**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 4: Heat map of blood pressure associations using –log10(P-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 < 5x10^-8), orange shows moderate significance (5x10^-8 ≤ P < 0.01) and yellow shows no significant association (P ≥ 0.01). SBP: systolic BP; DBP: diastolic BP; PP: pulse pressure.

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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 ≥ 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 ($r^2$ ≥ 0.2). The genomic inflation factor, $\lambda$, is reported (NB: LD Score regression analysis yields $\lambda$~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 registers. 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 (m$^2$) 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 available.

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 QC, 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 software. 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 approach\(^4\) 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 documentation\(^5\) 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 Biobank\(^5\). 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
’singleton’s 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
SNVs covered within ICBP-1000G data. In summary, a total of 218 SNVs from the GWAS discovery association signals were requested for lookups.

9. **Replication datasets**

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

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

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

- AGES: Age, gene/Enviroment Susceptibility-Reykjavik Study
- ARIC: Atherosclerosis Risk in Communities
- ASPS: Austrian Stroke Prevention Study
- BS8C: British 1958 birth cohort
- BHS: Busselton Health Study
- CHS: Cardiovascular Health Study
- COLAUS: Cohorte Lausannoise
- COROGENE: Genetic Predisposition of Coronary Heart Disease in Patients Verified with Coronary Angiogram (controls for this study are a part of the National FINRISK Studies)
- CROATIA-Korcula: CROATIA-Korcula
- CROATIA-Split: CROATIA-Split
- CROATIA-Vis: CROATIA-Vis
- EGCUT: Estonian Genome Center
- EGCUT2: Estonian Genome Center
- EPIC: European Prospective Investigation in Cancer and Nutrition
- ERF: Erasmus Rucphen Family
- Fenland Fenland Study
- FHS: Framingham Heart Study
- FINNIRISK CASE: Predicting CVD in FINRISK cohorts, cases
- FINNIRISK_ctrl: Predicting CVD in FINRISK cohorts, controls
- FUSION: Finland-United States Investigation of NIDDM Genetics Study
- GRAPHIC: Genetic Regulation of Ambulatory Blood Pressure in the Community
- H2000: Health 2000 controls
- Health ABC The Health Aging and Body Composition Study
HTO
INGI_VB: Italian Network of Genetic Isolates - Val Borbera
INGI-Cilent: Italian Network on Genetic Isolates - Carlantino Project
INGI-FVG: Genetic Park of Cilento and Vallo di Diano Project
INGI-CARL: Italian Network on Genetic Isolates - Friuli Venezia Giulia Genetic Park
IPM: Charles R. Bronfman Institute for Personalized Medicine (IPM) BioBank Genome Wide Association Study of Cardiovascular, Renal and Metabolic Phenotypes
KORAS3: Kooperative Gesundheitsforschung in der Region Augsburg
KORAS4: Cooperative Health Research in the Region of Augsburg (Survey 4)
LBC1921: Lothian Birth Cohort 1921
LBC1921: Lothian Birth Cohort 1936
LOLIPOP_EW610: London Life Sciences Prospective Population Study
MESA: Multi-Ethnic Study of Atherosclerosis
MICROS: MICROS
MIGen: Myocardial Infarction Genetics Consortium
NEDSA: Netherlands Study of Depression and Anxiety
NSPHS: The Northern Sweden Population Health Study
NTR: Netherlands Twin Register
ORCADES: Orkney Complex Disease Study
PHASE: Prospective Investigation of the Vasculature in Uppsala Seniors
PIVUS: Precocious Coronary Artery Disease
PROCARDIS: PHArmacogenetic Study of Statins in the Elderly at risk
RSI: Rotterdam Study 1
RSII: Rotterdam Study 2
RSIII: Rotterdam Study 3
SHIP: Study of Health in Pomerania
STR: Swedish Twin Register
TRAILS: Tracking Adolescents' Individual Live Surveys
TRAILS-CC: Tracking Adolescents' Individual Live Surveys - Clinical Cohort
ULSAM: Uppsala Longitudinal Study of Adult Men
WGHS: Women's Genome Health Study YFS The Young Finns Study
YFS: The Young Finns Study

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

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

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

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

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

PREVEND: The Prevention of REnal and Vascular ENd-stage Disease (PREVEND) study is an ongoing prospective population-based study of individuals from the Netherlands, investigating the natural course of increased levels of urinary albumin excretion and its relation to renal and cardiovascular disease. Further details are available on the study website: www.prevend.org.
The following consortia contributed to the replication of the UK Biobank exome lookups:

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

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

### 10. Meta-analyses

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

The UK Biobank-exome meta-analysis synthesized meta-analysis data of individuals of European ancestry from two BP exome consortia (European exome consortium and CHARGE BP exome consortium) for the lookup variants. As in the GWAS analysis the allele frequencies and strand 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 ≥ 1% and coverage in 1000G data, while recent simulations in the literature\(^{14}\) suggest a similar significance threshold of \( P < 3 \times 10^{-8} \) based on denser Whole-Genome Sequencing (WGS) studies filtered at MAF ≥ 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 Hochberg\(^ {15} \) and Benjamini and Yekutieli\(^ {16} \) 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:

\( \text{iGEN-BP}^{17} \): 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 ($P_{het} < 1 \times 10^{-8}$) were also removed. The 23 studies contributing to the East Asian ancestry meta-analysis are: AASC, CAGE-Amagasaki, CAGE_GWAS1, CAGE-KING_Ommi, 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+ consortium 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/).

The CHARGE BP exome consortium: 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) 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 $^1$H 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 Germany). 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) 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).

To find regulatory loops, from the identified novel GWAS loci, we took the location of either the sentinel SNV, if it was in a DNaseI 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.

**FORGE 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.

GenomeRunner\textsuperscript{24} 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.

Fantom5\textsuperscript{25} 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 3.0\textsuperscript{26} using a Euclidean distance similarity matrix and K=5. Clusters were visualized using Java Treeview\textsuperscript{27}.

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 protocol\textsuperscript{28}, 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-IITEM 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 \(2^{-\Delta\Delta Ct}\) method\textsuperscript{29}.

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References


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(1) Department of Social Medicine, University Medical Center Groningen, University of Groningen, The Netherlands
(2) Department of Human Nutrition, Wageningen University, The Netherlands
(3) Department of Cardiology, University Medical Center Groningen, University of Groningen, The Netherlands
(4) Lifelines Cohort Study, The Netherlands
(5) Interdisciplinary Center of Psychopathology of Emotion Regulation (ICPE), Department of Psychiatry, University Medical Center Groningen, University of Groningen, The Netherlands
(6) Department of Endocrinology, Erasmus Medical Center, Rotterdam, The Netherlands
(7) Department of Public Health, University Medical Center Utrecht, The Netherlands
(8) Department of Genetics, University Medical Center Groningen, University of Groningen, The Netherlands
(9) Department of Public and Occupational Health, VU Medical Center, Amsterdam, The Netherlands

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CHD Exome+ Consortium

Consortium Members


1. Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK
2. Department of Clinical Biochemistry Herlev Hospital, Copenhagen University Hospital, Herlev, Denmark
3. Centre for Non-Communicable Diseases, Karachi, Pakistan
4. Department of Biostatistics and Epidemiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA
5. Department of Health, National Institute for Health and Welfare, Helsinki, Finland
6. Institute of Molecular Medicine FIMM, University of Helsinki, Finland
7. Estonian Genome Center, University of Tartu, Tartu, Estonia
8. University of Glasgow, Glasgow, UK
9. Department of Gerontology and Geriatrics, Leiden University Medical Center, Leiden, The Netherlands
10. Mr. De Craen suddenly passed away January 2016
11. Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands
12. Development Management and Planning, Pfizer Worldwide Research and Development
13. Pfizer Worldwide Research and Development, Stockholm, Sweden
14. Genetics and Pharmacogenomics, Merck Research Laboratories, Boston, Massachusetts, USA
15. Merck Research Laboratories, Kenilworth, New Jersey, USA
16. The Interuniversity Cardiology Institute of the Netherlands, Utrecht, The Netherlands
17. Institute of Cardiovascular and Medical Sciences, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, UK
18. ICDDR, B; Mohakhali, Dhaka, Bangladesh
19. National Institute of Cardiovascular Diseases, Sher-e-Bangla Nagar, Dhaka, Bangladesh
20. The National Institute for Health Research Blood and Transplant Research Unit in Donor Health and Genomics, University of Cambridge, Cambridge, UK
21. University of Lille, Risk Factors and Molecular Determinants of aging-related diseases, Lille, France
22. Inserm, Lille, France
23. Centre Hospitalier Universitaire Lille, Public Health, Lille, France
24. Institute Pasteur de Lille, Lille, France
25. Department of Epidemiology and Public Health, EA 3430, University of Strasbourg, Strasbourg, France
26. Department of General and Interventional Cardiology, University Heart Center Hamburg, Germany
27. University Medical Center Hamburg-Eppendorf, Hamburg, Germany
28. Department of Epidemiology, UMR 1027-INSERM, Toulouse University-CHU Toulouse, Toulouse, France
29. Director, UKCRC Centre of Excellence for Public Health, Queens University, Belfast, Northern Ireland
30. Institute of Genetic Epidemiology, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany
31. Department of Medicine I, University Hospital Grosshadern, Ludwig-Maximilians-Universität, Munich, Germany
32. DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany
33. Research Center in Epidemiology and Preventive Medicine, Department of Clinical and Experimental Medicine, University of Insubria, Varese, Italy
34. A full list of members and affiliations appears in the Supplementary Note
35. Wellcome Trust Sanger Institute, Hinxton, UK
36. The National Institute for Health Research Blood and Transplant Research
Dentistry, Queen Mary University of London, London, UK
13. Estonian Genome Center, University of Tartu, Tartu, Estonia
14. Wellcome Trust Sanger Institute, Genome Campus, Hinxton, UK
15. Medical Research Council Human Genetics Unit, Medical Research Council Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK
16. University of Lund, Department of Clinical Sciences, Malmö, Sweden
17. University of Verona, Department of Medicine, Verona, Italy
18. Department of Haematology, University of Cambridge, Cambridge, UK
20. Department of Internal Medicine, Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, Michigan, USA
21. Medical Research Institute, University of Dundee, Ninewells Hospital and Medical School, Dundee, UK
22. Oxford Centre for Diabetes, Endocrinology, and Metabolism, Radcliffe Department of Medicine, University of Oxford, Oxford, UK
23. National Institute for Health Research Oxford Biomedical Research Centre, Oxford University Hospital Trusts, Oxford, UK
24. Section of Investigative Medicine, Imperial College London, London, UK
25. Department of Life Sciences, Brunel University London, London, UK
26. Institute of Biomedicine, Biocenter Oulu, University of Oulu, Oulu, Finland
27. Department of Gastroenterology and Metabolism, Poznan University of Medical Sciences, Poznan, Poland
28. Hospital for Children and Adolescents, Helsinki University Central Hospital and University of Helsinki, Helsinki, Finland
29. Department of Obstetrics and Gynaecology, Oulu University Hospital and University of Oulu, Oulu, Finland
30. Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, UK
31. Department of Cardiology, Ealing Hospital, Middlesex, UK
32. Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden
33. Section of Biology and Genetics, Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Italy
34. Human Genetics, Wellcome Trust Sanger Institute, Hinxton, UK
35. The National Institute for Health Research Blood and Transplant Research Unit in Donor Health and Genomics, University of Cambridge, Cambridge, UK
36. University Medical Center Groningen, University of Groningen, Department of Cardiology, The Netherlands
37. Center for Human Genetic Research, Massachusetts General Hospital, Boston, Massachusetts, USA
38. Program in Medical and Population Genetics, Broad Institute, 7 Cambridge Center, Cambridge, Massachusetts, USA
39. Department of Hygiene and Epidemiology, University of Ioannina Medical School, Ioannina, Greece
40. Farr Institute of Health Informatics Research, Institute of Health Informatics, University College London, London, London, UK
41. Department of Clinical Sciences, Genetic and Molecular Epidemiology Unit, Lund University, Malmö, Sweden
42. Department of Genetics, Physical Anthropology and Animal Physiology, Faculty of Science and Technology, University of the Basque Country (UPV/EHU), Bilbao, Spain
43. Medical Research Council Epidemiology Unit, University of Cambridge School of Clinical Medicine, Box 285 Institute of Metabolic Science, Cambridge Biomedical Campus, Cambridge, UK
44. Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK
45. Centre for Genomic and Experimental Medicine, Medical Research Council Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK
46. Department of Psychology, University of Edinburgh, Edinburgh, UK
47. Queensland Brain Institute, The University of Queensland, Brisbane, Queensland, Australia
48. Department of Twin Research and Genetic Epidemiology, King’s College London, UK
49. Department of Nutrition and Dietetics, School of Health Science and Education, Harokopio University, Athens, Greece
50. Department of Biobank Research, Umeå University, Umeå, Sweden
51. Centre for Global Health Research, Usher Institute for Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, UK
52. Faculty of Medicine, University of Split, Croatia
53. Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden
54. Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts, USA
55. Alzheimer Scotland Research Centre, University of Edinburgh, Edinburgh, UK
56. Institute of Cardiovascular and Medical Sciences, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, UK
57. Division of Endocrinology, Boston Children’s Hospital, Boston, Massachusetts, USA
58. Institute of Molecular and Cell Biology, Tartu, Estonia
59. Department of Cardiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
60. Department of Genetics, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
61. Durrer Center for Cardiogenetic Research, ICIN-Netherlands Heart Institute, Utrecht, The Netherlands
62. Division of Nephrology, Department of Internal Medicine and Medical Specialties, Columbus - Gemelli University Hospital, Catholic University, Rome, Italy
63. Department of Medical Sciences, Molecular Epidemiology and Science for Life Laboratory, Uppsala University, Uppsala, Sweden
64. Department of Medicine, Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, California, USA
65. Department of Medical Genetics, Center for Molecular Medicine, University Medical Center Utrecht, Utrecht, The Netherlands
66. Department of Epidemiology, Julius Center for Health Sciences and Primary Care, Utrecht, The Netherlands
67. Department of Public Health and Primary Care, Leiden University Medical Center, Leiden, The Netherlands
68. Imperial College Healthcare NHS Trust, London, UK
69. National Heart and Lung Institute, Imperial College London, London, UK
70. Institute of Reproductive and Developmental Biology, Imperial College London, London, UK
71. Department of Epidemiology and Biostatistics, Medical Research Council Public Health England
72. Centre for Life Course Epidemiology, Faculty of Medicine, University of Oulu, Oulu, Finland
73. Biocenter Oulu, University of Oulu, Oulu, Finland
74. Unit of Primary Care, Oulu University Hospital, Oulu, Finland
75. Dasman Diabetes Institute, Dasman, Kuwait
76. Centre for Vascular Prevention, Danube-University Krems, Krems, Austria
77. King Abdulaziz University, Jeddah, Saudi Arabia
78. School of Molecular, Genetic and Population Health Sciences, University of Edinburgh, Medical School, Teviot Place, Edinburgh, UK
79. HUNT Research Centre, Department of Public Health and General Practice, Norwegian University of Science and Technology, Levanger, Norway
80. St. Olav Hospital, Trondheim University Hospital, Trondheim, Norway
81. Department of Medicine, Levanger Hospital, Nord- Trøndelag Health Trust, Levanger, Norway
82. Department of Computational Medicine and Bioinformatics, University of Michigan, Ann Arbor, Michigan, USA
83. Department of Human Genetics, University of Michigan, Ann Arbor, Michigan, USA
84. Institute for Molecular Medicine Finland University of Helsinki, Helsinki, Finland
85. Psychiatric and Neurodevelopmental Genetics Unit, Department of Psychiatry, Massachusetts General Hospital, Boston, Massachusetts, USA
86. Department of Public Health, University of Helsinki, Finland
87. International Centre for Circulatory Health, Imperial College London, UK
88. Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland, Dublin, Ireland
89. Princess Al-Jawhara Al-Brahim Centre of Excellence in Research of Hereditary Disorders (PACER-HD), King Abdulaziz University, Jeddah, Saudi Arabia
90. Cardiovascular Research Center, Massachusetts General Hospital, Boston, Massachusetts, USA
91. Department of Medicine, Harvard Medical School, Boston, Massachusetts, USA
92. Institute of Cardiovascular Sciences, University of Manchester, Manchester, UK
93. Faculty of Population Health Sciences, Institute of Cardiovascular Science, University College London, London, UK
94. The Big Data Institute at the Li Ka Shing Centre for Health Information and Discovery, University of Oxford, Oxford, UK
Members of the Genetics of Type 2 Diabetes (GoT2D) and Type 2 Diabetes Genetic Exploration by Next-generation sequencing in multi-Ethnic Samples (T2D-GENES) Consortia (http://type2diabetesgenetics.org)


Members of the Genetics of Type 2 Diabetes (GoT2D) and Type 2 Diabetes Genetic Exploration by Next-generation sequencing in multi-Ethnic Samples (T2D-GENES) Consortia (http://type2diabetesgenetics.org)


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Members of the Genetics of Type 2 Diabetes (GoT2D) and Type 2 Diabetes Genetic Exploration by Next-generation sequencing in multi-Ethnic Samples (T2D-GENES) Consortia (http://type2diabetesgenetics.org)


Members of the Genetics of Type 2 Diabetes (GoT2D) and Type 2 Diabetes Genetic Exploration by Next-generation sequencing in multi-Ethnic Samples (T2D-GENES) Consortia (http://type2diabetesgenetics.org)

Affiliations

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

17. Medical Genomics and Metabolic Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland, USA.
18. Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts, USA.
19. Chronic Disease Epidemiology, Swiss Tropical and Public Health Institute, University of Basel, Basel, Switzerland.
20. Institute of Genetic Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany.
21. Department of Medicine I, University Hospital Grosshadern, Ludwig-Maximilians-Universität, Munich, Germany.
22. Institute of Medical Informatics, Biometry and Epidemiology, Chair of Genetic Epidemiology, Ludwig-Maximilians-Universität, Munich, Germany.
23. DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany.
24. The Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.
25. Department of Medicine, Section of Genetic Medicine, The University of Chicago, Chicago, Illinois, USA.
27. Human Genetics Center, School of Public Health, The University of Texas Health Science Center at Houston, Houston, Texas, USA.
28. Saw Swee Hock School of Public Health, National University of Singapore, National University Health System, Singapore.
29. Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts, USA.
31. The Jackson Laboratory for Genomic Medicine, Farmington, Connecticut, USA.
32. Departments of Computational Medicine & Bioinformatics and Human Genetics, University of Michigan, Ann Arbor, Michigan, USA.
33. Department of Clinical Sciences, Lund University Diabetes Centre, Genetic and Molecular Epidemiology Unit, Lund University, Malmö, Sweden.
34. Department of Epidemiology, Colorado School of Public Health, University of Colorado, Aurora, Colorado, USA.
35. Department of Endocrinology and Metabolism, Shanghai Diabetes Institute, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China.
36. Singapore Eye Research Institute, Singapore National Eye Centre, Singapore.
37. Department of Ophthalmology, Yong Loo Lin School of Medicine, National University of Singapore, National University Health System, Singapore.
38. The Eye Academic Clinical Programme, Duke-NUS Graduate Medical School, Singapore.
39. Interdisciplinary Program in Bioinformatics, Seoul National University, Seoul, Republic of Korea.
40. Department of Human Genetics, McGill University, Montreal, Quebec, Canada.
41. Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada.
42. Department of Epidemiology and Biostatistics, Imperial College London, London, UK.
43. Department of Cardiology, Ealing Hospital NHS Trust, Southall, Middlesex, UK.
44. Departments of Medicine and Genetics, Albert Einstein College of Medicine, New York, USA.
45. Department of Systems Pharmacology and Translational Therapeutics, University of Pennsylvania - Perelman School of Medicine, Philadelphia, Pennsylvania, USA.
46. Department of Genetics, University of Pennsylvania - Perelman School of Medicine, Philadelphia, Pennsylvania, USA.
47. Department of Medicine, University of Texas Health Science Center, San Antonio, Texas, USA.
48. Research, South Texas Veterans Health Care System, San Antonio, Texas, USA.
49. Faculty of Health Sciences, Institute of Clinical Medicine, Internal Medicine, University of Eastern Finland, Kuopio, Finland.
50. Kuopio University Hospital, Kuopio, Finland.
51. Center for Genomics and Personalized Medicine Research, Wake Forest School of Medicine, Winston-Salem, North Carolina, USA.
52. Center for Diabetes Research, Wake Forest School of Medicine, Winston-Salem, North Carolina, USA.
53. Department of Biochemistry, Wake Forest School of Medicine, Winston-Salem, North Carolina, USA.
54. Centre for Research in Epidemiology and Population Health, Inserm U1018, Villejuif, France.
55. German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany.
56. Department of Public Health and Caring Sciences, Geriatrics, Uppsala University, Uppsala, Sweden.
57. Centre for Chronic Disease Control, New Delhi, India.
58. The Charles Bronfman Institute for Personalized Medicine, The Icahn School of Medicine at Mount Sinai, New York, USA.
59. National Heart and Lung Institute, Cardiovascular Sciences, Hammersmith Campus, Imperial College London, London, UK.
60. Department of Genome Sciences, University of Washington School of Medicine, Seattle, Washington, USA.
61. Analytic and Translational Genetics Unit, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA.
62. Center for Human Genetic Research, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA.
63. Department of Psychiatry, Icahn Institute for Genomics and Multiscale Biology, Icahn School of Medicine at Mount Sinai, New York, USA.
64. Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK.
65. Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong, China.
66. Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea.
67. Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA.
68. NIHR Blood and Transplant Research Unit in Donor Health and Genomics, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK.
69. Department of Molecular Medicine and Biopharmaceutical Sciences, Graduate School of Convergence Science and Technology, and College of Medicine, Seoul National University, Seoul, Republic of Korea.
70. Department of Biostatistics and Epidemiology, University of Pennsylvania, Philadelphia, Pennsylvania, USA.
71. Center for Non-Communicable Diseases, Karachi, Pakistan.
72. Cardiovascular Division, Baylor College of Medicine, Houston, Texas, USA.
73. Department of Pediatrics, University of Texas Health Science Center, San Antonio, Texas, USA.
74. Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, National University Health System, Singapore.
75. Department of Epidemiology, Murcia Regional Health Council, IMIB-Arrixaca, Murcia, Spain.

76. CIBER Epidemiología y Salud Pública (CIBERESP), Spain.

77. Unit of Preventive Medicine and Public Health, School of Medicine, University of Murcia, Spain.

78. Cancer Research and Prevention Institute (ISPO), Florence, Italy.

79. Department of Medicine, University of Mississippi Medical Center, Jackson, Mississippi, USA.

80. South Texas Diabetes and Obesity Institute, Regional Academic Health Center, University of Texas Rio Grande Valley, Brownsville, Texas, USA.

81. Department of Genetics, Texas Biomedical Research Institute, San Antonio, Texas, USA.

82. Department of Internal Medicine, Section on Nephrology, Wake Forest School of Medicine, Winston-Salem, North Carolina, USA.

83. Center of Biostatistics and Bioinformatics, University of Mississippi Medical Center, Jackson, Mississippi, USA.

84. Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, National University Health System, Singapore.

85. Division of Human Genetics, Genome Institute of Singapore, A*STAR, Singapore.

86. CNRS-UMR8199, Lille University, Lille Pasteur Institute, Lille, France.

87. Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands.

88. Institute of Health Sciences, University of Oulu, Oulu, Finland.

89. Translational Laboratory in Genetic Medicine (TLGM), Agency for Science, Technology and Research (A*STAR), Singapore, Singapore.

90. Jackson Heart Study, University of Mississippi Medical Center, Jackson, Mississippi, USA.

91. College of Public Services, Jackson State University, Jackson, Mississippi, USA.

92. KG Jebsen Center for Diabetes Research, Department of Clinical Science, University of Bergen, Bergen, Norway.

93. Department of Pediatrics, Haukeland University Hospital, Bergen, Norway.

94. Institute of Human Genetics, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany.

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

96. Institute of Clinical Diabetology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University, Düsseldorf, Germany.

97. German Center for Diabetes Research (DZD), Neuherberg, Germany.

98. Institute of Regional Health Research, University of Southern Denmark, Odense, Denmark.

99. Department of Clinical Biochemistry, Vejle Hospital, Vejle, Denmark.

100. Department of Internal Medicine and Endocrinology, Vejle Hospital, Vejle, Denmark.


102. Abdominal Center: Endocrinology, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland.

103. Minerva Foundation Institute for Medical Research, Helsinki, Finland.

104. Department of Medicine, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland.

105. Division of Cardiovascular and Diabetes Medicine, Medical Research Institute, Ninewells Hospital and Medical School, Dundee, UK.

106. Estonian Genome Center, University of Tartu, Tartu, Estonia.

107. Department of Genetics, Harvard Medical School, Boston, Massachusetts, USA.

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

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

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

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

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

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


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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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


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

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

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

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

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

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

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


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.
9Department of Biostatistics, University of Washington, Seattle, WA, USA.
<table>
<thead>
<tr>
<th>Number</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>Human Genetics Center, School of Public Health, University of Texas Health Science Center at</td>
</tr>
<tr>
<td></td>
<td>Houston, Houston TX, USA.</td>
</tr>
<tr>
<td>10</td>
<td>The Charles Bronfman Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai,</td>
</tr>
<tr>
<td></td>
<td>New York, NY, USA.</td>
</tr>
<tr>
<td>11</td>
<td>DZHK (German Center for Cardiovascular Research), partner site Greifswald, Greifswald, Germany.</td>
</tr>
<tr>
<td>12</td>
<td>Interfaculty Institute for Genetics and Functional Genomics, University Medicine and Ernst-Moritz-</td>
</tr>
<tr>
<td></td>
<td>Arndt University Greifswald, Greifswald, Germany.</td>
</tr>
<tr>
<td>13</td>
<td>Institute for Translational Genomics and Population Sciences, Los Angeles Biomedical Research</td>
</tr>
<tr>
<td></td>
<td>Institute and Department of Pediatrics, Harbor-UCLA Medical Center, Torrance, CA, USA.</td>
</tr>
<tr>
<td>14</td>
<td>Columbia University Medical Center, 622 West 168th Street, PH 9 East, 107, New York, NY, USA.</td>
</tr>
<tr>
<td>15</td>
<td>George Washington University School of Medicine and Health Sciences, Washington DC, USA.</td>
</tr>
<tr>
<td>16</td>
<td>Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of</td>
</tr>
<tr>
<td></td>
<td>Cambridge, Cambridge, UK.</td>
</tr>
<tr>
<td>17</td>
<td>Centre for Cardiovascular Genetics, Institute of Cardiovascular Science, Rayne Building University</td>
</tr>
<tr>
<td></td>
<td>College London, London, WC1E 6JF, UK.</td>
</tr>
<tr>
<td>18</td>
<td>MRC Integrative Epidemiology Unit, School of Social and Community Medicine, University of Bristol,</td>
</tr>
<tr>
<td></td>
<td>Oakfield House, Oakfield Grove, Bristol BS8 2BN, UK.</td>
</tr>
<tr>
<td>19</td>
<td>Department of Biostatistics, University of Liverpool, Liverpool, L69 3GA, UK.</td>
</tr>
<tr>
<td>20</td>
<td>Department of Health Sciences, University of Leicester, Leicester, LE1 7RH, UK.</td>
</tr>
<tr>
<td>21</td>
<td>Joseph J. Zilber School of Public Health, University of Wisconsin, Milwaukee, WI, USA.</td>
</tr>
<tr>
<td>22</td>
<td>Division of Preventive Medicine, Brigham and Women's Hospital, Boston, MA, USA.</td>
</tr>
<tr>
<td>23</td>
<td>Vanderbilt Epidemiology Center, Vanderbilt Genetics Institute, Institute for Medicine and Public</td>
</tr>
<tr>
<td></td>
<td>Health, Vanderbilt University Medical Center, Nashville, TN, USA.</td>
</tr>
<tr>
<td>24</td>
<td>Icelandic Heart Association, Kopavogur, Iceland.</td>
</tr>
<tr>
<td>25</td>
<td>Institute of Molecular Medicine, University of Texas Health Science Center at Houston, Houston, TX,</td>
</tr>
<tr>
<td></td>
<td>USA.</td>
</tr>
<tr>
<td>26</td>
<td>Division of Public Health Sciences, Department of Biostatistical Sciences, Wake Forest School of</td>
</tr>
<tr>
<td></td>
<td>Medicine, Winston-Salem, NC, USA.</td>
</tr>
<tr>
<td>27</td>
<td>Genetic Epidemiology Unit, Department of Epidemiology, Erasmus Medical Center, 3015 CN</td>
</tr>
<tr>
<td></td>
<td>Rotterdam, the Netherlands.</td>
</tr>
<tr>
<td>28</td>
<td>Center of Biostatistics and Bioinformatics, University of Mississippi Medical Center, Jackson, MS,</td>
</tr>
<tr>
<td></td>
<td>USA.</td>
</tr>
<tr>
<td>29</td>
<td>The Bill and Melinda Gates Foundation, 500 Fifth Avenue North, Seattle, WA, USA.</td>
</tr>
<tr>
<td>30</td>
<td>Department of Mathematics and Statistics, Boston University, MA, USA.</td>
</tr>
<tr>
<td></td>
<td>Institution</td>
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<td>1</td>
<td>31Faculty of Medicine, University of Iceland, Reykjavik, Iceland.</td>
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<td>2</td>
<td>32Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA, USA.</td>
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<td>3</td>
<td>33Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA, USA.</td>
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<td>4</td>
<td>34Program in Medical and Population Genetics, Broad Institute of Harvard and MIT, Boston, MA, USA.</td>
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<td>5</td>
<td>35Division of Cardiology, Department of Medicine &amp; Department of Genetics, Washington University School of Medicine, Saint Louis, MO, USA.</td>
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<td>6</td>
<td>36Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA, USA.</td>
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<td>7</td>
<td>37Department of Cardiovascular Sciences, University of Leicester, Leicester, LE3 9QP, UK.</td>
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<td>8</td>
<td>38NIHR Leicester Cardiovascular Biomedical Research Unit, Glenfield Hospital, Leicester, LE3 9QP, UK.</td>
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<td>9</td>
<td>39Deutsches Herzzentrum München and Technische Universität München, München, Germany.</td>
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<tr>
<td>10</td>
<td>40Deutsches Zentrum für Herz- und Kreislaufforschung (DZHK), Munich Heart Alliance; Lazarettstraße 36, München, Germany.</td>
</tr>
<tr>
<td>11</td>
<td>41Princess Al-Jawhara Al-Brahim Centre of Excellence in Research of Hereditary Disorders (PACER-HD), King Abdulaziz University, Jeddah 21589, Saudi Arabia.</td>
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<td>12</td>
<td>42William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK.</td>
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<tr>
<td>13</td>
<td>43Department of Epidemiology, Johns Hopkins University, Baltimore, MD, USA.</td>
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<tr>
<td>14</td>
<td>44Center for Biomedicine, European Academy of Bozen/Bolzano (EURAC), affiliated to the University of Lübeck, Bolzano, Italy.</td>
</tr>
<tr>
<td>15</td>
<td>45Department of Genetic Epidemiology, Institute of Epidemiology and Preventive Medicine, University of Regensburg, Regensburg, Germany.</td>
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<tr>
<td>16</td>
<td>46Fred Hutchinson Cancer Research Center, Division of Public Health Sciences, Seattle, Washington, USA.</td>
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<tr>
<td>17</td>
<td>47Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute, Bethesda, MD, USA.</td>
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<td>18</td>
<td>48Survey Research Center, Institute for Social Research, University of Michigan, Ann Arbor, MI, USA.</td>
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<td>19</td>
<td>49Pennington Biomedical Research Center, Louisiana State University System, Baton Rouge, LA, USA.</td>
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<td>20</td>
<td>50Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA.</td>
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<tr>
<td>21</td>
<td>51Department of Epidemiology, Erasmus MC, Rotterdam, the Netherlands.</td>
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<td>22</td>
<td>52Department of Internal Medicine, Erasmus MC, Rotterdam, the Netherlands.</td>
</tr>
<tr>
<td>23</td>
<td>53Department of Preventive Medicine, Boston University School of Medicine, Boston, MA, USA.</td>
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<td>24</td>
<td>54Cardiology Section, Department of Medicine, Boston Veteran’s Administration Healthcare, Boston, MA, USA.</td>
</tr>
<tr>
<td>25</td>
<td>55Cardiovascular Division, Brigham and Women’s Hospital, Boston, MA, USA.</td>
</tr>
<tr>
<td>26</td>
<td>56Department of Medicine, Harvard Medical School, Boston, MA, USA.</td>
</tr>
</tbody>
</table>
57. Northwestern University School of Medicine, Chicago, IL, USA.
58. Departments of Human Genetics, University of Michigan, Ann Arbor MI, USA.
59. Departments of Internal Medicine, University of Michigan, Ann Arbor MI, USA.
60. Center for Complex Disease Genomics, McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA.
61. Laboratory of Epidemiology, Demography, and Biometry, National Institute on Aging, National Institutes of Health, Bethesda, MD, USA.
62. Neuroepidemiology Section, National Institute on Aging, National Institutes of Health, Bethesda, MD, USA.
63. Department of Internal Medicine B, University Medicine Greifswald, Greifswald, Germany.
64. Institute of Physiology, University of Greifswald, Greifswald-Karlsburg, Germany.
65. DZD (German Center for Diabetes Research), Site Greifswald, Germany.
66. Institute for Community Medicine, University Medicine Greifswald, Site Greifswald, Germany.
67. Department of Medical Research, Taichung Veterans General Hospital, Taichung, Taiwan.
68. Division of Endocrinology and Metabolism, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan.
69. School of Medicine, National Yang-Ming University, Taipei, Taiwan.
70. School of Medicine, Chung Shan Medical University, Taichung, Taiwan.
71. Institute of Medical Technology, National Chung-Hsing University, Taichung, Taiwan.
72. School of Medicine, National Defense Medical Center, Taipei, Taiwan.
73. Department of Obstetrics and Gynecology, Vanderbilt University Medical Center, Nashville, TN, USA.
74. Epidemiology & Prevention Center for Genomics and Personalized Medicine Research, Wake Forest Baptist Medical Center, Medical Center Boulevard, Winston-Salem, NC, USA.
75. Department of Medicine, University of Mississippi Medical Center, Jackson, MS, USA.
76. Harvard Medical School, Boston MA, USA
77. Department of Epidemiology, University of Washington, Seattle, WA, USA.
78. Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA.
79. Institute for Translational Genomics and Population Sciences, Los Angeles Biomedical Research Institute and Departments of Pediatrics and Medicine, Harbor-UCLA Medical Center, Torrance, CA, USA.
80. Department of Health Services, University of Washington, Seattle, WA, USA.
81. Group Health Research Institute, Group Health Cooperative, Seattle, WA, USA.
82. The Mindich Child Health and Development Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA.
Cardiology, Geneva University Hospitals, Rue Gabrielle-Perret-Gentil, 4,1211 Genève 14 Switzerland.

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