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ARTICLE

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 the 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 power 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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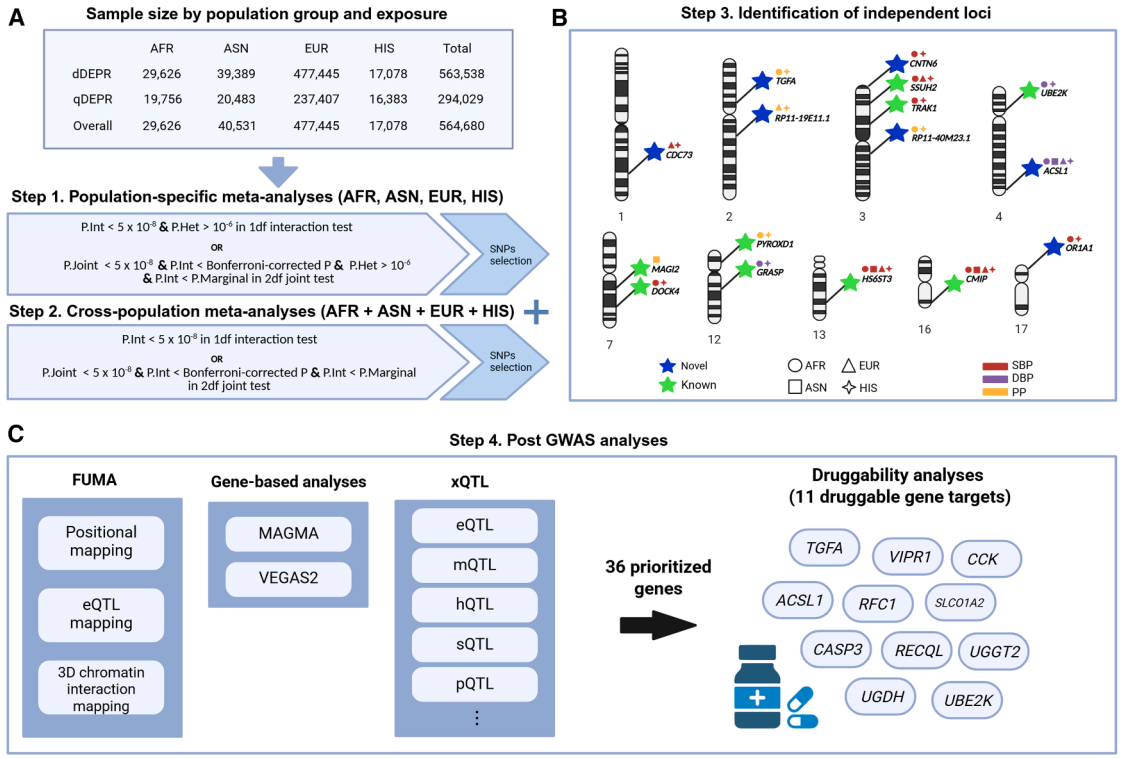

Figure 1. Study overview

(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) ≥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:

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

where DEPR was either dDEPR or qDEPR, and **C** was a vector of covariates, including age, age^2, 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 × covariate interaction terms with age, age^2, 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 × sex were excluded from the model. A 1-degree-of-freedom (1df) interaction test was performed to evaluate SNP × DEPR interaction effect alone under the null hypothesis that $\beta_{\mathrm{SNP}\times\mathrm{DEPR}} = 0$. A 2df joint test was used to simultaneously assess the SNP main effect and SNP × DEPR interaction effects, under the null hypothesis that $\beta_{\mathrm{SNP}} = \beta_{\mathrm{SNP}\times\mathrm{DEPR}} = 0$.[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:

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

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 × 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 × 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 GxE 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 ($p_{\mathrm{Int}} < 5 \times 10^{-8}$). In population-specific analyses, SNPs were also required to show no evidence of heterogeneity ($p_{\mathrm{Het}} > 10^{-6}$). (2) SNPs with significant 2df joint effects ($p_{\mathrm{Joint}} < 5 \times 10^{-8}$), p_{Int} < 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 $p_{\mathrm{Int}} < p_{\mathrm{Marginal}}$. False discovery rates (FDRs) were also calculated using EastyStrata2.

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 × 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 FUMA[33] 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 QTLbase[37] and Open Target Genetics[38] 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, NCIt, RxNorm, Wikidata, CancerCommons, CGI, ChEMBL, CIViC, ClearityFoundationBiomarkers, ClearityFoundationClinicalTrial, 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 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 ($p_{Int} < 5 \times 10^{-8}$) (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 ($p_{Joint} = 7.99 \times 10^{-9}$; $p_{Int} = 1.39 \times 10^{-7}$).

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 ($p_{Het} > 0.003$) (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 ($0.01 \leq MAF \leq 0.05$) and were rare in HIS (MAF < 0.01) (Table 1). Interestingly, rs115760284 (3p22.1) showed some heterogeneity between AFR and HIS ($I^2 > 80\%$, $p_{Het} < 0.01$), 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 ($p_{Het} > 0.003$). 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 ($p_{Int} < 5 \times 10^{-8}$) (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 ($p_{Int} < 5 \times 10^{-8}$) also showed evidence of an association with SBP through interaction with qDEPR using the 2df joint test ($p_{Joint} < 5 \times 10^{-8}$).

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 ($p_{Het} > 0.003$) 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 × 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	$p_{Sex.Het}$
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; $p_{Sex.Het}$, sex heterogeneity *p* value in two-sample *Z* tests.

[a]rs1664073690, rs10178576, and rs113521945: top SNPs at novel loci (at least 500 kbp away from any previously reported BP locus).

[b]rs1664073690: 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 CPMAs; heterogeneity *p* value across studies in ancestry-specific meta-analyses.

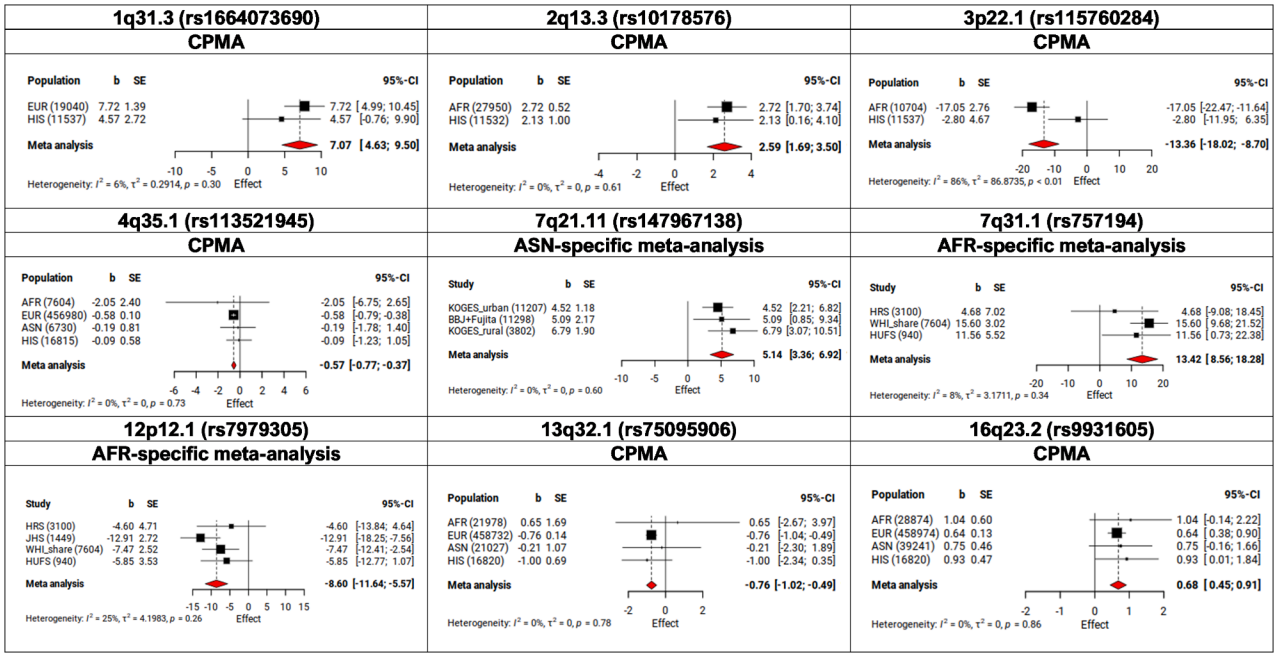

Figure 2. Forest plots of interaction effects at novel and known loci identified in the dDEPR analyses

Black squares and error bars represent the effect size and its 95% CI for each population in CPMAs 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 CPMAs, 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

Table 2. Novel and known loci associated with BP traits discovered through SNP × qDEPR 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	$p_{Sex.Het}$
2q14.2	2:118537183	A/G	rs77572777[a]	HIS-PP	0.99	0/0.02/0/0.01	*RP11-19E11.1*	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	*CNTN6*	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	0.23/0.02/0/0.06	*SSUH2*	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	*RP11-40M23.1*	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	*UBE2K*	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	*GRASP*	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	*OR1A1*	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; $p_{Sex.Het}$, sex heterogeneity p value in two-sample Z tests.

[a]rs77572777, rs148780833, rs748650739, rs140618249: top SNPs at novel loci.

[b]rs148780833, 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 CPMAs; 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

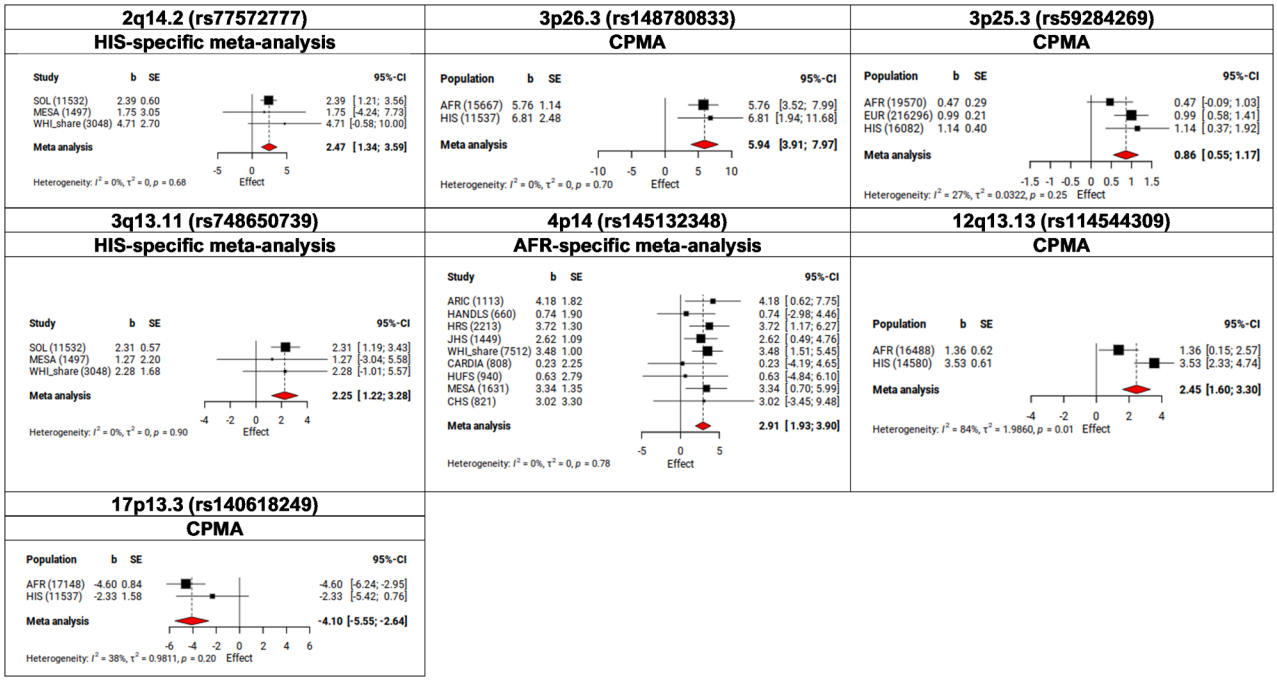

Figure 3. Forest plots of interaction effects at novel and known loci identified in the qDEPR analyses

Black squares and error bars represent the effect size and its 95% CI for each population in CPMAs 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 × 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-DPER 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-hypertensive 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] *SLCO1A2* (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 study[21] 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.l.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_SNPxEnvironment_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
OMIM, https://www.omim.org/

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