

Large-scale blood pressure GWAS accounting for gene-depression interactions in 564,680 individuals from diverse populations

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Summary

Gene-environment interactions may enhance our understanding of blood pressure (BP) biology. We conducted a meta-analysis of multi-population genome-wide association studies (GWASs) of BP traits accounting for gene-depressive symptomatology (DEPR) interactions. Our study included 564,680 adults from 67 cohorts and four population backgrounds: African (5%), Asian (7%), European (85%), and Hispanic (3%). We discovered seven previously unreported BP loci showing gene-DEPR interaction. These loci mapped to genes implicated in neurogenesis (*TGFA* and *CASP3*), lipid metabolism (*ACSL1*), neuronal apoptosis (*CASP3*), and synaptic activity (*CNTN6* and *DBI*). We also showed evidence for gene-DEPR interaction at nine known BP loci, further suggesting links between mood disturbance and BP regulation. Of the 16 identified loci, 11 were derived from non-European populations. Post-GWAS analyses prioritized 36 genes, including genes involved in synaptic functions (*DOCK4* and *MAGI2*) and neuronal signaling (*CCK*, *UGDH*, and *SLC01A2*). Integrative druggability analyses identified 11 druggable candidate gene targets linked to pathways involved in mood disorders as well as known anti-hypertensive drugs. Our findings emphasize the importance of considering gene-DEPR interactions on BP, particularly in non-European populations. Our prioritized genes and druggable targets highlight biological pathways connecting mood disorders and hypertension and suggest opportunities for BP drug repurposing and risk factor prevention, especially in individuals with DEPR.

Introduction

Hypertension and high blood pressure (BP) (MIM: 145500) are major risk factors for cardiovascular disease, stroke, chronic kidney disease, and vascular dementia,

significantly contributing to global morbidity and mortality.¹ Despite the widespread availability of effective anti-hypertensive medications, the prevalence of hypertension has doubled worldwide over the past three decades and is projected to affect 1.6 billion individuals by 2025.²

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Moreover, while the age-adjusted prevalence of hypertension has declined in some regions, global disparities in hypertension rates have widened.^{3,4}

Genetic and environmental factors can independently increase the risk of hypertension, but gene-environment interaction (GxE) may provide a more comprehensive

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understanding of the genetic contributions to the disease.^{5–7} A recent genome-wide association study (GWAS) of BP identified a total of 2,103 independent genetic signals, which accounts for approximately 60% of the heritability of BP.⁸ Consequently, a substantial portion of heritability remains unexplained. Incorporating GxE in genetic analyses of BP may yield additional information about its genetic architecture and provide avenues to improve health by more precisely characterizing risk of high BP in the context of potentially modifiable environmental, lifestyle, and behavioral risk factors.⁹

The influence of psychosocial factors on BP level is well known.^{10–12} Psychosocial stress increases the incidence of hypertension and is associated with poor hypertension control, unhealthy lifestyle behaviors, and non-compliance with treatment regimens.¹³ The relationship between depressive symptoms and BP is complex. While some studies have shown an association of depressive symptoms with incidence of hypertension,^{14–16} others have reported an association of depressive symptoms with lower BP levels.^{17–19} A recent study provided evidence of depression as a causal risk factor of hypertension using Mendelian randomization.²⁰ Our previous study examined the effect modification of genetic factors by dichotomous psychosocial factors on BP in up to 128,894 individuals.²¹ This highlighted the significance of gene-psychosocial factor interactions in gene discovery for BP, especially among individuals of African ancestry. However, the statistical power and population diversity of the study were limited. To address these shortcomings, we increased the sample size by up to 5-fold by incorporating currently available biobank data. In addition, we defined psychosocial exposures as both dichotomous and quantitative, potentially improving the statistical po-

wer to identify additional BP loci. We report genome-wide association meta-analyses of systolic BP (SBP), diastolic BP (DBP), and pulse pressure (PP) in the context of depressive symptomatology (DEPR) in a sample of up to 564,680 participants from populations of African (AFR), Asian (ASN), European (EUR), and Hispanic (HIS) backgrounds.

Methods

Study design and participants

All participating cohorts were part of the Gene-Lifestyle Interactions Working Group of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium.²² Except for the United Kingdom Biobank (UKB), the study included adult men and women aged 18 years or older from four population groups defined on the basis of self-reported participants' race and ethnicity: AFR (including self-reported Black), ASN (including East Asian and South Asian), EUR (including self-reported White), and HIS. The UKB used the Pan-UKB data to define population groups based on shared genetic similarity and demographic history.²³ GWASs considering the interaction between gene and DEPR were conducted within each individual study by population group. Population-specific meta-analyses were then performed using summary statistics, followed by cross-population meta-analyses (CPMAs) based on the population-specific results (Figure 1).

Ethics approval and consent

All participating studies obtained written informed consent from their participants and ethics approval from the appropriate institutional review boards. Details about the participating studies are provided in the [supplemental information](#).

BP traits

Three BP traits were considered as outcome variables: SBP, DBP, and PP. PP was calculated as the difference between SBP and

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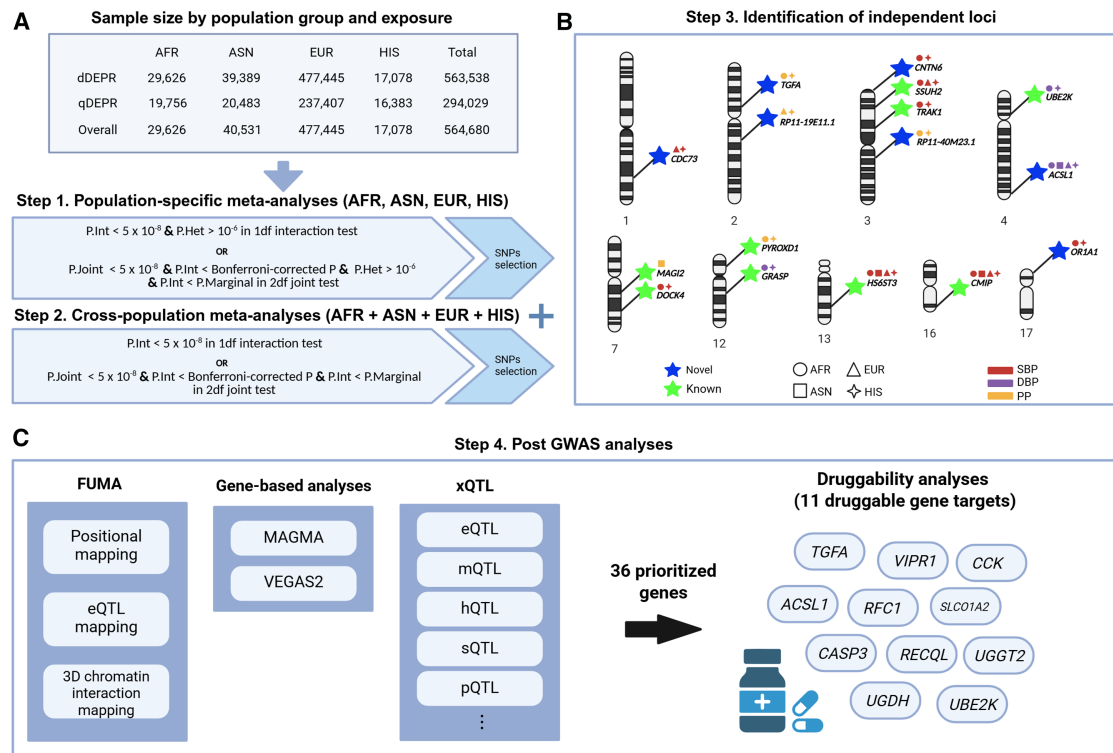


Figure 1. Study overview

(A) For each BP trait, association analyses were conducted accounting for SNP × depressive symptomatology (DEPR) interaction effects using two exposures: dichotomous DEPR (dDEPR) and quantitative DEPR (qDEPR). For each population group, study-specific results were combined to perform 1df interaction test and 2df joint test. Population-specific meta-analyses were carried out separately for each group—African (AFR), Asian (ASN), European (EUR), and Hispanic (HIS)—and subsequently combined for cross-population meta-analyses.

(B) A total of 16 independent loci were identified through SNP × DEPR interaction effects, including seven novel and nine known loci for BP.

(C) Gene prioritization was performed using FUMA, gene-based analyses, and xQTL. Druggability analyses of 36 prioritized genes identified 11 druggable gene targets.

DBP. When multiple BP readings were taken during the same examination, the average of all SBP or DBP readings were used. For participants taking anti-hypertensive medications, SBP and DBP values were adjusted by adding 15 mmHg and 10 mmHg, respectively, to the measured values.^{24,25} Extreme values for each BP variable were winsorized if they were more than 6 standard deviations (SDs) above or below the mean.

DEPR exposures

Each participating study collected information on DEPR using validated screening questionnaires. Across the studies, depressive symptoms were assessed using 13 distinct validated instruments, with additional variability arising from differences in the number of questionnaire items and scoring ranges (Table S1). Measurements of DEPR and BP were taken during the same examination. We defined two variables as exposures: dichotomous DEPR (dDEPR) and quantitative DEPR (qDEPR).

The dDEPR exposure was defined as a binary variable by dichotomizing DEPR measures using recommended standard cutoff points specific to each screening instrument. Individuals with higher depressive symptom score were categorized as the exposed group and coded as $E = 1$. The specific cutoff points used to define the dDEPR for each study are provided in Table S1. Descriptive statistics on depression score are provided in Table S2.

The qDEPR exposure was defined as a standardized residual after adjusting for age and sex effects within each cohort. For studies that included multiple population groups, the variable was computed separately for each population. First, DEPR scores were winsorized if a value was more than 6 SDs above or below the mean. The scores were then regressed on age, sex, and age × sex interaction in the sex-combined samples. The resulting age- and sex-adjusted residuals were standardized using the Z score in the combined sample. Thus, in each study, the mean and SD of qDEPR were approximately 0 and 1, respectively, as shown in Table S3. For the sex-stratified analyses, we used the same qDEPR estimates that were residualized and standardized in the sex-combined group used. No additional residualization or normalization was performed within the sex-specific group.

Genotype data

Most of the participating studies performed genotyping using Illumina or Affymetrix. Imputations were primarily carried out using Trans-Omics for Precision Medicine (TOPMed) or Haplotype Reference Consortium (HRC) reference panels. Details on genotyping and imputation are presented in Table S4. Before analysis, genotype data for each cohort were restricted to single-nucleotide polymorphism (SNP) mapping to autosomal chromosomes, with minor allele frequency (MAF) $\geq 0.1\%$ across all samples and an

imputation quality ≥ 0.3 . Indels (insertions and deletions) were also included.

Individual study statistical analyses

Each cohort performed analyses by population subgroup using two statistical models designed for different purposes. Model 1 was a joint-effect model that accounts for the SNP main effect, DEPR effect, and the interaction effect between SNP and DEPR:

$$E(\text{BP}) = \beta_0 + \beta_{\text{SNP}}\text{SNP} + \beta_{\text{DEPR}}\text{DEPR} + \beta_{\text{SNP} \times \text{DEPR}}\text{SNP} \times \text{DEPR} + \beta_C C,$$

where DEPR was either dDEPR or qDEPR, and **C** was a vector of covariates, including age, age², sex, field centers (if relevant), and population-specific principal components, as well as any additional cohort-specific covariates, if applicable (Table S4). In model 1, additional DEPR $\times$ covariate interaction terms with age, age², and sex were included in the model to minimize potential false-positive findings that could result from confounding effects.²⁶ For the sex-stratified analyses, both sex and DEPR $\times$ sex were excluded from the model. A 1-degree-of-freedom (1df) interaction test was performed to evaluate SNP $\times$ DEPR interaction effect alone under the null hypothesis that $\beta_{\text{SNP} \times \text{DEPR}} = 0$. A 2df joint test was used to simultaneously assess the SNP main effect and SNP $\times$ DEPR interaction effects, under the null hypothesis that $\beta_{\text{SNP}} = \beta_{\text{SNP} \times \text{DEPR}} = 0$.²⁷ When both the SNP main effect and interaction effects exist, the 2df joint test typically provides more power than the 1df interaction test.²⁷

Model 2 was an SNP marginal effect model:

$$E(\text{BP}) = \beta_0 + \beta_{\text{SNP}}\text{SNP} + \beta_C C.$$

The SNP marginal *p* value (p_{Marginal}) was used to identify SNPs with significant evidence of interaction effects by comparing p_{Marginal} to the 1df interaction *p* value (p_{Int}) in model 1. To ensure a fair comparison, we conducted a standard GWAS (model 2) with the same covariates used in model 1 other than the DEPR $\times$ covariate interaction terms.

Analyses excluded subjects without genotype data or with missing data for the DEPR exposure or any covariates. Each study selected one of the specialized software tools to run analyses: GEM (<https://github.com/large-scale-gxe-methods/GEM>), LinGxEscanR (<https://github.com/USCbiostats/LinGxEscanR>), or MMAP (<https://github.com/MMAP/MMAP.github.io>), as described in Table S4. For the studies with related subjects, MMAP was used to account for familial relatedness using linear mixed models.

Quality control of study-specific and meta-analyses results

Quality control (QC) was performed for both study-specific and meta-analyses results using EasyQC2 software (www.genepi-regensburg.de/easyqc2). For results submitted in build hg19, genomic coordinates were lifted over to build hg38. At the study-level, QC involved different SNP filters for the two exposures. For the dDEPR, SNPs were excluded if degree of freedom (df) was less than 20 in the unexposed, exposed, or total samples. The df was calculated as minor allele count $\times$ imputation quality score. For the qDEPR, SNPs were removed if the df was less than 20 in the total samples. To identify systematic errors in data preparation, allele frequency (AF) discrepancy, outliers, and missing data were assessed visually through comparison of results to reference panels derived by imputation of population-specific 1000

Genomes phase 3 version 5 (p3v5) panels to the TOPMed reference panels using the TOPMed imputation server. Any resulting concerns were addressed through consultation with the contributing studies. To evaluate study-level systematic inflation, genomic control (GC) inflation factors were also estimated (Table S5) and, thus, GC correction was not applied at the study level. Next, meta-level QC was performed within each population group (AFR: 18 cohorts; ASN: 8 cohorts, EUR: 36 cohorts, HIS: 5 cohorts) to assess improper transformation of BP variables, unstable numerical computation, and excessive inflation.

Meta-analyses

Meta-analyses were performed using an inverse-variance weighted fixed-effect model for the 1df interaction test and an inverse-covariance-matrix-weighted model for the 2df joint test,^{28,29} each method chosen to appropriately weight studies based on the precision of their estimates. Analyses were first conducted separately for each population group, after which the results were combined for CPMAs. The primary focus was on analyses within the sex-combined group, considering three phenotypes and two exposures. For the identified loci in the sex-combined group analyses, we performed sex-stratified analyses to assess differences in G $\times$ E by sex. The first GC correction was applied to the population-specific meta-analyses and subsequently once more to the CPMAs.²⁸ Quantile-quantile plots and GC inflation factors are shown in Figures S1–S10. In the 2df joint test, there were mild to moderate inflations, mainly due to the significance at previously reported loci for BP.

Identification of independent associated loci

EasyStrata2 software was used to prioritize the top loci among significant results identified in 1df interaction and 2df joint tests.³⁰ For the CPMAs, SNPs had to be present in at least two population groups with a minimum sample size of 20,000 individuals. In the EUR-specific meta-analyses, SNPs were reported if they appeared in at least three studies and in at least 3,000 individuals. These criteria were relaxed for other population groups due to smaller sample size, as shown in Table S6. Only SNPs with MAF greater than 1% were reported for both population-specific and cross-population meta-analyses. SNPs located within 1 Mb of the major histocompatibility complex (MHC) region were excluded.

We considered SNPs with significant evidence of DEPR interaction effects on BP as top SNPs based on the following criteria. (1) SNPs with significant 1df interaction effect ($p_{\text{Int}} < 5 \times 10^{-8}$). In population-specific analyses, SNPs were also required to show no evidence of heterogeneity ($p_{\text{Het}} > 10^{-6}$). (2) SNPs with significant 2df joint effects ($p_{\text{Joint}} < 5 \times 10^{-8}$), $p_{\text{Int}} < \text{Bonferroni-corrected } p$ value adjusted for the number of 2df joint variants identified in the respective CPMA or population-specific subgroup (e.g., for CPMA: dDEPR, $0.05/904 = 5.53 \times 10^{-5}$; for qDEPR, $0.05/316 = 1.58 \times 10^{-4}$), and $p_{\text{Int}} < p_{\text{Marginal}}$. False discovery rates (FDRs) were also calculated using EasyStrata2.

To identify independent loci among all significant variants, we grouped the significant variants within 500-kb regions and identified independent loci by linkage disequilibrium (LD) $r^2 < 0.1$, using TOPMed-imputed 1000 Genomes reference panels. If variants within regions were missing in the LD panels, the most significant variant within each region was reported. The independent loci were considered novel if the SNPs are located ± 500 kb away from the known loci previously reported in BP GWASs (Table S7). For the identified independent loci, we additionally

examined heterogeneity of the interaction effects by sex using the results from the sex-stratified analyses. Heterogeneity of SNP $\times$ DEPR effects between men and women was tested using two-sample Z tests.³¹ The significance threshold for heterogeneity tests was defined at the Bonferroni-corrected threshold based on the number of the identified independent loci.

DEPR-stratified analyses

For the SNPs identified in dDEPR analyses, we further derived SNP effect on BP by DEPR status using the joint model's summary statistics.³² For each SNP, the actual sample size and the number of exposed groups were used to derive summary statistics. This approach provides greater precision and avoids assumptions that may introduce errors.

Gene-based analyses

We performed gene-based tests on meta-analysis summary statistics for the 1df interaction results using Multi-Marker Analysis of Genomic Annotation (MAGMA) implemented in FUMA³³ and Versatile Gene-Based Association Study 2 (VEGAS2),³⁴ as the 2df joint test does not provide an interpretable interaction effect estimate and therefore could not be used for the gene-based analyses. Both tools computed gene-based p values by considering variants within each gene. The MAGMA method utilized a multiple linear regression model,³⁵ while VEGAS2 analyses were conducted using the "top10" parameter, which selects the top 10% variants within a gene, taking into account the number of variants and LD. This approach allowed us to include SNPs with stronger signals and exclude those that might dilute the summary statistics.³⁴ For both MAGMA and VEGAS2, we used 1000 Genomes phase 3 reference panels specific to AFR, EAS (for ASN), EUR, and AMR (for HIS) populations to compute LD for population-specific analyses. In MAGMA, the CPMA was conducted using the "all" 1000 Genomes phase 3 reference panel in the FUMA setting. For VEGAS2, we performed meta-analyses of population-specific gene-based results using Stouffer's method, with p values weighted by sample size. Gene-wide significance in MAGMA was defined as $p < 2.61 \times 10^{-6}$, correcting for 19,122 protein-coding genes. VEGAS2 included 19,263 protein-coding genes, leading to a gene-wide significance threshold of $p < 2.61 \times 10^{-6}$.

Gene-set- or pathway-based analysis

We conducted gene-set analysis using MAGMA in FUMA to identify associations between gene sets and biological pathways. The analyses were performed based on the gene-based results from MAGMA, with statistical significance threshold at $p < 2.94 \times 10^{-6}$, correcting for 17,009 gene sets. As a sensitivity analysis, we performed pathway-based analysis using VEGAS2Pathway,³⁶ based on population-specific gene-based association results generated with VEGAS2. The meta-analyses were conducted using Stouffer's method. VEGAS2Pathway included 2,748 pathways, resulting in a significance threshold of empirical $p < 1.82 \times 10^{-5}$.

Functional annotations

All identified independent loci were assessed for potential functional annotations using multiple tools. First, we used the FUMA v.1.5.2 to annotate functional information of the novel and known loci.³³ At the genomic region level, the FUMA SNP2GENE pipeline was used to prioritize genes based on the results of the top SNPs and SNPs in LD ($r^2 > 0.4$ within 250 kb)

through three gene-mapping approaches: positional mapping, GTEx v.8 expression quantitative trait locus (eQTL) mapping, and 3D chromatin interaction mapping (false discovery rate [FDR] $\leq 1 \times 10^{-6}$, 250 bp upstream and 500 bp downstream of the transcription start site [TSS] by default settings). At the variant level, we used QTLbase³⁷ and Open Target Genetics³⁸ databases to explore xQTLs that link our loci to tissue- or cell-type-specific functions. The xQTLs include gene expression (eQTLs), DNA methylation (mQTLs), histone modification (hQTLs), splicing event (sQTLs), protein expression (pQTLs), alternative polyadenylation (apaQTLs), and others. To investigate whether the identified loci were associated with other phenotypes, we utilized a phenome-wide association study (PheWAS) tool implemented in Open Targets genetics and GWAS ATLAS.³⁹ Using all the prioritized genes, we performed FUMA GENE2FUNC analysis to test enrichment of the gene sets and provide expression of those prioritized genes (adjusted p value < 0.05).

Druggability analyses

To assess the clinical potential of the candidate genes, we conducted integrative druggability analyses.⁴⁰ We first used the Drug-Gene Interaction database (DGIdb, v.4.2.0) to query high or medium priority and determine the potential druggability of the candidate gene targets. Genes were annotated for biological pathways and functions using the Kyoto Encyclopedia of Genes and Genomes (KEGG) database. Using DGIdb (<https://dgidb.org/about/overview/about-us>), We annotated the druggability target categories and queried all interacting drugs reported in 44 databases (Ensembl, HGNC, NCBI, ChemIDplus, Drugs@FDA, HemOnc, NCI, RxNorm, Wikidata, CancerCommons, CGI, ChEMBL, CIViC, ClarityFoundationBiomarkers, ClarityFoundationClinicalTrial, COSMIC, DoCM, DrugBank, DTC, FDA, GuidetoPharmacology, JAX-CKB, MyCancerGenome, MyCancerGenomeClinicalTrial, OncoKB, PharmGKB, TALC, TdgClinicalTrial, TEND, TTD, BaderLab, CarisMolecularIntelligence, dGene, FoundationOneGenes, GO, HingoraniCasas, HopkinsGroom, HumanProteinAtlas, IDG, MskImpact, Oncomine, Pharos, RussLampel, and Tempus). We queried protein targets for available active ligands in ChEMBL. We queried gene targets in the druggable genome using the most recent druggable genome list established from the NIH Illuminating the Druggable Genome Project (<https://github.com/druggablegenome/IDGTargets>) available through the Pharos web platform. We also queried FDA-approved drugs, late-stage clinical trials, and disease indications in the DrugBank, ChEMBL, and [ClinicalTrials.gov](https://clinicaltrials.gov) databases and provided results for the top MESH and DrugBank indications and clinical trials.

Results

Overview

A total of 564,680 individuals from four populations were included in the study, comprising 85% EUR, 7% ASN, 5% AFR, and 3% HIS. Overall, 52% of participants were female. Descriptive statistics are provided in [Table S8](#). Because the quantitative DEPR exposure was not available in some biobanks, sample sizes were larger for dDEPR than for qDEPR. As shown in [Figure 1](#), the dDEPR analyses included 563,538 individuals after excluding two studies where the number of individuals with DEPR (N_{exp}) was fewer than 10 ([Table S2](#)). Among individuals with dDEPR,

the median DEPR prevalence was 10.3%, with an interquartile range of 12.9% (Table S2). The qDEPR analyses consisted of 294,029 participants from EUR (80%), ASN (7%), AFR (7%), and HIS (6%) populations.

dDEPR analyses

We identified nine independent loci that showed evidence of association with BP traits modified by dDEPR in CPMAs or population-specific meta-analyses (Table 1). In the DEPR-stratified analyses, the directions of SNP effect observed in the exposed group were consistent with the directions of the corresponding interaction effects (Table S9). Of these, three loci tagged by rs1664073690 (1q31.3), rs10178576 (2q13.3), and rs113521945 (4q35.1) were novel. The other six loci tagged by rs115760284 (3p22.1), rs147967138 (7q21.11), rs757194 (7q31.1), rs7979305 (12p12.1), rs75095906 (13q32.1), and rs9931605 (16q23.2) were previously reported for BP (Table S10). Eight of the nine loci were identified via the 1df interaction test ($p_{\text{Int}} < 5 \times 10^{-8}$) (Table 1). In the 2df joint test, a total of 904 loci were associated with at least one BP trait (350 loci were associated with SBP, 337 loci were associated with DBP, and 364 loci were associated with PP). Among them, one previously reported BP locus (rs757194 on 7q31.1) showed evidence of association with SBP through interaction with dDEPR using the specified criteria ($p_{\text{Joint}} = 7.99 \times 10^{-9}$; $p_{\text{Int}} = 1.39 \times 10^{-7}$).

The three top SNPs at novel loci (1q31.3, 2q13.3, and 4q35.1) were identified in the CPMAs and showed no evidence of heterogeneity across population groups ($p_{\text{Het}} > 0.003$) (Table 1). Two of them were common variants with MAF greater than 0.05 in at least one population group, while one (rs1664073690 on 1q31.3) had a low frequency (MAF = 0.02). This variant was present at low frequency in EUR and HIS but was absent in both ASN and AFR. rs10178576 (2q13.3) was common in AFR (MAF = 0.11) but was not observed in either ASN or EUR populations (Figure 2). rs113521945 (4q35.1) was observed across all four population groups. While a significant interaction was observed only in EUR, the direction of the effect was consistent across all four groups (Figure 2).

Among the six top SNPs at known BP loci (3p22.1, 7q21.11, 7q31.1, 12p12.1, 13q32.1, and 16q23.2), four SNPs on 3p22.1, 7q21.11, 7q31.1, and 12p12.1 showed the most significant associations or were exclusively observed in non-EUR populations (Figure 2). Notably, three of them (rs115760284 on 3p22.1, rs757194 on 7q31.1, and rs7979305 on 12p12.1) were absent in both EUR and ASN but were present at low frequency in AFR ($0.01 \leq \text{MAF} \leq 0.05$) and were rare in HIS (MAF < 0.01) (Table 1). Interestingly, rs115760284 (3p22.1) showed some heterogeneity between AFR and HIS ($I^2 > 80\%$, $p_{\text{Het}} < 0.01$), with a greater effect size in AFR (Figure 2). Moreover, a locus on 7q21.11 was detected solely in the ASN population among 26,307 individuals, with no evidence of heterogeneity across ASN studies ($p_{\text{Het}} > 0.003$). Two loci tagged by rs75095906 (13q32.1) and rs9931605

(16q23.2) were identified in the CPMAs, with no evidence of heterogeneity by population group. Across all nine top SNPs identified in the dDEPR analyses, no evidence of sex heterogeneity was observed. However, four of the nine SNPs could not be evaluated due to a limited sample size in males passing QC.

qDEPR analyses

We identified seven independent loci that showed evidence of association with BP traits modified by qDEPR in CPMAs or population-specific meta-analyses (Table 2). Four loci tagged by rs77572777 (2q14.2), rs148780833 (3p26.3), rs748650739 (3q13.11), and rs140618249 (17p13.3) were not previously reported. The other three loci tagged by rs59284269 (3p25.3), rs145132348 (4p14), and rs114544309 (12q13.13) were previously reported for BP (Table S10). Five loci, including two not previously reported, were identified using the 1df interaction test ($p_{\text{Int}} < 5 \times 10^{-8}$) (Table 2). In the 2df joint test, a total of 316 loci were associated with at least one BP trait (144 loci were associated with SBP, 160 loci were associated with DBP, and 157 loci were associated with PP). Among them, two novel loci tagged by rs77572777 (2q14.2) and rs748650739 (3q13.11) were associated with PP through interaction with qDEPR. Notably, two of the novel loci—rs148780833 (3p26.3) and rs140618249 (17p13.3)—identified in the 1df test ($p_{\text{Int}} < 5 \times 10^{-8}$) also showed evidence of an association with SBP through interaction with qDEPR using the 2df joint test ($p_{\text{Joint}} < 5 \times 10^{-8}$).

The four top SNPs tagging the novel loci include rs77572777 (2q14.2) and rs748650739 (3q13.11) from the HIS-specific analyses and rs148780833 (3p26.3) and rs140618249 (17p13.3) from the CPMAs. None of these four SNPs showed evidence of heterogeneity across populations or studies ($p_{\text{Het}} > 0.003$) and all were of low frequency (MAF = 0.01–0.02). Except for rs77572777 on 2q14.2, the three other SNPs were polymorphic only in AFR and HIS populations.

Among the three known loci (3p25.3, 4p14, and 12q13.13) identified in the qDEPR analyses, two loci on 4p14 and 12q13.13 were not observed in the EUR population. Of these two, the 4p14 locus tagged by rs145132348 and identified in AFR-specific analyses showed no heterogeneity across AFR studies contributing to the meta-analyses in this population (Figure 3). The other locus on 12q13.13 tagged by rs114544309 and identified in CPMAs showed the most significant association in HIS, with some evidence of heterogeneity between AFR and HIS and a greater effect size in HIS (Figure 3). rs59284269 (3p25.3) identified in CPMAs showed no evidence of heterogeneity by population group. No evidence of sex heterogeneity was observed across all seven top SNPs identified in the qDEPR analyses.

Comparison between dDEPR and qDEPR analyses

Of the 16 identified loci (Tables 1 and 2), four top SNPs (rs77572777, rs148780833, rs748650739, and

Table 1. Novel and known loci associated with BP traits discovered through SNP $\times$ dDEPR interactions

Locus	CHR:position (hg38)	Alleles (E/A)	rsID	Analysis group	EAF	MAF, AFR/EUR/ ASN/HIS	Nearest gene	Position	Int effect	Int SE	p_{Int}	p_{Joint}	p_{FDR}^c	p_{Het}^d	Sample size	$p_{\text{Sex.Het}}$
1q31.3	1:194548555	A/G	rs1664073690 ^{a,b}	CPMA-SBP	0.98	0/0.02/0/0.01	CDC73	intergenic	7.07	1.25	1.44×10^{-8}	9.93×10^{-4}	0.09	0.30	30,577	N/A
2q13.3	2:70509396	C/T	rs10178576 ^a	CPMA-PP	0.91	0.11/0/0/0.02	TGFA	intronic	2.59	0.46	2.16×10^{-8}	5.11×10^{-7}	0.24	0.61	39,482	0.56
3p22.1	3:42213248	G/T	rs115760284	CPMA-SBP	0.01	0.01/0/0/0.003	TRAK1	intronic	-13.30	2.39	2.78×10^{-8}	0.048	0.10	0.01	22,241	N/A
4q35.1	4:184777291	A/G	rs113521945 ^a	CPMA-DBP	0.91	0.02/0.09/ 0.05/0.09	ACSL1	intronic	-0.57	0.10	2.72×10^{-8}	5.74×10^{-7}	0.26	0.71	488,129	0.05
7q21.11	7:78342531	A/T	rs147967138	ASN-PP	0.04	0/0/0.04/0	MAGI2	intronic	5.12	0.93	3.34×10^{-8}	2.89×10^{-7}	0.14	0.62	26,307	0.8
7q31.1	7:112203372	A/G	rs757194	AFR-SBP	0.03	0.03/0/0/0.006	DOCK4	intronic	13.62	2.58	1.39×10^{-7}	7.99×10^{-9}	0.05	0.73	11,644	N/A
12p12.1	12:21435910	C/T	rs7979305	AFR-PP	0.95	0.05/0/0/0.007	PYROXD1	intergenic	-8.63	1.56	3.09×10^{-8}	9.96×10^{-8}	0.18	0.26	13,093	N/A
13q32.1	13:96826633	A/G	rs75095906	CPMA-SBP	0.15	0.03/0.15/ 0.12/0.1	HS6ST3	intronic	-0.76	0.14	4.29×10^{-8}	2.45×10^{-5}	0.13	0.79	518,557	0.99
16q23.2	16:81545886	C/T	rs9931605	CPMA-SBP	0.81	0.83/0.81/ 0.78/0.77	CMIP	intronic	0.68	0.12	1.36×10^{-8}	1.23×10^{-5}	0.09	0.86	543,909	0.05

Allele E, effect allele; allele A, non-effect allele; EAF, effect allele frequency; MAF, minor allele frequency; AFR, African; EUR, European; ASN, Asian; HIS, Hispanic; Int effect, interaction effects estimated in the 1df interaction test (effect is in mmHg); Int SE, standard error of interaction effects estimated in the 1df interaction test; p_{Int} , p value of interaction effects in the 1df interaction test; p_{Joint} , p value of joint effects of SNP main effect and interaction effect in 2df joint test; $p_{\text{Sex.Het}}$, sex heterogeneity p value in two-sample Z tests.

^ars1664073690, rs10178576, and rs113521945: top SNPs at novel loci (at least 500 kbp away from any previously reported BP locus).

^brs1664073690: absent in the 1000 Genome phase 3 reference panels.

^c p_{FDR} : interaction FDR p value for 1df interaction test; joint FDR p value for 2df joint test.

^d p_{Het} : heterogeneity p value across population groups in CPMA; heterogeneity p value across studies in ancestry-specific meta-analyses.

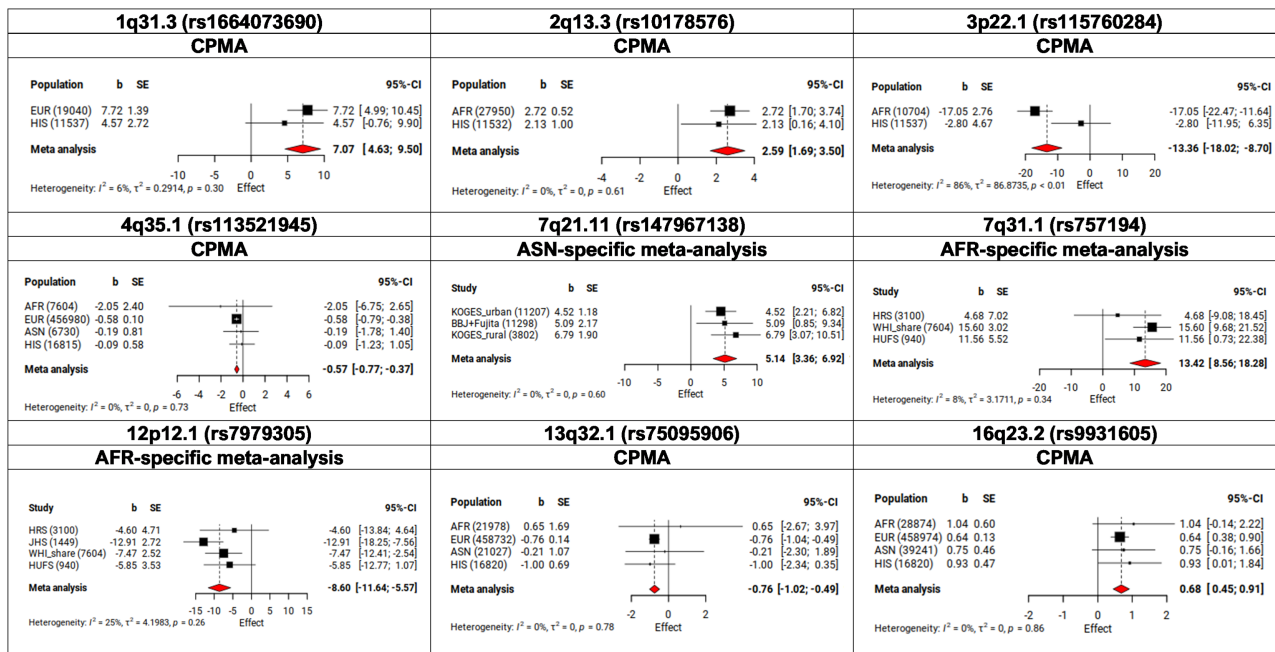


Figure 2. Forest plots of interaction effects at novel and known loci identified in the dDEPR analyses

Black squares and error bars represent the effect size and its 95% CI for each population in CPMA or for each study in population-specific meta-analyses. Red diamond represents the overall effect size calculated in the meta-analysis, where the center indicates the point estimate and its edges represent 95% CI of the estimate. CPMA, cross-population meta-analysis; AFR, African; ASN, Asian; EUR, European; HIS, Hispanic; b, the interaction effects estimated in the 1df interaction test (effect is in mmHg); SE, standard error of interaction effects estimated in the 1df interaction test; CI, confidence interval.

rs114544309) were identified exclusively in the qDEPR analyses (Figures S11 and S12). This appears to largely reflect differences in included studies in the two types of analyses (Figure S13). In the CPMA, approximately 15 million SNPs were included in the dDEPR analyses and 21 million SNPs in the qDEPR analyses. Notably, nearly 6 million SNPs were analyzed only in the qDEPR analyses, mainly because they were filtered out in the dDEPR analyses by the stringent study-level filters. Conversely, fewer than half a million SNPs were analyzed exclusively in dDEPR analyses, likely due to some large biobank samples where only dichotomous exposure was available while the quantitative exposure was not. The four SNPs identified only in qDEPR analyses were filtered out of the dDEPR analyses during study-level QC (rs148780833) or at meta-analysis QC because they were present in only one study (rs77572777 and rs748650739) or in only one population (rs114544309) (Figure S12). The remaining 12 loci were present in both dDEPR and qDEPR analyses. As illustrated in Figures S11 and S12, there was a consistency in direction between the two analyses even though magnitude of effects and statistical significance varied between them.

Gene-based and pathway analyses

Using 1df interaction test results, MAGMA and VEGAS2 ranked genes and pathways based on the combined association of SNPs within a gene with BPs. Both MAGMA and VEGAS2 gene-based tests identified a gene-wide significant association for *GLTPD2* (MIM: 620824), with similar

results observed for several other genes among the top 20 genes (Table S11). An additional gene, *TMEM199* (MIM: 616815), was discovered by VEGAS2. These two genes were not identified at genome-wide significance in the GWASs. Pathway analyses suggest DEPR-specific biochemical pathways that influence BP, including retinoid signaling, remodeling of acyl chains of phosphatidylethanolamine, nucleotide-binding oligomerization domain-containing 2 (NOD2) protein signaling, and response to stress (Table S12).

Functional annotation and gene prioritization

Functional annotation was conducted for all SNPs in LD ($r^2 > 0.4$), with the top SNPs tagging all identified novel and known BP loci. All the top SNPs were annotated as either intergenic or intronic variants, suggesting a potential role for regulatory mechanisms. Among 31 genes identified by FUMA, six genes were predicted to be highly intolerant to loss-of-function mutation based on probability of loss-of-function intolerance (pLI) score >0.9 , including *CMIP* (MIM: 610112), *ZBTB47* (MIM: 619969), *DOCK4* (MIM: 607679), *UBE2K* (MIM: 602846), *PDS5A* (MIM: 613200), and *GRASP* (MIM: 612027) (Table S13). Multiple genes exhibited high CADD scores (>12.37) among SNPs in LD, suggesting potential deleterious effects. Three additional genes were identified through associations with various xQTLs, namely *CASP3* (MIM: 600636), *DBI* (MIM: 125950), and *UGGT2* (MIM: 605898). PheWAS results showed associations with hematological-, psychiatric-, behavioral-, and

Locus	CHR-position (hg38)	Alleles (E/A)	rsID	Analysis group	EAF	MAF, AFR/EUR/ASN/HIS	Nearest gene	Position	Int effect	Int SE	p_{Int}	p_{Joint}	p_{FDR}^c	p_{Het}^d	Sample size	p_{SexHet}
2q14.2	2:118537183	A/G	rs77572777 ^a	HIS-PP	0.99	0/0/0/0/0.01	<i>RP11-19E11.1</i>	intergenic	2.48	0.44	3.55×10^{-5}	1.74×10^{-8}	0.06	0.47	16,077	0.60
3p26.3	3:1301059	C/T	rs148780833 ^{a,b}	CPMA-SBP	0.01	0.01/0/0/0.002	<i>CNTN6</i>	intronic	5.94	1.04	9.91×10^{-9}	2.85×10^{-9}	0.11	0.70	27,204	0.01
3p25.3	3:8726816	A/G	rs59284269	CPMA-SBP	0.09	0.23/0/0/0.06	<i>SSUH2</i>	intronic	0.86	0.16	4.29×10^{-8}	8.65×10^{-7}	0.18	0.25	25,1948	0.73
3q13.11	3:104214171	C/CA	rs748650739 ^{a,b}	HIS-PP	0.99	0.05/0/0/0.01	<i>RP11-40M23.1</i>	intergenic	2.25	0.48	3.76×10^{-5}	4.66×10^{-8}	0.08	0.94	16,077	0.16
4p14	4:39689605	C/T	rs145132348	AFR-DBP	0.02	0.03/0/0/0.006	<i>UBE2K</i>	intergenic	2.92	0.51	1.19×10^{-8}	6.33×10^{-8}	0.19	0.82	17,147	0.85
12q13.13	12:52010638	C/T	rs114544309	CPMA-DBP	0.01	0.02/0/0/0.008	<i>GRASP</i>	intronic	2.45	0.44	1.85×10^{-8}	2.56×10^{-7}	0.31	0.01	31,068	0.37
17p13.3	17:3225579	C/T	rs140618249 ^a	CPMA-SBP	0.98	0.02/0/0/0.004	<i>OR1A1</i>	intergenic	-4.10	0.74	3.18×10^{-8}	3.77×10^{-8}	0.18	0.20	28,685	0.50

Allele E, effect allele; Allele A, non-effect allele; EAF, effect allele frequency; MAF, minor allele frequency; AFR, African; EUR, European; ASN, Asian; HIS, Hispanic; Int effect, interaction effects estimated in the 1df interaction test (effect is in mmHg); Int SE, standard error of interaction effects estimated in the 1df interaction test; p_{Int} , p value of interaction effects in the 1df interaction test; p_{Joint} , p value of joint effects of SNP main effect and interaction effect in 2df joint test; p_{SexHet} , sex heterogeneity p value in two-sample Z tests.

^ars77572777, rs148780833, rs748650739, rs140618249: top SNPs at novel loci.

^brs148780833, rs748650739: absent in the 1000 Genome phase 3 reference panels.

^c p_{FDR} : interaction FDR p value for 1df interaction test; joint FDR p value for 2df joint test.

^d p_{Het} : heterogeneity p value across population groups in CPMA; heterogeneity p value across studies in ancestry-specific meta-analyses.

medication-related phenotypes, suggesting possible pleiotropic effects of the identified loci. Details on functional annotations are described in [Table S14](#).

A total of 36 genes were prioritized by functional annotations of both novel and known loci as well as gene-based analyses. These prioritized genes showed enrichment of gene expression in the brain and whole blood ([Figure S14](#)). Additionally, they demonstrated evidence of enrichment in two pathways involved in myogenesis and immune system in dendrite cells as well as enrichment in four potential microRNA regulatory targets ([Table S15](#)).

Druggability analyses

We investigated the potential druggability of the identified 36 candidate gene product targets using an integrative approach as previously described.⁴⁰ We queried dDEPR and qDEPR exposure candidate gene targets using the DGIdb, which identified 11 genes annotated as members of the druggable genome ([Table S16](#)). Several of these gene targets are implicated in metabolic pathways (*ACSL1* [MIM: 152425], *DBI*, *UGDH* [MIM: 603370], and *SLCO1A2* [MIM: 602883]), vascular wall signaling (*TGFA* [MIM: 190170], *CAV3* [MIM: 601253], *SSUH2* [MIM: 617479], and *DOCK4*), DNA-damage response or apoptosis (*CASP3*, *RFC1* [MIM: 102579], and *RECQL* [MIM: 600537]), and neuroactive ligand-receptor interaction (*VIPR1* [MIM: 192321] and *CCK* [MIM: 118440]). We identified 11 genes with FDA-approved drug interactions that have been evaluated in late-stage clinical trials using DrugBank, ChEMBL, and [ClinicalTrials.gov](#) databases ([Table S17](#)). Two of these gene targets (*CASP3* and *UGDH*) were identified as targets of aspirin, a well-established and safe drug used to treat pain and inflammation and to reduce cardiovascular events. *UBE2K* was identified as a target of the central nervous system stimulant dextroamphetamine, used to treat attention-deficit/hyperactivity disorder and narcolepsy, although its use has been federally controlled due to the high potential for abuse. *CCK* was also identified as a target of the vasodilator diazoxide, which is used to manage hypoglycemia due to pancreatic cancer or other conditions. Several genes (*CCK*, *SLCO1A2*, and *UGGT2*) were identified as targets of drugs (diazoxide, nadolol, and hydrochlorothiazide) used to treat hypertension, suggesting opportunities for drug repositioning and risk-factor prevention.

Discussion

In this large-scale genome-wide interaction study, we identified 16 genetic loci whose association with BP was modified by DEPR defined as a dichotomous or a quantitative exposure. These data provide support for molecular mechanisms connecting DEPR and BP and highlight several druggable gene targets that could be further

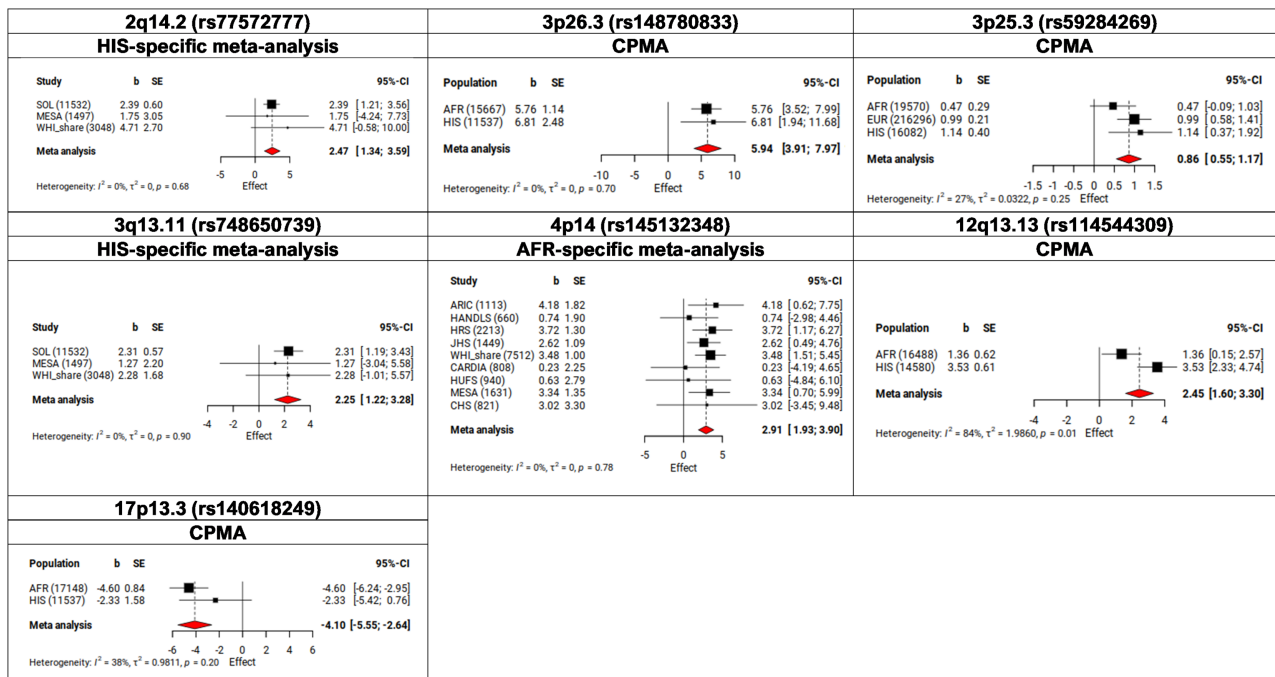


Figure 3. Forest plots of interaction effects at novel and known loci identified in the qDEPR analyses

Black squares and error bars represent the effect size and its 95% CI for each population in CPMA or for each study in population-specific meta-analyses. Red diamond represents the overall effect size calculated in the meta-analysis, where the center indicates the point estimate and its edges represent 95% CI of the estimate. CPMA, cross-population meta-analysis; AFR, African; ASN, Asian, EUR, European; HIS, Hispanic; b, the interaction effects estimated in the 1df interaction test (effect is in mmHg); SE, standard error of interaction effects estimated in the 1df interaction test; CI, confidence interval.

investigated for clinical potential for BP regulation in individuals with DEPR.

Nearly 70% of our findings were derived from non-EUR populations, likely due to differences in allele frequency across populations and/or to population differences in SNP $\times$ DEPR interaction effect sizes. Notably, several of the identified SNPs were monomorphic in EUR. Variations in MAF across population groups have been shown to contribute to differences in disease prevalence across populations.⁴¹ The risk of hypertension varies considerably across populations, being more prevalent in AFR and HIS populations.^{42,43} More than half of our findings come from AFR and/or HIS. AFR populations generally exhibit greater genetic diversity and more pronounced allele frequency differences compared to other populations.⁴⁴ Self-identified HIS populations in the United States include admixed individuals with varying proportions of EUR, AFR, and Amerindian genetic backgrounds, adding further complexity. Interestingly, patterns of associations were similar in AFR and HIS populations at several loci near the genes *TGFA*, *TRAK1* (MIM: 608112), *CNTN6* (MIM: 607220), and *OR1A1* (MIM: 618046). GWASs of BP have identified differences in BP loci by population groups, while partial generalization of BP loci between populations has also been reported.^{45–47} Thus, there is a critical need for expanding genetic studies of BP in non-EUR populations. In our study, among nine known BP loci identified with evidence for gene-DEPR interaction,

six loci (3p22.1, 7q21.11, 7q31.1, 12p12.1, 4p14, and 12q13.13) were derived from non-EUR populations, while they were previously discovered as BP loci in EUR population. This further underscores the importance of considering DEPR effect modification on BP for diverse populations.

Multiple studies have shown mixed results regarding the association between depressive symptomatology and hypertension.^{14,19,48} Despite this variability, depression has been consistently linked to an increased risk of cardiovascular morbidity and mortality.⁴⁹ Typically, depression arises in response to stressful events, and stress is a major risk factor for hypertension.⁵⁰ Both hypertension and depression show higher prevalence among individuals of non-EUR populations, highlighting significant racial and ethnic disparities.^{42,43,51,52}

Functional annotation of the novel loci revealed genes implicated in neurogenesis, lipid metabolism, neuronal apoptosis, and synaptic activity. A locus on chromosome 2 mapped to an intron of the *TGFA* gene, which encodes a ligand for the epidermal growth factor receptor and plays a crucial role in neural cell proliferation and differentiation.^{53,54} Previous studies suggested *TGFA*'s role in neurogenesis and angiogenesis in adult injured brain and the immune system.^{55,56} Furthermore, genetic variants in *TGFA* have been associated with response to antidepressant treatment in GWASs.^{57,58} *ACSL1* encodes an isozyme of the long-chain fatty-acid-coenzyme A ligase

family, which operates in lipid biosynthesis and fatty acid degradation. Animal models have demonstrated that *ACSL1* modulates lipid metabolism, inflammation, and oxidative stress in kidney disease.^{59,60} In fact, the kidney plays a critical role in BP regulation.⁶¹ The *ACSL1* locus was associated with DNA methylation levels (mQTL) of *ACSL1* in blood. Functional annotations of this previously unreported locus also highlight several additional genes, including *CASP3*. *CASP3* encodes a cysteine-aspartic acid protease (Caspase-3) that plays a critical role in neuronal apoptosis, neurogenesis, and synaptic activity.^{62–65} Notably, the *ACSL1* locus was associated with the splicing event of *CASP3* in brain tissue. Interestingly, a recent study highlighted the role of Caspase-3 in pathogenesis of depressive disorders.⁶⁶ *CNTN6* encodes Contactin-6, a neuronal cell adhesion molecule that facilitates neurite outgrowth and synaptogenesis.⁶⁷ Mutations in this gene increase the risk for autism spectrum disorders.⁶⁸ *DBI* encodes a diazepam-binding inhibitor, which is regulated by hormones and acts as a neuropeptide in brain synapses.⁶⁹ Our results showed an intergenic variant (rs77572777 on 2q14.2) with an eQTL of *DBI* in brain tissue. A previous study reported that *DBI* expression in the brain decreased with long-term social isolation stress.⁷⁰ An increased level of the protein encoded by *DBI* has been suggested as having prognostic value in cardiovascular disease.⁷¹

Several known loci for BP were identified through interactions with DEPR in our study and implicated several genes previously reported to be associated with mental disorders. These genes include *DOCK4*, *HS6ST3* (MIM: 609401), and *MAGI2* (MIM: 609401). The *DOCK4* locus was associated with SBP in the AFR population. *DOCK4* is a member of the dedicator of cytokinesis family and is involved in cell migration.⁷² Animal models have suggested a role of *DOCK4* in excitatory synaptic transmission and social behavior.⁷³ Variants in *DOCK4* have been associated with response to antidepressants, autism spectrum disorder, and schizophrenia.^{74,75} A recent GWAS of stress-induced vasomotion identified an association with variants in *DOCK4*, which were also linked to an increased risk of adverse cardiovascular events.⁷⁶ *HS6ST3* encodes heparin sulfate sulfotransferases involved in proliferation, inflammation, and blood coagulation. Variants within or near this gene have been associated with schizophrenia, major depressive disorder, and coronary artery calcified atherosclerotic plaque.^{77–79} *MAGI2* encodes a synaptic scaffolding molecule and shows high expression in the brain and postsynaptic density area of the spine.⁸⁰ In our data, the *MAGI2* locus was observed only in the ASN population, and variants in this gene have been associated with depressive symptoms in an East Asian cohort as well as in other population groups.^{81–83}

Our druggability analyses suggest potential opportunities for drug repurposing and risk-factor prevention. The identified genes include *CASP3* and *UGDH* as targets for aspirin and *CCK*, *SLC01A2*, and *UGGT2* for anti-hyper-

tensive medications. *UGDH* encodes an integral Golgi membrane protein involved in signal transduction and cell migration. A previous study has shown its nominal association with brain electrical activity linked to psychiatric conditions, including depression, and suggested that this association may be population specific.⁸⁴ This is consistent with our finding that the associated SNP (rs145132348 on 4p14) was identified only in individuals of AFR and HIS populations. *CCK* encodes cholecystokinin (CCK), a digestive enzyme and neuropeptide that regulates emotional states.^{85,86} Patients with major depression showed increased CCK levels in cerebrospinal fluid.⁸⁷ CCK enzyme also plays a role in BP regulation and predicts cardiovascular mortality in older women.^{88,89} *SLC01A2* (or *OATP1A2*) encodes a sodium-independent transporter that is crucial for transporting hormones across the blood-brain barrier to the central nervous system and has been suggested as a potential modulator of mood disorders.^{90–92} *UGGT2* encodes a soluble protein of the endoplasmic reticulum and has been associated with impulsive behaviors.^{93,94} It is important to note that some of these drug-gene interactions may also reflect the medication use for individuals with chronic depression and warrant follow-up to determine their direct impact on hypertension and cardiovascular risk.¹⁹

Findings from our prior study²¹ were generally not replicated in this study, likely due to the use of a different modeling strategy that includes additional adjustment for potential confounders. One notable exception is the reported gene-DEPR interaction at the *FSTL5* (MIM: 620128) locus, which was identified by the 2df joint test in a previous study, tagged by two SNPs (rs138187213 and rs5863461). In our dDEPR analyses, both SNPs showed associations in the 1df interaction test (rs138187213, $p_{\text{Int}} = 8.48 \times 10^{-4}$; rs5863461, $p_{\text{Int}} = 2.89 \times 10^{-4}$). Similar results were observed in the qDEPR analyses, with both SNPs showing evidence of interactions (rs138187213, $p_{\text{Int}} = 8.19 \times 10^{-5}$; rs5863461, $p_{\text{Int}} = 1.06 \times 10^{-4}$).

Our study benefits from a large sample size with diverse population backgrounds, which allows for a comprehensive analysis of the interactions across different populations. Moreover, our methodological approach using two complementary definitions of DEPR sought to enhance discoveries. The dDEPR analyses, with a larger sample size, provided greater statistical power, while the qDEPR analyses were designed to capture subtle variations in exposure and potentially reveal associations that might have been missed in the dDEPR analyses. Notably, we observed a substantial number of SNPs analyzed in qDEPR but not included in dDEPR, likely due to stringent filters required for binary exposure analyses. The qDEPR analyses enabled us to identify additional loci at genome-wide level, possibly due to the assumption of linearity between the exposure and outcome being met for those specific loci. Furthermore, the consistency of associations across both analytical approaches reinforces the robustness of our findings.

Several limitations should be acknowledged. First, the sample size for non-EUR population groups was relatively small compared to the EUR population, which may have limited the discovery of population-specific findings. For this reason, we combined East ASN and South ASN populations into a single population group, although that may have introduced heterogeneity. While combining distinct populations can introduce complexity due to underlying genetic and cultural differences, this approach was chosen to increase statistical power. Second, we relied on self-reported race and ethnicity information, which may have led to population groupings that do not fully capture underlying genetic diversity. This limitation also suggests that depressive symptoms may reflect sociodemographic factors that are not fully accounted for in our models. Third, DEPR was captured by several different validated instruments in the participating cohorts with different sensitivities and specificities to detect depressive symptoms, which may have introduced heterogeneity and measurement error, potentially reducing statistical power. Nevertheless, we chose to include all available cohorts in order to maximize sample size and retain the greatest statistical power possible. Lastly, while extensive functional annotation and druggability analyses provide biological validation and support for our findings, replication in independent samples was not possible in this study because dividing cohorts into discovery and replication analyses encountered insufficient power. Because we made extensive efforts at recruiting most of the studies known to have DEPR data, identifying suitable independent cohorts with large sample size and DEPR data availability for replication remains a major challenge. This is a particular issue for interactions identified only in non-European population groups, often in relatively modest sample sizes.

In conclusion, we identified multiple genetic loci associated with BP traits that were modified by DEPR. These data emphasize the importance of considering DEPR as an effect modifier in BP gene discovery, particularly in non-European populations. They also provide insights into the genetic basis of the relationships between DEPR and BP and highlight the potential of applying such information to enhance more personalized approaches to hypertension management in individuals with DEPR.

Data and code availability

- Due to restrictions in the written informed consent and local regulations, individual genotype-level data from this project could not be shared. Summary statistics are available at the CHARGE (Cohorts for Heart and Aging Research in Genomics Epidemiology) dbGaP summary site (phs000930 [https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000930.v1.p1]).
- All analyses supporting the conclusions of this meta-analysis were conducted using the following open-source software (see [web resources](#)): LinGxEscanR, GEM v.1.4.1, MMAP, EasyQC2, EasyStrata2, and METAL.

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Author contributions

S.L., W.J.G., T.W.W., L.J.B., L.d.I.F., D.C.R., and M.F. contributed to conception and design of the study; H.C., W.J.G., J.R.O., T.W.W., and J.L.M. were involved in the development of software; and S.L., C.L.M., and M.F. prepared the initial manuscript draft. All other co-authors contributed to data acquisition, analysis, and interpretation as well as critical revision of the manuscript.

Declaration of interests

C.L.M. has received funding from AstraZeneca on an unrelated project. B.M.P. serves on the Steering Committee of the Yale Open Data Access Project funded by Johnson & Johnson. D.C. received consulting fees from Trimedics. H.J.G. has received travel grants and speaker's honoraria from Neuraxpharm, Servier, Indorsia, and Janssen Cilag.

Supplemental information

Supplemental information can be found online at <https://doi.org/10.1016/j.xhgg.2026.100566>.

Web resources

Drug-Gene Interaction database (DGIdb), <https://dgidb.org/about/overview/about-us>
 EasyQC2 and EasyStrata2, www.genepi-regensburg.de/easyqc2
 GEM v.1.4.1, <https://github.com/large-scale-gxe-methods/GEM>
 LinGxEscanR, <https://github.com/USCbiostats/LinGxEscanR>
 METAL, <https://csg.sph.umich.edu/abecasis/metal/download/>,
https://genome.sph.umich.edu/wiki/Meta_Analysis_of_SNPx_Environment_Interaction
 MMAP, <https://github.com/MMAP/MMAP.github.io>
 NIH Illuminating the Druggable Genome Project, <https://github.com/druggablegenome/IDGTargets>
 NIH NCBI clinical trials, [ClinicalTrials.gov](https://clinicaltrials.gov)
 OMIM, <https://www.omim.org/>

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Supplemental information

Large-scale blood pressure GWAS accounting

for gene-depression interactions in 564,680

individuals from diverse populations

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Supplemental Material

1. Study Descriptions

AGES (Age Gene/Environment Susceptibility Reykjavik Study): The AGES Reykjavik study originally comprised a random sample of 30,795 men and women born in 1907-1935 and living in Reykjavik in 1967. A total of 19,381 people attended, resulting in a 71% recruitment rate. The study sample was divided into six groups by birth year and birth date within month. One group was designated for longitudinal follow up and was examined in all stages; another was designated as a control group and was not included in examinations until 1991. Other groups were invited to participate in specific stages of the study. Between 2002 and 2006, the AGES Reykjavik study re-examined 5,764 survivors of the original cohort who had participated before in the Reykjavik Study.

ARIC (Atherosclerosis Risk in Communities): The ARIC study is a population-based prospective cohort study of cardiovascular disease sponsored by the National Heart, Lung, and Blood Institute (NHLBI). ARIC included 15,792 individuals, predominantly European American and African American, aged 45-64 years at baseline (1987-89), chosen by probability sampling from four US communities. Cohort members completed three additional triennial follow-up examinations, a fifth exam in 2011-2013, a sixth exam in 2016-2017, and a seventh exam in 2018-2019, an eighth exam in 2020, a ninth exam in 2021-2022, a tenth exam in 2023, and an eleventh exam in 2024-2025. The ARIC study has been described in detail previously (PMC8667593; Wright JD, Folsom AR, Coresh J, et al. The ARIC (Atherosclerosis Risk In Communities) Study: JACC Focus Seminar 3/8. J Am Coll Cardiol. 2021 Jun 15;77(23):2939-2959).

ASPREE (ASpirin in Reducing Events in the Elderly): The ASPREE study (n=19,114) is a randomized double-blind, placebo-controlled clinical trial, which aimed to determine whether daily 100-mg aspirin extended disability-free survival in healthy adults aged 70 years and older (65 years of age and older for U.S. minorities) with no history of diagnosed cardiovascular diseases, dementia, physical disability, or other life-threatening illness at enrolment. The design and protocol of the ASPREE trial have been reported previously.¹⁻⁴ All participants provided written informed consent. The study was approved by the Monash University and Alfred Hospital Human Research Ethics Committee (390/15) in Australia and site-specific Institutional Review Boards in the United States and registered on Clinicaltrials.gov (NCT01038583).

Out of the 19,114 ASPREE trial participants, a total of 12,031 genotyped, unrelated participants (genetic relationship <0.05) aged ≥70 years with European ancestry (determined by genetic principal component analysis) were included in the CHARGE gene-lifestyle interaction studies.

1. McNeil, J.J., Woods, R.L., Nelson, M.R. et al., 2017. Baseline characteristics of participants in the ASPREE (ASpirin in Reducing Events in the Elderly) study. *The Journals of Gerontology: Series A*, 72(11), 1586-1593.

2. McNeil, J.J., Woods, R.L., Nelson, M.R. et al., 2018. Effect of aspirin on disability-free survival in the healthy elderly. *New England Journal of Medicine*, 379(16), 1499-1508.
3. McNeil, J.J., Wolfe, R., Woods, R.L. et al., 2018. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. *New England Journal of Medicine*, 379(16), 1509-1518.
4. McNeil, J.J., Nelson, M.R., Woods, R.L. et al., 2018. Effect of aspirin on all-cause mortality in the healthy elderly. *New England Journal of Medicine*, 379(16), 1519-1528.

ASPS (The Austrian Stroke Prevention Study): The ASPS study is a single center prospective follow-up study on the effects of vascular risk factors on brain structure and function in the normal elderly population of the city of Graz, Austria. The procedure of recruitment and diagnostic work-up of study participants has been described previously ^{1,2}. A total of 2007 European Caucasian participants were randomly selected from the official community register stratified by gender and 5 year age groups. Individuals were excluded from the study if they had a history of neuropsychiatric disease, including previous stroke, transient ischemic attacks, and dementia, or an abnormal neurologic examination determined on the basis of a structured clinical interview and a physical and neurologic examination. During two study periods between September 1991 and March 1994 and between January 1999 and December 2003 an extended diagnostic work-up including magnetic resonance imaging and neuropsychological testing was done in 1076 individuals aged 45 to 85 years randomly selected from the entire cohort: 509 from the first period and 567 from the second. Genotyping was performed in 996 participants. The study protocol was approved by the ethics committee of the Medical University of Graz, Austria, and written informed consent was obtained from all subjects.

¹ Schmidt R, Fazekas F, Kapeller P, Schmidt H, Hartung HP. Mri white matter hyperintensities: Three year follow-up of the austrian stroke prevention study. *Neurology*. 1999;53:132-139

² Schmidt R, Lechner H, Fazekas F, Niederkorn K, Reinhart B, Grieshofer P, et al. Assessment of cerebrovascular risk profiles in healthy persons: Definition of research goals and the austrian stroke prevention study (asps). *Neuroepidemiology*. 1994;13:308-313

ASPS-Fam (Austrian Stroke Prevention Family Study): The Austrian Stroke Prevention Family Study (ASPS-Fam) is a prospective single-center, community-based study on the cerebral effects of vascular risk factors in the normal elderly population of the city of Graz, Austria ^{1,2}. The ASPS-Fam represents an extension of the Austrian Stroke Prevention Study (ASPS), which was established in 1991 ^{3,4}. Between 2006 and 2013, study participants of the ASPS and their first grade relatives were invited to enter ASPS-Fam. Inclusion criteria were no history of previous stroke or dementia and a normal neurologic examination. A total of 419 individuals from 176 families were included into the study. The number of members per family ranged from two to six. The entire cohort underwent an extended diagnostic workup including clinical history, blood tests, cognitive testing, magnetic resonance imaging and a thorough vascular risk factor assessment. The study protocol was approved by the ethics committee of the Medical University of Graz, Austria, and written informed consent was obtained from all subjects.

¹ Seiler, S. et al. Magnetization transfer ratio relates to cognitive impairment in normal elderly. *Frontiers in aging neuroscience* 6, 263, doi:10.3389/fnagi.2014.00263 (2014).

² Ghadery, C. et al. R2* mapping for brain iron: associations with cognition in normal aging. *Neurobiology of aging* 36, 925-932, doi:10.1016/j.neurobiolaging.2014.09.013 (2015).

³ Schmidt, R. et al. Assessment of cerebrovascular risk profiles in healthy persons: definition of research goals and the Austrian Stroke Prevention Study (ASPS). *Neuroepidemiology* 13, 308-313, doi:10.1159/000110396 (1994).

⁴ Schmidt, R., Fazekas, F., Kapeller, P., Schmidt, H. & Hartung, H. P. MRI white matter hyperintensities: three-year follow-up of the Austrian Stroke Prevention Study. *Neurology* 53, 132-139 (1999).

BBJ (Biobank Japan Project): The BBJ is a national biobank project and a nationwide hospital-based genome cohort that enrolled patients from 12 collaborating medical institutions since 2013 (<https://biobankjp.org/en/index.html>). The BBJ consists of DNA samples and clinical data, including laboratory data, related to 47 target diseases from approximately 200,000 patients (Nagai et al, *J Epidemiol* 2017). Genotyping was performed on the Illumina HumanOmniExpressExome BeadChip or a combination of the Illumina HumanOmniExpress and HumanExome BeadChips (Terao et al, *Nature* 2020). Genotypes were imputed using our new reference panel developed by using 3,256 high depth whole genome sequencing data from Japanese population combined with the 1000 Genome project (Tanaka et al, *JACI* 2021). **Of note, part of the patients diagnosed with depression were recruited by Fujita Health University between 2008 and 2022. These patients were diagnosed by certified psychiatrists based on the DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition). Genotyping for these patients was conducted using the Illumina HumanOmniExpressExome BeadChip.** All patients recruited for the BioBank Japan Project **and Fujita Health University** provided written informed consent. All relevant ethical regulations were complied with throughout this study.

BES (Beijing Eye Study): The Beijing Eye Study is a population-based study that assesses the associated and risk factors of ocular and general diseases in a Chinese population. The study was initialized in 2001 and collected data from 4439 subjects aged ≥ 40 years and living in seven communities in the Beijing area. Three of these communities were located in a rural district and four were located in an urban district. The BES was followed-up in 2006, with 3251 of the original subjects participating, and in 2011, with 2695 subjects returning for the follow-up examination. At the examinations in 2006 and 2011, trained research staffs asked the subjects questions from a standard questionnaire providing information on the family status, level of education, income, quality of life, psychic depression, physical activity, and known major systemic diseases. Fasting blood samples were taken for measurement of concentrations of substances such as blood lipids, glucose, and glycosylated hemoglobin. Individuals were classified as self-reported non-smokers or self-reported current smokers. Alcohol consumption

habits based on number of drinks per day were collected. Physical activity was assessed in questions on the number of hours per day and number of days per week spent on intensively or moderately performed sport activities, spent on walking, on riding a bicycle, and spent on sitting. All variables used in analyses were taken from examinations in 2006 or in 2011. The BES subjects were genotyped on two arrays, Illumina Human610-Quad (N = 832) and Illumina OmniExpress (N = 814).

BHS (Bogalusa Heart Study): The BHS study is population-based panel study to investigate the early natural history of cardiovascular disease and risk factors from childhood to adulthood among a biracial sample (65% white and 35% African American) of residents from Bogalusa, Louisiana. The study was established in 1973 by Dr. Gerald Berenson. To date, 9 surveys were conducted in children and adolescents aged 4 to 17 years, and 11 surveys were conducted among adults aged 18 to 51 years who were examined previously as children. At each survey, a standard questionnaire was used by trained research staffs to collect participants' information on family status, levels of education, income, medical history and health behaviors. Clinical measures were collected following stringent protocols. The current study included 630 participants who were born between 1959 and 1979, examined at least once in childhood, and surveyed during the follow-up visit between 2013 and 2016. Genome-wide genotypes were assayed using the Illumina Human610 BeadChip. The genotype data were further imputed to the TOPMed reference panel using the TOPMed Imputation Server following a stringent genotype imputation protocol developed by the University of Michigan.

BioVU (VUMC): BioVU is Vanderbilt's biorepository of de-identified samples extracted from discarded blood collected during routine clinical testing and linked to de-identified medical records in the Synthetic Derivative (SD). The SD consists of de-identified clinical data obtained from patients attending all clinics associated with the Vanderbilt University Medical Center hospital system. Clinical data are abstracted from multiple sources including diagnostic and procedure codes, basic demographics, discharge summaries, progress notes, health history, multi-disciplinary assessments, laboratory values, imaging reports, medication orders, and pathology reports.

Blood pressure measures extracted from EHR records reflect the earliest outpatient measurements taken after and within 1-year exposure assessment in adults ≥ 18 years of age. When measurements were available for multiple days for the earliest time since exposure measurement, a visit was randomly chosen. When the chosen visit had multiple measurements per-day, an average measurement was computed.

CARDIA (The Coronary Artery Risk Development in Young Adults): CARDIA is a prospective multicenter study of the development and determinants of clinical and subclinical cardiovascular disease and their risk factors. It began in 1985-1986 with a group of 5,115 black and white men and women aged 18-30 years, recruited from four US centers. The recruitment was done from the total community in

Birmingham, AL, from selected census tracts in Chicago, IL and Minneapolis, MN; and from the Kaiser Permanente health plan membership in Oakland, CA. The participants were selected so that there would be approximately the same number of people in subgroups of race, gender, education (high school or less and more than high school) and age (18-24 and 25-30). These same participants were asked to participate in follow-up examinations during 1987-1988 (Year 2), 1990-1991 (Year 5), 1992-1993 (Year 7), 1995-1996 (Year 10), 2000-2001 (Year 15), 2005-2006 (Year 20), 2010-2011 (Year 25), 2015-2016 (Year 30), and 2020-2022 (Year 35).

Data collection protocols have been described previously (Friedman, 1988). Weight, height, systolic blood pressure and diastolic blood pressure were measured using standard protocols with participants wearing light clothing and no shoes. Morning venous blood samples were obtained after an overnight fast of at least 8 hours. Total cholesterol and triglycerides were measured enzymatically, HDL-C was determined by precipitation with dextran sulfate magnesium chloride, and LDL cholesterol was calculated using the Friedewald equation. Fasting plasma glucose and insulin were measured with the hexokinase-ultraviolet and radioimmunoassay methods, respectively (Linco Research, St Charles, MO, USA).

Written informed consent was obtained from participants at each examination and all study protocols were approved by the institutional review boards of the participating institutions.

Friedman GD, Cutter GR, Donahue RP, Hughes GH, Hulley SB, Jacobs DR Jr, Liu K, Savage PJ. CARDIA: study design, recruitment, and some characteristics of the examined subjects. *J Clin Epidemiol.* 1988;41(11):1105-16. PMID: 3204420.

CFS (The Cleveland Family Study) is the largest family-based study of sleep apnea worldwide, consisting of 2,284 individuals (46% African American) from 361 families studied on up to 4 occasions over a period of 16 years. The study was begun in 1990 with the initial aims of quantifying the familial aggregation of sleep apnea. NIH renewals provided expansion of the original cohort (including increased minority recruitment) and longitudinal follow-up, with the last exam occurring in February 2006. 632 African Americans were genotyped on the Affymetrix array 6.0 platform through the CARE Consortium with suitable genotyping quality control. A further 122 African-Americans had genotyping based on the Illumina OmniExpress + Exome platform. Genomes were imputed by TOPMed imputation server separately.

CHS (Cardiovascular Health Study): CHS is a population-based cohort study of risk factors for cardiovascular disease in adults 65 years of age or older conducted across four field centers (1). The original predominantly European ancestry cohort of 5,201 persons was recruited in 1989-1990 from random samples of the Medicare eligibility lists and an additional predominately African-American cohort of 687 persons was enrolled in 1992-93 for a total sample of 5,888. Blood samples were drawn from all participants at their baseline examination and DNA was subsequently extracted from available samples. European ancestry participants were excluded from the GWAS study sample due to prevalent

coronary heart disease, congestive heart failure, peripheral vascular disease, valvular heart disease, stroke, or transient ischemic attack at baseline. After QC, genotyping was successful for 3271 European ancestry and 823 African-American participants. CHS was approved by institutional review committees at each site and individuals in the present analysis gave informed consent including consent to use of genetic information for the study of cardiovascular disease.

1. Fried LP, Borhani NO, Enright P, Furberg CD, Gardin JM, Kronmal RA, et al. The Cardiovascular Health Study: design and rationale. *Ann Epidemiol* 1991; 1:263-76.

FHS (Framingham Heart Study): FHS began in 1948 with the recruitment of an original cohort of 5,209 men and women (mean age 44 years; 55 percent women). In 1971 a second generation of study participants was enrolled; this cohort (mean age 37 years; 52% women) consisted of 5,124 children and spouses of children of the original cohort. A third-generation cohort of 4,095 children of offspring cohort participants (mean age 40 years; 53 percent women) was enrolled in 2002-2005 and are seen every 4 to 8 years. Details of study designs for the three cohorts are summarized elsewhere. At each clinic visit, a medical history was obtained with a focus on cardiovascular content, and participants underwent a physical examination including measurement of height and weight from which BMI was calculated.

GAPP - Genetic and phenotypic determinants of blood pressure and other cardiovascular risk factors:

GAPP is a population-based prospective cohort study involving a representative sample of initially healthy adults aged 25-41 years at baseline and residing in the Principality of Liechtenstein. Exclusion criteria were the presence of cardiovascular disease, diabetes, obstructive sleep apnea and a body mass index >35kg/m². A standardized 12-lead ECG was obtained in all participants. Baseline characteristics were obtained in all participants using standard methodology. The main goal of GAPP is to assess the mechanisms for the development of cardiovascular risk factors over time.

GENOA (Genetic Epidemiology Network of Arteriopathy): The Genetic Epidemiology Network of Arteriopathy (GENOA) study, a part of the Family Blood Pressure Program (FBPP Investigators, 2002), consists of hypertensive sibships that were recruited for linkage and association studies in order to identify genes that influence blood pressure and its target organ damage (Daniels, 2004). In the initial phase of the GENOA study (Phase I: 1995-2000), all members of sibships containing ≥ 2 individuals with essential hypertension clinically diagnosed before age 60 were invited to participate, including both hypertensive and normotensive siblings. During the first exam, 1,583 European Americans from Rochester, MN and 1,854 African Americans from Jackson, MS were recruited. In the second phase of the GENOA study (Phase II: 2001-2004), 1,241 European American and 1,482 African American participants were successfully re-recruited to measure potential target organ damage due to hypertension. In a GENOA follow-up study (2009–2011), 752 African Americans participated in a third examination that included an assessment of depression. Since African American probands in GENOA were recruited in part through the Jackson, MS field center for Atherosclerosis Risk in Communities (ARIC), we excluded ARIC participants from GENOA analysis.

FBPP Investigators. (2002) Multi-center genetic study of hypertension: The Family Blood Pressure Program (FBPP). *Hypertension* 39(1): 3-9.

Daniels, P.R., Kardia, S.L., Hanis, C.L., Brown, C.A., Hutchinson, R., Boerwinkle, E., Turner, S.T., and Genetic Epidemiology Network of Arteriopathy study. (2004). Familial Aggregation of Hypertension Treatment and Control in the Genetic Epidemiology Network of Arteriopathy (GENOA) Study. *Am J Med* 116(10): 676-681.

HANDLS (Healthy Aging in Neighborhoods of Diversity across the Life Span): HANDLS is a community-based, longitudinal epidemiologic study examining the influences of race and socioeconomic status (SES) on the development of age-related health disparities among a sample of socioeconomically diverse African Americans and whites. This unique study will assess over a 20-year period physical parameters and also evaluate genetic, biologic, demographic, and psychosocial, parameters of African American and white participants in higher and lower SES to understand the driving factors behind persistent black-white health disparities in overall longevity, cardiovascular disease, and cognitive decline. The study recruited 3,722 participants from Baltimore, MD with a mean age of 47.7 years, 2,200 African Americans and 1,522 whites, with 41% reporting household incomes below the 125% poverty delimiter.

Genotyping was done on a subset of self-reporting African American participants by the Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health (NIH). A larger genotyping effort included a small subset of self-reporting European ancestry samples. This research was supported by the Intramural Research Program of the NIH, NIA and the National Center on Minority Health and Health Disparities.

HCHS/SOL: The Hispanic Community Health Study / Study of Latinos (HCHS/SOL) is a multicenter prospective cohort of 16,000 Hispanic/Latino adults designed to investigate the role of acculturation in disease, and to identify other traits that impact Hispanic/Latino health. HCHS/SOL is the most diverse and comprehensive study of Hispanic/Latino health, with participants of Cuban, Puerto Rican, Dominican, Mexican or Central/South American origin. Participants were recruited through four sites affiliated with San Diego State University, Northwestern University in Chicago, Albert Einstein College of Medicine in Bronx, New York, and the University of Miami, using a census block and household sampling design. Study participants who were self-identified Hispanic/Latino and aged 18-74 years underwent extensive psychosocial, clinical assessments, and biospecimen collection during the baseline visit (2008-2011). A re-examination of the HCHS/SOL cohort was conducted during 2015-2017, and visit 3, which began in 2020, is ongoing. Annual telephone follow-up interviews have been conducted since study inception to determine health outcomes of interest. (dbGaP study accession number: phs000555).

HCS (Hunter Community Study): The HCS is a community-based longitudinal investigation that was commenced in Australia in 2004-2005. The study aims to investigate retired and near-retired persons by sampling older Australians aged 55–85, randomly selected from electoral rolls in a regional area on the heavily populated east coast (New South Wales). There were 3253 participants who completed at least some baseline measures. Follow-up was obtained through health record linkage up to 2017, representing over 10 years of health outcomes and hospitalizations.

HRS (Health & Retirement Study): The Health and Retirement Study (HRS) is a longitudinal survey of a representative sample of Americans over the age of 50. The total sample ever interviewed consists of over 43,000 persons in 26,500 households. Respondents are interviewed every two years about income and wealth, health and use of health services, work and retirement, and family connections. DNA was extracted from saliva collected during a face-to-face interview in the respondents' homes. These data represent respondents who provided DNA samples and signed consent forms in 2006, 2008, 2010, and 2012. Respondents were removed if they had missing genotype or phenotype data.

1. Juster, F. T., Suzman, R. (1995). An Overview of the Health and Retirement Study, *Journal of Human Resources* 30:Suppl: S7-S56.
2. Sonnega A, Faul JD, Ofstedal MB, Langa KM, Phillips JWR, Weir DR. Cohort Profile: the Health and Retirement Study (HRS). *Int. J. Epidemiol.* 2014; 43 (2): 576-585. PMID: 24671021.
3. Crimmins, E.M., Faul, J., Guyer H., Langa K.M., Ofstedal M.B., Sonnega, A., Wallace R.B., and Weir D.R. (2013). Documentation of Biomarkers in the 2006 and 2008 Health and Retirement Study. HRS Documentation Report DR-012.
<https://hrsdata.isr.umich.edu/sites/default/files/documentation/data-descriptions/Biomarker2006and2008%20%281%29.pdf>

HUFS (Howard University Family Study): HUFS followed a population-based selection strategy designed to be representative of African American families living in the Washington, DC metropolitan area. The major objectives of the HUFS were to study the genetic and environmental basis of common complex diseases including hypertension, obesity, and associated phenotypes. Participants were sought through door-to-door canvassing, advertisements in local print media and at health fairs and other community gatherings. In order to maximize the utility of this cohort for the study of multiple common traits, families were not ascertained based on any phenotype. During a clinical examination, demographic information was collected by interview.

INGI-FVG (INGI-Friuli Venezia Giulia) is a population-based study started in 2008 with follow-up in 2014/2015, carried out in six villages of the Friuli Venezia Giulia (FVG) region, North-Eastern of Italy (Erto-

Casso, Clauzetto, Illegio, Sauris, San Martino del Carso and Val di Resia). These populations belong to the Italian Network of Genetic Isolates (INGI), a project that aims to study the genetic basis of complex diseases and phenotypes, taking advantage of these populations' genetic and environmental homogeneity (doi: 10.1038/s41431-019-0551-x). Demographic data and detailed familial and individual medical history were collected for all the voluntarily enrolled participants. In addition, participants underwent specialist evaluations, e.g., cardiovascular, neurological, psychiatric, in-depth sensorial, stomatological, etc. All pathologies were classified according to the International Classification of Diseases-10 (ICD-10). The cohort accounts for 1927 genotyped samples from three to 92 years of age. All participants signed a written informed consent to the study before their enrollment; parents or legal guardians signed the informed consent for underage participants. The ethical committee of the Institute for Maternal and Child Health – IRCCS “Burlo Garofolo” approved the study under the univocal code Prot. CE/V-78, 06/08/2007. All study procedures were performed under the ethical principles expressed by the Helsinki Declaration.

INGI-VBI (INGI-Val Borbera): is a collection of samples from seven small villages in the Borbera Valley, a geographically isolated valley located within the Apennine Mountains, in the southern part of Piedmont, North-Western of Italy. These populations belong to the Italian Network of Genetic Isolates (INGI), a project that aims to study the genetic basis of complex diseases and phenotypes, taking advantage of these populations' genetic and environmental homogeneity (doi: 10.1038/s41431-019-0551-x). Individuals with an age range from 18 to 87 years old were voluntarily enrolled. Demographic data and detailed familial and individual medical history were collected for all the participants. In addition, participants underwent specialist evaluations, e.g., neurological, psychiatric, in-depth sensorial, etc. Genotyping and phenotypic data for 1785 samples are available. Written informed consent for participation was obtained from all subjects. The project was approved by the Ethical committee of the San Raffaele Hospital (Milan, Italy). All study procedures were performed under the ethical principles expressed by the Helsinki Declaration.

JHS (Jackson Heart Study): The JHS is a longitudinal, community-based observational cohort study investigating the role of environmental and genetic factors in the development of cardiovascular disease in African Americans. Between 2000 and 2004, a total of 5306 participants were recruited from a tri-county area (Hinds, Madison, and Rankin Counties) that encompasses Jackson, MS. Details of the design and recruitment for the Jackson Heart Study cohort has been previously published [1-3]. Briefly, approximately 30% of participants were former members of the Atherosclerosis Risk in Communities (ARIC) study. The remainder were recruited by either 1) random selection from the Accudata list, 2) commercial listing, 3) a constrained volunteer sample, in which recruitment was distributed among defined demographic cells in proportions designed to mirror those in the overall population, or through the Jackson Heart Study Family Study. All JHS participants self-identified as Black or African American. Median % similarity to African reference panels (such as 1000G) is >80% for JHS participants in prior work. For this meta-analysis JHS was included in the African population subgroup.

1. Wyatt SB, Diekelmann N, Henderson F, Andrew ME, Billingsley G, Felder SH, et al. A community-driven model of research participation: the Jackson Heart Study Participant Recruitment and Retention Study. *Ethn Dis*. 2003;13(4):438-55. PubMed PMID: 14632263.
2. Taylor HA, Jr., Wilson JG, Jones DW, Sarpong DF, Srinivasan A, Garrison RJ, et al. Toward resolution of cardiovascular health disparities in African Americans: design and methods of the Jackson Heart Study. *Ethn Dis*. 2005;15(4 Suppl 6):S6-4-17. PubMed PMID: 16320381.
3. Fuqua SR, Wyatt SB, Andrew ME, Sarpong DF, Henderson FR, Cunningham MF, et al. Recruiting African-American research participation in the Jackson Heart Study: methods, response rates, and sample description. *Ethn Dis*. 2005;15(4 Suppl 6):S6-18-29. PubMed PMID: 16317982.

KoGES (Korean Genome and Epidemiology Study): KoGES is a large-scale prospective cohort study with a comprehensive range of phenotypic measures and biological samples collected on approximately 210,000 individuals. KoGES's long-term objective is to develop comprehensive and applicable healthcare guidelines for common complex diseases in Koreans, reduce the burden of chronic diseases and improve the quality of life. KoGES includes population-based cohorts, the community-based Ansan and Ansong study, the urban community-based health examinee study, and the rural community-based cardiovascular disease association study. The cohorts consist of community-dwellers and participants recruited from the national health examinee registry, men and women, aged ≥ 40 years at baseline. A total of 72,000 samples were genotyped with KoreanChip, a customized array optimized for the Korean population, and imputed using IMPUTE4 with 1000 Genomes Project Phase 3 data and the Korean reference genome as a reference panel. Measures of the baseline recruitment, and only genotyped samples that met the following exclusion criteria were used in the analyses: low call rate ($<97\%$), excessive heterozygosity, excessive singletons, gender discrepancy, and cryptic first-degree relatives. SNPs with low HWE p value ($<10^{-6}$) or low call rate ($<95\%$) were excluded. Variants with imputation quality score (IQS) < 0.8 and MAF $< 1\%$ were excluded after imputation.

1. Kim, Yeonjung, Bok-Ghee Han, and KoGES Group. "Cohort profile: the Korean genome and epidemiology study (KoGES) consortium." *International journal of epidemiology* 46.2 (2017): e20-e20.
2. Moon, Sanghoon, et al. "The Korea Biobank Array: design and identification of coding variants associated with blood biochemical traits." *Scientific reports* 9.1 (2019): 1-11.
3. Nam, Kisung, Jangho Kim, and Seunggeun Lee. "Genome-wide study on 72,298 individuals in Korean biobank data for 76 traits." *Cell Genomics* 2.10 (2022): 100189.

LBC1921 (Lothian Birth Cohort 1921): LBC1921 consists of 550 relatively healthy individuals, most of whom took part in the Scottish Mental Survey of 1932 at the age of ~ 11 years old. They were recruited to a study to determine influences on cognitive ageing at age ~ 79 years, when almost all lived

independently in the Lothian region of Scotland. They have taken part in five waves of testing in later life (at mean ages 79, 83, 87, 90 and 92 years). At each wave they underwent a series of cognitive and physical tests.^{1,2}

1. Deary IJ, Gow AJ, Pattie A, Starr JM. Cohort profile: the Lothian Birth Cohorts of 1921 and 1936. *Int J Epidemiol* 2012;41:1576-1584.

2. Taylor AM, Pattie A, Deary IJ. Cohort Profile Update: The Lothian Birth Cohorts of 1921 and 1936. *Int J Epidemiol* 2018;47:1042-1042r

LBC1936 (Lothian Birth Cohort 1936): LBC1936 consists of 1091 relatively healthy individuals, most of whom took part in the Scottish Mental Survey of 1947 at the age of ~11 years old. They were recruited to a study to determine influences on cognitive ageing at age ~70 years, when almost all lived independently in the Lothian region of Scotland. They have taken part in six waves of testing in later life (at mean ages 70, 73, 76, 79, 82 and 86 years). At each wave they underwent a series of cognitive and physical tests.^{1,2}

1. Deary IJ, Gow AJ, Pattie A, Starr JM. Cohort profile: the Lothian Birth Cohorts of 1921 and 1936. *Int J Epidemiol* 2012;41:1576-1584.

2. Taylor AM, Pattie A, Deary IJ. Cohort Profile Update: The Lothian Birth Cohorts of 1921 and 1936. *Int J Epidemiol* 2018;47:1042-1042r

Lifelines: (<https://lifelines.nl/>) Lifelines is a multi-disciplinary prospective population-based cohort study using a unique three-generation design to examine the health and health-related behaviors 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, behavioral, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multimorbidity. In addition, the Lifelines project comprises a number of cross-sectional sub-studies, which investigate specific age-related conditions. These include investigations into metabolic and hormonal diseases, including obesity, cardiovascular and renal diseases, pulmonary diseases and allergy, cognitive function and depression, and musculoskeletal conditions. All survey participants are between 18 and 90 years old at the time of enrollment. Recruitment has been going on since the end of 2006, and over 130,000 participants had been included by April 2013. At the baseline examination, the participants in the study were asked to fill in a questionnaire (on paper or online) before the first visit. During the first and second visit, the first or second part of the questionnaire, respectively, are checked for completeness, a number of investigations are conducted, and blood and urine samples are taken. Lifelines is a facility that is open for all researchers. Information on application and data access procedure is summarized on www.lifelines.nl. (Scholtens S, Smidt N, Swertz MA, Bakker SJ, Dotinga A, Vonk JM, et al. Cohort Profile: LifeLines, a three-generation cohort study and biobank. *Int J Epidemiol*. 2014 Dec 14.)

Lifelines was genotyped in 2 stages: the first stage consisted of ~15,000 participants and used the Illumina CytoSNP chip; the second stage included ~35,000 participants and used the Illumina GSA chip. Due to the differences in genotyping, these two groups are analysed separately. Samples that are present, or have close relatives in both groups, are excluded from the CytoSNP dataset prior to analysis.

LLFS (The Long Life Family Study): LLFS is a longitudinal, population-based multigenerational family cohort designed to study genetic, behavioral, and environmental factors in families exhibiting exceptional longevity. Families were sampled from four clinical centers: Boston University Medical Center in Boston, MA; Columbia College of Physicians and Surgeons in New York City, NY; the University of Pittsburgh in Pittsburgh, PA, USA; and the University of Southern Denmark, Denmark. The characteristics, recruitment, eligibility, and enrollment were previously described (PMID: 21258136, PMID: 34739053). The first clinical exam started in 2006 and recruited 4,953 individuals in 539 two-generational families that demonstrated clustering for exceptional survival in the upper generation. The second clinical exam (2014-2017) revisited 2,933 European descent individuals from 528 families. The third clinical exam (2021-) is recruiting the participants from second exam and a few new ones from the grandchild generation. The individuals were genotyped using ~2.3 million SNPs from the Illumina Omni chip, then imputed on Version R2 of the TOPMed reference panel using the Michigan Imputation Server (<https://imputation.biodatacatalyst.nih.gov/#!>), which used Eagle v2.4 for phasing and minimac4 v1.3.3 for imputation.

MESA (Multi-Ethnic Study of Atherosclerosis) The Multi-Ethnic Study of Atherosclerosis (MESA) is a study of the characteristics of subclinical cardiovascular disease and the risk factors that predict progression to clinically overt cardiovascular disease or progression of the subclinical disease. MESA consisted of a diverse, population-based sample of an initial 6,814 asymptomatic men and women aged 45-84. 38 percent of the recruited participants were white, 28 percent African American, 22 percent Hispanic, and 12 percent Asian, predominantly of Chinese descent. Participants were recruited from six field centers across the United States: Wake Forest University, Columbia University, Johns Hopkins University, University of Minnesota, Northwestern University and University of California - Los Angeles. Participants are being followed for identification and characterization of cardiovascular disease events, including acute myocardial infarction and other forms of coronary heart disease (CHD), stroke, and congestive heart failure; for cardiovascular disease interventions; and for mortality. The first examination took place over two years, from July 2000 - July 2002. It was followed by five examination periods that were 17-20 months in length, including the recently completed Exam 6 (2016-2018). MESA Exam 7 is approved and now being planned. Participants have been contacted every 9 to 12 months throughout the study to assess clinical morbidity and mortality. Informed consent was obtained for extensive data sharing (dbGaP) and genetic/omic studies, including candidate genes (NHLBI CARE), genome-wide scans (NHLBI SHARE), exome sequencing (NHLBI ESP) and, most recently, the NHLBI TOPMed program.

1. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, Greenland P, Jacob DR Jr,

Kronmal R, Liu K, Nelson JC, O'Leary D, Saad MF, Shea S, Szklo M, Tracy RP. Multi-ethnic study of atherosclerosis: objectives and design. *Am J Epidemiol*. 2002 Nov 1;156(9):871-81. PubMed PMID: 12397006.

NEO (The Netherlands Epidemiology of Obesity study): The NEO was designed for extensive phenotyping to investigate pathways that lead to obesity-related diseases. The NEO study is a population-based, prospective cohort study that includes 6,671 individuals aged 45–65 years, with an oversampling of individuals with overweight or obesity. At baseline, information on demography, lifestyle, and medical history have been collected by questionnaires. In addition, samples of 24-h urine, fasting and postprandial blood plasma and serum, and DNA were collected. Genotyping was performed using the Illumina HumanCoreExome chip, which was subsequently imputed to the 1000 genome reference panel. Participants underwent an extensive physical examination, including anthropometry, electrocardiography, spirometry, and measurement of the carotid artery intima-media thickness by ultrasonography. In random subsamples of participants, magnetic resonance imaging of abdominal fat, pulse wave velocity of the aorta, heart, and brain, magnetic resonance spectroscopy of the liver, indirect calorimetry, dual energy X-ray absorptiometry, or accelerometry measurements were performed. The collection of data started in September 2008 and completed at the end of September 2012. Participants are currently being followed for the incidence of obesity-related diseases and mortality.

NESDA: The Netherlands Study of Depression and Anxiety (NESDA) is an ongoing longitudinal cohort study to examine the prevalence, long-term course and consequences of depressive and anxiety disorders in the adult population. A detailed description of the study can be found elsewhere¹. Briefly, a total of 2981 participants, consisting of a healthy control group, people with a history of depressive or anxiety disorder and people with current depressive and/or anxiety disorder, were recruited from community (19%), primary care (54%), and outpatient psychiatric clinics (27%), and included at the baseline assessment in 2004-2007. Inclusion criteria were a lifetime diagnosis of major depressive disorder or anxiety disorder, age 18-65 years, and self-reported western European ancestry. Excluded were those who were not fluent in Dutch, and those with a primary diagnosis of psychotic disorder, obsessive compulsive disorder, bipolar disorder, or severe substance use or dependence. Biological sample collection and biobanking procedures (i.e. blood sampling and DNA isolation) took place during the baseline visit and has been previously described in detail ².

NESDA samples were genotyped using either the Perlegen-Affymetrix 5.0, or Affymetrix 6.0 genotyping chip and called with BirdSeed. SNPs were excluded if unmapped or mapped to multiple locations, call rate<95%, MAF<0.01, HWE p-value<10⁻⁵, unmapped to build 36, allele frequency difference with 1000Genomes reference >20%, or palindromic SNPs with allele frequency>35%. Samples were removed if call rate<90%, deviant heterozygosity, abs(PLINK F)>0.1, sex mismatch, unexpected relatedness, or non-Caucasian. Imputation was performed with Impute software using the 1000Genomes Phase 1 Integrated Release 3 ALL reference panel.

1. Penninx BW, Beekman AT, Smit JH, et al. The Netherlands study of depression and anxiety (NESDA): Rationale, objectives and methods. *International journal of methods in psychiatric research*. 2008;17(3):121-140.

2. Boomsma DI, Willemsen G, Sullivan PF, et al. Genome-wide association of major depression: Description of samples for the GAIN major depressive disorder study: NTR and NESDA biobank projects. *European Journal of Human Genetics*. 2008;16(3):335.

SHIP (Study of Health in Pomerania): The Study of Health In Pomerania (SHIP) is a prospective longitudinal population-based cohort study in Mecklenburg-Western Pomerania assessing the prevalence and incidence of common diseases and their risk factors (PMID: 20167617 and 35348705). SHIP encompasses the two independent cohorts SHIP-START and SHIP-TREND. Participants aged 20 to 79 with German citizenship and principal residency in the study area were recruited from a random sample of residents living in the three local cities, 12 towns as well as 17 randomly selected smaller towns. Individuals were randomly selected stratified by age and sex in proportion to population size of the city, town or small towns, respectively. A total of 4,308 participants were recruited between 1997 and 2001 in the SHIP-START cohort. Between 2008 and 2012 a total of 4,420 participants were recruited in the SHIP-TREND cohort. Individuals were invited to the SHIP study center for a computer-assisted personal interviews and extensive physical examinations. The study protocol was approved by the medical ethics committee of the University of Greifswald. Oral and written informed consent was obtained from each of the study participants.

Genome-wide SNP-typing was performed using the Affymetrix Genome-Wide Human SNP Array 6.0 (SHIP-START samples), the Illumina Infinium HumanOmni2.5 BeadChip, or the Illumina Infinium Global Screening Array (SHIP-TREND samples). Array processing was carried out in accordance with the manufacturer's standard recommendations. Genotypes were determined using the Birdseed2 clustering algorithm for SHIP-START, GenomeStudio Genotyping Module v1.0, and GenomeStudio 2.0 Genotyping Module (GenCall) for SHIP-TREND.

Singapore Prospective Study Program (SP2) – for contributing data SP2-1M and SP2-610

SP2 (Singapore Prospective Study Program):

The SP2 (Singapore Prospective Study Program) is a population-based study of diabetes and cardiovascular disease in Singapore. Participants were between the ages of 24-95 years between 2003 and 2007. A total of 5,157 participants completed a questionnaire and the subsequent clinical examinations. Of the 5,517 subjects, 2,098 Chinese were genotyped on a combination of Illumina 610, 1M arrays. Fasting HDL-C, TC and TG were measured by an automated analyzer autoanalyzer (ADVIA 2400, Bayer Diagnostics). LDL-C was calculated from Friedewald formula. [1, 2].

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SWAN (The Study of Women's Health Across the Nation):

The **Study of Women's Health Across the Nation (SWAN)** is a multi-site, multiracial/ethnic longitudinal study of women's health designed to describe the biological, behavioral, and psychosocial characteristics that occur during midlife and the menopausal transition. In addition to characterizing reproductive aging, SWAN focuses on the impact of menopause on age-related chronic diseases, such as diabetes, cardiovascular disease, depression, bone loss and osteoporosis, as well as physical and cognitive functioning. The SWAN cohort was enrolled in 1996-97 and consists of 3302 community-based women from seven sites with data from five race/ethnic groups: Black (n=935), Chinese (n=250), Hispanic (n=286), Japanese (n=281), and White (n=1550). To be eligible for enrollment women had to be aged 42 to 52 years old, have an intact uterus and at least one ovary, have had a menstrual period in the previous three months, and not be taking hormones. SWAN participants have completed 15 approximately annual follow-up visits since enrollment. During follow-up visits 5 and 6 (2001-2003), 1757 women from six sites were consented to provide genetic materials for whom extracted DNA was successfully obtained for 1536 women: Black (n=410), Chinese (n=151), Hispanic (n=0), Japanese (n=168), and White (n=807). This analysis was done separately for Whites and Blacks.

Sowers MF, Crawford S, Sternfeld B, Morganstein DG, Gold EB, Greendale G, Evans D, Neer R, Matthews K, Sherman S, Lo A, Weiss G, Kelsey J. SWAN: A multi-center, multi-ethnic, community-based cohort study of women and the menopausal transition. In: Lobo RA, Kelsey JL, Marcus R, editors. Menopause: biology and pathobiology. San Diego, CA: Academic Press; 2000. p. 175-88

UKBB (UK Biobank): UK Biobank (UKB, www.ukbiobank.ac.uk) is a large longitudinal biobank study in the United Kingdom which was established to improve understanding of the genetic and environmental causes of common diseases including cardiovascular diseases. In addition to self-reported disease outcomes and extensive health and life-style questionnaire data, UKB participants are being tracked through their NHS records and national registries (including cause of death and Hospital Episode Statistics). In 2017, UKB released the genotypes of 488,377 participants profiled with a custom SNP array. Genotyping QC was performed centrally by UKB, and genotypes imputed to Haplotype Reference Consortium (HRC) panel were released for 488,377 participants. Sample selection for the Gene-Lifestyle Interaction projects was based on available datasets for traits and lifestyle measures.

WHI (Women's Health Initiative): is a long-term national health study that focuses on strategies for preventing common diseases such as heart disease, cancer and fracture in postmenopausal women. A total of 161,838 women aged 50–79 years old were recruited from 40 clinical centers in the US between 1993 and 1998(1, 2). WHI consists of an observational study, two clinical trials of postmenopausal hormone therapy (HT, estrogen alone or estrogen plus progestin), a calcium and vitamin D supplement trial, and a dietary modification trial. Study recruitment and exclusion criteria have been described previously(1, 2). Recruitment was done through mass mailing to age-eligible women obtained from voter registration, driver's license and Health Care Financing Administration or other insurance list, with emphasis on recruitment of minorities and older women. Exclusions included participation in other randomized trials, predicted survival < 3 years, alcoholism, drug dependency, mental illness and

dementia. For

the CT, women were ineligible if they had a systolic BP > 200 mm Hg or diastolic BP > 105 mm Hg, a history of hypertriglyceridemia or breast cancer. Study protocols and consent forms were approved by the IRB at all participating institutions. Socio-demographic characteristics, lifestyle, medical history and self-reported medications were collected using standardized questionnaires at the screening visit. Genome wide association study (GWAS) non-overlapping samples are composed of (a) a case-control study (WHI Genomics and Randomized Trials Network – GARNET, which included all coronary heart disease, stroke, venous thromboembolic events and selected diabetes cases that happened during the active intervention phase in the WHI HT clinical trials and aged matched controls), (b) women selected to be "representative" of the HT trial (mostly younger white HT subjects that were also enrolled in the WHI memory study - WHIMS) and (c) the WHI SNP Health Association Resource (WHI SHARe), a randomly selected sample of 8,515 African American and 3,642 Hispanic women from WHI. Genotyping was performed using Affymetrix 6.0 (WHI-SHARe), HumanOmniExpressExome-8v1_B (WHIMS) and Illumina HumanOmni1-Quad v1-0 B (GARNET). Quality control of the GWAS data included variant and sample call rates >95%, and included identification of genetically related individuals. Principal components were computed using methods developed by Price et al(3). Imputation was performed using the TOPMed Imputation Server and freeze 8 reference multi-ethnic panel (build hg38). Due to some overlap of WHI participants with the TOPMed reference panel, we re-calculated the estimated imputation quality based on only the samples not on TOPMed reference panel, to account for the over-estimation of imputation quality given by the imputation software(4). Variants with an imputation quality (Rsq) <0.3 were filtering out. After QC and exclusions from analysis protocol, the number of women included in analysis is 4,423 whites for GARNET, 5,202 white for WHIMS, 7,919 for SHARe African American and 3,377 for SHARe Hispanics. Analyses were performed using LinGxEScanR software.

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YFS (The Cardiovascular Risk in Young Finns Study): The YFS is a population-based follow up-study started in 1980. The main aim of the YFS is to determine the contribution made by childhood lifestyle, biological and psychological measures to the risk of cardiovascular diseases in adulthood. In 1980, over 3,500 children and adolescents all around Finland participated in the baseline study. The follow-up studies have been conducted mainly with 3-year intervals. The latest 30-year follow-up study was conducted in 2010-11 (ages 33-49 years) with 2,063 participants. The study was approved by the local ethics committees (University Hospitals of Helsinki, Turku, Tampere, Kuopio and Oulu) and was conducted following the guidelines of the Declaration of Helsinki. All participants gave their written informed consent.

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The expert technical assistance in the statistical analyses by Leo-Pekka Lyytikäinen and Irina Lisinen is gratefully acknowledged.

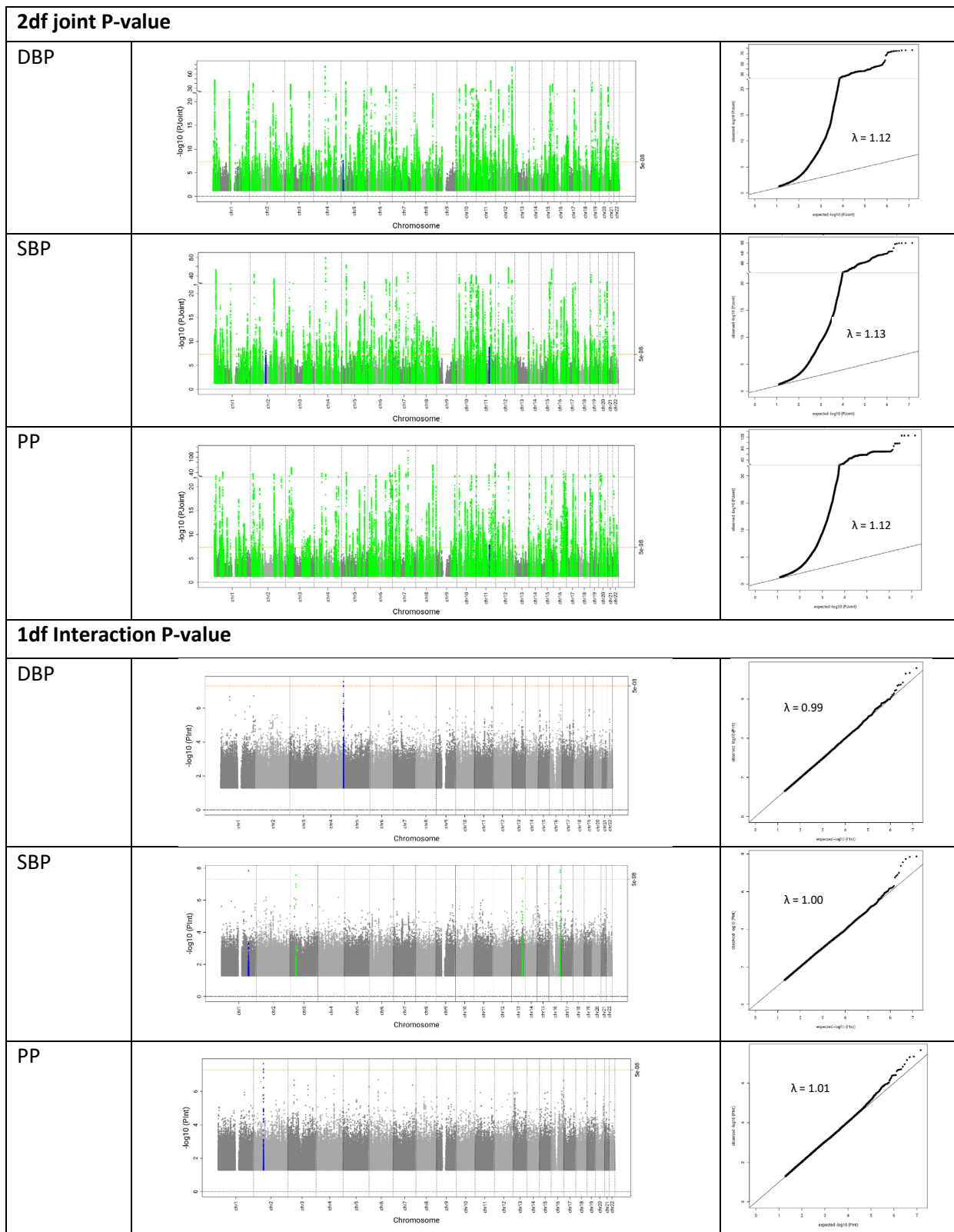


Figure S1. Manhattan and Quantile-quantile (QQ) plots for the 2df joint and 1df interaction P-values in cross-population dDEPR analyses (Green: known, Blue: novel). In the Manhattan plots, the $-\log_{10}(\text{P-value})$ is shown on the y-axis and chromosomal position on the x-axis. The genome-wide significance threshold ($P < 5 \times 10^{-8}$) is indicated by the yellow line. The QQ plots display the empirically observed P-value quantiles on the y-axis and the expected quantiles under the null on the x-axis. Genomic inflation factors (λ) were computed using two genomic control approaches.

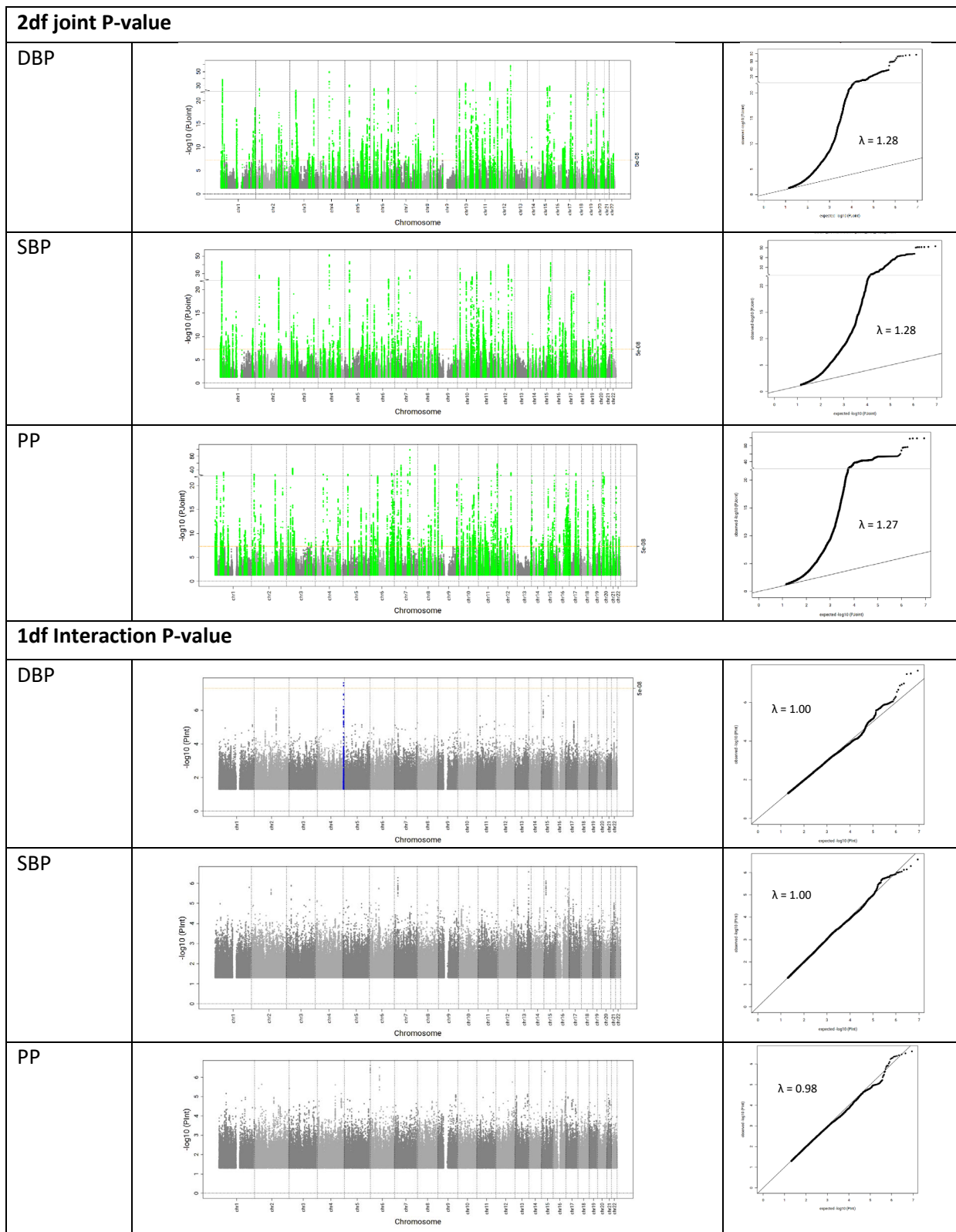


Figure S2. Manhattan and QQ plots for the 2df joint and 1df interaction P-values in EUR-specific dDEPR analyses (Green: known, Blue: novel). In the Manhattan plots, the $-\log_{10}(\text{P-value})$ is shown on the y-axis and chromosomal position on the x-axis. The genome-wide significance threshold ($P < 5 \times 10^{-8}$) is indicated by the yellow line. The QQ plots display the empirically observed P-value quantiles on the y-axis and the expected quantiles under the null on the x-axis. Genomic inflation factors (λ) were computed using one genomic control approach.

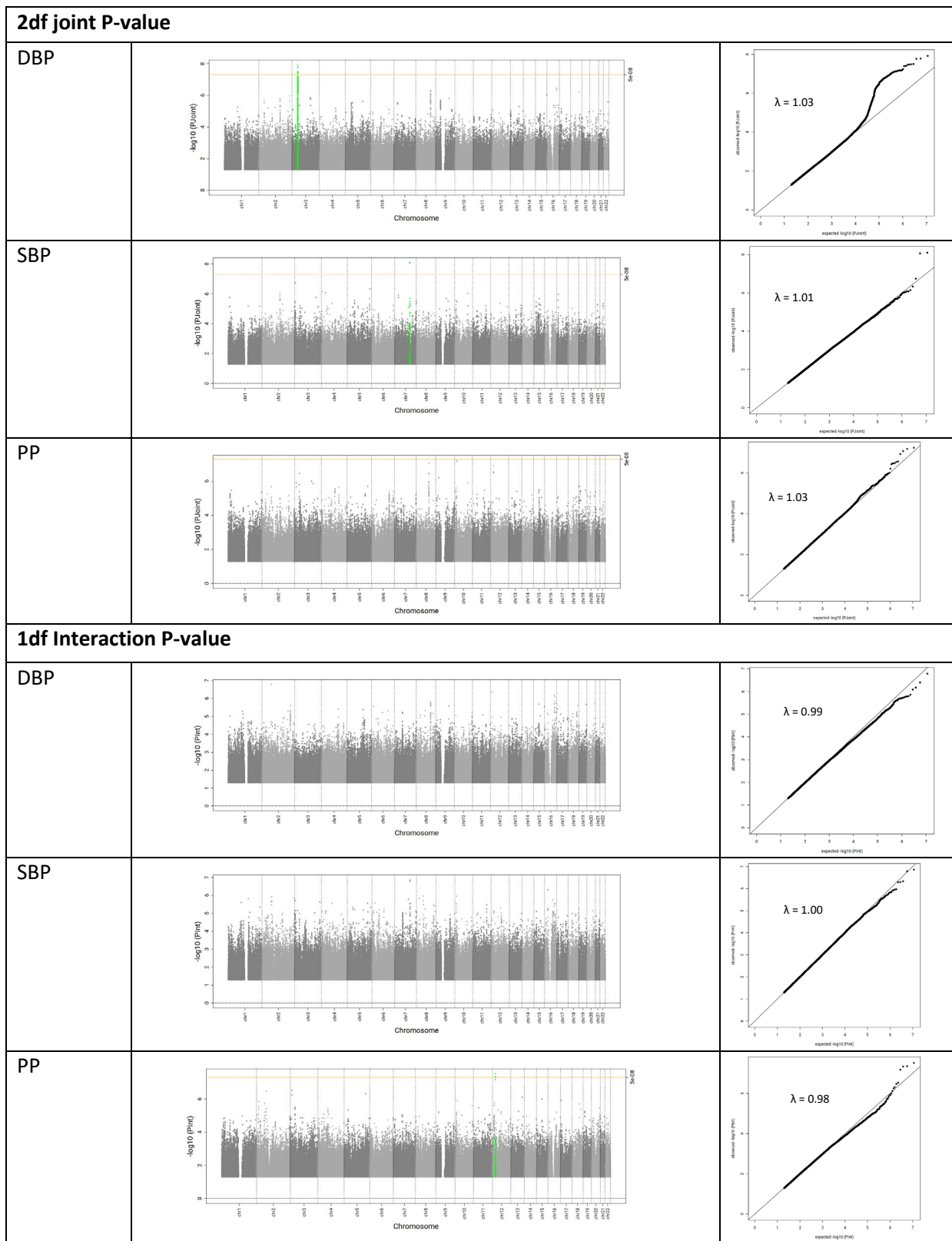


Figure S3. Manhattan and QQ plots for the 2df joint and 1df interaction P-values in AFR-specific dDEPR analyses (Green: known, Blue: novel). In the Manhattan plots, the $-\log_{10}(\text{P-value})$ is shown on the y-axis and chromosomal position on the x-axis. The genome-wide significance threshold ($P < 5 \times 10^{-8}$) is indicated by the yellow line. The QQ plots display the empirically observed P-value quantiles on the y-axis and the expected quantiles under the null on the x-axis. Genomic inflation factors (λ) were computed using one genomic control approach.

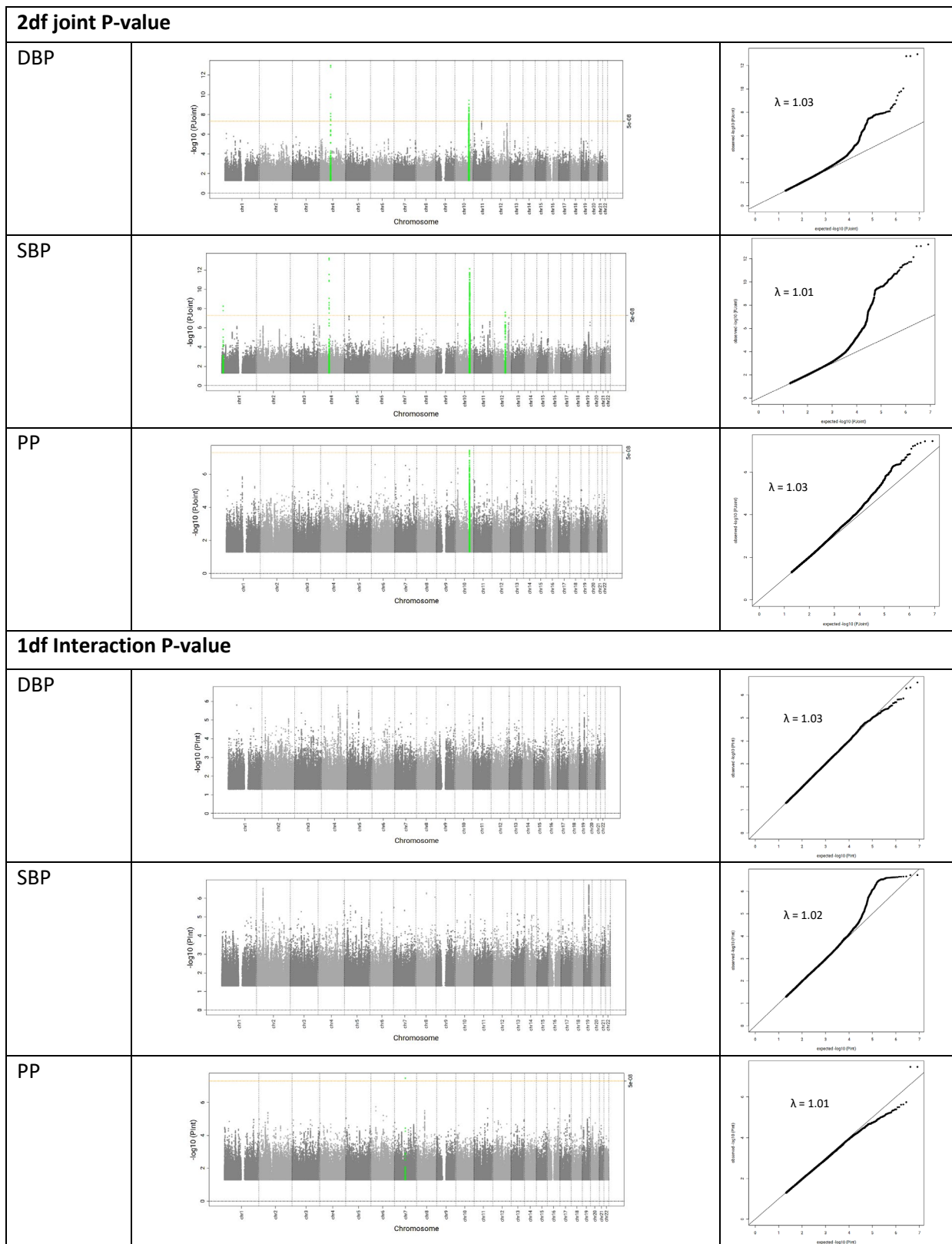


Figure S4. Manhattan and QQ plots for the 2df joint and 1df interaction P-values in ASN-specific dDEPR analyses (Green: known, Blue: novel). In the Manhattan plots, the $-\log_{10}(\text{P-value})$ is shown on the y-axis and chromosomal position on the x-axis. The genome-wide significance threshold ($P < 5 \times 10^{-8}$) is indicated by the yellow line. The QQ plots display the empirically observed P-value quantiles on the y-axis and the expected quantiles under the null on the x-axis. Genomic inflation factors (λ) were computed using one genomic control approach.

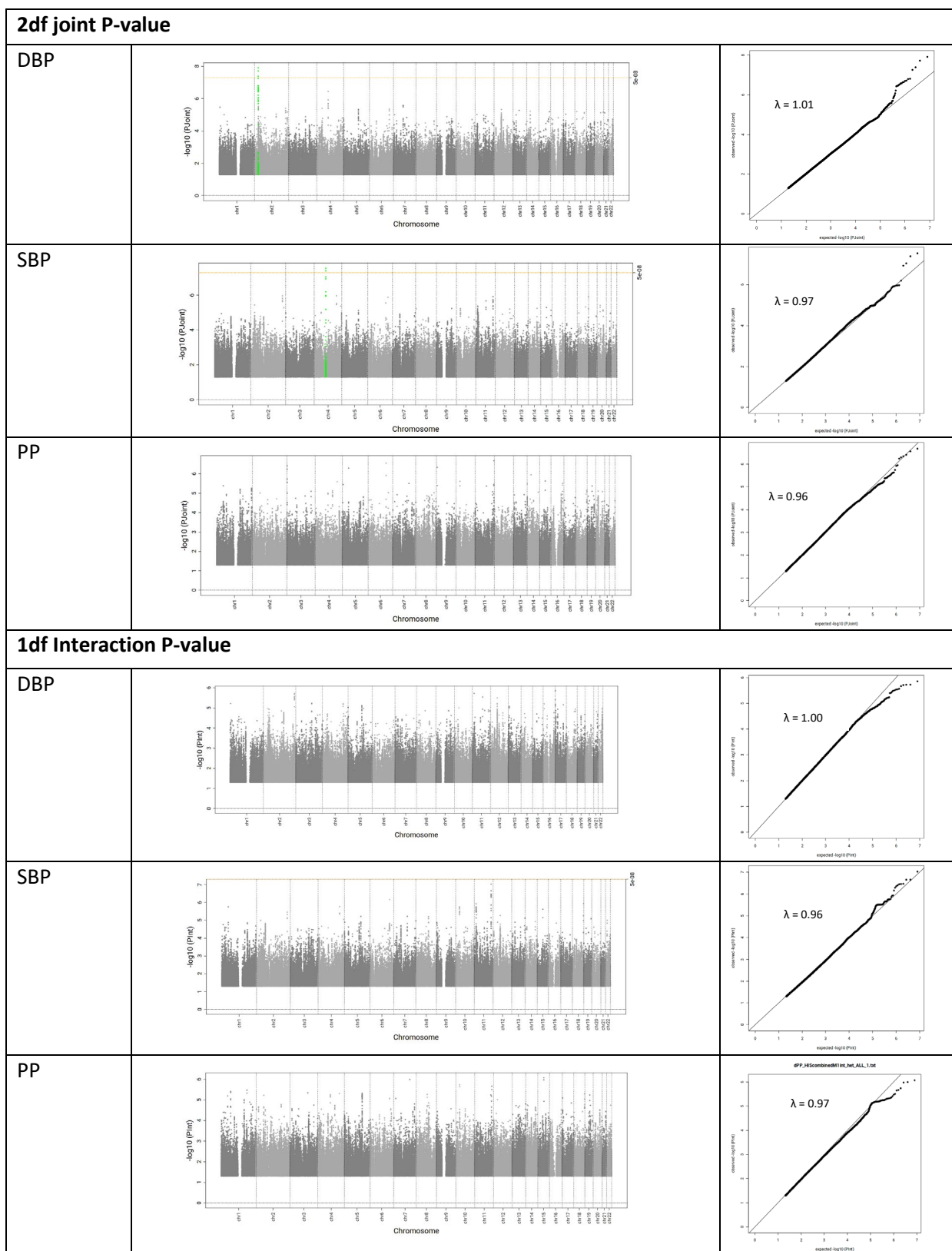


Figure S5. Manhattan and QQ plots for the 2df joint and 1df interaction P-values in HIS-specific dDEPR analyses (Green: known, Blue: novel). In the Manhattan plots, the $-\log_{10}(\text{P-value})$ is shown on the y-axis and chromosomal position on the x-axis. The genome-wide significance threshold ($P < 5 \times 10^{-8}$) is indicated by the yellow line. The QQ plots display the empirically observed P-value quantiles on the y-axis and the expected quantiles under the null on the x-axis. Genomic inflation factors (λ) were computed using one genomic control approach.

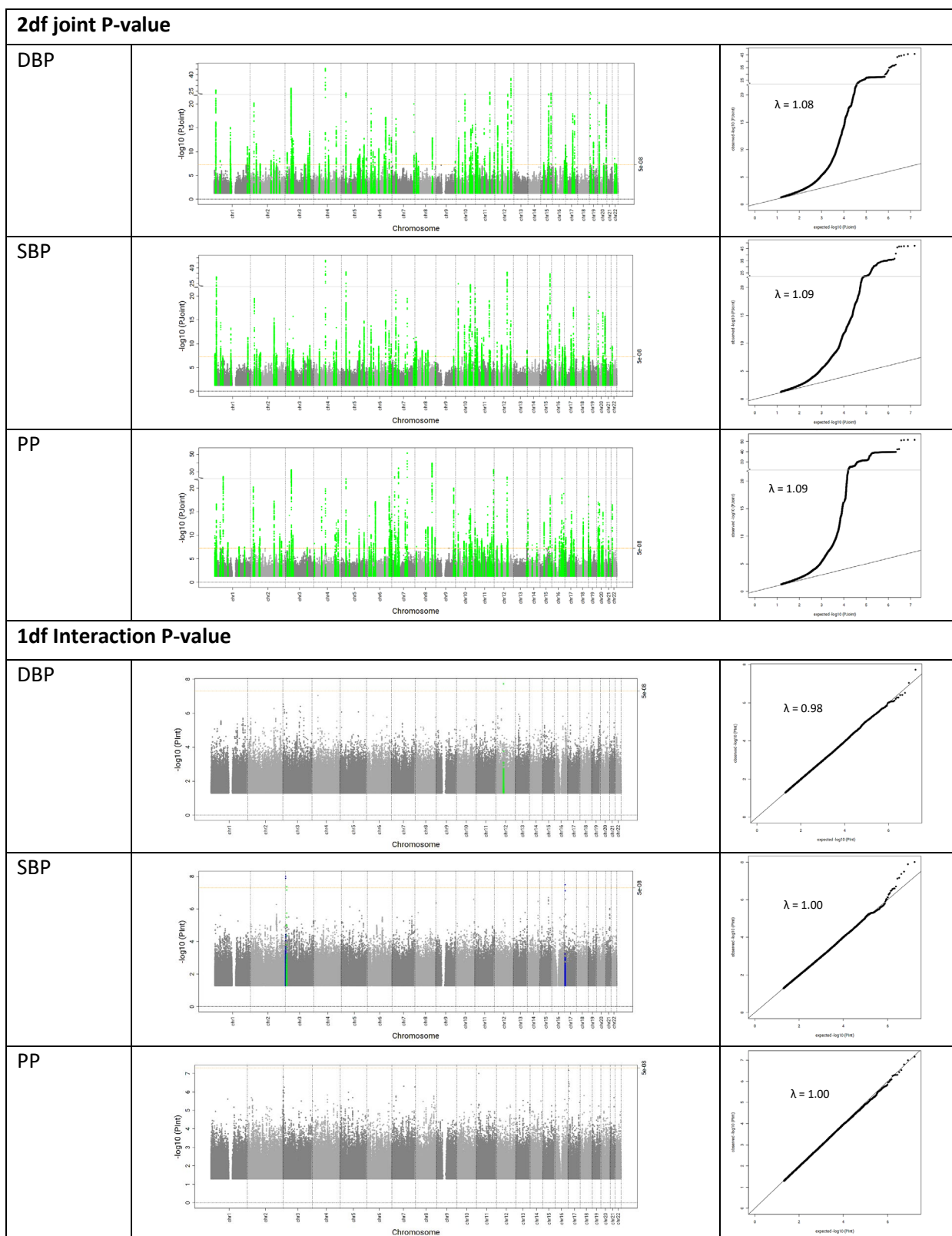


Figure S6. Manhattan and QQ plots for the 2df joint and 1df interaction P-values in cross-population qDEPR analyses (Green: known, Blue: novel). In the Manhattan plots, the $-\log_{10}(\text{P-value})$ is shown on the y-axis and chromosomal position on the x-axis. The genome-wide significance threshold ($P < 5 \times 10^{-8}$) is indicated by the yellow line. The QQ plots display the empirically observed P-value quantiles on the y-axis and the expected quantiles under the null on the x-axis. Genomic inflation factors (λ) were computed using two genomic control approaches.

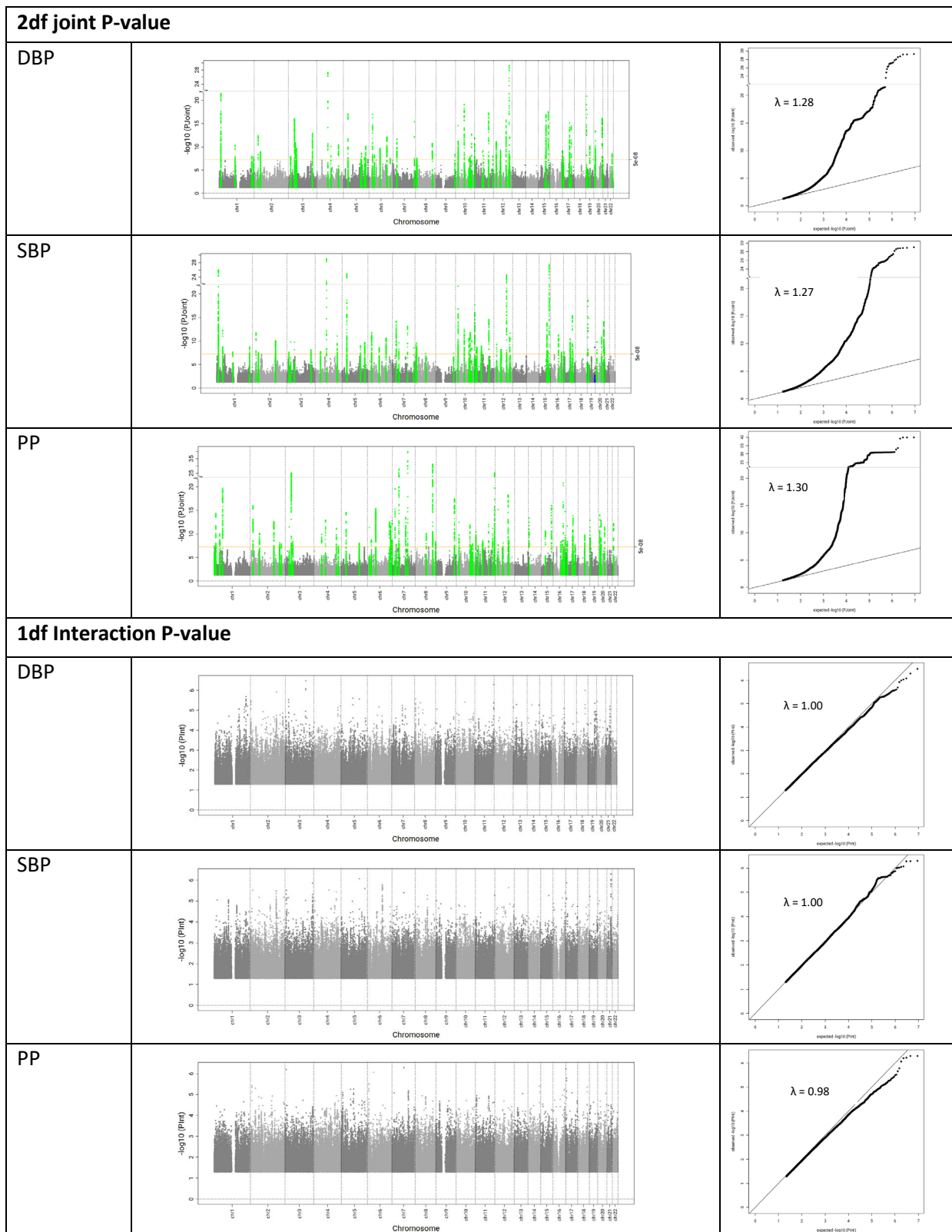


Figure S7. Manhattan and QQ plots for the 2df joint and 1df interaction P-values in EUR-specific qDEPR analyses (Green: known, Blue: novel). In the Manhattan plots, the $-\log_{10}(\text{P-value})$ is shown on the y-axis and chromosomal position on the x-axis. The genome-wide significance threshold ($P < 5 \times 10^{-8}$) is indicated by the yellow line. The QQ plots display the empirically observed P-value quantiles on the y-axis and the expected quantiles under the null on the x-axis. Genomic inflation factors (λ) were computed using one genomic control approach.

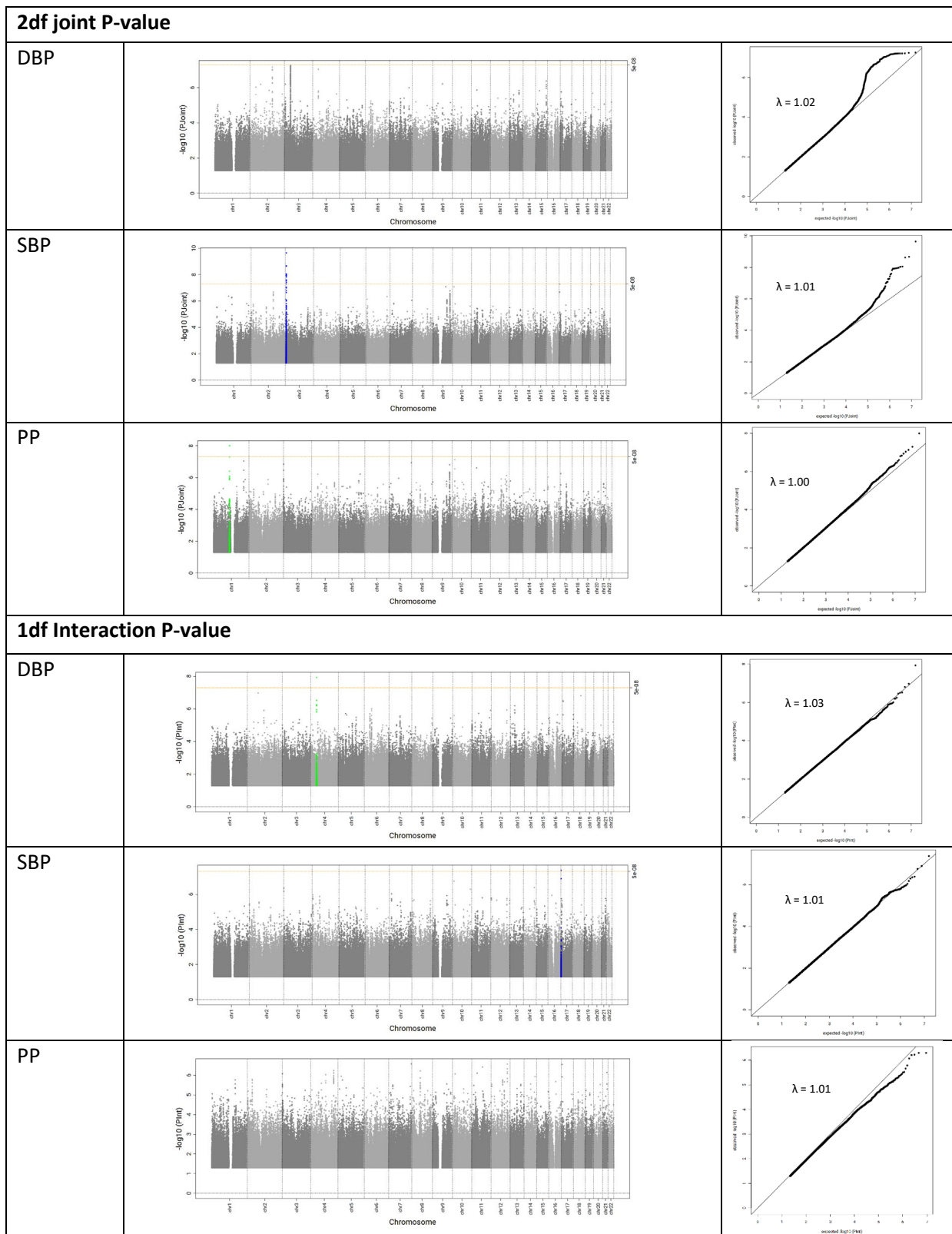


Figure S8. Manhattan and QQ plots for the 2df joint and 1df interaction P-values in AFR-specific qDEPR analyses (Green: known, Blue: novel). In the Manhattan plots, the $-\log_{10}(\text{P-value})$ is shown on the y-axis and chromosomal position on the x-axis. The genome-wide significance threshold ($P < 5 \times 10^{-8}$) is indicated by the yellow line. The QQ plots display the empirically observed P-value quantiles on the y-axis and the expected quantiles under the null on the x-axis. Genomic inflation factors (λ) were computed using one genomic control approach.

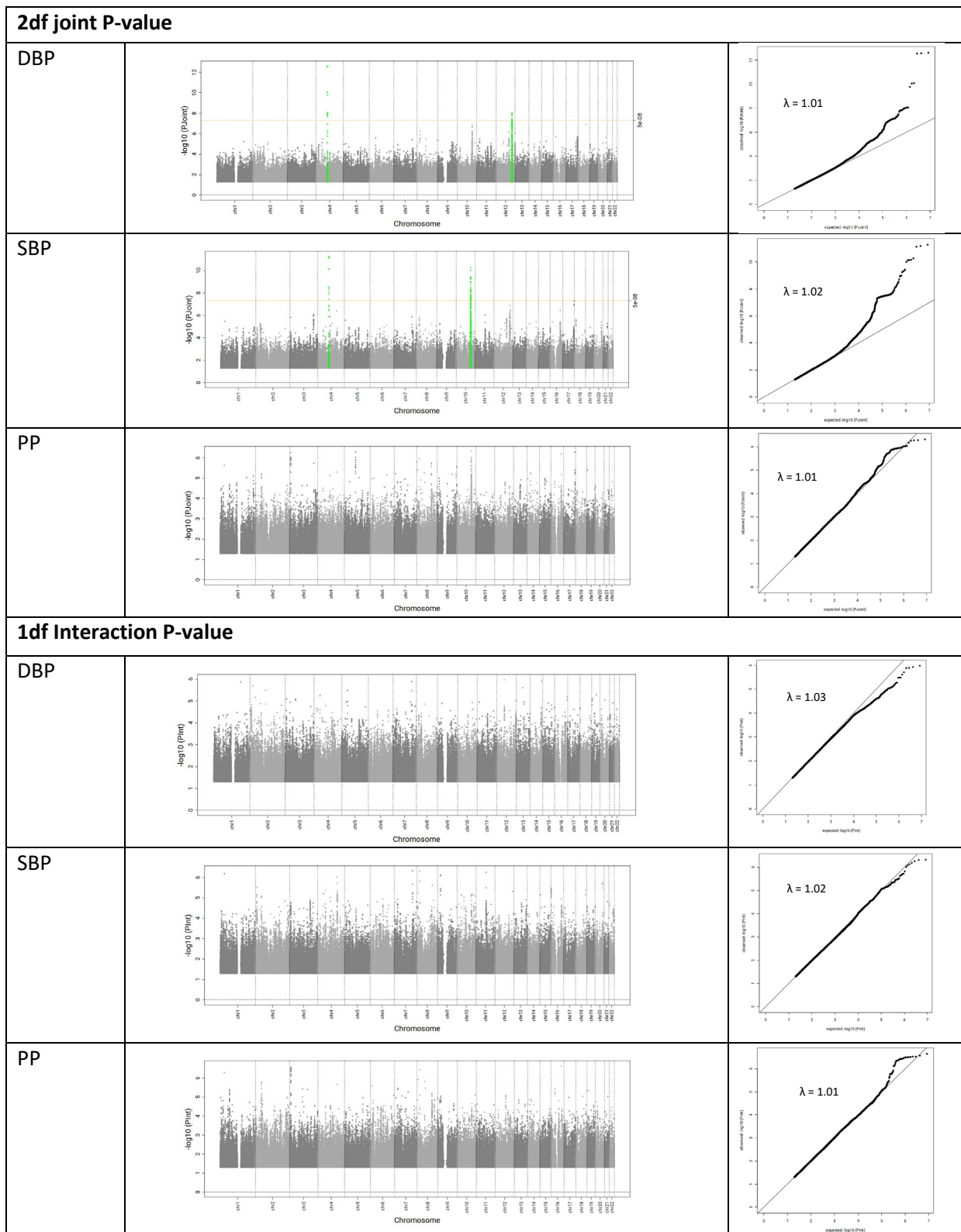


Figure S9. Manhattan and QQ plots for the 2df joint and 1df interaction P-values in ASN-specific qDEPR analyses (Green: known, Blue: novel). In the Manhattan plots, the $-\log_{10}(\text{P-value})$ is shown on the y-axis and chromosomal position on the x-axis. The genome-wide significance threshold ($P < 5 \times 10^{-8}$) is indicated by the yellow line. The QQ plots display the empirically observed P-value quantiles on the y-axis and the expected quantiles under the null on the x-axis. Genomic inflation factors (λ) were computed using one genomic control approach.

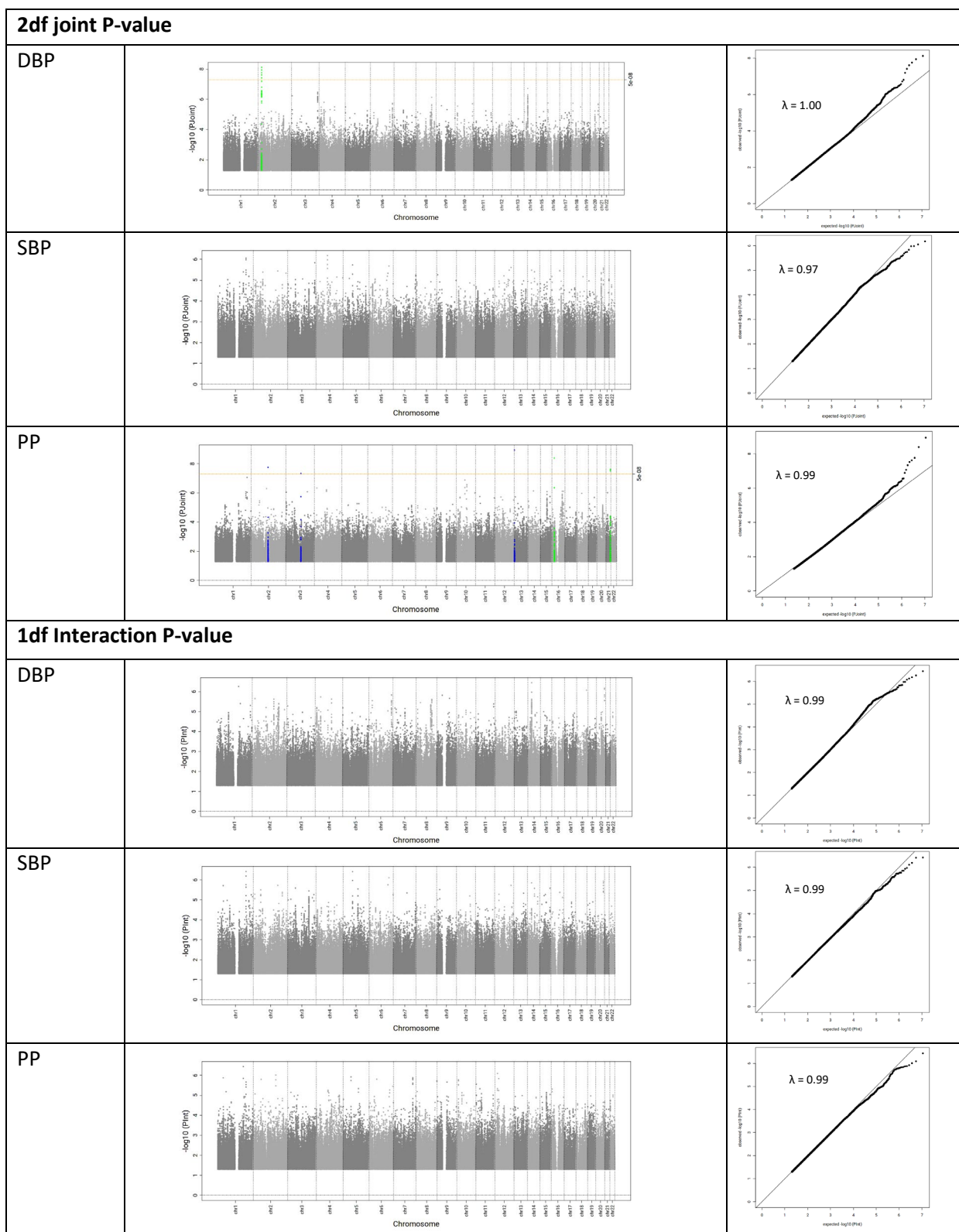


Figure S10. Manhattan and QQ plots for the 2df joint and 1df interaction P-values in HIS-specific qDEPR analyses (Green: known, Blue: novel). In the Manhattan plots, the $-\log_{10}(\text{P-value})$ is shown on the y-axis and chromosomal position on the x-axis. The genome-wide significance threshold ($P < 5 \times 10^{-8}$) is indicated by the yellow line. The QQ plots display the empirically observed P-value quantiles on the y-axis and the expected quantiles under the null on the x-axis. Genomic inflation factors (λ) were computed using one genomic control approach.

dDEPR	qDEPR																																																																								
1q31.3 (rs1664073690)																																																																									
<table><tr><th>Population</th><th>b</th><th>SE</th><th>95%-CI</th></tr><tr><td>EUR (19040)</td><td>7.72</td><td>1.39</td><td>7.72 [4.99; 10.45]</td></tr><tr><td>HIS (11537)</td><td>4.57</td><td>2.72</td><td>4.57 [-0.76; 9.90]</td></tr><tr><td>Meta analysis</td><td></td><td></td><td>7.07 [4.63; 9.50]</td></tr></table> Heterogeneity: $I^2 = 6\%$, $\tau^2 = 0.2914$, $p = 0.30$	Population	b	SE	95%-CI	EUR (19040)	7.72	1.39	7.72 [4.99; 10.45]	HIS (11537)	4.57	2.72	4.57 [-0.76; 9.90]	Meta analysis			7.07 [4.63; 9.50]	<table><tr><th>Population</th><th>b</th><th>SE</th><th>95%-CI</th></tr><tr><td>EUR (52546)</td><td>0.89</td><td>0.46</td><td>0.89 [-0.01; 1.78]</td></tr><tr><td>HIS (11537)</td><td>1.19</td><td>1.41</td><td>1.19 [-1.57; 3.96]</td></tr><tr><td>Meta analysis</td><td></td><td></td><td>0.92 [0.06; 1.77]</td></tr></table> Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.84$	Population	b	SE	95%-CI	EUR (52546)	0.89	0.46	0.89 [-0.01; 1.78]	HIS (11537)	1.19	1.41	1.19 [-1.57; 3.96]	Meta analysis			0.92 [0.06; 1.77]																																								
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SP2_1M (915)	1.66	1.62	1.66 [-1.51; 4.83]																																																																						
KOGES_rural (3802)	1.74	0.78	1.74 [0.22; 3.26]																																																																						
SP2_610 (930)	2.08	1.95	2.08 [-1.75; 5.91]																																																																						
KOGES_urban (11207)	0.85	0.40	0.85 [0.06; 1.63]																																																																						
MESA (775)	-3.30	2.39	-3.30 [-7.99; 1.38]																																																																						
BES_610 (585)	0.69	4.66	0.69 [-8.45; 9.83]																																																																						
BES_omni (557)	-3.67	3.02	-3.67 [-9.58; 2.24]																																																																						
Meta analysis			0.95 [0.29; 1.60]																																																																						
7q31.1 (rs757194)																																																																									
<table><tr><th>Study</th><th>b</th><th>SE</th><th>95%-CI</th></tr><tr><td>HRS (3100)</td><td>4.68</td><td>7.02</td><td>4.68 [-9.08; 18.45]</td></tr><tr><td>WHLshare (7604)</td><td>15.60</td><td>3.02</td><td>15.60 [9.68; 21.52]</td></tr><tr><td>HUFS (940)</td><td>11.56</td><td>5.52</td><td>11.56 [0.73; 22.38]</td></tr><tr><td>Meta analysis</td><td></td><td></td><td>13.42 [8.56; 18.28]</td></tr></table> Heterogeneity: $I^2 = 8\%$, $\tau^2 = 3.1711$, $p = 0.34$	Study	b	SE	95%-CI	HRS (3100)	4.68	7.02	4.68 [-9.08; 18.45]	WHLshare (7604)	15.60	3.02	15.60 [9.68; 21.52]	HUFS (940)	11.56	5.52	11.56 [0.73; 22.38]	Meta analysis			13.42 [8.56; 18.28]	<table><tr><th>Study</th><th>b</th><th>SE</th><th>95%-CI</th></tr><tr><td>ARIC (1113)</td><td>2.58</td><td>2.57</td><td>2.58 [-2.45; 7.62]</td></tr><tr><td>HANDLS (660)</td><td>-2.78</td><td>3.48</td><td>-2.78 [-9.60; 4.05]</td></tr><tr><td>HRS (2214)</td><td>0.39</td><td>1.99</td><td>0.39 [-3.51; 4.28]</td></tr><tr><td>JHS (1449)</td><td>0.03</td><td>1.52</td><td>0.03 [-2.96; 3.01]</td></tr><tr><td>WHLshare (7512)</td><td>4.74</td><td>1.05</td><td>4.74 [2.68; 6.81]</td></tr><tr><td>CARDIA (808)</td><td>1.86</td><td>2.56</td><td>1.86 [-3.15; 6.87]</td></tr><tr><td>CHS (821)</td><td>8.23</td><td>4.26</td><td>8.23 [-0.11; 16.57]</td></tr><tr><td>GENOA (368)</td><td>-2.33</td><td>4.19</td><td>-2.33 [-10.55; 5.88]</td></tr><tr><td>HUFS (940)</td><td>3.24</td><td>2.10</td><td>3.24 [-0.88; 7.35]</td></tr><tr><td>MESA (1631)</td><td>-1.67</td><td>2.42</td><td>-1.67 [-6.41; 3.07]</td></tr><tr><td>SWAN (366)</td><td>-4.85</td><td>4.54</td><td>-4.85 [-13.75; 4.05]</td></tr><tr><td>Meta analysis</td><td></td><td></td><td>2.12 [0.89; 3.35]</td></tr></table> Heterogeneity: $I^2 = 48\%$, $\tau^2 = 3.6145$, $p = 0.04$	Study	b	SE	95%-CI	ARIC (1113)	2.58	2.57	2.58 [-2.45; 7.62]	HANDLS (660)	-2.78	3.48	-2.78 [-9.60; 4.05]	HRS (2214)	0.39	1.99	0.39 [-3.51; 4.28]	JHS (1449)	0.03	1.52	0.03 [-2.96; 3.01]	WHLshare (7512)	4.74	1.05	4.74 [2.68; 6.81]	CARDIA (808)	1.86	2.56	1.86 [-3.15; 6.87]	CHS (821)	8.23	4.26	8.23 [-0.11; 16.57]	GENOA (368)	-2.33	4.19	-2.33 [-10.55; 5.88]	HUFS (940)	3.24	2.10	3.24 [-0.88; 7.35]	MESA (1631)	-1.67	2.42	-1.67 [-6.41; 3.07]	SWAN (366)	-4.85	4.54	-4.85 [-13.75; 4.05]	Meta analysis			2.12 [0.89; 3.35]
Study	b	SE	95%-CI																																																																						
HRS (3100)	4.68	7.02	4.68 [-9.08; 18.45]																																																																						
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SWAN (366)	-4.85	4.54	-4.85 [-13.75; 4.05]																																																																						
Meta analysis			2.12 [0.89; 3.35]																																																																						
12p12.1 (rs7979305)																																																																									

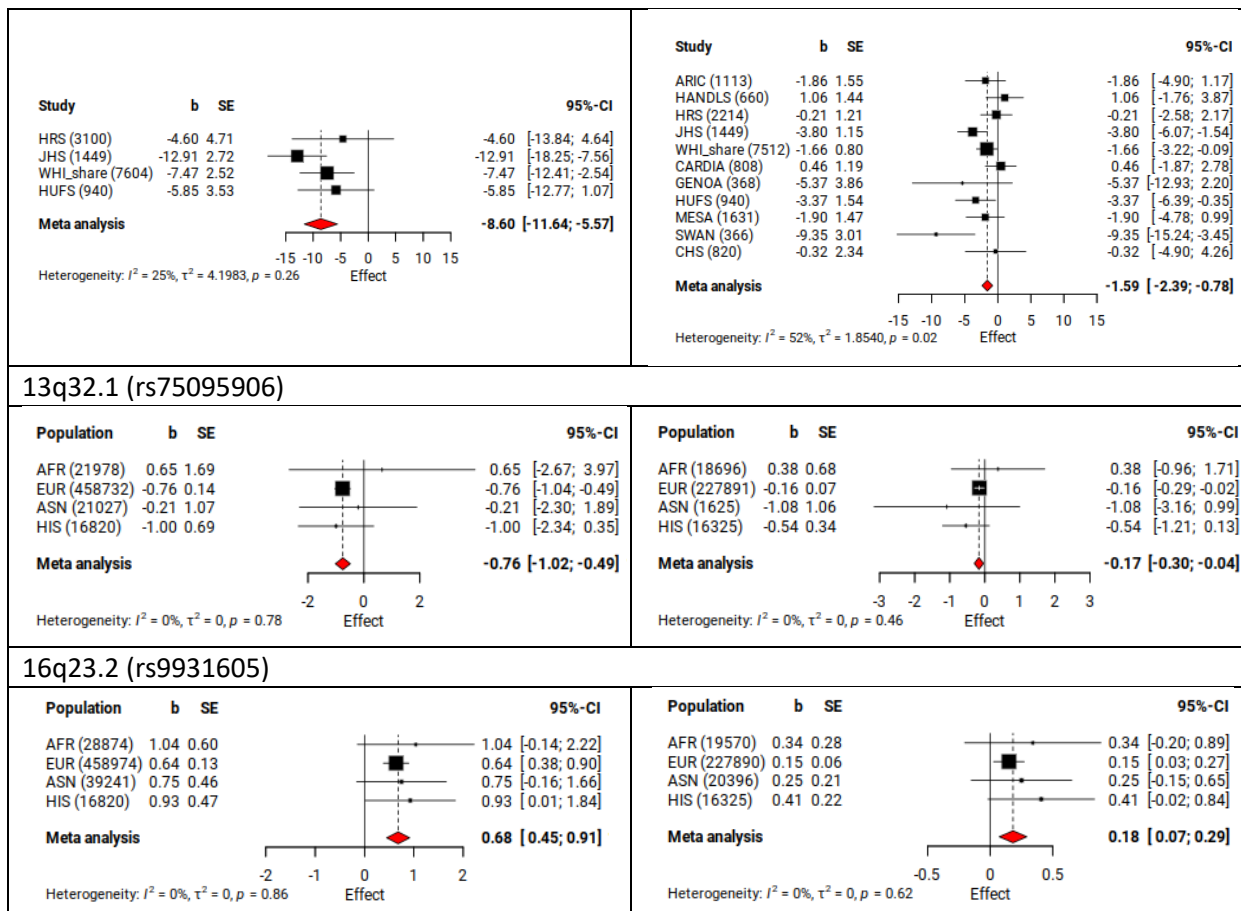
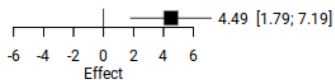
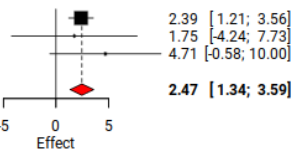
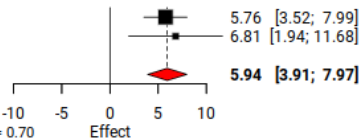
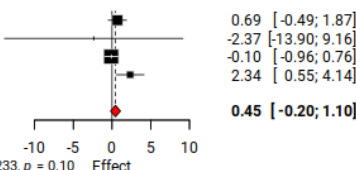
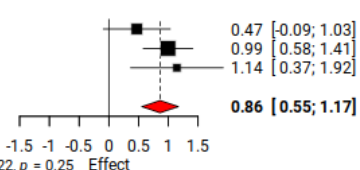
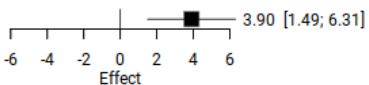
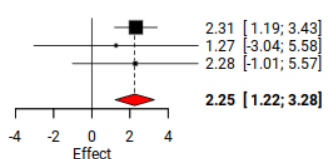
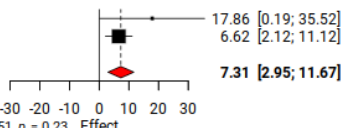
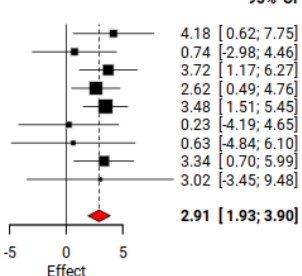
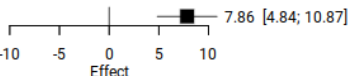
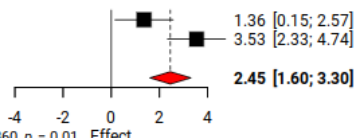


Figure S11. Comparison of SNP x DEPR effects at novel and known loci identified in dDEPR analyses between dDEPR and qDEPR models. For the cross-population meta-analyses, the labels on the left correspond to population names. For the population-specific analyses, the labels correspond to the individual studies contributing data for each population. On the right, the effect size (b), standard error (SE), and 95% confidence interval (95% CI) for each study or population are shown. Squares represent the b estimate, with horizontal lines indicating the 95% CI. Diamonds represent the meta-analyzed effect estimate, with the lateral points indicating the corresponding 95% CI. I^2 quantifies the proportion of variation due to heterogeneity (0-100%), and τ^2 represents the between study variance. The heterogeneity p-values (p) are shown. Solid vertical line denotes the null effect.

dDEPR	qDEPR
2q14.2 (rs77572777)	
Study b SE 95%-CI SOL (11532) 4.49 1.38 4.49 [1.79; 7.19] 	Study b SE 95%-CI SOL (11532) 2.39 0.60 2.39 [1.21; 3.56] MESA (1497) 1.75 3.05 1.75 [-4.24; 7.73] WHL_share (3048) 4.71 2.70 4.71 [-0.58; 10.00] Meta analysis 2.47 [1.34; 3.59]  Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.68$
3p26.3 (rs148780833)	
Not available	Population b SE 95%-CI AFR (15667) 5.76 1.14 5.76 [3.52; 7.99] HIS (11537) 6.81 2.48 6.81 [1.94; 11.68] Meta analysis 5.94 [3.91; 7.97]  Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.70$
3p25.3 (rs59284269)	
Population b SE 95%-CI AFR (29839) 0.69 0.60 0.69 [-0.49; 1.87] ASN (11298) -2.37 5.88 -2.37 [-13.90; 9.16] EUR (374086) -0.10 0.44 -0.10 [-0.96; 0.76] HIS (13034) 2.34 0.92 2.34 [-0.55; 4.14] Meta analysis 0.45 [-0.20; 1.10]  Heterogeneity: $I^2 = 52\%$, $\tau^2 = 0.8233$, $p = 0.10$	Population b SE 95%-CI AFR (19570) 0.47 0.29 0.47 [-0.09; 1.03] EUR (216296) 0.99 0.21 0.99 [0.58; 1.41] HIS (16082) 1.14 0.40 1.14 [0.37; 1.92] Meta analysis 0.86 [0.55; 1.17]  Heterogeneity: $I^2 = 27\%$, $\tau^2 = 0.0322$, $p = 0.25$
3q13.11 (rs748650739)	
Study b SE 95%-CI SOL (11532) 3.90 1.23 3.90 [1.49; 6.31] 	Study b SE 95%-CI SOL (11532) 2.31 0.57 2.31 [1.19; 3.43] MESA (1497) 1.27 2.20 1.27 [-3.04; 5.58] WHL_share (3048) 2.28 1.68 2.28 [-1.01; 5.57] Meta analysis 2.25 [1.22; 3.28]  Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.90$
4p14 (rs145132348)	
Study b SE 95%-CI HRS (3099) 17.86 9.01 17.86 [0.19; 35.52] JHS (1449) 6.62 2.30 6.62 [2.12; 11.12] Meta analysis 7.31 [2.95; 11.67]  Heterogeneity: $I^2 = 31\%$, $\tau^2 = 19.8451$, $p = 0.23$	Study b SE 95%-CI ARIC (1113) 4.18 1.82 4.18 [0.62; 7.75] HANDLS (660) 0.74 1.90 0.74 [-2.98; 4.46] HRS (2213) 3.72 1.30 3.72 [1.17; 6.27] JHS (1449) 2.62 1.09 2.62 [0.49; 4.76] WHL_share (7512) 3.48 1.00 3.48 [1.51; 5.45] CARDIA (808) 0.23 2.25 0.23 [-4.19; 4.65] HUFS (940) 0.63 2.79 0.63 [-4.84; 6.10] MESA (1631) 3.34 1.35 3.34 [0.70; 5.99] CHS (821) 3.02 3.30 3.02 [-3.45; 9.48] Meta analysis 2.91 [1.93; 3.90]  Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.78$
12q13.13 (rs114544309)	
Population b SE 95%-CI HIS (11532) 7.86 1.54 7.86 [4.84; 10.87] 	Population b SE 95%-CI AFR (16488) 1.36 0.62 1.36 [0.15; 2.57] HIS (14580) 3.53 0.61 3.53 [2.33; 4.74] Meta analysis 2.45 [1.60; 3.30]  Heterogeneity: $I^2 = 84\%$, $\tau^2 = 1.9860$, $p = 0.01$
17p13.3 (rs140618249)	

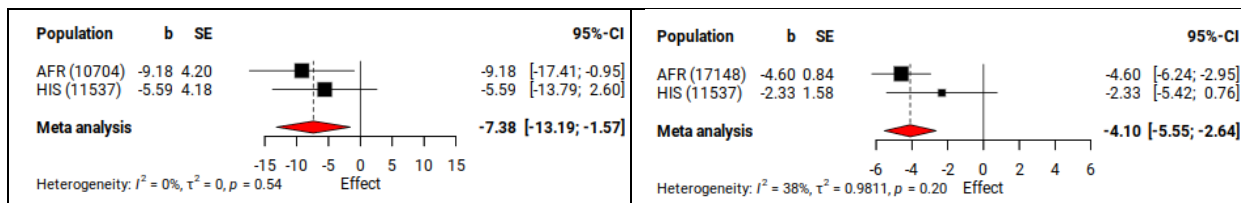


Figure S12. Comparison of SNP x DEPR effects at novel and known loci identified in qDEPR analyses between dDEPR and qDEPR models. For the cross-population meta-analyses, the labels on the left correspond to population names. For the population-specific analyses, the labels correspond to the individual studies contributing data for each population. On the right, the effect size (b), standard error (SE), and 95% confidence interval (95% CI) for each study or population are shown. Squares represent the b estimate, with horizontal lines indicating the 95% CI. Diamonds represent the meta-analyzed effect estimate, with the lateral points indicating the corresponding 95% CI. I^2 quantifies the proportion of variation due to heterogeneity (0-100%), and τ^2 represents the between study variance. The heterogeneity p-values (p) are shown. Solid vertical line denotes the null effect.

	DBP	SBP	PP
CPMA			
AFR			
ASN			
EUR			
HIS			

Figure S13. Number of SNPs in dDEPR (D) and qDEPR (Q) analyses across three BP traits in population-specific and cross-population meta-analyses (CPMA). For comparison between dDEPR and qDEPR analyses, each Venn diagram reports the total number of SNPs contributing to the respective analysis.

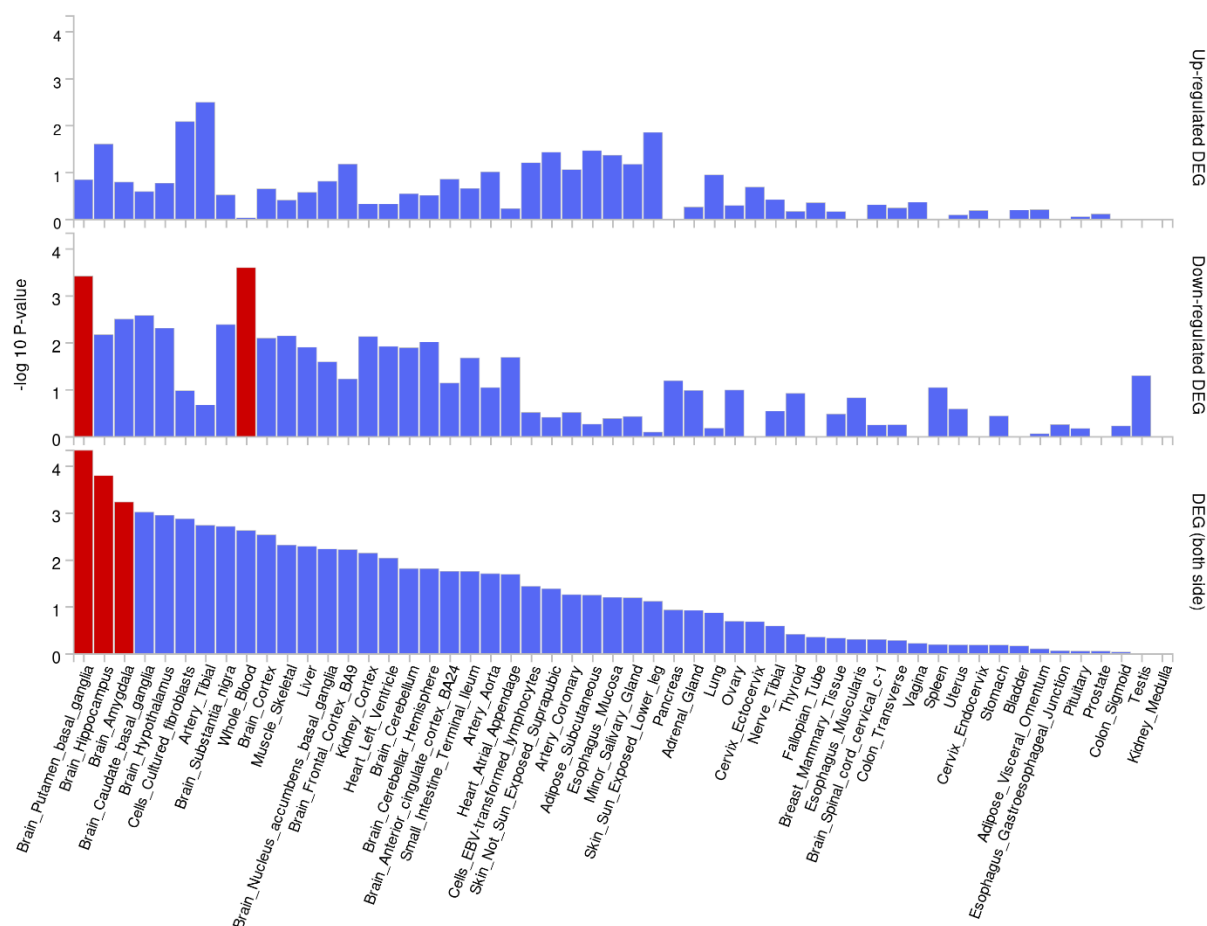


Figure S14. Enrichment of the prioritized genes mapped to novel and known BP loci in differentially expressed genes (DEG) sets from GTEx v8 54 tissue types. Significantly enriched DEG sets (Bonferroni-corrected $p < 0.05$) are highlighted in red.