

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 Ansung 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.nhlbi.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.

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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.

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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.

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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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AGES (Age Gene/Environment Susceptibility Reykjavik Study): This study has been funded by NIH contract N01-AG012100, HSSN271201200022C, the NIA Intramural Research Program, an Intramural Research Program Award (ZIAEY000401) from the National Eye Institute, an award from the National Institute on Deafness and Other Communication Disorders (NIDCD) Division of Scientific Programs (IAA Y2-DC_1004-02), Hjartavernd (the Icelandic Heart Association), and the Althingi (the Icelandic Parliament). The study is approved by the Icelandic National Bioethics Committee, VSN: 00-063. The researchers are indebted to the participants for their willingness to participate in the study.

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FHS (Framingham Heart Study): This research was conducted in part using data and resources from the Framingham Heart Study of the National Heart Lung and Blood Institute of the National Institutes of Health and Boston University School of Medicine. The analyses reflect intellectual input and resource development from the Framingham Heart Study investigators participating in the SNP Health Association Resource (SHARe) project. This work was partially supported by the National Heart, Lung and Blood Institute's Framingham Heart Study (Contract Nos. N01-HC-25195 and HSN268201500001I) and its contract with Affymetrix, Inc for genotyping services (Contract No. N02-HL-6-4278). This research was partially supported by grant R01DK122503 from the National Institute of Diabetes and Digestive and Kidney Diseases (MPIs: Kari North, Anne Justice, and Ching-Ti Liu).

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

SP2 (Singapore Prospective Study Program): The SP2 study is supported by individual research and clinical scientist award schemes from the National Medical Research Council (NMRC) and the Biomedical Research Council (BMRC) of Singapore, the Singapore Ministry of Health, National University of Singapore and National University Health System, Singapore. The Genome Institute of Singapore, Agency for Science, Technology and Research, Singapore provided services for genotyping.

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2020 – Present; Joel Finkelstein, PI 1999 – 2020; Robert Neer, PI 1994 – 1999; Rush University, Rush University Medical Center, Chicago, IL – Imke Janssen, PI 2020 – Present; Howard Kravitz, PI 2009 – 2020; Lynda Powell, PI 1994 – 2009; University of California, Davis/Kaiser – Elaine Waetjen and Monique Hedderson, PIs 2020 – Present; Ellen Gold, PI 1994 - 2020; University of California, Los Angeles – Arun Karlamangla, PI 2020 – Present; Gail Greendale, PI 1994 - 2020; Albert Einstein College of Medicine, Bronx, NY – Carol Derby, PI 2011 – present, Rachel Wildman, PI 2010 – 2011; Nanette Santoro, PI 2004 – 2010; University of Medicine and Dentistry – New Jersey Medical School, Newark – Gerson Weiss, PI 1994 – 2004; and the University of Pittsburgh, Pittsburgh, PA – Rebecca Thurston, PI 2020 – Present; Karen Matthews, PI 1994 - 2020.

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and Turku University Hospital Medical Funds (grant X51001); Juho Vainio Foundation; Paavo Nurmi Foundation; Finnish Foundation for Cardiovascular Research ; Finnish Cultural Foundation; Tampere Tuberculosis Foundation; Emil Aaltonen Foundation; Yrjö Jahnesson Foundation; Signe and Ane Gyllenberg Foundation; and Diabetes Research Foundation of Finnish Diabetes Association.

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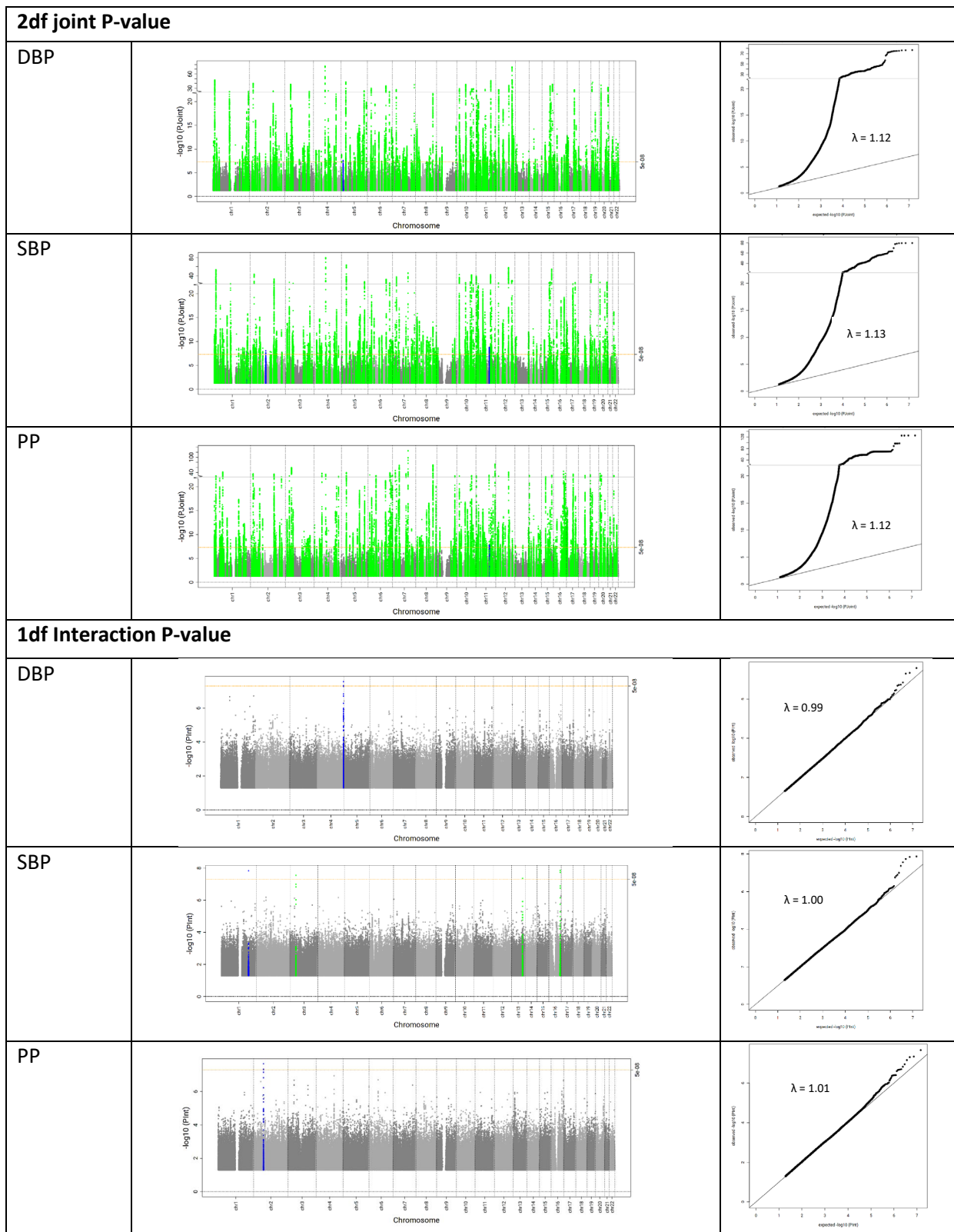


Figure S1. Manhattan and Quantile-quantile (QQ) plots for the 2df joint and 1df interaction P-values in cross-population dDEPR analyses (Green: known, Blue: novel). In the Manhattan plots, the $-\log_{10}(\text{P-value})$ is shown on the y-axis and chromosomal position on the x-axis. The genome-wide 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.

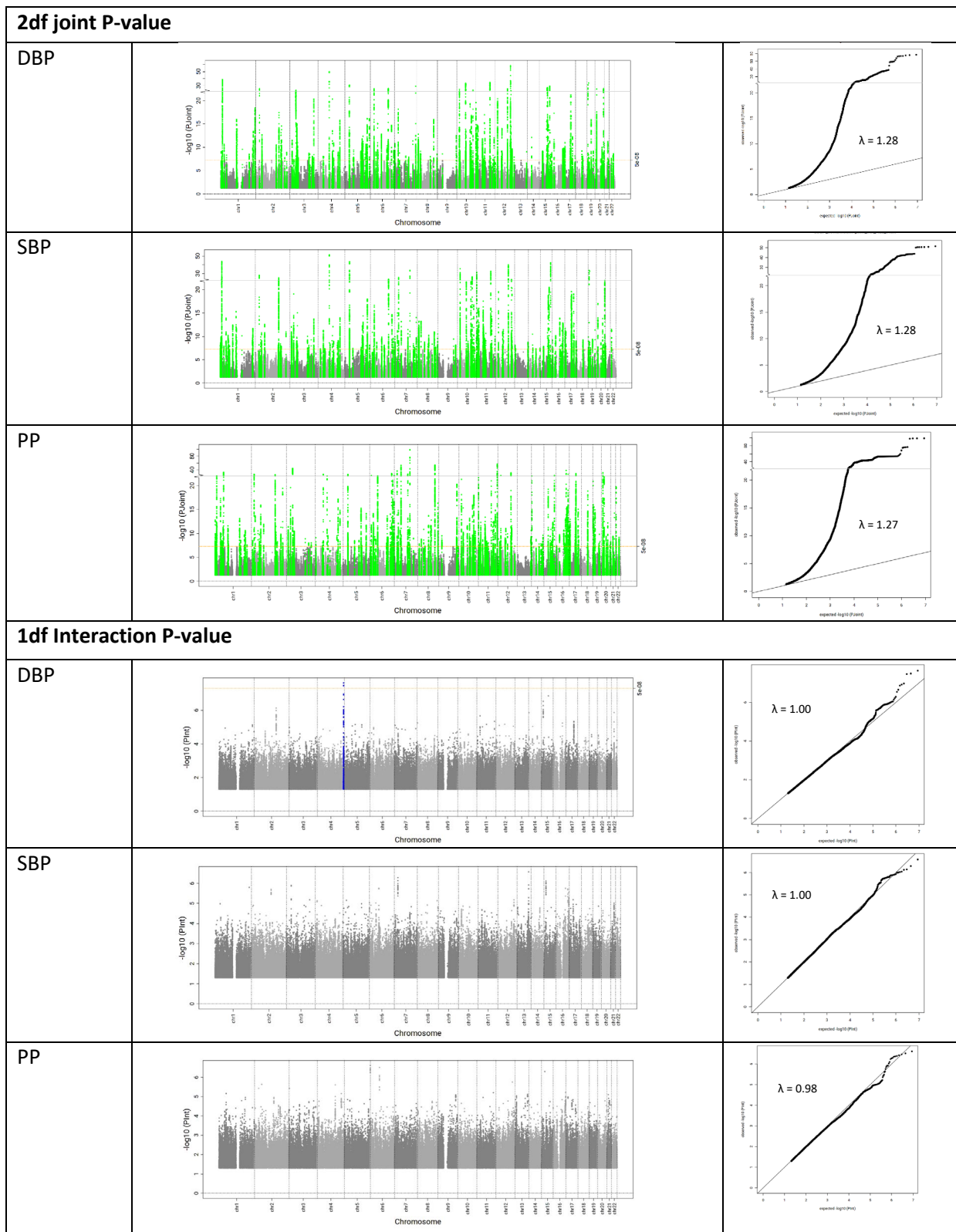


Figure S2. Manhattan and QQ plots for the 2df joint and 1df interaction P-values in EUR-specific dDEPR analyses (Green: known, Blue: novel). In the Manhattan plots, the $-\log_{10}(\text{P-value})$ is shown on the y-axis and chromosomal position on the x-axis. The genome-wide significance threshold ($P < 5 \times 10^{-8}$) 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.

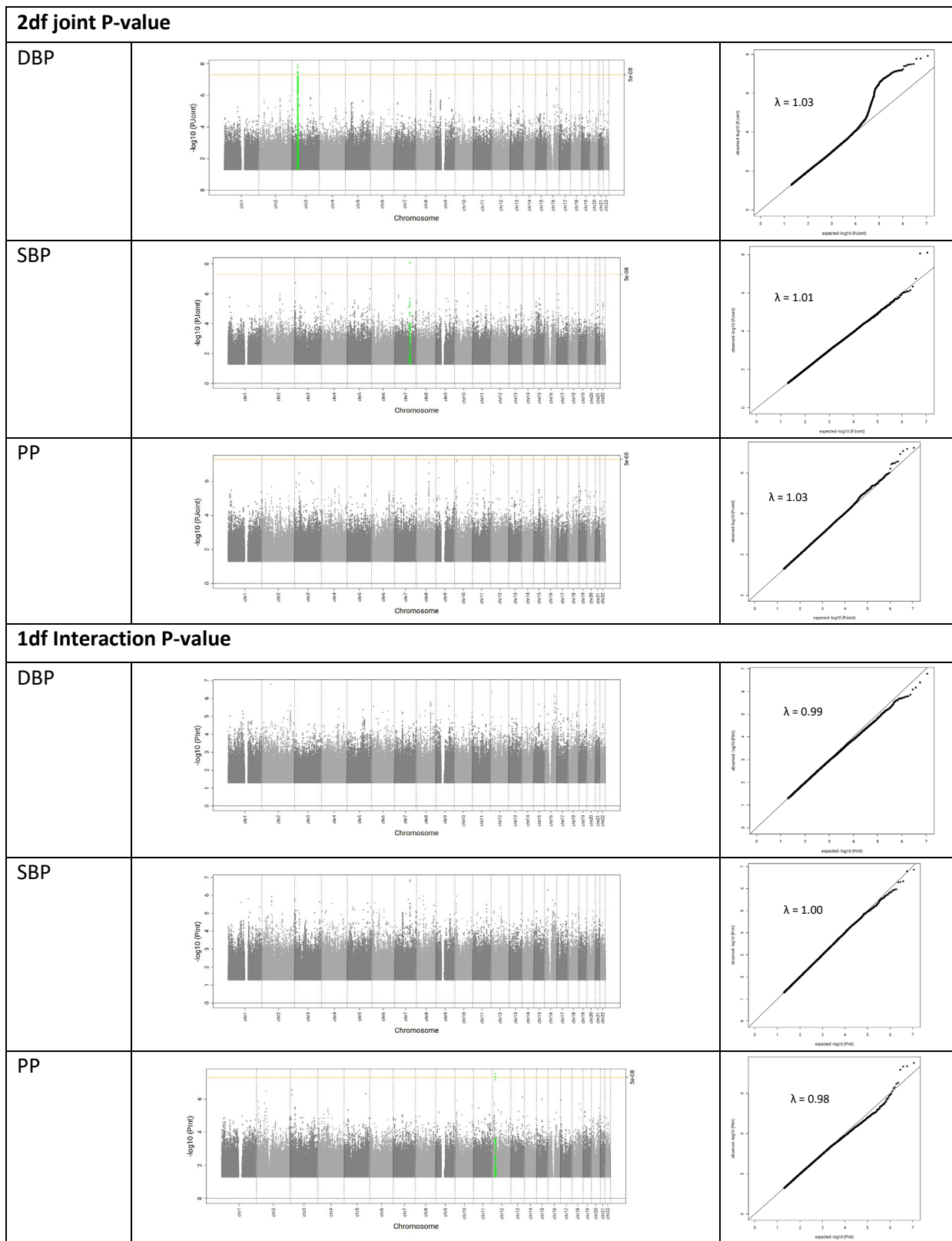


Figure S3. Manhattan and QQ plots for the 2df joint and 1df interaction P-values in AFR-specific dDEPR analyses (Green: known, Blue: novel). In the Manhattan plots, the $-\log_{10}(\text{P-value})$ is shown on the y-axis and chromosomal position on the x-axis. The genome-wide significance threshold ($P < 5 \times 10^{-8}$) 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.

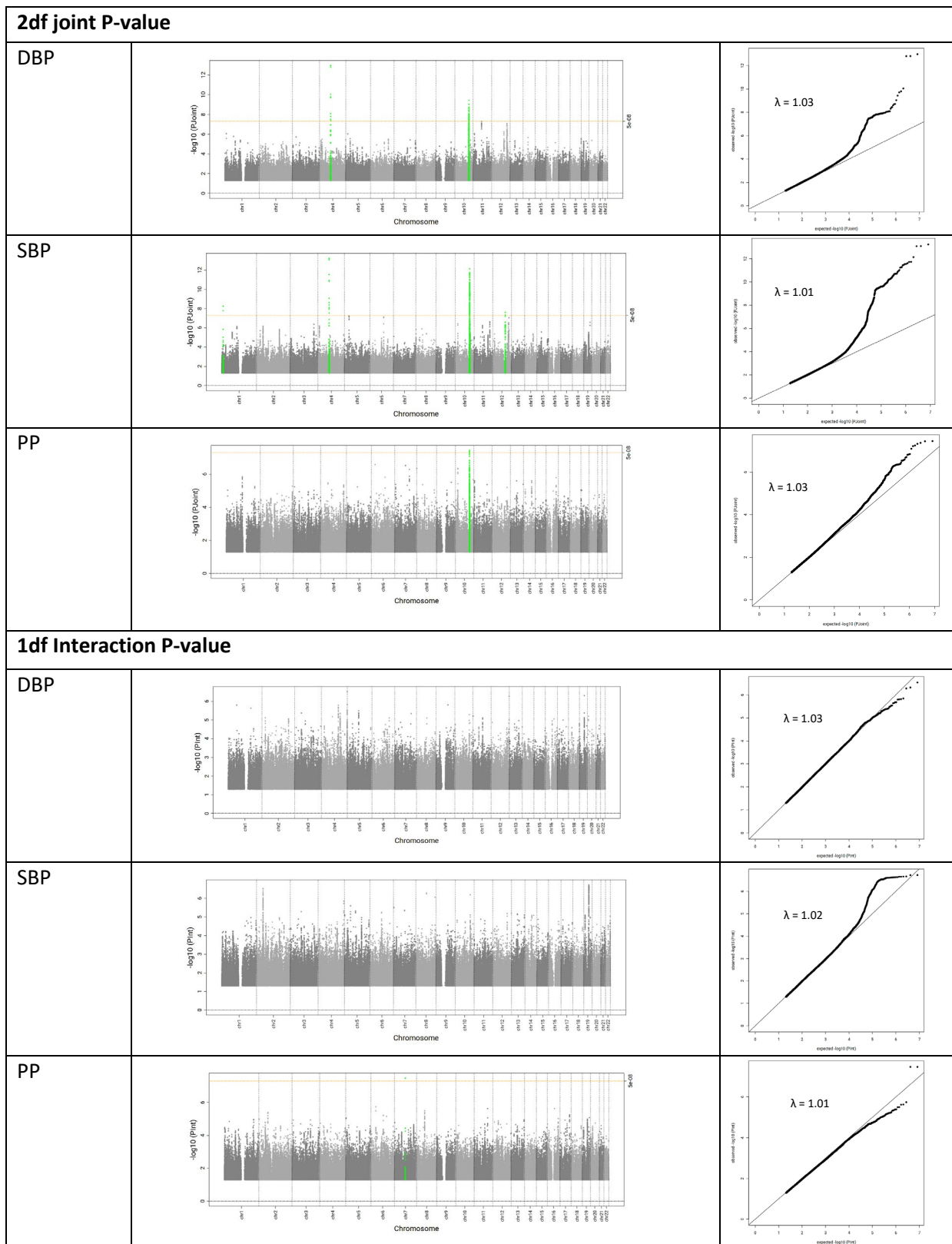


Figure S4. Manhattan and QQ plots for the 2df joint and 1df interaction P-values in ASN-specific dDEPR analyses (Green: known, Blue: novel). In the Manhattan plots, the $-\log_{10}(\text{P-value})$ is shown on the y-axis and chromosomal position on the x-axis. The genome-wide significance threshold ($P < 5 \times 10^{-8}$) 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.

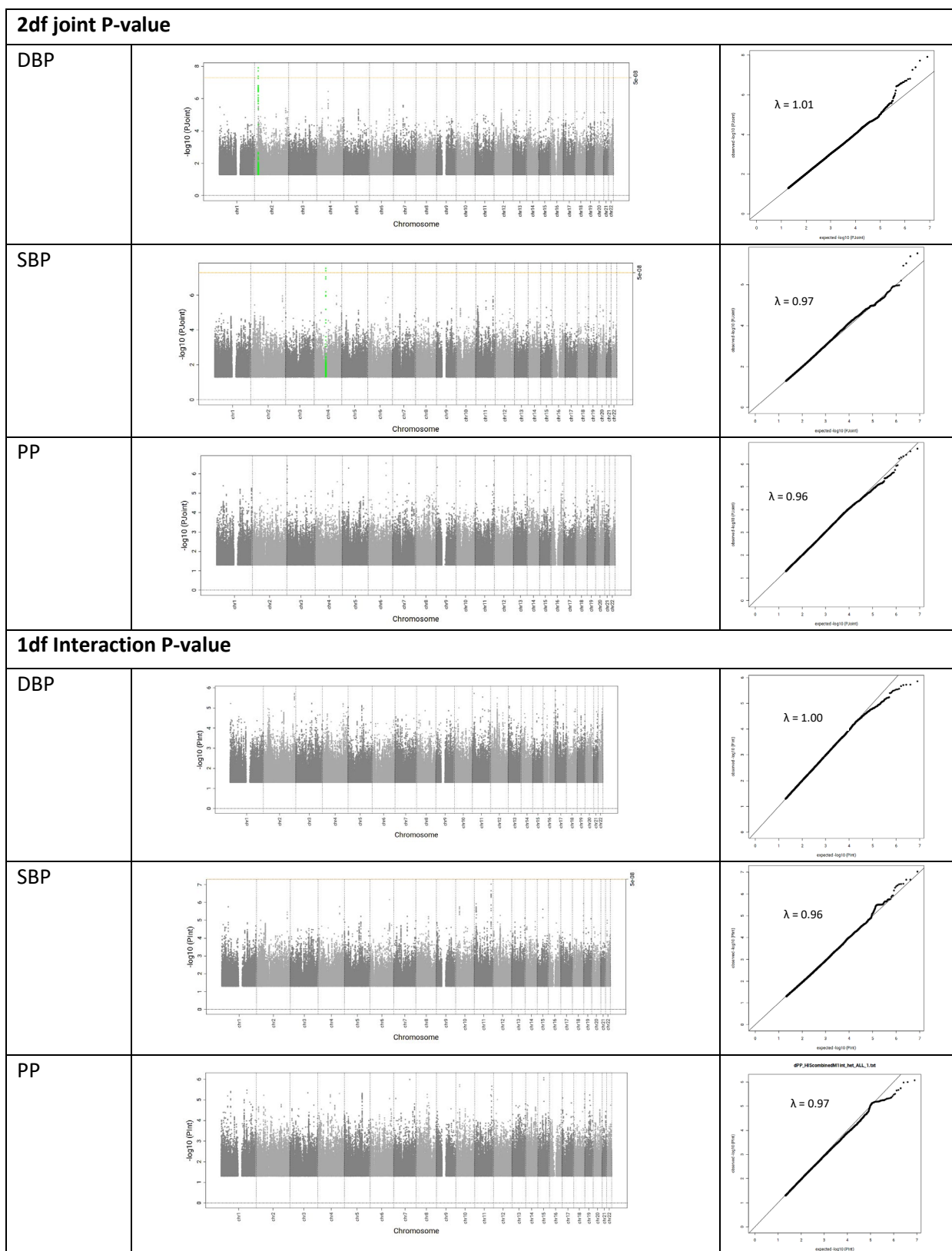


Figure S5. Manhattan and QQ plots for the 2df joint and 1df interaction P-values in HIS-specific dDEPR analyses (Green: known, Blue: novel). In the Manhattan plots, the $-\log_{10}(\text{P-value})$ is shown on the y-axis and chromosomal position on the x-axis. The genome-wide significance threshold ($P < 5 \times 10^{-8}$) 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.

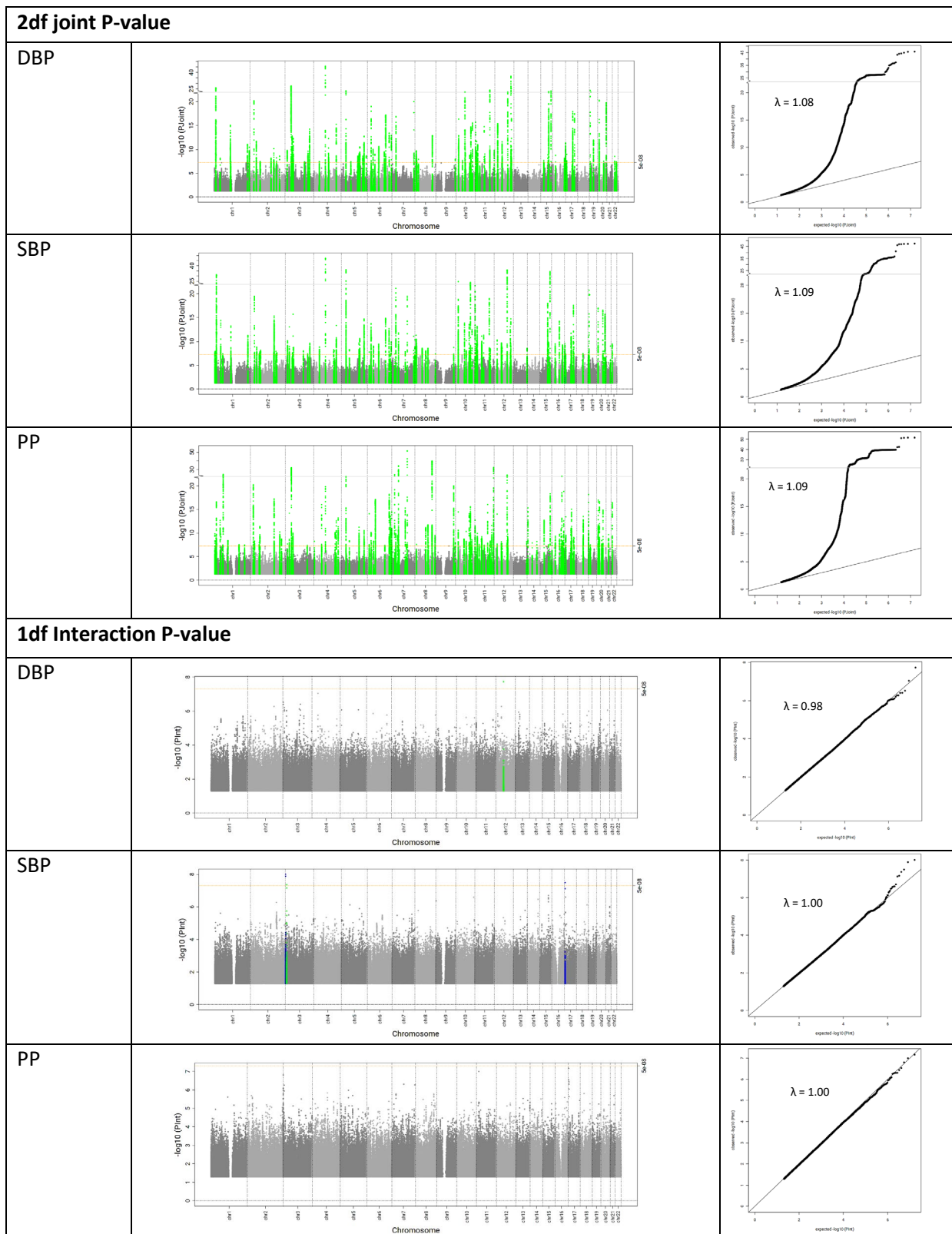


Figure S6. Manhattan and QQ plots for the 2df joint and 1df interaction P-values in cross-population qDEPR analyses (Green: known, Blue: novel). In the Manhattan plots, the $-\log_{10}(\text{P-value})$ is shown on the y-axis and chromosomal position on the x-axis. The genome-wide significance threshold ($P < 5 \times 10^{-8}$) 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.

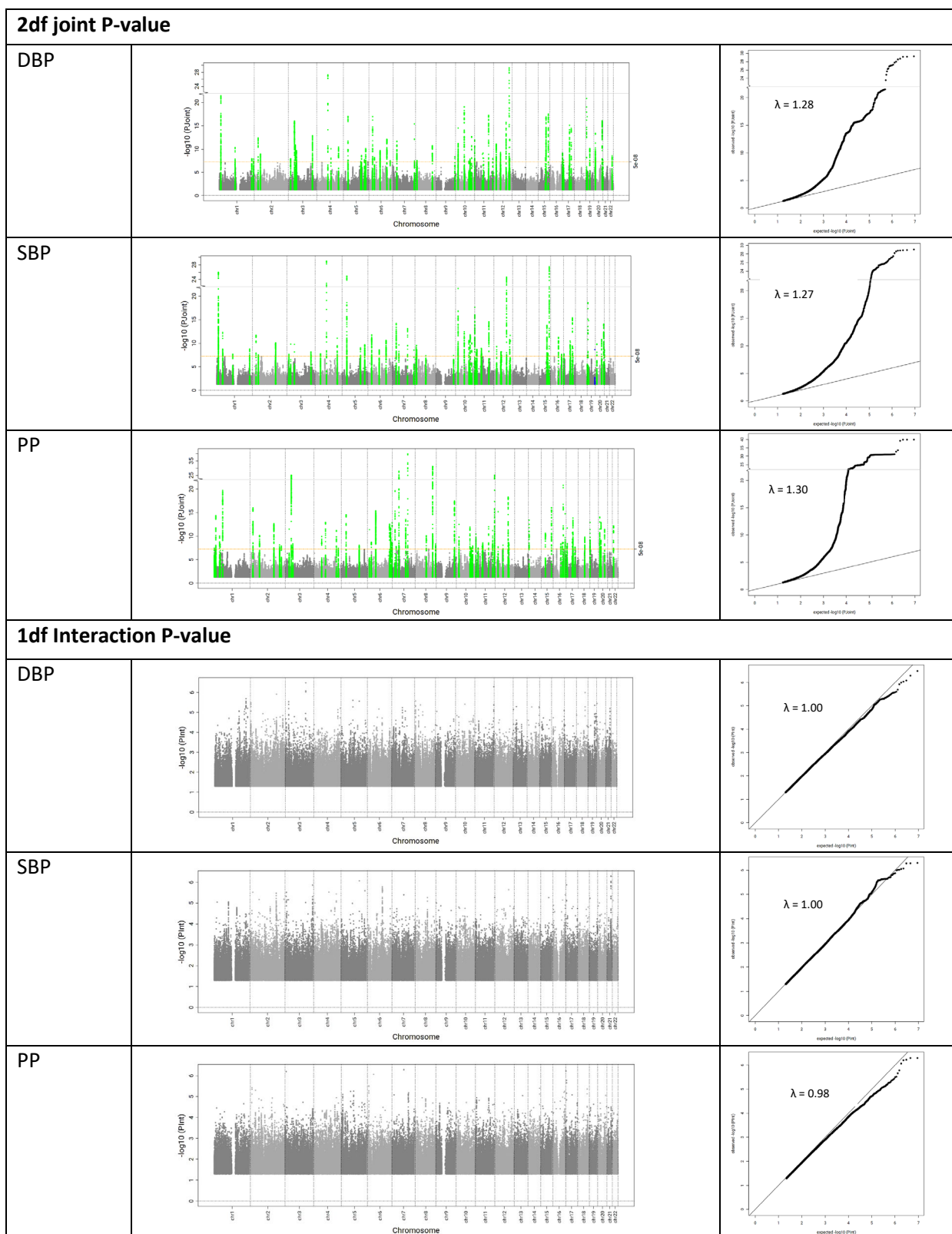


Figure S7. Manhattan and QQ plots for the 2df joint and 1df interaction P-values in EUR-specific qDEPR analyses (Green: known, Blue: novel). In the Manhattan plots, the $-\log_{10}(\text{P-value})$ is shown on the y-axis and chromosomal position on the x-axis. The genome-wide significance threshold ($P < 5 \times 10^{-8}$) 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.

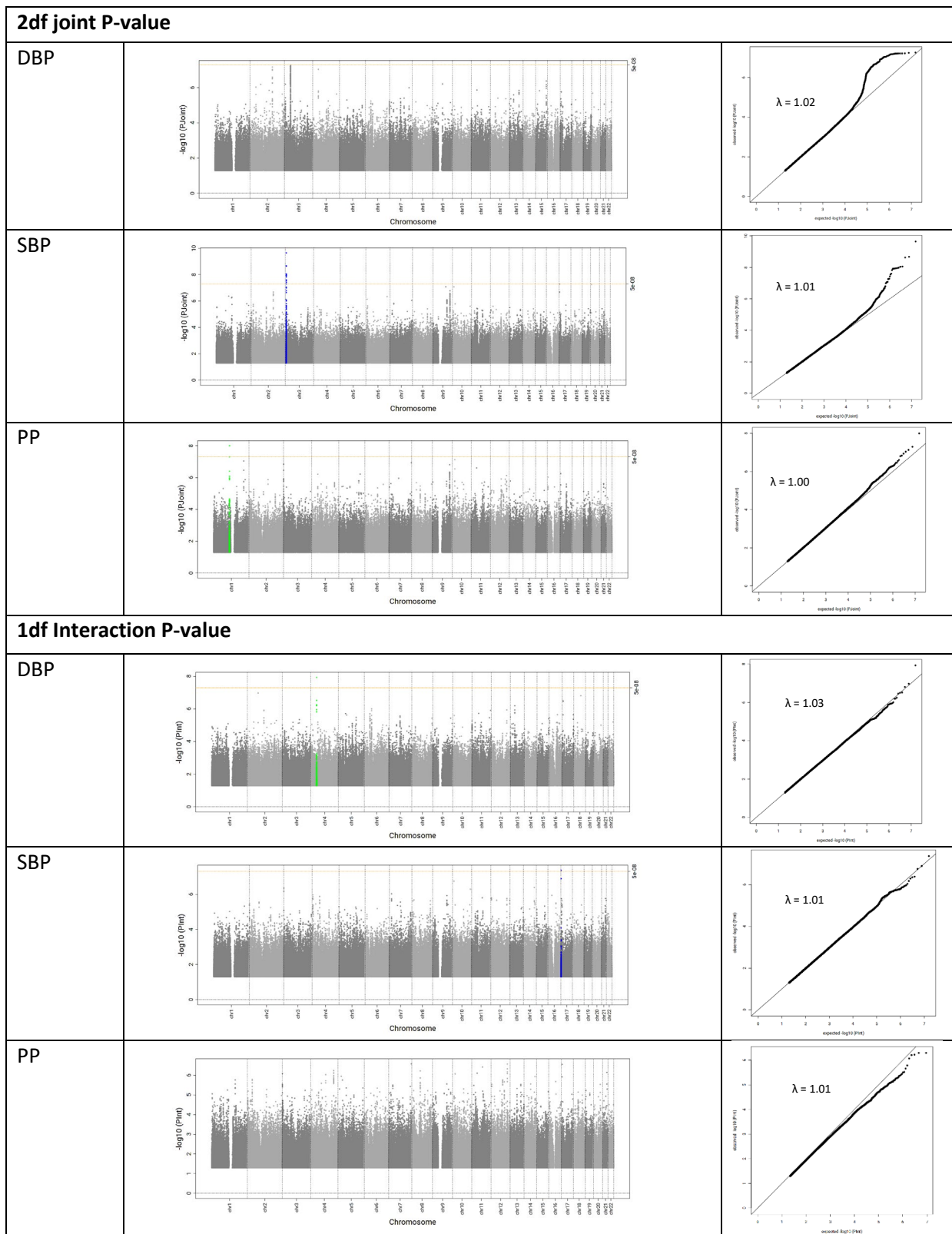


Figure S8. Manhattan and QQ plots for the 2df joint and 1df interaction P-values in AFR-specific qDEPR analyses (Green: known, Blue: novel). In the Manhattan plots, the $-\log_{10}(\text{P-value})$ is shown on the y-axis and chromosomal position on the x-axis. The genome-wide significance threshold ($P < 5 \times 10^{-8}$) 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.

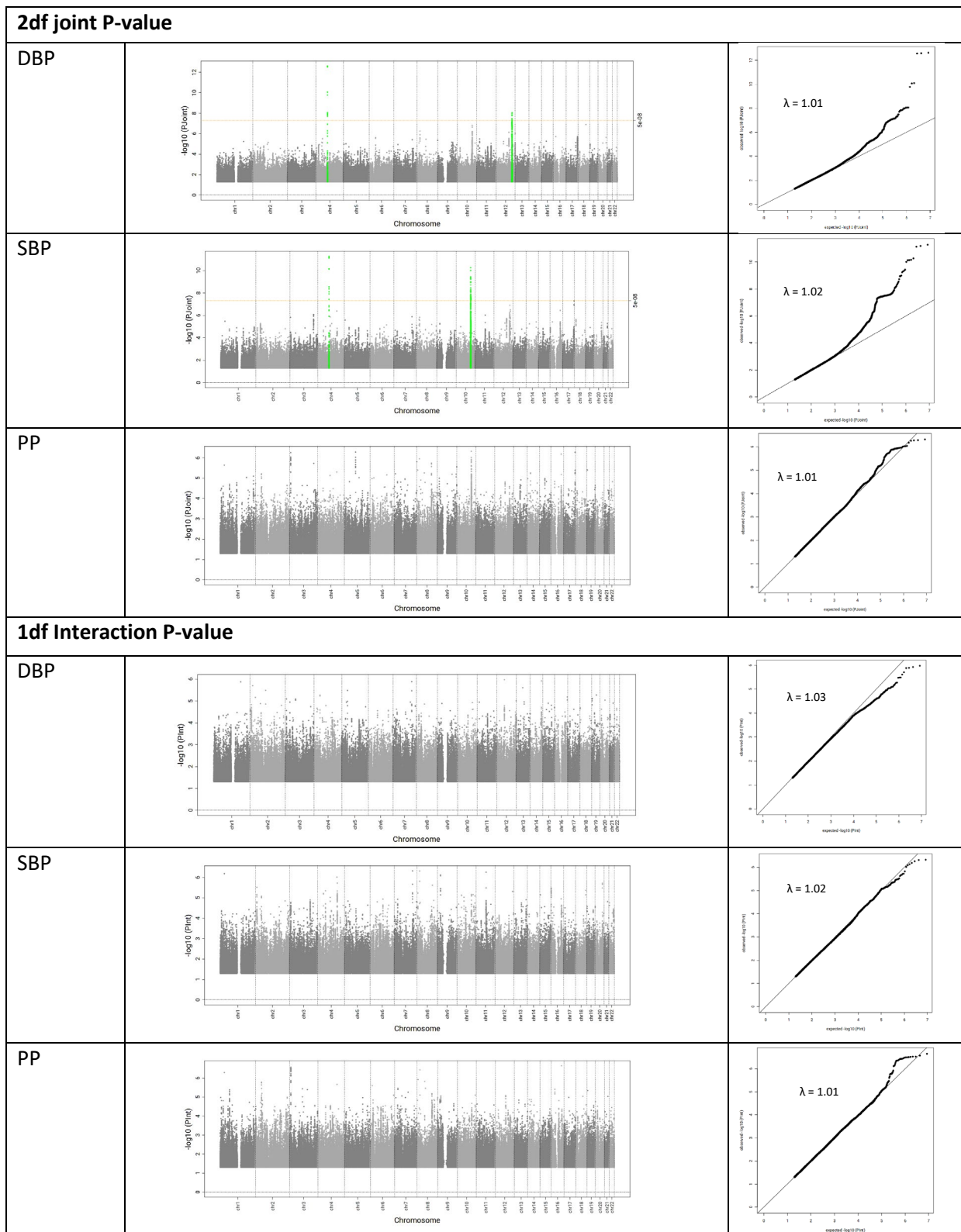


Figure S9. Manhattan and QQ plots for the 2df joint and 1df interaction P-values in ASN-specific qDEPR analyses (Green: known, Blue: novel). In the Manhattan plots, the $-\log_{10}(\text{P-value})$ is shown on the y-axis and chromosomal position on the x-axis. The genome-wide significance threshold ($P < 5 \times 10^{-8}$) 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.

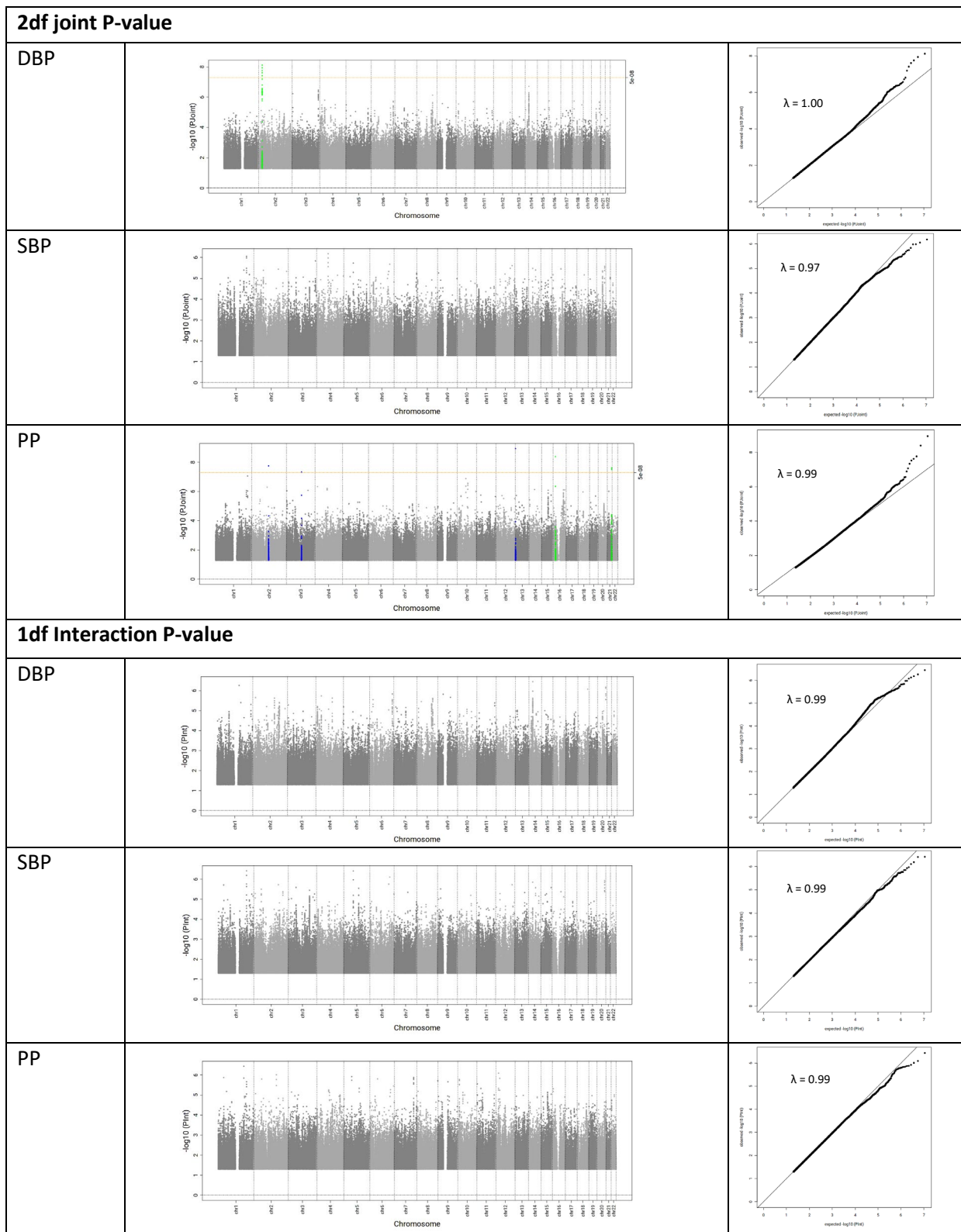


Figure S10. Manhattan and QQ plots for the 2df joint and 1df interaction P-values in HIS-specific qDEPR analyses (Green: known, Blue: novel). In the Manhattan plots, the $-\log_{10}(\text{P-value})$ is shown on the y-axis and chromosomal position on the x-axis. The genome-wide significance threshold ($P < 5 \times 10^{-8}$) 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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<table><tr><th>Population</th><th>b</th><th>SE</th><th>95%-CI</th></tr><tr><td>AFR (27950)</td><td>2.72</td><td>0.52</td><td>2.72 [1.70; 3.74]</td></tr><tr><td>HIS (11532)</td><td>2.13</td><td>1.00</td><td>2.13 [0.16; 4.10]</td></tr><tr><td>Meta analysis</td><td></td><td></td><td>2.59 [1.69; 3.50]</td></tr></table> Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.61$	Population	b	SE	95%-CI	AFR (27950)	2.72	0.52	2.72 [1.70; 3.74]	HIS (11532)	2.13	1.00	2.13 [0.16; 4.10]	Meta analysis			2.59 [1.69; 3.50]	<table><tr><th>Population</th><th>b</th><th>SE</th><th>95%-CI</th></tr><tr><td>AFR (19569)</td><td>0.83</td><td>0.24</td><td>0.83 [0.37; 1.30]</td></tr><tr><td>HIS (16077)</td><td>0.56</td><td>0.45</td><td>0.56 [-0.33; 1.45]</td></tr><tr><td>Meta analysis</td><td></td><td></td><td>0.78 [0.36; 1.19]</td></tr></table> Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.60$	Population	b	SE	95%-CI	AFR (19569)	0.83	0.24	0.83 [0.37; 1.30]	HIS (16077)	0.56	0.45	0.56 [-0.33; 1.45]	Meta analysis			0.78 [0.36; 1.19]																																								
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<table><tr><th>Population</th><th>b</th><th>SE</th><th>95%-CI</th></tr><tr><td>AFR (10704)</td><td>-17.05</td><td>2.76</td><td>-17.05 [-22.47; -11.64]</td></tr><tr><td>HIS (11537)</td><td>-2.80</td><td>4.67</td><td>-2.80 [-11.95; 6.35]</td></tr><tr><td>Meta analysis</td><td></td><td></td><td>-13.36 [-18.02; -8.70]</td></tr></table> Heterogeneity: $I^2 = 86\%$, $\tau^2 = 86.8735$, $p < 0.01$	Population	b	SE	95%-CI	AFR (10704)	-17.05	2.76	-17.05 [-22.47; -11.64]	HIS (11537)	-2.80	4.67	-2.80 [-11.95; 6.35]	Meta analysis			-13.36 [-18.02; -8.70]	<table><tr><th>Population</th><th>b</th><th>SE</th><th>95%-CI</th></tr><tr><td>AFR (15227)</td><td>-1.97</td><td>0.98</td><td>-1.97 [-3.90; 0.05]</td></tr><tr><td>HIS (11537)</td><td>-1.86</td><td>1.95</td><td>-1.86 [-5.68; 1.96]</td></tr><tr><td>Meta analysis</td><td></td><td></td><td>-1.95 [-3.67; -0.23]</td></tr></table> Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.96$	Population	b	SE	95%-CI	AFR (15227)	-1.97	0.98	-1.97 [-3.90; 0.05]	HIS (11537)	-1.86	1.95	-1.86 [-5.68; 1.96]	Meta analysis			-1.95 [-3.67; -0.23]																																								
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<table><tr><th>Population</th><th>b</th><th>SE</th><th>95%-CI</th></tr><tr><td>AFR (7604)</td><td>-2.05</td><td>2.40</td><td>-2.05 [-6.75; 2.65]</td></tr><tr><td>EUR (456980)</td><td>-0.58</td><td>0.10</td><td>-0.58 [-0.79; -0.38]</td></tr><tr><td>ASN (6730)</td><td>-0.19</td><td>0.81</td><td>-0.19 [-1.78; 1.40]</td></tr><tr><td>HIS (16815)</td><td>-0.09</td><td>0.58</td><td>-0.09 [-1.23; 1.05]</td></tr><tr><td>Meta analysis</td><td></td><td></td><td>-0.57 [-0.77; -0.37]</td></tr></table> Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.73$	Population	b	SE	95%-CI	AFR (7604)	-2.05	2.40	-2.05 [-6.75; 2.65]	EUR (456980)	-0.58	0.10	-0.58 [-0.79; -0.38]	ASN (6730)	-0.19	0.81	-0.19 [-1.78; 1.40]	HIS (16815)	-0.09	0.58	-0.09 [-1.23; 1.05]	Meta analysis			-0.57 [-0.77; -0.37]	<table><tr><th>Population</th><th>b</th><th>SE</th><th>95%-CI</th></tr><tr><td>AFR (16207)</td><td>-0.78</td><td>0.52</td><td>-0.78 [-1.81; 0.24]</td></tr><tr><td>EUR (227871)</td><td>-0.05</td><td>0.05</td><td>-0.05 [-0.15; 0.05]</td></tr><tr><td>ASN (1061)</td><td>0.28</td><td>0.82</td><td>0.28 [-1.33; 1.89]</td></tr><tr><td>HIS (16320)</td><td>-0.16</td><td>0.27</td><td>-0.16 [-0.69; 0.38]</td></tr><tr><td>Meta analysis</td><td></td><td></td><td>-0.06 [-0.15; 0.04]</td></tr></table> Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.52$	Population	b	SE	95%-CI	AFR (16207)	-0.78	0.52	-0.78 [-1.81; 0.24]	EUR (227871)	-0.05	0.05	-0.05 [-0.15; 0.05]	ASN (1061)	0.28	0.82	0.28 [-1.33; 1.89]	HIS (16320)	-0.16	0.27	-0.16 [-0.69; 0.38]	Meta analysis			-0.06 [-0.15; 0.04]																								
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7q21.11 (rs147967138)																																																																									
<table><tr><th>Study</th><th>b</th><th>SE</th><th>95%-CI</th></tr><tr><td>KOGES_urban (11207)</td><td>4.52</td><td>1.18</td><td>4.52 [2.21; 6.82]</td></tr><tr><td>BBJ+Fujita (11298)</td><td>5.09</td><td>2.17</td><td>5.09 [0.85; 9.34]</td></tr><tr><td>KOGES_rural (3802)</td><td>6.79</td><td>1.90</td><td>6.79 [3.07; 10.51]</td></tr><tr><td>Meta analysis</td><td></td><td></td><td>5.14 [3.36; 6.92]</td></tr></table> Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.60$	Study	b	SE	95%-CI	KOGES_urban (11207)	4.52	1.18	4.52 [2.21; 6.82]	BBJ+Fujita (11298)	5.09	2.17	5.09 [0.85; 9.34]	KOGES_rural (3802)	6.79	1.90	6.79 [3.07; 10.51]	Meta analysis			5.14 [3.36; 6.92]	<table><tr><th>Study</th><th>b</th><th>SE</th><th>95%-CI</th></tr><tr><td>SP2_1M (915)</td><td>1.66</td><td>1.62</td><td>1.66 [-1.51; 4.83]</td></tr><tr><td>KOGES_rural (3802)</td><td>1.74</td><td>0.78</td><td>1.74 [0.22; 3.26]</td></tr><tr><td>SP2_610 (930)</td><td>2.08</td><td>1.95</td><td>2.08 [-1.75; 5.91]</td></tr><tr><td>KOGES_urban (11207)</td><td>0.85</td><td>0.40</td><td>0.85 [0.06; 1.63]</td></tr><tr><td>MESA (775)</td><td>-3.30</td><td>2.39</td><td>-3.30 [-7.99; 1.38]</td></tr><tr><td>BES_610 (585)</td><td>0.69</td><td>4.66</td><td>0.69 [-8.45; 9.83]</td></tr><tr><td>BES_omni (557)</td><td>-3.67</td><td>3.02</td><td>-3.67 [-9.58; 2.24]</td></tr><tr><td>Meta analysis</td><td></td><td></td><td>0.95 [0.29; 1.60]</td></tr></table> Heterogeneity: $I^2 = 16\%$, $\tau^2 = 0$, $p = 0.31$	Study	b	SE	95%-CI	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]																
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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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Meta analysis			2.12 [0.89; 3.35]																																																																						
12p12.1 (rs7979305)																																																																									

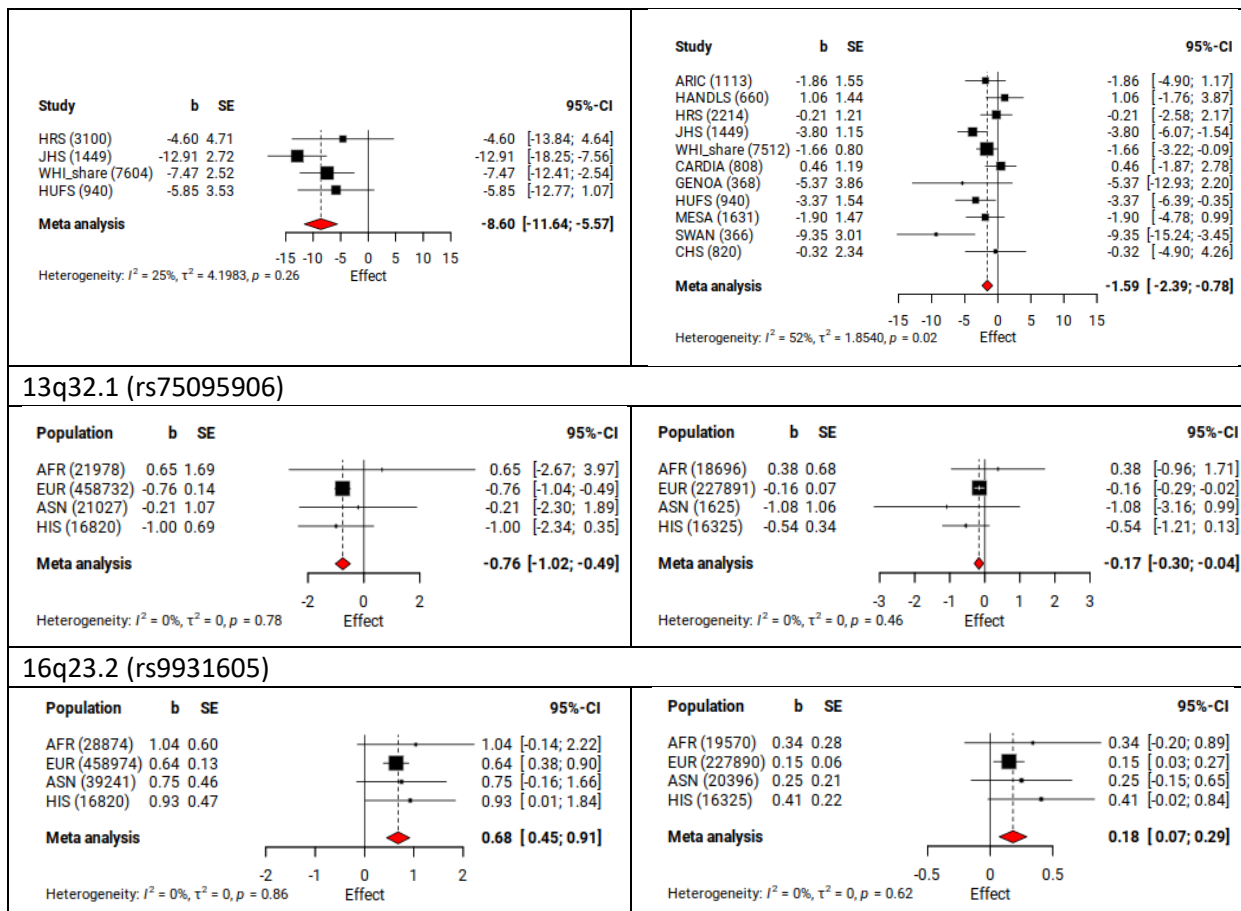
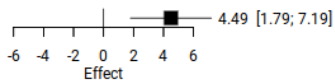
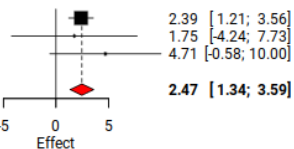
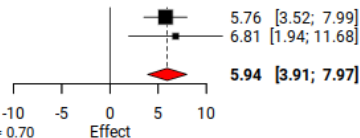
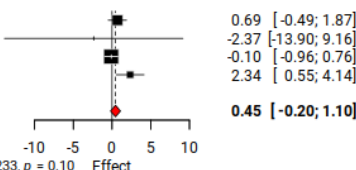
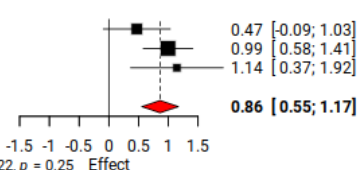
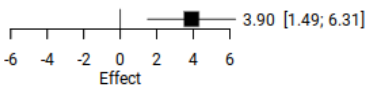
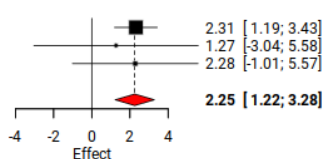
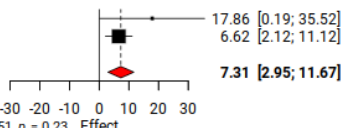
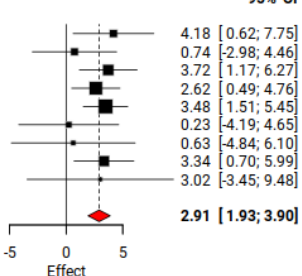
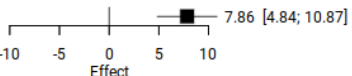
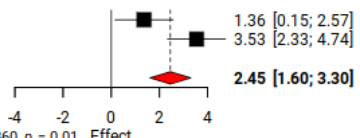


Figure S11. Comparison of SNP x DEPR effects at novel and known loci identified in dDEPR analyses between dDEPR and qDEPR models. For the cross-population meta-analyses, the labels on the left correspond to population names. For the population-specific analyses, the labels correspond to the individual 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)	

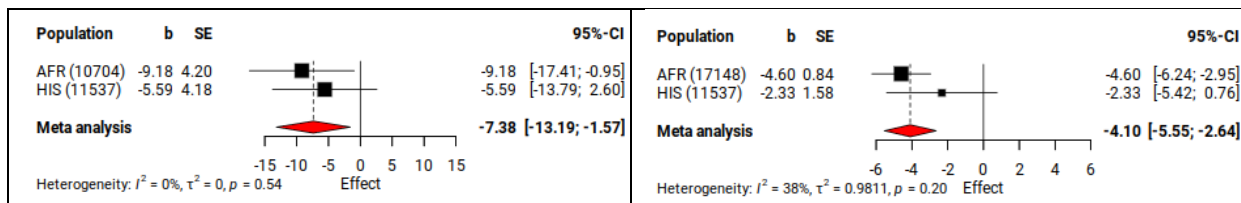


Figure S12. Comparison of SNP x DEPR effects at novel and known loci identified in qDEPR analyses between dDEPR and qDEPR models. For the cross-population meta-analyses, the labels on the left correspond to population names. For the population-specific analyses, the labels correspond to the individual 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.

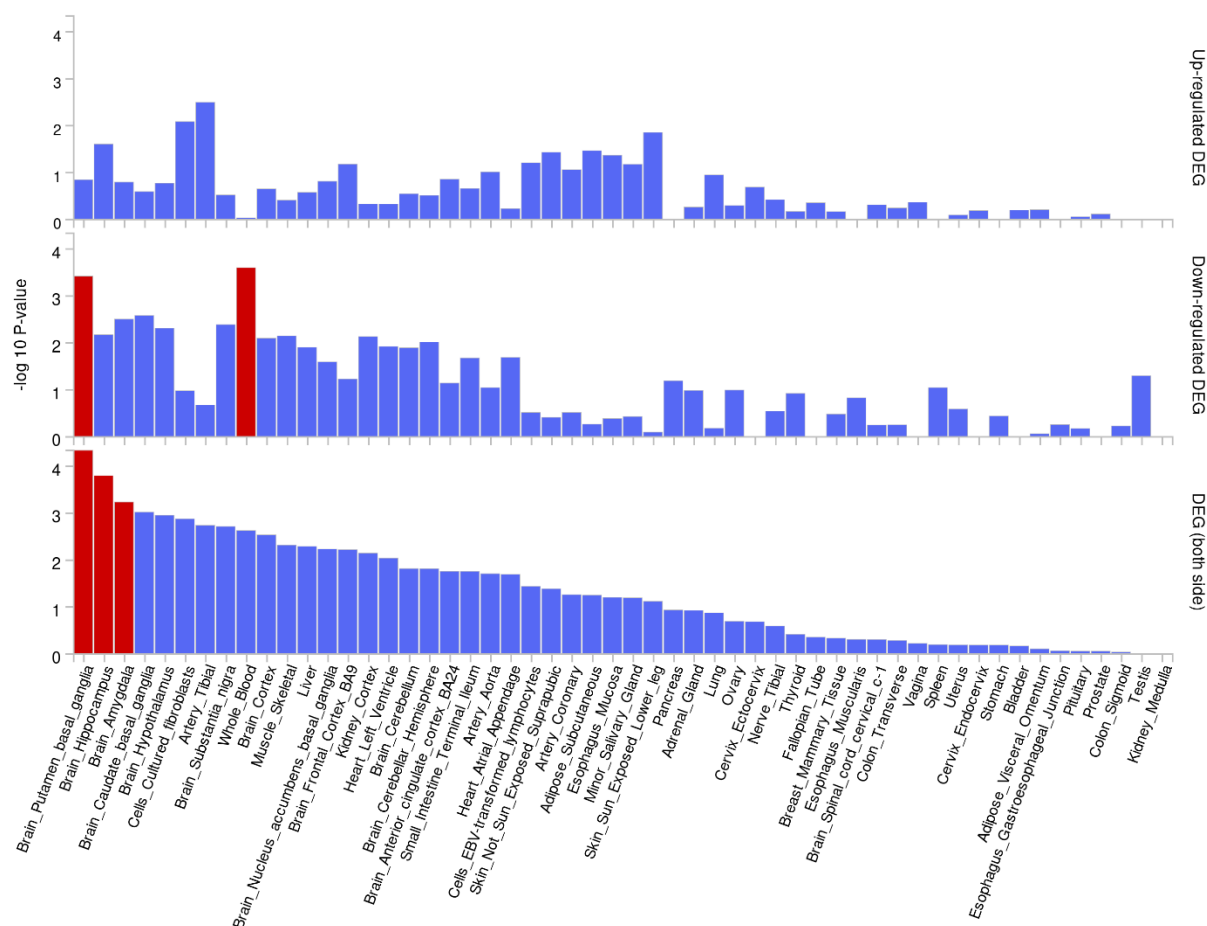


Figure S14. Enrichment of the prioritized genes mapped to novel and known BP loci in differentially expressed genes (DEG) sets from GTEx v8 54 tissue types. Significantly enriched DEG sets (Bonferroni-corrected $p < 0.05$) are highlighted in red.