hence variants reaching an $r^2 \geq 0.2$ threshold within 500kb downstream and upstream of the LD-lookup SNVs were identified and assigned to loci sets. A locus set is composed of all SNVs linked by LD regardless of their association P -value and whether previously reported or not. For example, if SNV A is in LD with SNV B, and SNV B is in LD with SNV C, but SNV A and C are not in direct LD; SNV A, B and C would be part of the same locus set as SNV B is in LD with both A and C. The loci were then classified into three different types: (i) non-significant previously reported locus, if it contained at least one SNV from the set of previously reported-LD variants but did not reach any of the lookup thresholds so was not contained in the list of SNVs for replication, (ii) UK Biobank-GWAS locus, if it contained at least one SNV reaching the lookup criteria threshold from the GWAS discovery, (iii) UK Biobank-exome locus, otherwise, containing SNVs which exclusively came from the UK Biobank-exome discovery lookups and are not in LD with any of the GWAS discovery lookups and are therefore not contained in a UK Biobank-GWAS locus. All UK Biobank GWAS and exome top-loci were screened to check for the presence of previously reported LD variants, to distinguish our novel discovery loci from previously reported BP loci.

A second stage of loci assignment was performed on the novel and previously reported loci to identify potential secondary signals within these loci. Each novel locus was reduced only to the set of SNVs which met the lookup criteria thresholds, and these remaining SNVs were reassigned to new locus subsets by $r^2 \geq 0.2$, and denoted as signals. This allows the partitioning of loci into separate, independent signals, not in direct LD with each other, i.e. some loci may have multiple pairwise-independent ($r^2 < 0.2$) signals within a 1Mb region. Similarly, in order to identify potential secondary signals in the previously reported loci, each locus was reduced to the variants in LD meeting the lookup thresholds, and these variants were reassigned to new locus subsets. All subsets which contained at least one variant in direct LD with the previously reported SNVs were removed, leaving the remaining subsets as potential secondary signals. If validated, these potential secondary signals at novel and

previously reported loci could then be subsequently tested for statistical independence by conditional analysis.

These final sets, novel and previously reported, are referred to as the discovery association signals. For each discovery association signal we identified the most significantly associated SNV within the set, with minimum P -value across all three BP traits, and refer to this as the sentinel SNV. Similarly, for any novel loci containing multiple signals within the 1Mb locus region, the sentinel signal was identified as the most significant SNV.

All SNVs within the loci were mapped to genes (GRCh37.75) when the variant localized within 5kb of the start or end of the gene's transcription (bedtools v2.17). Any genes which were annotated from previously reported-LD variants were listed, and referred to as previously reported BP genes (**Supplementary Table 27**).

A signal was classified as secondary within a previously reported region if it satisfied at least one of the following conditions: i) it is a secondary signal from a locus that contains at least one previously reported-LD variant (as above), ii) at least one of the SNVs within the signal's corresponding locus maps to a previously reported BP gene or feature (**Supplementary Table 28**), such as long non-coding RNA, pseudogenes, or long non-coding transcripts, iii) the sentinel SNV is within 500kb of a previously reported BP-associated SNV, or iv) the signal is within the HLA region (chr 6: 25–34 Mb) as for simplicity, due to the complicated LD structure, we treat the entire HLA region as a previously reported BP region.

All other signals are classified as not previously reported, in order to be followed-up as potential novel loci.

8. Selection of variants for follow-up

For the primary discovery analysis, the sentinel signal SNV at each novel locus was considered for validation and then any other validated SNV signals within the 1Mb locus region were considered as potential secondary signals for conditional analysis investigation.

Due to the slightly different coverage from the imputation strategies and reference panels used by ICBP-1000G and UK Biobank, the list of UK Biobank-GWAS lookup signals was cross-referenced with the list of SNVs available within the ICBP-1000G data, in order to check that any SNVs selected for follow-up were covered within ICBP-1000G for possible replication. Of the total 235 SNVs selected for replication, 218 were covered within ICBP-1000G data, either directly or by proxies, or with an alternative SNV available within the locus. The proxies were in high LD with the sentinel SNV ($r^2 > 0.8$; using LD calculated within UK Biobank), for which the proxy with the highest r^2 , then closest position to the sentinel SNV was selected. For loci where the sentinel SNV was not covered either directly or by a proxy, the most significantly associated SNV across all BP traits with $P < 1 \times 10^{-6}$ within the LD set, which was covered within ICBP-1000G data, was selected as the alternative SNV. Only 17 loci could not be followed-up, due to a lack of coverage in the replication resources (**Supplementary Table 3**). However, most of these signals were sets containing only a few associated SNVs, including many 'singletons' with only one SNV within the LD set at the $P < 1 \times 10^{-6}$ lookup threshold, and therefore less likely to be covered in ICBP-1000G, and perhaps more likely to be potential spurious findings. We further checked that each SNV selected for follow-up had concordant single nucleotide polymorphism (SNP) vs Indel status in both UK Biobank and ICBP-1000G. Similarly, of the 54 previously reported BP loci containing potential secondary SNVs, 51 loci could be followed-up with the potential secondary

403 SNVs covered within ICBP-1000G data. In summary, a total of 218 SNVs from the GWAS discovery
404 association signals were requested for lookups.

405 9. **Replication datasets**

406 The following studies contributed to the replication of the UK Biobank-GWAS lookups. More
407 information on the individual cohorts can be found within **Supplementary Table 4** (study
408 characteristics, summary descriptives, genetic data information and quality control applied):

409 ICBP-1000G: The International Consortium for Blood Pressure GWAS 1000G analyses.

410 The individual studies who contributed to the ICBP-1000G discovery analyses are listed below:

411 AGES: Age, gene/Environment Susceptibility-Reykjavik Study

412 ARIC: Atherosclerosis Risk in Communities

413 ASPS: Austrian Stroke Prevention Study

414 B58C: British 1958 birth cohort

415 BHS: Busselton Health Study

416 CHS: Cardiovascular Health Study

417 COLAUS: Cohorte Lausannoise

418 COROGENE: Genetic Predisposition of Coronary Heart Disease in Patients Verified with Coronary
419 Angiogram (controls for this study are a part of the National FINRISK Studies)

420 CROATIA-Korcula: CROATIA-Korcula

421 CROATIA-Split: CROATIA-Split

422 CROATIA-Vis: CROATIA-Vis

423 EGCUT: Estonian Genome Center

424 EGCUT2: Estonian Genome Center

425 EPIC: European Prospective Investigation in Cancer and Nutrition

426 ERF: Erasmus Rucphen Family

427 Fenland Fenland Study

428 FHS: Framingham Heart Study

429 FINNRISK CASE: Predicting CVD in FINRISK cohorts, cases

430 FINRISK_ctrl: Predicting CVD in FINRISK cohorts, controls

431 FUSION: Finland-United States Investigation of NIDDM Genetics Study

432 GRAPHIC: Genetic Regulation of Ambulatory Blood Pressure in the Community

433 H2000: Health 2000 controls

434 Health ABC The Health Aging and Body Composition Study

435 HTO

436 INGI_VB: Italian Network of Genetic Isolates - Val Borbera

437 INGI-Cilento: Italian Network on Genetic Isolates - Carlantino Project

438 INGI-FVG: Genetic Park of Cilento and Vallo di Diano Project

439 INIG-CARL: Italian Network on Genetic Isolates - Friuli Venezia Giulia Genetic Park

440 IPM: Charles R. Bronfman Institute for Personalized Medicine (IPM) BioBank Genome Wide
441 Association Study of Cardiovascular, Renal and Metabolic Phenotypes

442 KORAS3: Kooperative Gesundheitsforschung in der Region Augsburg

443 KORAS4: Cooperative Health Research in the Region of Augsburg (Survey 4)

444 LBC1921: Lothian Birth Cohort 1921

445 LBC1921: Lothian Birth Cohort 1936

446 LOLIPOP_EW610: London Life Sciences Prospective Population Study

447 MESA: Multi-Ethnic Study of Atherosclerosis

448 MICROS: MICROS

449 MIGen: Myocardial Infarction Genetics Consortium

450 NESDA: Netherlands Study of Depression and Anxiety

451 NSPHS: The Northern Sweden Population Health Study

452 NTR: Netherlands Twin Register

453 ORCADES: Orkney Complex Disease Study

454 PHASE: Prospective Investigation of the Vasculature in Uppsala Seniors

455 PIVUS: Precocious Coronary Artery Disease

456 PROCARDIS: PHarmacogenetic Study of Statins in the Elderly at risk

457 RSI: Rotterdam Study 1

458 RSII: Rotterdam Study 2

459 RSIII: Rotterdam Study 3

460 SHIP: Study of Health in Pomerania

461 STR: Swedish Twin Register

462 TRAILS: Tracking Adolescents' Individual Live Surveys

463 TRAILS-CC: Tracking Adolescents' Individual Live Surveys - Clinical Cohort

464 ULSAM: Uppsala Longitudinal Study of Adult Men

465 WGHS: Women's Genome Health Study YFS The Young Finns Study

466 YFS: The Young Finns Study

467 ASCOT⁶: The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) includes (19,342 hypertensives)
468 enrolled in a randomised controlled trial of calcium channel blocker based regimen or a beta-blocker
469 based regimen with blood pressure greater than 140/90 mm Hg on treatment of 160/100 mm Hg off
470 treatment and followed for 5.5 years. Only a subset of the participants consented to DNA extraction
471 for genetic studies. Data was genotyped separately for patients from UK/Ireland (ASCOT-UK: N =
472 3,803) and Scandinavia (ASCOT-SC: N = 2,462).

473 BRIGHT⁷: The MRC British Genetics of Hypertension study (2,001 hypertensives) included white
474 European individuals with hypertension drawn from the upper 5% of the blood pressure distribution
475 and usually on treatment subjected to GWAS.

476 EGCUT⁸: The Estonian Biobank is the population-based biobank of the Estonian Genome Center of the
477 University of Tartu (EGCUT). The project is conducted according to the Estonian Gene Research Act
478 and all participants have signed broad informed consent. The cohort size is currently 51,535 people
479 from 18 years of age and up. All subjects are volunteers and were recruited randomly by general
480 practitioners (GP) and physicians in hospitals. A Computer Assisted Personal Interview is conducted at
481 the doctor's office to record personal data (place of birth, place(s) of living, nationality etc.),
482 genealogical data (family history spanning four generations), educational and occupational history,
483 lifestyle data (physical activity, dietary habits – food frequency questionnaire, smoking, alcohol
484 consumption, women's health, quality of life). The EGCUT database has been linked with the national
485 registries and hospital databases for obtaining up-to-date phenotypic information, including but not
486 limiting to Death Registry, Health Insurance Registry and epicrisis from major hospitals. Medical
487 history and current health status are recorded according to the ICD10, medication according to the
488 ATC. Anthropometric measurements, blood pressure (sitting position at the end of the interview), and
489 resting heart rate are measured; 30-50 mL of venous blood are collected into EDTA Vacutainers. These
490 are transported to the central laboratory of the EGCUT at +4...+6 °C (in 6 to 36h) where DNA, plasma
491 and WBC are immediately isolated and kept in aliquots in MAPI straws in liquid N₂. All procedures are
492 run according to ISO 9000-2008 (www.biobank.ee)

493 GenScot⁹: Generation Scotland: Scottish Family Health Study (GS:SFHS) is a family-based genetic
494 epidemiology study of ~24,000 volunteers from ~7000 families across Scotland with the capacity for
495 follow-up through record linkage and re-contact. Participants completed a demographic, health and
496 lifestyle questionnaire and provided biological samples including DNA, and ~21,500 participants
497 underwent detailed clinical assessment, including anthropometric, cardiovascular, respiratory,
498 cognition and mental health (<http://www.ed.ac.uk/generation-scotland>).

499 Lifelines¹⁰: This is a multi-disciplinary prospective population-based cohort study examining in a
500 unique three-generation design the health and health-related behaviours of 165,000 persons living in
501 the North East region of The Netherlands. It employs a broad range of investigative procedures in
502 assessing the biomedical, socio-demographic, behavioural, physical and psychological factors which
503 contribute to the health and disease of the general population, with a special focus on multimorbidity
504 and complex genetics. Details of the protocol have been described elsewhere
505 (<https://www.lifelines.nl/lifelines-research/news>).

506 PREVEND¹¹: The Prevention of RENal and Vascular ENd-stage Disease (PREVEND) study is an ongoing
507 prospective population-based study of individuals from the Netherlands, investigating the natural
508 course of increased levels of urinary albumin excretion and its relation to renal and cardiovascular
509 disease. Further details are available on the study website: www.prevend.org.

510

511 The following consortia contributed to the replication of the UK Biobank exome lookups:

512 European exome consortium¹²: Consortium comprises 51 studies from various European countries
513 within 3 contributing consortia (CHD exome+ consortium, ExomeBP consortium, T2D-
514 GENES/GoT2DGenes consortium). Samples from all studies were genotyped using a version of the
515 Illumina exome array. Central QC was performed to identify studies with QC issues and remove
516 variants failing quality thresholds. 3 quantitative traits were analysed (DBP, SBP, PP) with and without
517 applying inverse rank normalisation, and HTN was analysed as a binary trait. The 51 contributing
518 studies are: Airwave, ASCOT_SC, ASCOT_UK, 1958BC, BRIGHT_CASES, BRIGHT_CONTROLS, CROATIA-
519 Korcula, DIABNORD, EGCUT, FENLAND, FINRISK97/02, GS:SFHS, GLACIER_Controls, GODARTS_diab,
520 GODARTS_nondiab, GRAPHIC, HELICMANOLIS, HUNT, INCIPE, LBC1921, LBC1936, LIFELINES, MDC,
521 Northern Finland Birth Cohorts 1966 and 1986, OBB, PIVUS/ULSAM, TwinsUK, UHP, UKHLS, ADDITION,
522 DPS, DR'S EXTRA Study, FIN-D2D 2007, FINRISK 2007, FUSION, Health 2006/2008, Inter99, PPP, SDC,
523 SDR/ANDIS, VejleCases, VejleCtrl, CCHS, CGPS, CIHDS, EPIC-CVD, EPIC-InterAct, MORGAM, PROSPER,
524 WOSCOPS.

525 CHARGE BP exome consortium¹³: The CHARGE BP exome Consortium includes 16 studies from the
526 CHARGE+ consortium including a total of 146,562 samples, of which N=120,473 are European
527 ancestry. Samples from all studies were genotyped using Illumina Infinium Human Exome Array (v 1.0
528 or 1.1). QC was performed either centrally (10 studies) or by individual cohorts (6 studies) to identify
529 studies with QC issues and remove variants failing quality thresholds. Four quantitative traits (DBP,
530 SBP, mean arterial pressure, pulse pressure) were analysed with and without applying inverse rank
531 normalisation. Hypertension was analysed as a binary trait. The 16 contributing studies are: AGES,
532 ARIC, BioVU, CARDIA, CHS, FamHS, FHS, Health ABC, HRS, JHS, MESA, Mt. Sinai, Rotterdam Study, SHIP,
533 WGHS, Women's Health Initiative.

534 **10. Meta-analyses**

535 The UK Biobank-GWAS replication meta-analysis combined the ICBP-1000G meta-analysis data with
536 the lookup results from the seven other replication studies. As the ICBP-1000G data had been
537 generated from a large meta-analysis of many studies, N-effective was provided, calculated as the
538 product of the sample size and imputation quality per SNV within each study and summed over the
539 whole ICBP-1000G meta-analysis. We therefore used N-effective as the input N for ICBP-1000G within
540 METAL. For the seven individual studies, to take account of imputation quality and apply further QC
541 prior to analysis, SNVs with imputation quality < 0.3 were excluded from the meta-analysis input, and
542 sample size N was used for all remaining SNVs. Allele frequencies and strand alignments were tracked
543 for consistency within the meta-analysis. For consistency with the SNVs present in the replication data
544 sets, the results for the proxy SNVs were used within the UK Biobank discovery input for the variants
545 that required proxies or alternative SNVs to the sentinel SNVs for the UK Biobank-GWAS lookups.
546 Overall, sentinel and proxy SNVs had similar levels of association in the UK Biobank-BP discovery
547 analysis (**Supplementary Table 2**). Genomic control (GC) had already been applied to the ICBP-1000G
548 meta-analysis and their post-GC results were used as the input into our meta-analysis. No further GC
549 corrections were applied in METAL for our UK Biobank-GWAS replication or combined meta-analyses.

550 The UK Biobank-exome meta-analysis synthesized meta-analysis data of individuals of European
551 ancestry from two BP exome consortia (European exome consortium and CHARGE BP exome
552 consortium) for the lookup variants. As in the GWAS analysis the allele frequencies and strand
553 alignments were tracked for consistency within the meta-analysis.

11. Significance thresholds

We note that the standard genome-wide significance threshold ($P < 5 \times 10^{-8}$) is suitable for validation from our combined meta-analysis. The UK Biobank-GWAS analysis follows up 9.8 million SNVs with $MAF \geq 1\%$ and coverage in 1000G data, while recent simulations in the literature¹⁴ suggest a similar significance threshold of $P < 3 \times 10^{-8}$ based on denser Whole-Genome Sequencing (WGS) studies filtered at $MAF \geq 1\%$ with an LD-independence r^2 threshold of 0.8. In addition, we require replication support of $P < 0.01$ which is more stringent than a range of thresholds calculated according to False Discovery Rate (FDR) which gives FDR thresholds of $0.03 < P < 0.04$ using the approaches proposed by Benjamini and Hochberg¹⁵ and Benjamini and Yekutieli¹⁶ respectively. As a further protection against false positive findings, we require concordance in direction of effect between the discovery and replication resources.

12. Conditional analyses

Within the novel loci containing potential secondary validated SNVs within the 1Mb locus region, i.e. in addition to the sentinel SNV, conditional analysis was performed, conditioning on the sentinel SNV, to test for independence of the secondary SNV according to a 1.5 fold threshold for reduction in P -value, with adjustment for covariates as in the discovery GWAS. For novel loci with more than one secondary SNV, conditional analysis results were considered for all pairwise combinations of SNVs within the locus, sequentially in order of main discovery association significance, to conclude with a set of pairwise conditionally independent SNV association signals.

For previously reported loci, each validated secondary known signal is matched to its corresponding locus according to the criteria which defined it as a secondary signal at that locus, i.e. either (i) the locus that it was partitioned from during the annotation pipeline, (ii) matching according to the annotated gene in common, or (iii) the locus containing the previously reported SNV which is within 500kb. As noted above, signals within the HLA region were excluded from further conditional analysis. For each of these loci the previously reported SNV(s) within the region are listed (**Supplementary Table 12**). Within SNPTEST, a conditional analysis is run for each previously reported region containing a validated secondary signal, allowing the region of analysis to cover both the previously reported locus and the secondary signal.

Further rounds of conditional analysis are performed for regions containing more than one independent validated secondary signal. The secondary signals are ordered by significance according to the UK Biobank discovery association P -values for their validated BP trait, and a second round of analysis then conditions further on the most associated secondary signal as well as the sentinel SNV to assess whether any further SNVs pass the 1.5 fold threshold test of independence. This iterative conditioning process continues until no remaining secondary SNVs pass the conditional test.

13. Lookups in non-European ancestries

The following consortia and studies contributed to the non-European ancestry lookups:

iGEN-BP¹⁷: The International Genomics of Blood Pressure Consortium (iGEN-BP) genome-wide association was analyzed in a total of 31,516 individuals of East Asian ancestry and 33,126 of South Asian ancestry. Imputation was carried out using haplotypes from HapMap Phase 2. Quality control checks included on the distribution of effect sizes across phenotypes and comparison of allele frequencies against those expected from HapMap populations. There were between 2,127,883 (SBP) and 2,166,286 (hypertension) SNPs for analysis after quality control. Associations of SNPs with

phenotype were tested in each cohort separately in single-marker tests, using regression analysis and an additive genetic model. Principal components and other study-specific factors were included as covariates to account for population substructure. Test statistics from each cohort were then corrected for their respective genomic control inflation factor to adjust for residual population substructure. SNPs with information score <0.5 and minor allele frequency (MAF) <1% (weighted average across the cohorts) as well as sample size <50% of the maximum n for the phenotype were removed. SNPs showing heterogeneity of effect ($P_{\text{het}} < 1 \times 10^{-8}$) were also removed. The 23 studies contributing to the East Asian ancestry meta-analysis are: AASC, CAGE-Amagasaki, CAGE_GWAS1, CAGE-KING_Omni, CAGE-KING_Quad, CLHNS, GenSalt, KARE, NHAPC, SCES, SiMES, SP2-1m, SP2-550, SP2-610, SRS_Cases, SRS_Controls, TWSC, Vanderbilt_birdsuite, Vanderbilt_panscan, Vanderbilt_CRC_GWAS (SHANGHAI1), Vanderbilt_CRC_GWAS (SHANGHAI2), Vanderbilt_upperGI (SMHS), Vanderbilt_upperGI (SWHS). The 13 studies contributing to the South Asian ancestry meta-analysis are: AIDHS/SDS_Cases, AIDHS/SDS_Controls, LOLIPOP_IA300, LOLIPOP_IA610_Cases, LOLIPOP_IA610_Controls, LOLIPOP_IAP, PROMIS_GWAS1_Cases, PROMIS_GWAS1_Controls, PROMIS_GWAS2_Cases, PROMIS_GWAS2_Controls, RHS, RHS_610K, SINDI.

The CHD exome+ consortium¹⁸ contributed South Asian samples from two studies: N=5,756 individuals from BRAVE (Bangladesh Risk of Acute Vascular Events study) and N=22,094 individuals from PROMIS (Pakistan Risk of Myocardial Infarction Study; <http://www.phpc.cam.ac.uk/ceu/research/promis/>).

CHARGE BP exome consortium¹³: The CHARGE BP Exome Consortium also contributed samples of African (N=21,503) and Hispanic (N=4,586) ancestry.

Note: Only SNVs available in at least 60% of the samples within each study were considered within the non-European lookup analyses.

14. Airwave Study data

The Airwave Health Monitoring Study (Airwave)¹⁹ was used as an independent cohort for risk score analyses (see Methods Online) and for analysis of metabolomics data. The Airwave analyses included 14,002 participants with imputed genetic data. Systolic and diastolic blood pressures were measured as three consecutive readings using a digital blood pressure monitor (Omron HEM 705-CP digital BP monitor). Mean SBP and DBP adjusted for medication (as previously defined) were calculated from available readings and were used as dependent variables in the analyses.

Genetic risk scores (GRS) were constructed from a combination of both previously reported and validated novel SNVs. Genetic dosages were extracted from the Airwave 1000G imputed data, extending to proxies ($r^2 > 0.8$) if required. The previously reported BP variants were filtered by LD (r^2 of 0.2) and of the remaining 152 independent SNVs, 144 SNVs were covered exactly, and proxies were available for another 2 SNVs, providing a total of 146 pairwise-independent SNVs. All the 115 validated novel variants were available in the Airwave data. Weights were applied to all previously reported and novel SNVs in the GRS, as described in the Online Methods and in Supplementary Table 21.

From the Airwave plasma ¹H NMR metabolomics dataset measured using MRC-NIHR National Phenome Centre protocols, we undertook a lipoprotein subclass analysis using a regression-based prediction of lipid concentrations to characterise lipids (cholesterol, free cholesterol, phospholipids and triglycerides) and apolipoproteins (Apo-A1, ApoA2 and Apo-B) for VLDL, IDL, LDL and HDL classes, as well as six subclasses of VLDL and LDL and four subclasses HDL (data provided by Brucker Biospin GmbH, Rheinstetten Germany²⁰). Overall, 105 different lipoprotein subclasses were generated from the deconvolution the CH₃-group signal of the lipoproteins at 0.8ppm. (**Supplementary Table 19**).

15. Cardiovascular outcomes data in UK Biobank

To classify cardiovascular disease (CVD) outcomes we used self-reported baseline information on CVD prevalence available in UKB, and linkage to Hospital Episodes Statistics (HES) and mortality data. HES provide detailed information for participants admitted to hospital and includes coded data on diagnoses and operations. Coronary artery disease, stroke and peripheral artery disease were classified using International Classification of Disease (ICD) 9 and 10 codes and operation codes (**Supplementary Table 24**). The large UK Biobank cohort with sufficient numbers of cardiovascular events enables the assessment of cardiovascular risk within the same data set, noting that results are still independent, as the variants within the GRS are selected for their association with BP, not for cardiovascular outcomes.

16. Functional analyses

A structured approach was used to identify candidate regulatory variants, using two sources of regulatory information for annotation: ENCODE annotated DNase I sites in 123 cell types (wgEncodeAwgDnaseMasterSites) and a reference data set of over 3 million DNase “footprint variants”. Footprint variants were defined by Moyerbrailean et al, (2016)²¹ from a set of functional regulatory regions that integrate sequence position weight matrices with ENCODE and NIH Roadmap DNase I footprinting data to predict the impact of a sequence change on transcription factor binding in a panel of 650 cell-types. All variants in LD ($r^2 \geq 0.8$) with the sentinel SNV were reviewed and the variant with the lowest imputed *P*-value (for the same trait association as the sentinel) overlapping a DNase site was selected as the best regulatory candidate in each locus.

Hi-C analyses: Since SNVs in intergenic regulatory regions may act through long-range promoter-enhancer/silencer chromatin interactions, we aim to identify distant target genes of SNVs using chromatin folding data. Chromatin interaction can be assayed with the Hi-C technique, which identifies interacting genomic regions from the number of paired-end sequence reads that connect two genomic regions after crosslinking the cells, digesting the genome with a restriction enzyme and ligating fragment ends that are held together by 3D chromatin interactions. The 3D folding of the genome is tissue specific, therefore In order to identify potential target genes of SNVs, we used a cell type relevant to the BP phenotype, human umbilical vein endothelial cells (HUVEC)²²

To find regulatory loops, from the identified novel GWAS loci, we took the location of either the sentinel SNV, if it was in a DNase hypersensitivity site (DHS), or the next most significant SNV for the same trait within a DHS and therefore potentially a regulatory SNV. Then using 5kb resolution HUVEC Hi-C data, taking only reads MAPQ>30, we identified the strongest SNV interacting regions after Knight&Ruiz (KR) normalisation of interaction strength and distance normalization. Taking the strongest interaction where the interacting region overlapped with a promoter region, as annotated by the ChIPseeker R package, we defined the potential target genes of these regulatory SNVs.

Enrichment testing: In order to distinguish enrichment of the novel discovery from the previously reported variants, we performed two sets of enrichment analyses. The first only included the novel SNVs and their proxies in high LD ($r^2 \geq 0.8$) (**Table 1**), and the second investigated all novel SNVs together with previously reported and secondary SNVs and their proxies in high LD ($r^2 \geq 0.8$). The two analyses allow us to identify properties of our novel findings as well as highlighting mechanisms (e.g. pathways, tissues, cells, etc.) for all BP-associated variants.

FORGE²³ analysis: FORGE compares the frequency of query SNVs in different cell types with a reference set of 1204 control SNVs from the NHGRI GWAS catalog with discovery *P*-values $< 5 \times 10^{-8}$ in European

ancestry populations. For each cell-type and *P*-value threshold, the enrichment of query SNVs mapping to footprints is expressed as a *P*-value derived from a logistic mixed effect model.

GenomeRunner²⁴ analysis of histone marks: GenomeRunner tests whether co-localization of a set of BP-associated SNVs with genome annotation features is significantly different from what would be expected by chance for a similar sized random set of SNVs. Tracks of histone modifications obtained by ChIP-seq from ENCODE were used for the assessment of histone marks, and significant enrichment of histone marks was investigated in a wide range of cell types. We also tested for cell type specificity of enrichments of SNV sets, which compares whether a cell type-specific enrichment is significantly different from the overall enrichment of a SNV set.

Fantom5²⁵ analysis of tissue clustering: Cardiovascular relevant tissue expression was investigated, using Fantom5 reference transcript expression data (fantom.gsc.riken.jp/5). Kmeans clustering was performed on novel BP-associated genes with Gene Cluster 3.0²⁶ using a Euclidean distance similarity matrix and K=5. Clusters were visualized using Java Treeview²⁷.

17. Experimental studies

Gene expression associated with sentinel SNVs in *SF3A3*, *ADAMTS7*, *NOX4* was tested using vascular smooth muscle cells (VSMCs) and endothelial cells (ECs) isolated from human umbilical cord artery and vein (Royal London hospital, UK) respectively according to established protocol²⁸, and approved by the appropriate local ethics committee (08/H0704/140). VSMCs and ECs were harvested from flasks and suspended in 500μL lysis buffer (10 mM Tris PH 8.0, 10 mmol/L EDTA, 100 mmol/L NaCl, 0.5 % w/v SDS), and were then administered 250μL 5mmol/L NaCl. The mixture was centrifuged at 12,000g for 5min and the supernatant transferred to a fresh eppendorf then 500μL isopropanol added. The DNA pellet was collected and washed with 500μL 70% ethanol, then resolved in 40μL nuclear free water. The concentration of DNA was quantified by NanoDrop and adjusted to 5ng/μL for further genotyping. The Kbiosciences Competitive Allelic-specific PCR SNP genotyping system (KASPar; LGC Genomics Kbiosciences) was used for genotyping according to product introductions. Primers targeting the allelic specific DNA amplification were designed by Primer-Picker (Kbiosciences) (**Supplementary Table 29**). 10ng DNA from each sample plus the master mix was plated in a 384-well plate and subjected to PCR (ABI 7900HT machine).

Total RNA was extracted from human VSMCs and ECs, using the SV total RNA isolation system (Promega), then reverse transcribed into complementary DNA (cDNA) with the ImProm-ITM Reverse Transcription System (Promega) according to manufacturer's instructions. qRT-PCR for *SF3A3*, *ADAMTS7*, *NOX4* and 18S (internal control) was performed on cDNA in duplicate by using Power Up SYBR® Green PCR Master Mix kit (Life Technologies) according to the product guide using real-time quantitative PCR instrument (ABI 7900HT machine). Three pairs of primers were designed (**Supplementary Table 29**) and tested specificity and only primer pairs that had good specificity were chosen for the qPCR. The expression levels of *SF3A3*, *ADAMTS7* and *NOX4* relative to 18S from independently repeated experiments were then determined by the $2^{-\Delta\Delta Ct}$ method²⁹.

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817 ⁽⁵⁾, E.F.C. van Rossum ⁽⁶⁾, H.A. Smit ⁽⁷⁾, M. Swertz ⁽⁸⁾, E.A.L.M. Verhagen ⁽⁹⁾

818 ⁽¹⁾ Department of Social Medicine, University Medical Center Groningen, University of
819 Groningen, The Netherlands

820 ⁽²⁾ Department of Human Nutrition, Wageningen University, The Netherlands

821 ⁽³⁾ Department of Cardiology, University Medical Center Groningen, University of Groningen,
822 The Netherlands

823 ⁽⁴⁾ Lifelines Cohort Study, The Netherlands

824 ⁽⁵⁾ Interdisciplinary Center of Psychopathology of Emotion Regulation (ICPE), Department of
825 Psychiatry, University Medical Center Groningen, University of Groningen, The Netherlands

826 ⁽⁶⁾ Department of Endocrinology, Erasmus Medical Center, Rotterdam, The Netherlands

827 ⁽⁷⁾ Department of Public Health, University Medical Center Utrecht, The Netherlands

828 ⁽⁸⁾ Department of Genetics, University Medical Center Groningen, University of Groningen, The
829 Netherlands

830 ⁽⁹⁾ Department of Public and Occupational Health, VU Medical Center, Amsterdam, The
831 Netherlands

832

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850

851

Consortium Members

852 CHD Exome+ Consortium

853 Praveen Surendran¹, Robin Young¹, Daniel R. Barnes¹, James R. Staley¹, Daniel F. Freitag¹, Sune
854 Fallgaard. Nielsen², Asif Rasheed³, Maria Samuel³, Wei Zhao⁴, Jukka Kontto⁵, Markus Perola^{5,6,7}, Muriel
855 Caslake⁸, Anton JM. de Craen^{9,10}, Stella Trompet^{9,11}, Maria Uria-Nickelsen¹², Anders Malarstig¹³,
856 Dermot F. Reily¹⁴, Maarten Hoek¹⁵, Thomas Vogt¹⁵, J Wouter. Jukema^{11,16}, Naveed Sattar¹⁷, Ian Ford⁸,
857 Chris J. Packard⁸, Dewan S. Alam¹⁸, Abdulla al Shafi. Majumder¹⁹, Emanuele Di Angelantonio^{1,20}, Rajiv
858 Chowdhury¹, Philippe Amouyel^{21,22,23,24}, Dominique Arveiler²⁵, Stefan Blankenberg^{26,27}, Jean
859 Ferrières²⁸, Frank Kee²⁹, Kari Kuulasmaa⁵, Martina Müller-Nurasyid^{30,31,32}, Giovanni Veronesi³³, Jarmo
860 Virtamo⁵, EPIC-CVD Consortium³⁴, Philippe Frossard³, Børge Grønne. Nordestgaard², Danish
861 Saleheen^{4,3,1}, John Danesh^{1,35,20}, Adam S. Butterworth^{1,36}, Joanna MM. Howson¹

- 862 1. Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of
863 Cambridge, Cambridge, UK
- 864 2. Department of Clinical Biochemistry Herlev Hospital, Copenhagen University Hospital, Herlev,
865 Denmark
- 866 3. Centre for Non-Communicable Diseases, Karachi, Pakistan
- 867 4. Department of Biostatistics and Epidemiology, Perelman School of Medicine, University of
868 Pennsylvania, Philadelphia, Pennsylvania, USA
- 869 5. Department of Health, National Institute for Health and Welfare, Helsinki, Finland
- 870 6. Institute of Molecular Medicine FIMM, University of Helsinki, Finland
- 871 7. Estonian Genome Center, University of Tartu, Tartu, Estonia
- 872 8. University of Glasgow, Glasgow, UK
- 873 9. Department of Gerontology and Geriatrics, Leiden University Medical Center, Leiden, The
874 Netherlands
- 875 10. Mr. De Craen suddenly passed away January 2016
- 876 11. Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands
- 877 12. Development Management and Planning, Pfizer Worldwide Research and Development
- 878 13. Pfizer Worldwide Research and Development, Stockholm, Sweden
- 879 14. Genetics and Pharmacogenomics, Merck Research Laboratories, Boston, Massachusetts, USA.
- 880 15. Merck Research Laboratories, Kenilworth, New Jersey, USA
- 881 16. The Interuniversity Cardiology Institute of the Netherlands, Utrecht, The Netherlands
- 882 17. Institute of Cardiovascular and Medical Sciences, College of Medical, Veterinary and Life
883 Sciences, University of Glasgow, Glasgow, UK
- 884 18. ICDDR, B; Mohakhali, Dhaka, Bangladesh
- 885 19. National Institute of Cardiovascular Diseases, Sher-e-Bangla Nagar, Dhaka, Bangladesh
- 886 20. The National Institute for Health Research Blood and Transplant Research Unit in Donor Health
887 and Genomics, University of Cambridge, Cambridge, UK
- 888 21. University of Lille, Risk Factors and Molecular Determinants of aging-related diseases, Lille,
889 France
- 890 22. Inserm, Lille, France
- 891 23. Centre Hospitalier Universitaire Lille, Public Health, Lille, France
- 892 24. Institute Pasteur de Lille, Lille, France
- 893 25. Department of Epidemiology and Public Health, EA 3430, University of Strasbourg, Strasbourg,
894 France
- 895 26. Department of General and Interventional Cardiology, University Heart Center Hamburg,
896 Germany

- 897 27. University Medical Center Hamburg-Eppendorf, Hamburg, Germany
898 28. Department of Epidemiology, UMR 1027- INSERM, Toulouse University-CHU Toulouse, Toulouse,
899 France
900 29. Director, UKCRC Centre of Excellence for Public Health, Queens University, Belfast, Northern
901 Ireland
902 30. Institute of Genetic Epidemiology, Helmholtz Zentrum München - German Research Center for
903 Environmental Health, Neuherberg, Germany
904 31. Department of Medicine I, University Hospital Grosshadern, Ludwig-Maximilians-Universität,
905 Munich, Germany
906 32. DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich,
907 Germany
908 33. Research Center in Epidemiology and Preventive Medicine, Department of Clinical and
909 Experimental Medicine, University of Insubria, Varese, Italy
910 34. A full list of members and affiliations appears in the Supplementary Note
911 35. Wellcome Trust Sanger Institute, Hinxton, UK
912 36. The National Institute for Health Research Blood and Transplant Research
913
914

915 **Exome BP Consortium**

916 Fotios Drenos ^{1,2}, Helen Warren ^{3,4}, James P Cook ^{5,6}, Kate Witkowska ^{3,4}, Vinicius Tragante ⁷, Hanieh
 917 Yaghootkar ⁸, Nicholas Masca ^{9,10}, Teresa Ferreira ¹¹, Olga Giannakopoulou ¹², Andrew Tinker ^{12,4},
 918 Magdalena Harakalova ⁷, Evelin Mihailov ¹³, Lorraine Southam ^{11,14}, Jonathan Marten ¹⁵, Cristiano Fava
 919 ^{16,17}, Therese Ohlsson ¹⁶, Angela Matchan ¹⁴, Kathleen E Stirrups ^{12,18}, Susan Shaw-Hawkins ³, Aki S
 920 Havulinna ¹⁹, He Zhang ²⁰, Louise A Donnelly ²¹, Christopher J Groves ²², N William Rayner ^{22,11,14}, Matt
 921 J Neville ^{22,23}, Neil R Robertson ^{11,22}, Andrianos M Yiorkas ^{24,25}, Karl-Heinz Herzig ^{26,27}, Eero Kajantie
 922 ^{19,28,29}, Weihua Zhang ^{30,31}, Lars Lannfelt ³², Giovanni Malerba ³³, Nicole Soranzo ^{34,18,35}, Elisabetta
 923 Trabetti ³³, Niek Verweij ^{36,38,37}, Evangelos Evangelou ^{30,39}, Alireza Moayyeri ^{30,40}, Anne-Claire Vergnaud
 924 ³⁰, Christopher P Nelson ^{9,10}, Alaitz Poveda ^{41,42}, Tibor V Varga ⁴¹, Jian'an Luan ⁴³, Robert A Scott ⁴³, Sarah
 925 E Harris ^{44,45}, David CM Liewald ^{44,46}, Riccardo Marioni ^{44,45,47}, Cristina Menni ⁴⁸, Aliko-Eleni Farmaki ⁴⁹,
 926 Göran Hallmans ⁵⁰, Frida Renström ^{41,50}, Jennifer E Huffman ^{15,23}, Ozren Polasek ^{51,52}, Igor Rudan ⁵¹, Paul
 927 W Franks ^{41,53,54}, George Dedoussis ⁴⁹, Timothy D Spector ⁴⁸, Ian J Deary ^{44,46}, John M Starr ^{44,55}, Nick J
 928 Wareham ⁴³, Morris J Brown ¹², Anna F Dominiczak ⁵⁶, John M Connell ²¹, Tõnu Esko ^{13,57,38}, Reedik Mägi
 929 ¹³, Andres Metspalu ^{13,58}, Rudolf A de Boer ⁵⁹, Peter van der Meer ⁵⁹, Pim van der Harst ^{59,60,61}, Giovanni
 930 Gambaro ⁶², Erik Ingelsson ^{63,64}, Lars Lind ⁶³, Paul IW de Bakker ^{65,66}, Mattijs E Numans ^{67,66}, John C
 931 Chambers ^{30,31,68}, Jaspal S Kooner ^{31,69,65}, Alexandra IF Blakemore ^{24,25}, Steve Franks ⁷⁰, Marjo-Riitta
 932 Jarvelin ^{71,72,73,74}, Fredrik Karpe ^{22,23}, Jaakko Tuomilehto ^{19,75,76,77}, Alex SF Doney ²¹, Andrew D Morris ⁷⁸,
 933 Colin Palmer ²¹, Oddgeir Lingaas Holmen ^{79,80}, Kristian Hveem ^{79,81}, Cristen J Willer ^{20,82,83}, Aarno Palotie
 934 ^{38,84,85}, Samuli Ripatti ^{84,86,14}, Veikko Salomaa ¹⁹, Mark I McCarthy ^{22,23,11}, Neil Poulter ⁸⁷, Alice V Stanton
 935 ⁸⁸, Peter Sever ⁸⁷, Panos Deloukas ^{12,89}, Paul Elliott ⁷¹, Eleftheria Zeggini ¹⁴, Sekar Kathiresan ^{37,91,90,38},
 936 Olle Melander ¹⁶, Sandosh Padmanabhan ⁵⁶, David Porteous ⁴⁵, Caroline Hayward ¹⁵, Martin D Tobin ⁵,
 937 Mark J Caulfield ^{3,4}, Anubha Mahajan ¹¹, Andrew P Morris ^{11,6}, Maciej Tomaszewski ^{9,10,92}, Nilesh J
 938 Samani ^{9,10}, Folkert W Asselbergs ^{7,61,93}, Cecilia M Lindgren ^{94,38,11}, Louise V Wain ⁵, Patricia B Munroe
 939 ^{3,4}

- 940
- 941 1. Medical Research Council Integrative Epidemiology Unit, School of Social and Community
 942 Medicine, University of Bristol, Oakfield House, Oakfield Grove, Bristol, UK
- 943 2. Centre for Cardiovascular Genetics, Institute of Cardiovascular Science, Rayne Building University
 944 College London, London, UK
- 945 3. Clinical Pharmacology, William Harvey Research Institute, Queen Mary University of London,
 946 London, UK
- 947 4. National Institute for Health Research Barts Cardiovascular Biomedical Research Unit, Queen Mary
 948 University of London, London, UK
- 949 5. Department of Health Sciences, University of Leicester, Leicester, UK
- 950 6. Department of Biostatistics, University of Liverpool, Liverpool, UK
 951 and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
- 952 7. Department of Cardiology, University Medical Center Utrecht, Utrecht, The Netherlands
- 953 8. Genetics of Complex Traits, Institute of Biomedical and Clinical Science, University of Exeter
 954 Medical School, Exeter, UK
- 955 9. Department of Cardiovascular Sciences, University of Leicester, Leicester, UK
- 956 10. National Institute for Health Research Leicester Biomedical Research Unit in Cardiovascular
 957 Disease, Leicester, UK
- 958 11. Wellcome Trust Centre for Human Genetics, Nuffield Department of Medicine, University of
 959 Oxford, Oxford, UK
- 960 12. Heart Centre, William Harvey Research Institute, Barts and The London School of Medicine and

961 Dentistry, Queen Mary University of London, London, UK
 962 13. Estonian Genome Center, University of Tartu, Tartu, Estonia
 963 14. Wellcome Trust Sanger Institute, Genome Campus, Hinxton, UK
 964 15. Medical Research Council Human Genetics Unit, Medical Research Council Institute of Genetics
 965 and Molecular Medicine, University of Edinburgh, Edinburgh, UK
 966 16. University of Lund, Department of Clinical Sciences, Malmö, Sweden
 967 17. University of Verona, Department of Medicine, Verona, Italy
 968 18. Department of Haematology, University of Cambridge, Cambridge, UK
 969 19. Department of Health, National Institute for Health and Welfare, Helsinki, Finland
 970 20. Department of Internal Medicine, Division of Cardiovascular Medicine, University of Michigan,
 971 Ann Arbor, Michigan, USA
 972 21. Medical Research Institute, University of Dundee, Ninewells Hospital and Medical School,
 973 Dundee, UK
 974 22. Oxford Centre for Diabetes, Endocrinology, and Metabolism, Radcliffe Department of Medicine,
 975 University of Oxford, Oxford, UK
 976 23. National Institute for Health Research Oxford Biomedical Research Centre, Oxford University
 977 Hospital Trusts, Oxford, UK
 978 24. Section of Investigative Medicine, Imperial College London, London, UK
 979 25. Department of Life Sciences, Brunel University London, London, UK
 980 26. Institute of Biomedicine, Biocenter Oulu, University of Oulu, Oulu, Finland
 981 27. Department of Gastroenterology and Metabolism, Poznan University of Medical Sciences,
 982 Poznan, Poland
 983 28. Hospital for Children and Adolescents, Helsinki University Central Hospital and University of
 984 Helsinki, Helsinki, Finland
 985 29. Department of Obstetrics and Gynaecology, Oulu University Hospital and University of Oulu,
 986 Oulu, Finland
 987 30. Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London,
 988 London, UK
 989 31. Department of Cardiology, Ealing Hospital, Middlesex, UK
 990 32. Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden
 991 33. Section of Biology and Genetics, Department of Neurosciences, Biomedicine and Movement
 992 Sciences, University of Verona, Verona, Italy
 993 34. Human Genetics, Wellcome Trust Sanger Institute, Hinxton, UK
 994 35. The National Institute for Health Research Blood and Transplant Research Unit in Donor Health
 995 and Genomics, University of Cambridge, Cambridge, UK
 996 36. University Medical Center Groningen, University of Groningen, Department of Cardiology, The
 997 Netherlands
 998 37. Center for Human Genetic Research, Massachusetts General Hospital, Boston, Massachusetts,
 999 USA
 1000 38. Program in Medical and Population Genetics, Broad Institute, 7 Cambridge Center,
 1001 Cambridge, Massachusetts, USA
 1002 39. Department of Hygiene and Epidemiology, University of Ioannina Medical School, Ioannina,
 1003 Greece
 1004 40. Farr Institute of Health Informatics Research, Institute of Health Informatics, University College
 1005 London, London, UK

- 1006 41. Department of Clinical Sciences, Genetic and Molecular Epidemiology Unit, Lund University,
1007 Malmö, Sweden
- 1008 42. Department of Genetics, Physical Anthropology and Animal Physiology, Faculty of Science and
1009 Technology, University of the Basque Country (UPV/EHU), Bilbao, Spain
- 1010 43. Medical Research Council Epidemiology Unit, University of Cambridge School of Clinical
1011 Medicine, Box 285 Institute of Metabolic Science, Cambridge Biomedical Campus, Cambridge, UK
- 1012 44. Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK
- 1013 45. Centre for Genomic and Experimental Medicine, Medical Research Council Institute of Genetics
1014 and Molecular Medicine, University of Edinburgh, Edinburgh, UK
- 1015 46. Department of Psychology, University of Edinburgh, Edinburgh, UK
- 1016 47. Queensland Brain Institute, The University of Queensland, Brisbane, Queensland, Australia
- 1017 48. Department of Twin Research and Genetic Epidemiology, King's College London, UK
- 1018 49. Department of Nutrition and Dietetics, School of Health Science and Education, Harokopio
1019 University, Athens, Greece
- 1020 50. Department of Biobank Research, Umeå University, Umeå, Sweden
- 1021 51. Centre for Global Health Research, Usher Institute for Population Health Sciences and
1022 Informatics, University of Edinburgh, Edinburgh, UK
- 1023 52. Faculty of Medicine, University of Split, Croatia
- 1024 53. Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden
- 1025 54. Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts, USA
- 1026 55. Alzheimer Scotland Research Centre, University of Edinburgh, Edinburgh, UK
- 1027 56. Institute of Cardiovascular and Medical Sciences, College of Medical, Veterinary and Life
1028 Sciences, University of Glasgow, Glasgow, UK
- 1029 57. Division of Endocrinology, Boston Children's Hospital, Boston, Massachusetts, USA
- 1030 58. Institute of Molecular and Cell Biology, Tartu, Estonia
- 1031 59. Department of Cardiology, University of Groningen, University Medical Center Groningen,
1032 Groningen, The Netherlands
- 1033 60. Department of Genetics, University of Groningen, University Medical Center Groningen,
1034 Groningen, The Netherlands
- 1035 61. Durrer Center for Cardiogenetic Research, ICIN-Netherlands Heart Institute, Utrecht, The
1036 Netherlands
- 1037 62. Division of Nephrology, Department of Internal Medicine and Medical Specialties, Columbus -
1038 Gemelli University Hospital, Catholic University, Rome, Italy
- 1039 63. Department of Medical Sciences, Molecular Epidemiology and Science for Life Laboratory,
1040 Uppsala University, Uppsala, Sweden
- 1041 64. Department of Medicine, Division of Cardiovascular Medicine, Stanford University School of
1042 Medicine, Stanford, California, USA
- 1043 65. Department of Medical Genetics, Center for Molecular Medicine, University Medical Center
1044 Utrecht, Utrecht, The Netherlands
- 1045 66. Department of Epidemiology, Julius Center for Health Sciences and Primary Care, University
1046 Medical Center Utrecht, Utrecht, The Netherlands
- 1047 67. Department of Public Health and Primary Care, Leiden University Medical Center, Leiden, The
1048 Netherlands
- 1049 68. Imperial College Healthcare NHS Trust, London, UK
- 1050 69. National Heart and Lung Institute, Imperial College London, London, UK

1051 70. Institute of Reproductive and Developmental Biology, Imperial College London, London, UK
 1052 71. Department of Epidemiology and Biostatistics, Medical Research Council Public Health England
 1053 Centre for Environment and Health, School of Public Health, Faculty of Medicine, Imperial College
 1054 London, St. Mary's Campus, London, UK
 1055 72. Centre for Life Course Epidemiology, Faculty of Medicine, University of Oulu, Oulu, Finland
 1056 73. Biocenter Oulu, University of Oulu, Oulu, Finland
 1057 74. Unit of Primary Care, Oulu University Hospital, Oulu, Finland
 1058 75. Dasman Diabetes Institute, Dasman, Kuwait
 1059 76. Centre for Vascular Prevention, Danube-University Krems, Krems, Austria
 1060 77. King Abdulaziz University, Jeddah, Saudi Arabia
 1061 78. School of Molecular, Genetic and Population Health Sciences, University of Edinburgh, Medical
 1062 School, Teviot Place, Edinburgh, UK
 1063 79. HUNT Research Centre, Department of Public Health and General Practice, Norwegian University
 1064 of Science and Technology, Levanger, Norway
 1065 80. St. Olav Hospital, Trondheim University Hospital, Trondheim, Norway
 1066 81. Department of Medicine, Levanger Hospital, Nord- Trøndelag Health Trust, Levanger, Norway
 1067 82. Department of Computational Medicine and Bioinformatics, University of Michigan, Ann Arbor,
 1068 Michigan, USA
 1069 83. Department of Human Genetics, University of Michigan, Ann Arbor, Michigan, USA
 1070 84. Institute for Molecular Medicine Finland University of Helsinki, Helsinki, Finland
 1071 85. Psychiatric and Neurodevelopmental Genetics Unit, Department of Psychiatry, Massachusetts
 1072 General Hospital, Boston, Massachusetts, USA
 1073 86. Department of Public Health, University of Helsinki, Finland
 1074 87. International Centre for Circulatory Health, Imperial College London, UK
 1075 88. Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland, Dublin, Ireland
 1076 89. Princess Al-Jawhara Al-Brahim Centre of Excellence in Research of Hereditary Disorders (PACER-
 1077 HD), King Abdulaziz University, Jeddah, Saudi Arabia
 1078 90. Cardiovascular Research Center, Massachusetts General Hospital, Boston, Massachusetts, USA
 1079 91. Department of Medicine, Harvard Medical School, Boston, Massachusetts, USA
 1080 92. Institute of Cardiovascular Sciences, University of Manchester, Manchester, UK
 1081 93. Faculty of Population Health Sciences, Institute of Cardiovascular Science, University College
 1082 London, London, UK
 1083 94. The Big Data Institute at the Li Ka Shing Centre for Health Information and Discovery, University
 1084 of Oxford, Oxford, UK
 1085
 1086
 1087

1088 **Members of the Genetics of Type 2 Diabetes (GoT2D) and Type 2 Diabetes Genetic Exploration by**
 1089 **Next-generation sequencing in multi-Ethnic Samples**
 1090 **(T2D-GENES) Consortia (<http://type2diabetesgenetics.org>)**
 1091
 1092 Christian Fuchsberger¹, Jason Flannick^{2,3}, Tanya M Teslovich¹, Anubha Mahajan⁴, Vineeta Agarwala^{2,5},
 1093 Kyle J Gaulton⁴, Clement Ma¹, Pierre Fontanillas², Loukas Moutsianas⁴, Davis J McCarthy^{4,6}, Manuel A
 1094 Rivas⁴, John R B Perry^{4,7,8,9}, Xueling Sim¹, Thomas W Blackwell¹, Neil R Robertson^{4,10}, N William
 1095 Rayner^{4,10,11}, Pablo Cingolani^{12,13}, Adam E Locke¹, Juan Fernandez Taj⁴, Heather M Highland¹⁴, Josee
 1096 Dupuis^{15,16}, Peter S Chines¹⁷, Cecilia M Lindgren^{2,4}, Christopher Hartl², Anne U Jackson¹, Han Chen^{15,18},
 1097 Jeroen R Huyghe¹, Martijn van de Bunt^{4,10}, Richard D Pearson⁴, Ashish Kumar^{4,19}, Martina Müller-
 1098 Nurasyid^{20,21,22,23}, Niels Grarup²⁴, Heather M Stringham¹, Eric R Gamazon²⁵, Jaehoon Lee²⁶, Yuhui Chen⁴,
 1099 Robert A Scott⁸, Jennifer E Below²⁷, Peng Chen²⁸, Jinyan Huang²⁹, Min Jin Go³⁰, Michael L Stitzel³¹,
 1100 Dorota Pasko⁷, Stephen C J Parker³², Tibor V Varga³³, Todd Green², Nicola L Beer¹⁰, Aaron G Day-
 1101 Williams¹¹, Teresa Ferreira⁴, Tasha Fingerlin³⁴, Momoko Horikoshi^{4,10}, Cheng Hu³⁵, Iksoo Huh²⁶,
 1102 Mohammad Kamran Ikram^{36,37,38}, Bong-Jo Kim³⁰, Yongkang Kim²⁶, Young Jin Kim³⁰, Min-Seok Kwon³⁹,
 1103 Juyoung Lee³⁰, Selyeong Lee²⁶, Keng-Han Lin¹, Taylor J Maxwell²⁷, Yoshihiko Nagai^{13,40,41}, Xu Wang²⁸,
 1104 Ryan P Welch¹, Joon Yoon³⁹, Weihua Zhang^{42,43}, Nir Barzilai⁴⁴, Benjamin F Voight^{45,46}, Bok-Ghee Han³⁰,
 1105 Christopher P Jenkinson^{47,48}, Teemu Kuulasmaa⁴⁹, Johanna Kuusisto^{49,50}, Alisa Manning², Maggie C Y
 1106 Ng^{51,52}, Nicholette D Palmer^{51,52,53}, Beverley Balkau⁵⁴, Alena Stančáková⁴⁹, Hanna E Abboud^{47‡}, Heiner
 1107 Boeing⁵⁵, Vilmantas Giedraitis⁵⁶, Dorairaj Prabhakaran⁵⁷, Omri Gottesman⁵⁸, James Scott⁵⁹, Jason
 1108 Carey², Phoenix Kwan¹, George Grant², Joshua D Smith⁶⁰, Benjamin M Neale^{2,61,62}, Shaun Purcell^{2,62,63},
 1109 Adam S Butterworth⁶⁴, Joanna M M Howson⁶⁴, Heung Man Lee⁶⁵, Yingchang Lu⁵⁸, Soo-Heon Kwak⁶⁶,
 1110 Wei Zhao⁶⁷, John Danesh^{11,64,68}, Vincent K L Lam⁶⁵, Kyong Soo Park^{66,69}, Danish Saleheen^{70,71}, Wing Yee
 1111 So⁶⁵, Claudia H T Tam⁶⁵, Uzma Afzal⁴², David Aguilar⁷², Rector Arya⁷³, Tin Aung^{36,37,38}, Edmund Chan⁷⁴,
 1112 Carmen Navarro^{75,76,77}, Ching-Yu Cheng^{28,36,37,38}, Domenico Palli⁷⁸, Adolfo Correa⁷⁹, Joanne E Curran⁸⁰,
 1113 Denis Rybin¹⁵, Vidya S Farook⁸¹, Sharon P Fowler⁴⁷, Barry I Freedman⁸², Michael Griswold⁸³, Daniel
 1114 Esten Hale⁷³, Pamela J Hicks^{51,52,53}, Chiea-Chuen Khor^{28,36,37,84,85}, Satish Kumar⁸⁰, Benjamin Lehne⁴²,
 1115 Dorothée Thuillier⁸⁶, Wei Yen Lim²⁸, Jianjun Liu^{28,85}, Yvonne T van der Schouw⁸⁷, Marie Loh^{42,88,89},
 1116 Solomon K Musani⁹⁰, Sobha Puppala⁸¹, William R Scott⁴², Loïc Yengo⁸⁶, Sian-Tsung Tan^{43,59}, Herman A
 1117 Taylor Jr⁷⁹, Farook Thameem⁴⁷, Gregory Wilson Sr⁹¹, Tien Yin Wong^{36,37,38}, Pål Rasmus Njølstad^{92,93},
 1118 Jonathan C Levy¹⁰, Massimo Mangino⁹, Lori L Bonnycastle¹⁷, Thomas Schwarzmayer⁹⁴, João Fadista⁹⁵,
 1119 Gabriela L Surdulescu⁹, Christian Herder^{96,97}, Christopher J Groves¹⁰, Thomas Wieland⁹⁴, Jette Bork-
 1120 Jensen²⁴, Ivan Brandslund^{98,99}, Cramer Christensen¹⁰⁰, Heikki A Koistinen^{101,102,103,104}, Alex S F Doney¹⁰⁵,
 1121 Leena Kinnunen¹⁰¹, Tõnu Esko^{2,106,107,108}, Andrew J Farmer¹⁰⁹, Liisa Hakaste^{102,110,111}, Dylan Hodgkiss⁹,
 1122 Jasmina Kravic⁹⁵, Valeriya Lyssenko⁹⁵, Mette Hollensted²⁴, Marit E Jørgensen¹¹², Torben
 1123 Jørgensen^{113,114,115}, Claes Ladenvall⁹⁵, Johanne Marie Justesen²⁴, Annemari Käräjämäki^{116,117}, Jennifer
 1124 Kriebel^{97,118,119}, Wolfgang Rathmann¹²⁰, Lars Lannfelt⁵⁶, Torsten Lauritzen¹²¹, Narisu Narisu¹⁷, Allan
 1125 Linneberg^{113,122,123}, Olle Melander¹²⁴, Lili Milani¹⁰⁶, Matt Neville^{10,125}, Marju Orho-Melander¹²⁶, Lu
 1126 Qi^{127,128}, Qibin Qi^{127,129}, Michael Roden^{96,97,130}, Olov Rolandsson¹³¹, Amy Swift¹⁷, Anders H Rosengren⁹⁵,
 1127 Kathleen Stirrups¹¹, Andrew R Wood⁷, Evelin Mihailov¹⁰⁶, Christine Blancher¹³², Mauricio O Carneiro²,
 1128 Jared Maguire², Ryan Poplin², Khalid Shakir², Timothy Fennell², Mark DePristo², Martin Hrabé de
 1129 Angelis^{97,133,134}, Panos Deloukas^{135,136}, Anette P Gjesing²⁴, Goo Jun^{1,27}, Peter Nilsson¹³⁷, Jacquelyn
 1130 Murphy², Robert Onofrio², Barbara Thorand^{97,118}, Torben Hansen^{24,138}, Christa Meisinger^{97,118}, Frank B
 1131 Hu^{29,127}, Bo Isomaa^{110,139}, Fredrik Karpe^{10,125}, Liming Liang^{18,29}, Annette Peters^{23,97,118}, Cornelia
 1132 Huth^{97,118}, Stephen P O'Rahilly¹⁴⁰, Colin N A Palmer¹⁴¹, Oluf Pedersen²⁴, Rainer Rauramaa¹⁴², Jaakko
 1133 Tuomilehto^{101,143,144,145,146}, Veikko Salomaa¹⁴⁶, Richard M Watanabe^{147,148,149}, Ann-Christine Syvänen¹⁵⁰,

1134 Richard N Bergman¹⁵¹, Dwaipayan Bharadwaj¹⁵², Erwin P Bottinger⁵⁸, Yoon Shin Cho¹⁵³, Giriraj R
 1135 Chandak¹⁵⁴, Juliana C N Chan^{65,155,156}, Kee Seng Chia²⁸, Mark J Daly⁶¹, Shah B Ebrahim⁵⁷, Claudia
 1136 Langenberg⁸, Paul Elliott^{42,157}, Kathleen A Jablonski¹⁵⁸, Donna M Lehman⁴⁷, Weiping Jia³⁵, Ronald C W
 1137 Ma^{65,155,156}, Toni I Pollin¹⁵⁹, Manjinder Sandhu^{11,64}, Nikhil Tandon¹⁶⁰, Philippe Froguel^{86,161}, Inês
 1138 Barroso^{11,140}, Yik Ying Teo^{28,162,163}, Eleftheria Zeggini¹¹, Ruth J F Loos⁵⁸, Kerrin S Small⁹, Janina S Ried²⁰,
 1139 Ralph A DeFronzo⁴⁷, Harald Grallert^{97,118,119}, Benjamin Glaser¹⁶⁴, Andres Metspalu¹⁰⁶, Nicholas J
 1140 Wareham⁸, Mark Walker¹⁶⁵, Eric Banks², Christian Gieger^{20,118,119}, Erik Ingelsson^{4,166}, Hae Kyung Im²⁵,
 1141 Thomas Illig^{119,167,168}, Paul W Franks^{33,127,131}, Gemma Buck¹³², Joseph Trakalo¹³², David Buck¹³², Inga
 1142 Prokopenko^{4,10,161}, Reedik Mägi¹⁰⁶, Lars Lind¹⁶⁹, Yossi Farjoun¹⁷⁰, Katharine R Owen^{10,125}, Anna L
 1143 Gloyn^{4,10,125}, Konstantin Strauch^{20,22}, Tiinamaija Tuomi^{102,110,111,171}, Jaspal Singh Kooner^{43,59,172}, Jong-
 1144 Young Lee³⁰, Taesung Park^{26,39}, Peter Donnelly^{4,6}, Andrew D Morris^{173,174}, Andrew T Hattersley¹⁷⁵,
 1145 Donald W Bowden^{51,52,53}, Francis S Collins¹⁷, Gil Atzmon^{44,176}, John C Chambers^{42,43,172}, Timothy D
 1146 Spector⁹, Markku Laakso^{49,50}, Tim M Strom^{94,177}, Graeme I Bell¹⁷⁸, John Blangero⁸⁰, Ravindranath
 1147 Duggirala⁸¹, E Shyong Tai^{28,74,179}, Gilean McVean^{4,180}, Craig L Hanis²⁷, James G Wilson¹⁸¹, Mark
 1148 Seielstad^{182,183}, Timothy M Frayling⁷, James B Meigs¹⁸⁴, Nancy J Cox²⁵, Rob Sladek^{13,40,185}, Eric S
 1149 Lander¹⁸⁶, Stacey Gabriel², Noël P Burt², Karen L Mohlke¹⁸⁷, Thomas Meitinger^{94,177}, Leif Groop^{95,171},
 1150 Goncalo Abecasis¹, Jose C Florez^{2,62,188,189}, Laura J Scott¹, Andrew P Morris^{4,106,190}, Hyun Min Kang¹,
 1151 Michael Boehnke¹, David Altshuler^{2,3,107,188,189,191}, Mark I McCarthy^{4,10,125}

1152

1153 Affiliations

- 1154 1. Department of Biostatistics and Center for Statistical Genetics, University of Michigan, Ann
 1155 Arbor, Michigan, USA.
- 1156 2. Program in Medical and Population Genetics, Broad Institute, Cambridge, Massachusetts,
 1157 USA.
- 1158 3. Department of Molecular Biology, Massachusetts General Hospital, Boston, Massachusetts,
 1159 USA.
- 1160 4. Wellcome Trust Centre for Human Genetics, Nuffield Department of Medicine, University of
 1161 Oxford, Oxford, UK.
- 1162 5. Harvard-MIT Division of Health Sciences and Technology, Massachusetts Institute of
 1163 Technology, Cambridge, Massachusetts, USA.
- 1164 6. Department of Statistics, University of Oxford, Oxford, UK.
- 1165 7. Genetics of Complex Traits, University of Exeter Medical School, University of Exeter, Exeter,
 1166 UK.
- 1167 8. MRC Epidemiology Unit, Institute of Metabolic Science, University of Cambridge, Cambridge,
 1168 UK.
- 1169 9. Department of Twin Research and Genetic Epidemiology, King's College London, London, UK.
- 1170 10. Oxford Centre for Diabetes, Endocrinology and Metabolism, Radcliffe Department of
 1171 Medicine, University of Oxford, Oxford, UK.
- 1172 11. Department of Human Genetics, Wellcome Trust Sanger Institute, Hinxton, Cambridgeshire,
 1173 UK.
- 1174 12. School of Computer Science, McGill University, Montreal, Quebec, Canada.
- 1175 13. McGill University and Génome Québec Innovation Centre, Montreal, Quebec, Canada.
- 1176 14. Human Genetics Center, The University of Texas Graduate School of Biomedical Sciences at
 1177 Houston, The University of Texas Health Science Center at Houston, Houston, Texas, USA.
- 1178 15. Department of Biostatistics, Boston University School of Public Health, Boston,
 1179 Massachusetts, USA.
- 1180 16. National Heart, Lung, and Blood Institute's Framingham Heart Study, Framingham,
 1181 Massachusetts, USA.

- 1182 17. Medical Genomics and Metabolic Genetics Branch, National Human Genome Research
1183 Institute, National Institutes of Health, Bethesda, Maryland, USA.
- 1184 18. Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts, USA.
- 1185 19. Chronic Disease Epidemiology, Swiss Tropical and Public Health Institute, University of Basel,
1186 Basel, Switzerland.
- 1187 20. Institute of Genetic Epidemiology, Helmholtz Zentrum München, German Research Center for
1188 Environmental Health, Neuherberg, Germany.
- 1189 21. Department of Medicine I, University Hospital Grosshadern, Ludwig-Maximilians-Universität,
1190 Munich, Germany.
- 1191 22. Institute of Medical Informatics, Biometry and Epidemiology, Chair of Genetic Epidemiology,
1192 Ludwig-Maximilians-Universität, Munich, Germany.
- 1193 23. DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance,
1194 Munich, Germany.
- 1195 24. The Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and
1196 Medical Sciences, University of Copenhagen, Copenhagen, Denmark.
- 1197 25. Department of Medicine, Section of Genetic Medicine, The University of Chicago, Chicago,
1198 Illinois, USA.
- 1199 26. Department of Statistics, Seoul National University, Seoul, Republic of Korea.
- 1200 27. Human Genetics Center, School of Public Health, The University of Texas Health Science
1201 Center at Houston, Houston, Texas, USA.
- 1202 28. Saw Swee Hock School of Public Health, National University of Singapore, National University
1203 Health System, Singapore.
- 1204 29. Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts, USA.
- 1205 30. Center for Genome Science, Korea National Institute of Health, Chungcheongbuk-do, Republic
1206 of Korea.
- 1207 31. The Jackson Laboratory for Genomic Medicine, Farmington, Connecticut, USA.
- 1208 32. Departments of Computational Medicine & Bioinformatics and Human Genetics, University of
1209 Michigan, Ann Arbor, Michigan, USA.
- 1210 33. Department of Clinical Sciences, Lund University Diabetes Centre, Genetic and Molecular
1211 Epidemiology Unit, Lund University, Malmö, Sweden.
- 1212 34. Department of Epidemiology, Colorado School of Public Health, University of Colorado,
1213 Aurora, Colorado, USA.
- 1214 35. Department of Endocrinology and Metabolism, Shanghai Diabetes Institute, Shanghai Jiao
1215 Tong University Affiliated Sixth People's Hospital, Shanghai, China.
- 1216 36. Singapore Eye Research Institute, Singapore National Eye Centre, Singapore.
- 1217 37. Department of Ophthalmology, Yong Loo Lin School of Medicine, National University of
1218 Singapore, National University Health System, Singapore.
- 1219 38. The Eye Academic Clinical Programme, Duke-NUS Graduate Medical School, Singapore.
- 1220 39. Interdisciplinary Program in Bioinformatics, Seoul National University, Seoul, Republic of
1221 Korea.
- 1222 40. Department of Human Genetics, McGill University, Montreal, Quebec, Canada.
- 1223 41. Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada.
- 1224 42. Department of Epidemiology and Biostatistics, Imperial College London, London, UK.
- 1225 43. Department of Cardiology, Ealing Hospital NHS Trust, Southall, Middlesex, UK.
- 1226 44. Departments of Medicine and Genetics, Albert Einstein College of Medicine, New York, USA.
- 1227 45. Department of Systems Pharmacology and Translational Therapeutics, University of
1228 Pennsylvania - Perelman School of Medicine, Philadelphia, Pennsylvania, USA.

- 1229 46. Department of Genetics, University of Pennsylvania - Perelman School of Medicine,
1230 Philadelphia, Pennsylvania, USA.
- 1231 47. Department of Medicine, University of Texas Health Science Center, San Antonio, Texas, USA.
- 1232 48. Research, South Texas Veterans Health Care System, San Antonio, Texas, USA.
- 1233 49. Faculty of Health Sciences, Institute of Clinical Medicine, Internal Medicine, University of
1234 Eastern Finland, Kuopio, Finland.
- 1235 50. Kuopio University Hospital, Kuopio, Finland.
- 1236 51. Center for Genomics and Personalized Medicine Research, Wake Forest School of Medicine,
1237 Winston-Salem, North Carolina, USA.
- 1238 52. Center for Diabetes Research, Wake Forest School of Medicine, Winston-Salem, North
1239 Carolina, USA.
- 1240 53. Department of Biochemistry, Wake Forest School of Medicine, Winston-Salem, North
1241 Carolina, USA.
- 1242 54. Centre for Research in Epidemiology and Population Health, Inserm U1018, Villejuif, France.
- 1243 55. German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany.
- 1244 56. Department of Public Health and Caring Sciences, Geriatrics, Uppsala University, Uppsala,
1245 Sweden.
- 1246 57. Centre for Chronic Disease Control, New Delhi, India.
- 1247 58. The Charles Bronfman Institute for Personalized Medicine, The Icahn School of Medicine at
1248 Mount Sinai, New York, USA.
- 1249 59. National Heart and Lung Institute, Cardiovascular Sciences, Hammersmith Campus, Imperial
1250 College London, London, UK.
- 1251 60. Department of Genome Sciences, University of Washington School of Medicine, Seattle,
1252 Washington, USA.
- 1253 61. Analytic and Translational Genetics Unit, Department of Medicine, Massachusetts General
1254 Hospital, Boston, Massachusetts, USA.
- 1255 62. Center for Human Genetic Research, Department of Medicine, Massachusetts General
1256 Hospital, Boston, Massachusetts, USA.
- 1257 63. Department of Psychiatry, Icahn Institute for Genomics and Multiscale Biology, Icahn School
1258 of Medicine at Mount Sinai, New York, USA.
- 1259 64. Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK.
- 1260 65. Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong,
1261 China.
- 1262 66. Department of Internal Medicine, Seoul National University College of Medicine, Seoul,
1263 Republic of Korea.
- 1264 67. Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA.
- 1265 68. NIHR Blood and Transplant Research Unit in Donor Health and Genomics, Department of
1266 Public Health and Primary Care, University of Cambridge, Cambridge, UK.
- 1267 69. Department of Molecular Medicine and Biopharmaceutical Sciences, Graduate School of
1268 Convergence Science and Technology, and College of Medicine, Seoul National University,
1269 Seoul, Republic of Korea.
- 1270 70. Department of Biostatistics and Epidemiology, University of Pennsylvania, Philadelphia,
1271 Pennsylvania, USA.
- 1272 71. Center for Non-Communicable Diseases, Karachi, Pakistan.
- 1273 72. Cardiovascular Division, Baylor College of Medicine, Houston, Texas, USA.
- 1274 73. Department of Pediatrics, University of Texas Health Science Center, San Antonio, Texas, USA.
- 1275 74. Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore,
1276 National University Health System, Singapore.

- 1277 75. Department of Epidemiology, Murcia Regional Health Council, IMIB-Arrixaca, Murcia, Spain.
- 1278 76. CIBER Epidemiología y Salud Pública (CIBERESP), Spain.
- 1279 77. Unit of Preventive Medicine and Public Health, School of Medicine, University of Murcia,
- 1280 Spain.
- 1281 78. Cancer Research and Prevention Institute (ISPO), Florence, Italy.
- 1282 79. Department of Medicine, University of Mississippi Medical Center, Jackson, Mississippi, USA.
- 1283 80. South Texas Diabetes and Obesity Institute, Regional Academic Health Center, University of
- 1284 Texas Rio Grande Valley, Brownsville, Texas, USA.
- 1285 81. Department of Genetics, Texas Biomedical Research Institute, San Antonio, Texas, USA.
- 1286 82. Department of Internal Medicine, Section on Nephrology, Wake Forest School of Medicine,
- 1287 Winston-Salem, North Carolina, USA.
- 1288 83. Center of Biostatistics and Bioinformatics, University of Mississippi Medical Center, Jackson,
- 1289 Mississippi, USA.
- 1290 84. Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore,
- 1291 National University Health System, Singapore.
- 1292 85. Division of Human Genetics, Genome Institute of Singapore, A*STAR, Singapore.
- 1293 86. CNRS-UMR8199, Lille University, Lille Pasteur Institute, Lille, France.
- 1294 87. Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht,
- 1295 Utrecht, Netherlands.
- 1296 88. Institute of Health Sciences, University of Oulu, Oulu, Finland.
- 1297 89. Translational Laboratory in Genetic Medicine (TLGM), Agency for Science, Technology and
- 1298 Research (A*STAR), Singapore, Singapore.
- 1299 90. Jackson Heart Study, University of Mississippi Medical Center, Jackson, Mississippi, USA.
- 1300 91. College of Public Services, Jackson State University, Jackson, Mississippi, USA.
- 1301 92. KG Jebsen Center for Diabetes Research, Department of Clinical Science, University of Bergen,
- 1302 Bergen, Norway.
- 1303 93. Department of Pediatrics, Haukeland University Hospital, Bergen, Norway.
- 1304 94. Institute of Human Genetics, Helmholtz Zentrum München, German Research Center for
- 1305 Environmental Health, Neuherberg, Germany.
- 1306 95. Department of Clinical Sciences, Diabetes and Endocrinology, Lund University Diabetes
- 1307 Centre, Malmö, Sweden.
- 1308 96. Institute of Clinical Diabetology, German Diabetes Center, Leibniz Center for Diabetes
- 1309 Research at Heinrich Heine University, Düsseldorf, Germany.
- 1310 97. German Center for Diabetes Research (DZD), Neuherberg, Germany.
- 1311 98. Institute of Regional Health Research, University of Southern Denmark, Odense, Denmark.
- 1312 99. Department of Clinical Biochemistry, Vejle Hospital, Vejle, Denmark.
- 1313 100. Department of Internal Medicine and Endocrinology, Vejle Hospital, Vejle, Denmark.
- 1314 101. Department of Health, National Institute for Health and Welfare, Helsinki, Finland.
- 1315 102. Abdominal Center: Endocrinology, University of Helsinki and Helsinki University Central
- 1316 Hospital, Helsinki, Finland.
- 1317 103. Minerva Foundation Institute for Medical Research, Helsinki, Finland.
- 1318 104. Department of Medicine, University of Helsinki and Helsinki University Central Hospital,
- 1319 Helsinki, Finland.
- 1320 105. Division of Cardiovascular and Diabetes Medicine, Medical Research Institute, Ninewells
- 1321 Hospital and Medical School, Dundee, UK.
- 1322 106. Estonian Genome Center, University of Tartu, Tartu, Estonia.
- 1323 107. Department of Genetics, Harvard Medical School, Boston, Massachusetts, USA.
- 1324 108. Division of Endocrinology, Boston Children's Hospital, Boston, Massachusetts, USA.

1325 109. Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK.
 1326 110. Folkhälsan Research Centre, Helsinki, Finland.
 1327 111. Research Programs Unit, Diabetes and Obesity, University of Helsinki, Helsinki, Finland.
 1328 112. Steno Diabetes Center, Gentofte, Denmark.
 1329 113. Research Centre for Prevention and Health, Capital Region of Denmark, Glostrup, Denmark.
 1330 114. Department of Public Health, Institute of Health Sciences, University of Copenhagen,
 1331 Copenhagen, Denmark.
 1332 115. Faculty of Medicine, Aalborg University, Aalborg, Denmark.
 1333 116. Department of Primary Health Care, Vaasa Central Hospital, Vaasa, Finland.
 1334 117. Diabetes Center, Vaasa Health Care Center, Vaasa, Finland.
 1335 118. Institute of Epidemiology II, Helmholtz Zentrum München, German Research Center for
 1336 Environmental Health, Neuherberg, Germany.
 1337 119. Research Unit of Molecular Epidemiology, Helmholtz Zentrum München, German Research
 1338 Center for Environmental Health, Neuherberg, Germany.
 1339 120. Institute for Biometrics and Epidemiology, German Diabetes Center, Leibniz Center for
 1340 Diabetes Research at Heinrich Heine University, Düsseldorf, Germany.
 1341 121. Department of Public Health, Section of General Practice, Aarhus University, Aarhus,
 1342 Denmark.
 1343 122. Department of Clinical Experimental Research, Rigshospitalet, Glostrup, Denmark.
 1344 123. Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of
 1345 Copenhagen, Copenhagen, Denmark.
 1346 124. Department of Clinical Sciences, Hypertension and Cardiovascular Disease, Lund University,
 1347 Malmö, Sweden.
 1348 125. Oxford NIHR Biomedical Research Centre, Oxford University Hospitals Trust, Oxford, UK.
 1349 126. Department of Clinical Sciences, Diabetes and Cardiovascular Disease, Genetic Epidemiology,
 1350 Lund University, Malmö, Sweden.
 1351 127. Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts, USA.
 1352 128. Channing Division of Network Medicine, Department of Medicine, Brigham and Women's
 1353 Hospital and Harvard Medical School, Boston, Massachusetts, USA.
 1354 129. Department of Epidemiology and Population Health, Albert Einstein College of Medicine, New
 1355 York, USA.
 1356 130. Department of Endocrinology and Diabetology, Medical Faculty, Heinrich-Heine University,
 1357 Düsseldorf, Germany.
 1358 131. Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden.
 1359 132. High Throughput Genomics, Oxford Genomics Centre, Wellcome Trust Centre for Human
 1360 Genetics, Nuffield Department of Medicine, University of Oxford, Oxford, UK.
 1361 133. Institute of Experimental Genetics, Helmholtz Zentrum München, German Research Center
 1362 for Environmental Health, Neuherberg, Germany.
 1363 134. Center of Life and Food Sciences Weihenstephan, Technische Universität München, Freising-
 1364 Weihenstephan, Germany.
 1365 135. William Harvey Research Institute, Barts and The London School of Medicine and Dentistry,
 1366 Queen Mary University of London, London, UK.
 1367 136. Princess Al-Jawhara Al-Brahim Centre of Excellence in Research of Hereditary Disorders
 1368 (PACER-HD), King Abdulaziz University, Jeddah, Saudi Arabia.
 1369 137. Department of Clinical Sciences, Medicine, Lund University, Malmö, Sweden.
 1370 138. Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark.
 1371 139. Department of Social Services and Health Care, Jakobstad, Finland.

1372 140. Metabolic Research Laboratories, Institute of Metabolic Science, University of Cambridge,
1373 Cambridge, UK.

1374 141. Pat Macpherson Centre for Pharmacogenetics and Pharmacogenomics, Ninewells Hospital
1375 and Medical School, University of Dundee, Dundee, UK.

1376 142. Foundation for Research in Health, Exercise and Nutrition, Kuopio Research Institute of
1377 Exercise Medicine, Kuopio, Finland.

1378 143. Center for Vascular Prevention, Danube University Krems, Krems, Austria.

1379 144. Diabetes Research Group, King Abdulaziz University, Jeddah, Saudi Arabia.

1380 145. Instituto de Investigacion Sanitaria del Hospital Universario LaPaz (IdiPAZ), University Hospital
1381 LaPaz, Autonomous University of Madrid, Madrid, Spain.

1382 146. National Institute for Health and Welfare, Helsinki, Finland.

1383 147. Department of Preventive Medicine, Keck School of Medicine, University of Southern
1384 California, Los Angeles, California, USA.

1385 148. Department of Physiology & Biophysics, Keck School of Medicine, University of Southern
1386 California, Los Angeles, California, USA.

1387 149. Diabetes and Obesity Research Institute, Keck School of Medicine, University of Southern
1388 California, Los Angeles, California, USA.

1389 150. Department of Medical Sciences, Molecular Medicine and Science for Life Laboratory, Uppsala
1390 University, Uppsala, Sweden.

1391 151. Cedars-Sinai Diabetes and Obesity Research Institute, Los Angeles, California, USA.

1392 152. Functional Genomics Unit, CSIR-Institute of Genomics & Integrative Biology (CSIR-IGIB), New
1393 Delhi, India.

1394 153. Department of Biomedical Science, Hallym University, Chuncheon, Republic of Korea.

1395 154. CSIR-Centre for Cellular and Molecular Biology, Hyderabad, Telangana, India.

1396 155. Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong, Hong Kong,
1397 China.

1398 156. Hong Kong Institute of Diabetes and Obesity, The Chinese University of Hong Kong, Hong
1399 Kong, China.

1400 157. MRC-PHE Centre for Environment and Health, Imperial College London, London, UK.

1401 158. The Biostatistics Center, The George Washington University, Rockville, Maryland, USA.

1402 159. Department of Medicine, Division of Endocrinology, Diabetes and Nutrition, and Program in
1403 Personalized and Genomic Medicine, University of Maryland School of Medicine, Baltimore, Maryland,
1404 USA.

1405 160. Department of Endocrinology and Metabolism, All India Institute of Medical Sciences, New
1406 Delhi, India.

1407 161. Department of Genomics of Common Disease, School of Public Health, Imperial College
1408 London, London, UK.

1409 162. Life Sciences Institute, National University of Singapore, Singapore.

1410 163. Department of Statistics and Applied Probability, National University of Singapore, Singapore.

1411 164. Endocrinology and Metabolism Service, Hadassah-Hebrew University Medical Center,
1412 Jerusalem, Israel.

1413 165. The Medical School, Institute of Cellular Medicine, Newcastle University, Newcastle, UK.

1414 166. Department of Medical Sciences, Molecular Epidemiology and Science for Life Laboratory,
1415 Uppsala University, Uppsala, Sweden.

1416 167. Hannover Unified Biobank, Hannover Medical School, Hanover, Germany.

1417 168. Institute for Human Genetics, Hannover Medical School, Hanover, Germany.

1418 169. Department of Medical Sciences, Uppsala University, Uppsala, Sweden.

1419 170. Data Sciences and Data Engineering, Broad Institute, Cambridge, Massachusetts, USA.

1420 171. Institute for Molecular Medicine Finland (FIMM), University of Helsinki, Helsinki, Finland.
1421 172. Imperial College Healthcare NHS Trust, Imperial College London, London, UK.
1422 173. Clinical Research Centre, Centre for Molecular Medicine, Ninewells Hospital and Medical
1423 School, Dundee, UK.
1424 174. The Usher Institute to the Population Health Sciences and Informatics, University of
1425 Edinburgh, Edinburgh, UK.
1426 175. University of Exeter Medical School, University of Exeter, Exeter, UK.
1427 176. Department of Natural Science, University of Haifa, Haifa, Israel.
1428 177. Institute of Human Genetics, Technische Universität München, Munich, Germany.
1429 178. Departments of Medicine and Human Genetics, The University of Chicago, Chicago, Illinois,
1430 USA.
1431 179. Cardiovascular & Metabolic Disorders Program, Duke-NUS Medical School Singapore,
1432 Singapore.
1433 180. Li Ka Shing Centre for Health Information and Discovery, University of Oxford, Oxford, UK.
1434 181. Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson,
1435 Mississippi, USA.
1436 182. Department of Laboratory Medicine & Institute for Human Genetics, University of California,
1437 San Francisco, San Francisco, California, USA.
1438 183. Blood Systems Research Institute, San Francisco, California, USA.
1439 184. General Medicine Division, Massachusetts General Hospital and Department of Medicine,
1440 Harvard Medical School, Boston, Massachusetts, USA.
1441 185. Division of Endocrinology and Metabolism, Department of Medicine, McGill University,
1442 Montreal, Quebec, Canada.
1443 186. Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA.
1444 187. Department of Genetics, University of North Carolina, Chapel Hill, North Carolina, USA.
1445 188. Department of Medicine, Harvard Medical School, Boston, Massachusetts, USA.
1446 189. Diabetes Research Center (Diabetes Unit), Department of Medicine, Massachusetts General
1447 Hospital, Boston, Massachusetts, USA.
1448 190. Department of Biostatistics, University of Liverpool, Liverpool, UK.
1449 191. Department of Biology, Massachusetts Institute of Technology, Cambridge, Massachusetts,
1450 USA.
1451
1452 ‡ Deceased.
1453
1454

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. Bis⁶, Kenneth Rice⁸, Alanna C. Morrison⁹, Yingchang Lu¹⁰, Stefan Weiss^{11,12}, Xiuqing Guo¹³, Walter Palmas¹⁴, Lisa W. Martin¹⁵, Yii-Der Ida Chen¹³, Praveen Surendran¹⁶, Fotios Drenos^{17,18}, James P. Cook^{19,20}, Paul L. Auer²¹, Audrey Y. Chu^{1,3,22}, Ayush Giri²³, Wei Zhao⁵, Johanna Jakobsdottir²⁴, Li-An Lin²⁵, Jeanette M. Stafford²⁶, Najaf Amin²⁷, Hao Mei²⁸, Jie Yao¹³, Arend Voorman²⁹, CHD Exome Plus Consortium†, ExomeBP Consortium†, GoT2D Consortium/GoT2DGenes consortium†, Martin G. Larson^{1,2,30}, Megan L. Grove⁹, Albert V. Smith^{24,31}, Shih-Jen Hwang^{1,3}, Han Chen³², Tianxiao Huan^{1,3}, Gulum Kosova^{33,34}, Nathan O. Stitzel³⁵, Sekar Kathiresan^{34,36}, Nilesh Samani^{37,38}, Heribert Schunkert^{39,40}, Panos Deloukas^{41,42}, Myocardial Infarction Genetics and CARDIoGRAM Exome Consortia Investigator†, Man Li⁴³, Christian Fuchsberger⁴⁴, Cristian Pattaro⁴⁴, Mathias Gorski⁴⁵, CKDGen Consortium†, Charles Kooperberg⁴⁶, George J. Papanicolaou⁴⁷, Jacques E. Rossouw⁴⁷, Jessica D. Faul⁴⁸, Sharon L.R. Kardia⁵, Claude Bouchard⁴⁹, Leslie J. Raffel⁵⁰, André G. Uitterlinden^{51,52}, Oscar H. Franco⁵¹, Ramachandran S. Vasan^{1,53}, Christopher J. O'Donnell^{1,54,55,56}, Kent D. Taylor¹³, Kiang Liu⁵⁷, Erwin P. Bottinger¹⁰, Omri Gottesman¹⁰, E. Warwick Daw⁴, Franco Giulianini²², Santhi Ganesh^{58,59}, Elias Salfati⁶⁰, Tamara B. Harris⁶¹, Lenore J. Launer⁶², Marcus Dörr^{11,63}, Stephan B. Felix^{11,63}, Rainer Rettig^{11,64}, Henry Völzke^{11,65,66}, Eric Kim¹³, Wen-Jane Lee⁶⁷, I-Te Lee^{68,69,70}, Wayne H-H Sheu^{68,69,71,72}, Krystal S. Tsosie²³, Digna R. Velez Edwards^{23,73}, Yongmei Liu⁷⁴, Adolfo Correa⁷⁵, David R. Weir⁴⁸, Uwe Völker^{11,12}, Paul M. Ridker^{22,76}, Eric Boerwinkle⁹, Vilmundur Gudnason^{24,31}, Alexander P. Reiner⁷⁷, Cornelia M. van Duijn²⁷, Ingrid B. Borecki⁴, Todd L. Edwards^{23,78}, Aravinda Chakravarti⁶⁰, Jerome I. Rotter⁷⁹, Bruce M. Psaty^{6,77,80,81}, Ruth J.F. Loos^{10,82}, Myriam Fornage²⁵, Georg Ehret^{60,83#}, Christopher Newton-Cheh^{33,34,84#}, Daniel Levy^{1,3#@}, Daniel I. Chasman^{22,76#@}

¹Framingham Heart Study, National Heart, Lung, and Blood Institute, Framingham, MA, USA.

²Department of Biostatistics, School of Public Health, Boston University, Boston, MA, USA.

³The Population Sciences Branch, National Heart, Lung, and Blood Institute, Bethesda, MD, USA.

⁴Division of Statistical Genomics, Department of Genetics & Center for Genome Sciences and Systems Biology, Washington University School of Medicine, St. Louis, MO, USA.

⁵Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, MI, USA.

⁶Cardiovascular Health Research Unit, Department of Medicine, University of Washington, Seattle, WA, USA.

⁷Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA.

⁸Department of Biostatistics, University of Washington, Seattle, WA, USA.

1488 ⁹Human Genetics Center, School of Public Health, University of Texas Health Science Center at
1489 Houston, Houston TX, USA.

1490 ¹⁰The Charles Bronfman Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai,
1491 New York, NY, USA.

1492 ¹¹DZHK (German Center for Cardiovascular Research), partner site Greifswald, Greifswald, Germany.

1493 ¹²Interfaculty Institute for Genetics and Functional Genomics, University Medicine and Ernst-Moritz-
1494 Arndt University Greifswald, Greifswald, Germany.

1495 ¹³Institute for Translational Genomics and Population Sciences, Los Angeles Biomedical Research
1496 Institute and Department of Pediatrics, Harbor-UCLA Medical Center, Torrance, CA, USA.

1497 ¹⁴Columbia University Medical Center, 622 West 168th Street, PH 9 East, 107, New York, NY, USA.

1498 ¹⁵George Washington University School of Medicine and Health Sciences, Washington DC, USA.

1499 ¹⁶Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of
1500 Cambridge, Cambridge, UK.

1501 ¹⁷Centre for Cardiovascular Genetics, Institute of Cardiovascular Science, Rayne Building University
1502 College London, London, WC1E 6JF, UK.

1503 ¹⁸MRC Integrative Epidemiology Unit, School of Social and Community Medicine, University of Bristol,
1504 Oakfield House, Oakfield Grove, Bristol BS8 2BN, UK.

1505 ¹⁹Department of Biostatistics, University of Liverpool, Liverpool, L69 3GA, UK.

1506 ²⁰Department of Health Sciences, University of Leicester, Leicester, LE1 7RH, UK.

1507 ²¹Joseph J. Zilber School of Public Health, University of Wisconsin, Milwaukee, WI, USA.

1508 ²²Division of Preventive Medicine, Brigham and Women's Hospital, Boston, MA, USA.

1509 ²³Vanderbilt Epidemiology Center, Vanderbilt Genetics Institute, Institute for Medicine and Public
1510 Health, Vanderbilt University Medical Center, Nashville, TN, USA.

1511 ²⁴Icelandic Heart Association, Kopavogur, Iceland.

1512 ²⁵Institute of Molecular Medicine, University of Texas Health Science Center at Houston, Houston, TX,
1513 USA.

1514 ²⁶Division of Public Health Sciences, Department of Biostatistical Sciences, Wake Forest School of
1515 Medicine, Winston-Salem, NC, USA.

1516 ²⁷Genetic Epidemiology Unit, Department of Epidemiology, Erasmus Medical Center, 3015 CN
1517 Rotterdam, the Netherlands.

1518 ²⁸Center of Biostatistics and Bioinformatics, University of Mississippi Medical Center, Jackson, MS,
1519 USA.

1520 ²⁹The Bill and Melinda Gates Foundation, 500 Fifth Avenue North, Seattle, WA, USA.

1521 ³⁰Department of Mathematics and Statistics, Boston University, MA, USA.

1522 ³¹Faculty of Medicine, University of Iceland, Reykjavik, Iceland.

1523 ³²Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA, USA.

1524 ³³Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA, USA.

1525 ³⁴Program in Medical and Population Genetics, Broad Institute of Harvard and MIT, Boston, MA, USA.

1526 ³⁵Division of Cardiology, Department of Medicine & Department of Genetics, Washington University

1527 School of Medicine, Saint Louis, MO, USA.

1528 ³⁶ Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA, USA.

1529 ³⁷Department of Cardiovascular Sciences, University of Leicester, Leicester, LE3 9QP, UK.

1530 ³⁸NIHR Leicester Cardiovascular Biomedical Research Unit, Glenfield Hospital, Leicester, LE3 9QP, UK.

1531 ³⁹Deutsches Herzzentrum Mǃnchen and Technische Universitǃt Mǃnchen, Mǃnchen, Germany.

1532 ⁴⁰Deutsches Zentrum fǃr Herz- und Kreislau fforschung (DZHK), Munich Heart Alliance; Lazarettstra ǃe

1533 36, Mǃnchen, Germany.

1534 ⁴¹Princess Al-Jawhara Al-Brahim Centre of Excellence in Research of Hereditary Disorders (PACER-HD),

1535 King Abdulaziz University, Jeddah 21589, Saudi Arabia.

1536 ⁴²William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen

1537 Mary University of London, London, UK.

1538 ⁴³Department of Epidemiology, Johns Hopkins University, Baltimore, MD, USA.

1539 ⁴⁴Center for Biomedicine, European Academy of Bozen/Bolzano (EURAC), affiliated to the University

1540 of Lǃbeck, Bolzano, Italy.

1541 ⁴⁵Department of Genetic Epidemiology, Institute of Epidemiology and Preventive Medicine, University

1542 of Regensburg, Regensburg, Germany.

1543 ⁴⁶Fred Hutchinson Cancer Research Center, Division of Public Health Sciences, Seattle, Washington,

1544 USA.

1545 ⁴⁷Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute, Bethesda, MD, USA.

1546 ⁴⁸Survey Research Center, Institute for Social Research, University of Michigan, Ann Arbor, MI, USA.

1547 ⁴⁹Pennington Biomedical Research Center, Louisiana State University System, Baton Rouge, LA, USA.

1548 ⁵⁰Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA.

1549 ⁵¹Department of Epidemiology, Erasmus MC, Rotterdam, the Netherlands.

1550 ⁵²Department of Internal Medicine, Erasmus MC, Rotterdam, the Netherlands.

1551 ⁵³Department of Preventive Medicine, Boston University School of Medicine, Boston, MA, USA.

1552 ⁵⁴Cardiology Section, Department of Medicine, Boston Veteran's Administration Healthcare, Boston,

1553 MA, USA.

1554 ⁵⁵Cardiovascular Division, Brigham and Women's Hospital, Boston, MA, USA.

1555 ⁵⁶Department of Medicine, Harvard Medical School, Boston, MA, USA.

1556 ⁵⁷Northwestern University School of Medicine, Chicago, IL, USA.

1557 ⁵⁸Departments of Human Genetics, University of Michigan, Ann Arbor MI, USA.

1558 ⁵⁹Departments of Internal Medicine, University of Michigan, Ann Arbor MI, USA.

1559 ⁶⁰Center for Complex Disease Genomics, McKusick-Nathans Institute of Genetic Medicine, Johns
 1560 Hopkins University School of Medicine, Baltimore, MD, USA.

1561 ⁶¹Laboratory of Epidemiology, Demography, and Biometry, National Institute on Aging, National
 1562 Institutes of Health, Bethesda, MD, USA.

1563 ⁶²Neuroepidemiology Section, National Institute on Aging, National Institutes of Health, Bethesda,
 1564 MD, USA.

1565 ⁶³Department of Internal Medicine B, University Medicine Greifswald, Greifswald, Germany.

1566 ⁶⁴Institute of Physiology, University of Greifswald, Greifswald-Karlsburg, Germany.

1567 ⁶⁵DZD (German Center for Diabetes Research), Site Greifswald, Germany.

1568 ⁶⁶Institute for Community Medicine, University Medicine Greifswald, Site Greifswald, Germany.

1569 ⁶⁷Department of Medical Research, Taichung Veterans General Hospital, Taichung, Taiwan.

1570 ⁶⁸Division of Endocrinology and Metabolism, Department of Internal Medicine, Taichung Veterans
 1571 General Hospital, Taichung, Taiwan.

1572 ⁶⁹School of Medicine, National Yang-Ming University, Taipei, Taiwan.

1573 ⁷⁰School of Medicine, Chung Shan Medical University, Taichung, Taiwan.

1574 ⁷¹Institute of Medical Technology, National Chung-Hsing University, Taichung, Taiwan.

1575 ⁷²School of Medicine, National Defense Medical Center, Taipei, Taiwan.

1576 ⁷³Department of Obstetrics and Gynecology, Vanderbilt University Medical Center, Nashville, TN, USA.

1577 ⁷⁴Epidemiology & Prevention Center for Genomics and Personalized Medicine Research, Wake Forest
 1578 Baptist Medical Center, Medical Center Boulevard, Winston-Salem, NC, USA.

1579 ⁷⁵Department of Medicine, University of Mississippi Medical Center, Jackson, MS, USA.

1580 ⁷⁶Harvard Medical School, Boston MA, USA

1581 ⁷⁷Department of Epidemiology, University of Washington, Seattle, WA, USA.

1582 ⁷⁸Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA.

1583 ⁷⁹Institute for Translational Genomics and Population Sciences, Los Angeles Biomedical Research
 1584 Institute and Departments of Pediatrics and Medicine, Harbor-UCLA Medical Center, Torrance, CA,
 1585 USA.

1586 ⁸⁰Department of Health Services, University of Washington, Seattle, WA, USA.

1587 ⁸¹Group Health Research Institute, Group Health Cooperative, Seattle, WA, USA.

1588 ⁸²The Mindich Child Health and Development Institute, Icahn School of Medicine at Mount Sinai, New
 1589 York, NY, USA.

1590 ⁸³Cardiology, Geneva University Hospitals, Rue Gabrielle-Perret-Gentil, 4,1211 Genève 14 Switzerland.

1591 ⁸⁴Cardiovascular Research Center, Massachusetts General Hospital, Boston, MA, USA.

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