SUPPLEMENTARY INFORMATION

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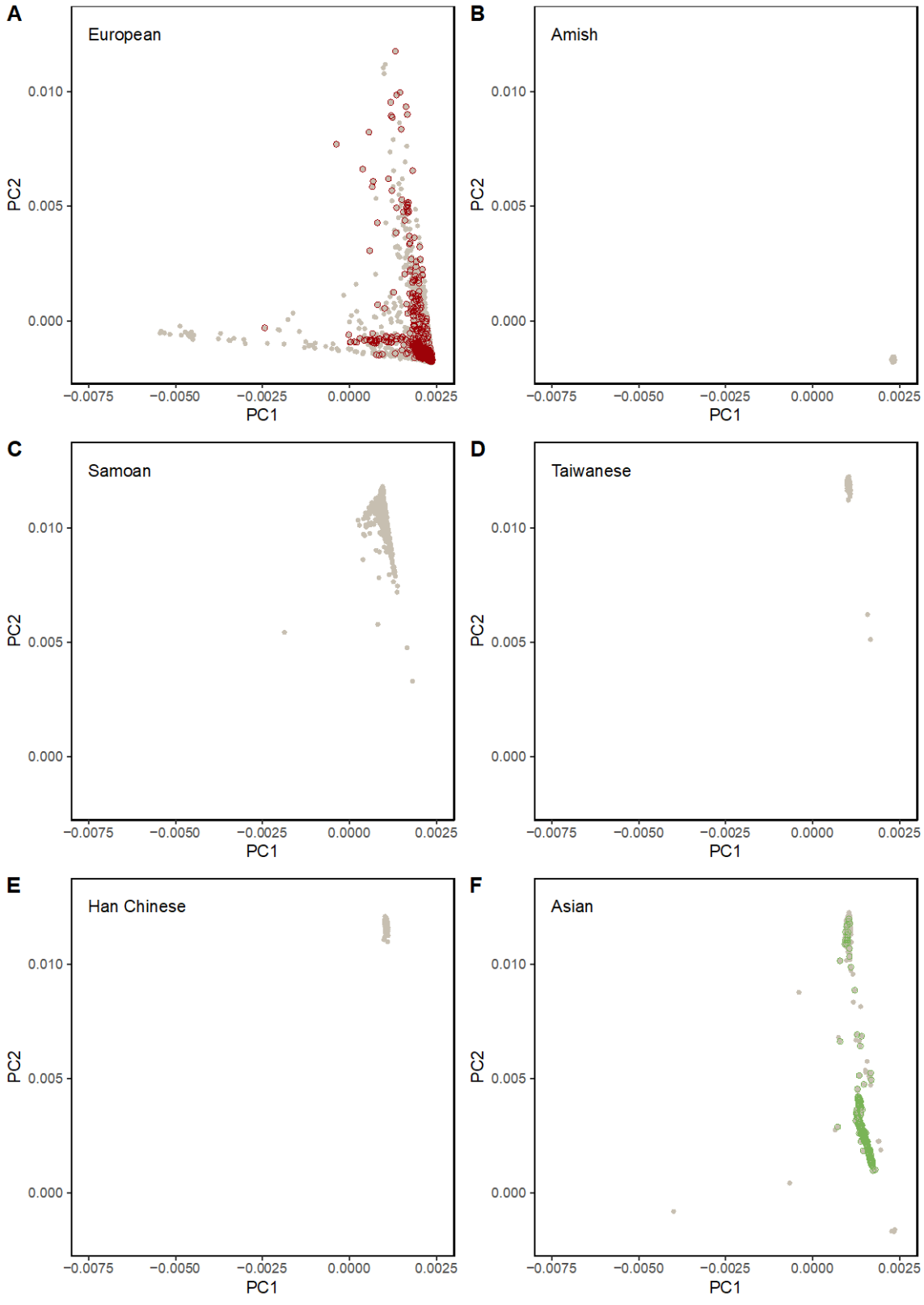
Supplementary Figure 1. Scatter plots of PC1 *vs.* PC2 by population group

Individuals with reported population memberships in each population group are denoted by filled circles in grey. Unfilled circles in colors represent inferred population memberships (N = 8,015), using Harmonized Ancestry and Race/Ethnicity (HARE) method (see methods for details). A) European, B) Amish, C) Samoan, D) Taiwanese, E) Han Chinese, F) Asian, G) Puerto Rican, H) Cuban, I) Central American, J) South American, K) Mexican, L) Costa Rican, M) Dominican, N) Barbadian, O) African/African American/Black.



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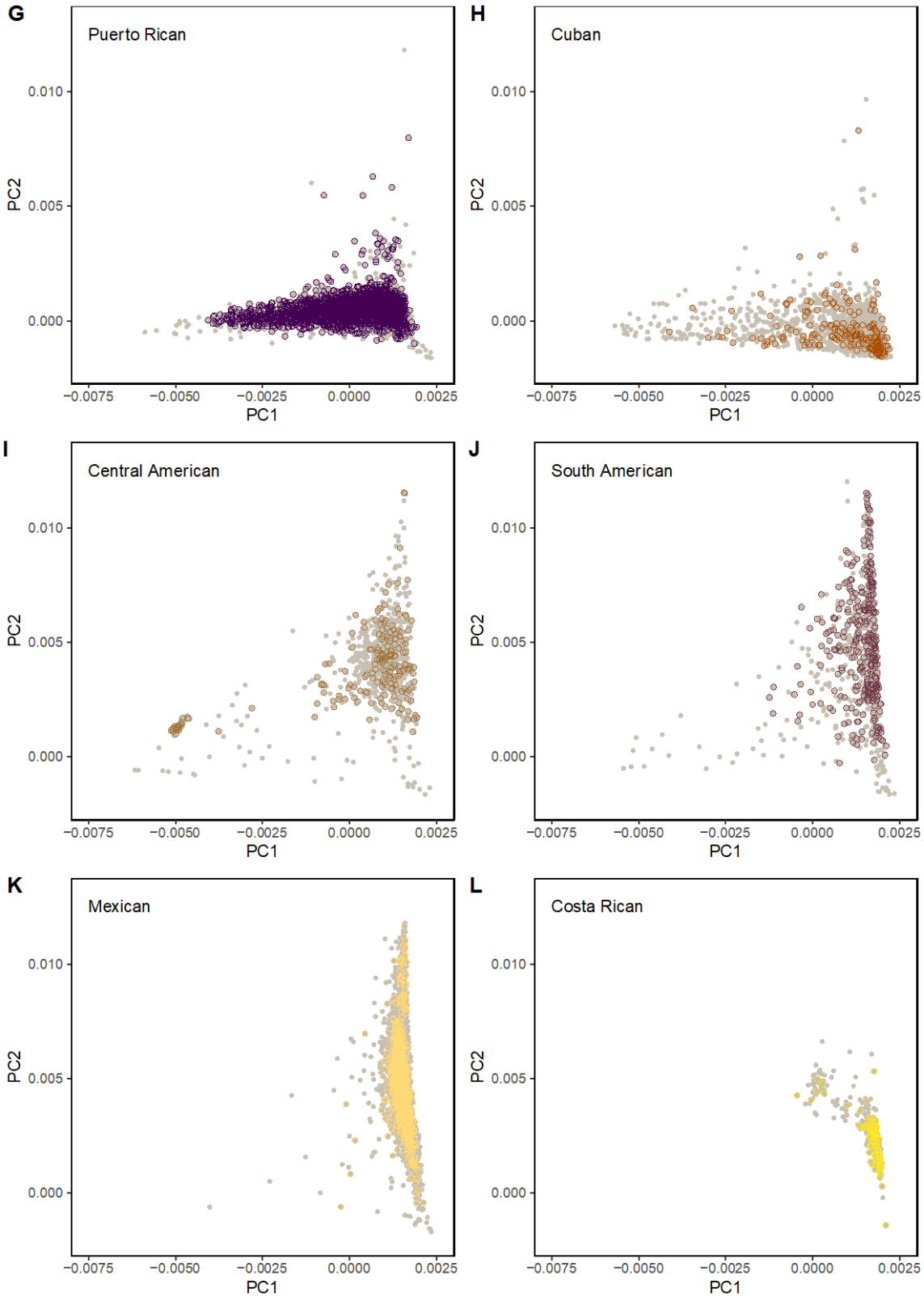

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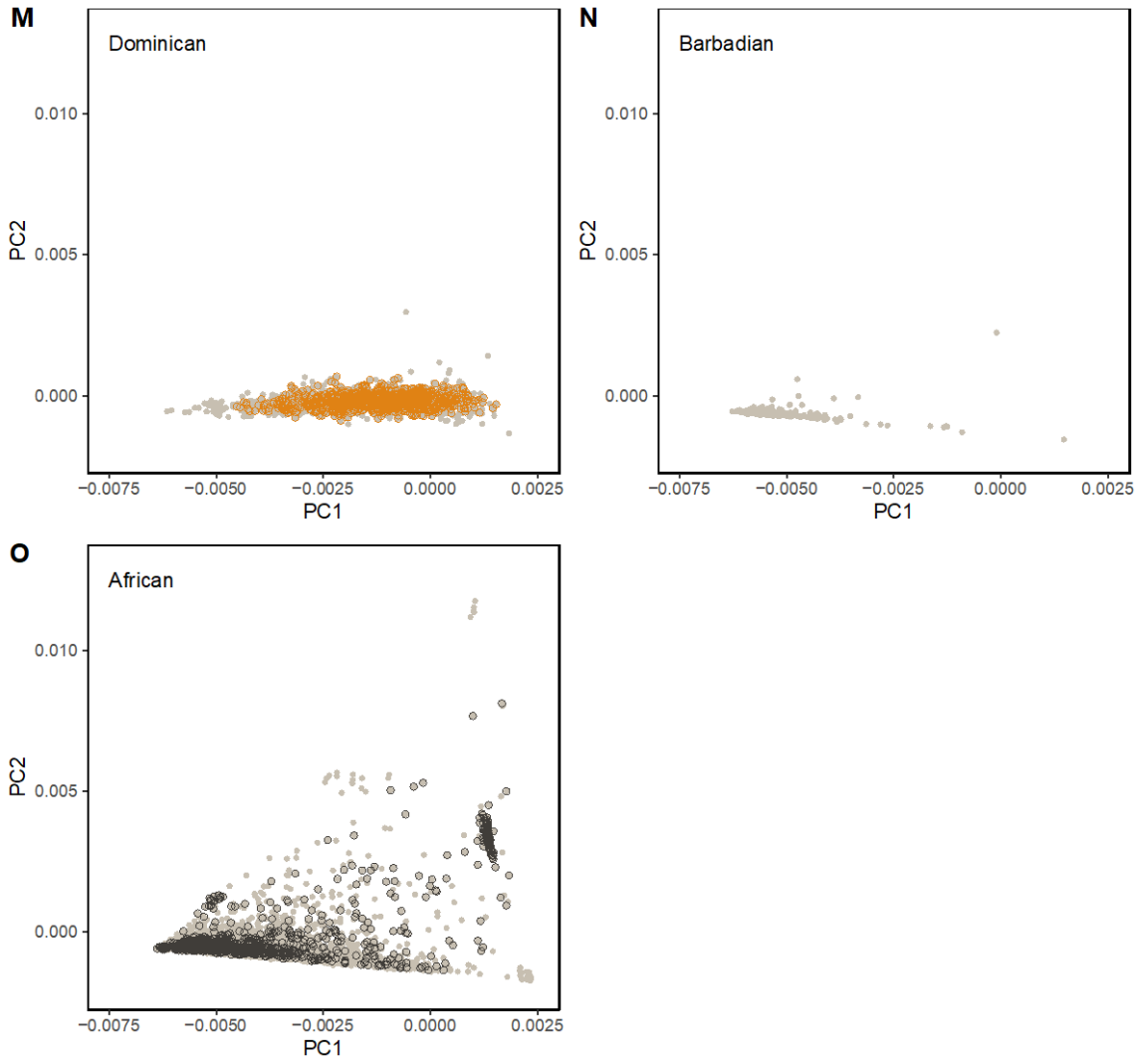
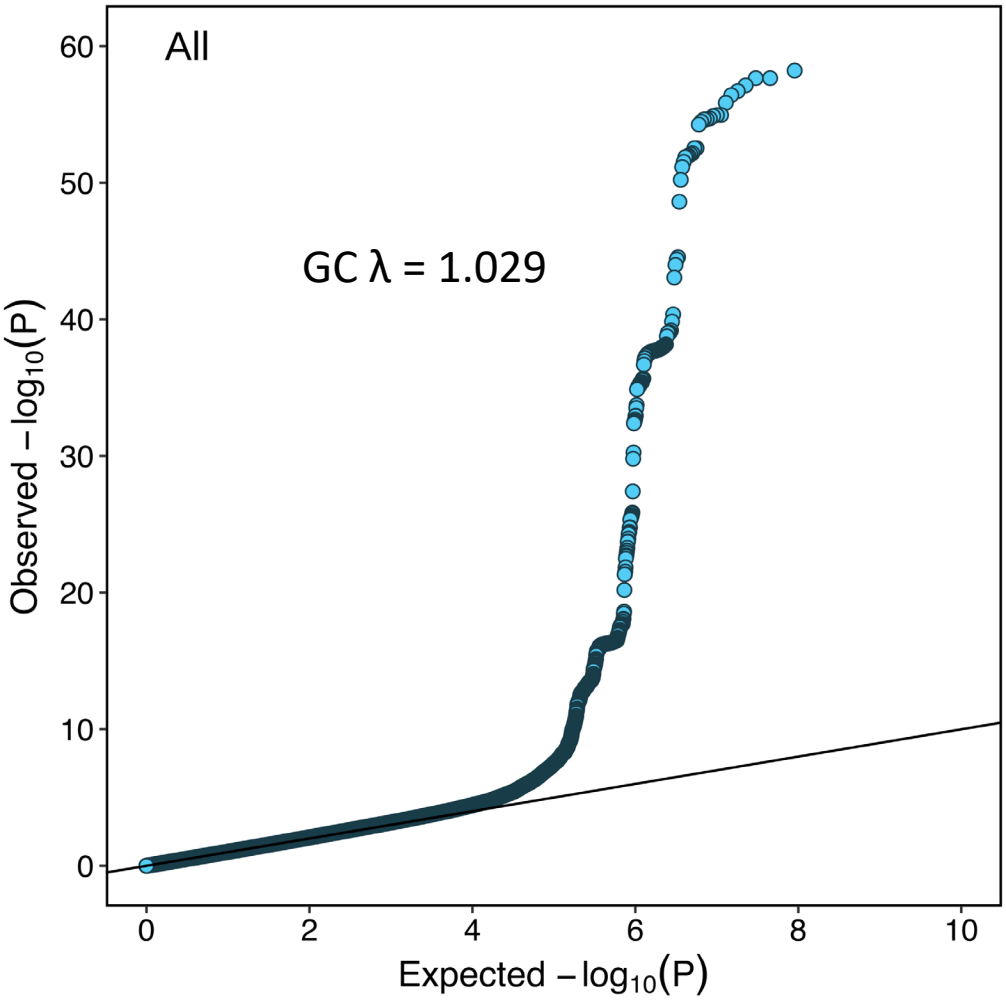


Supplementary Figure 2. QQ plot of primary BMI GWAS

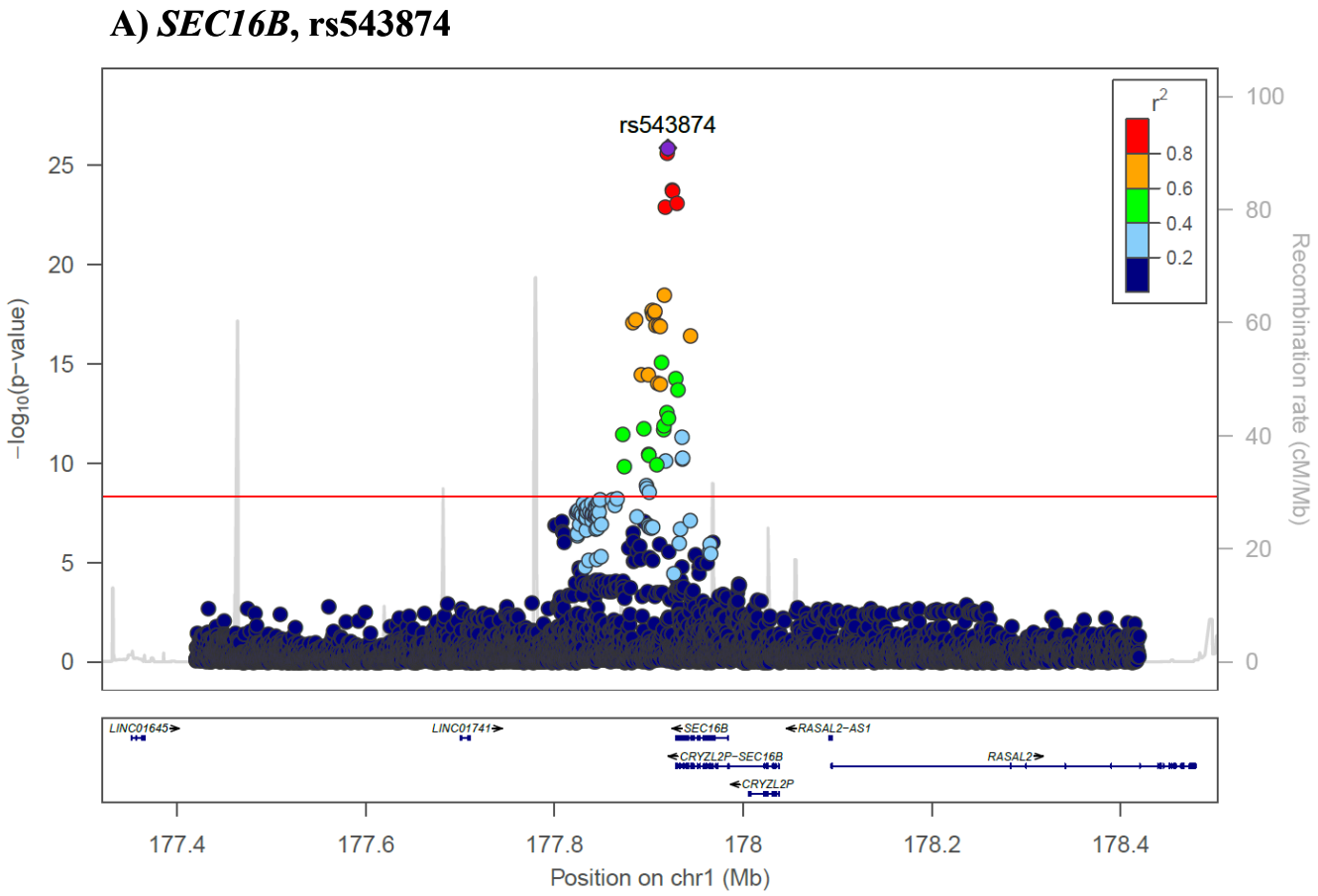
Quantile-quantile plot of multi-population, single variant analysis (N = 88,873 individuals, N = 90,142,062 variants).



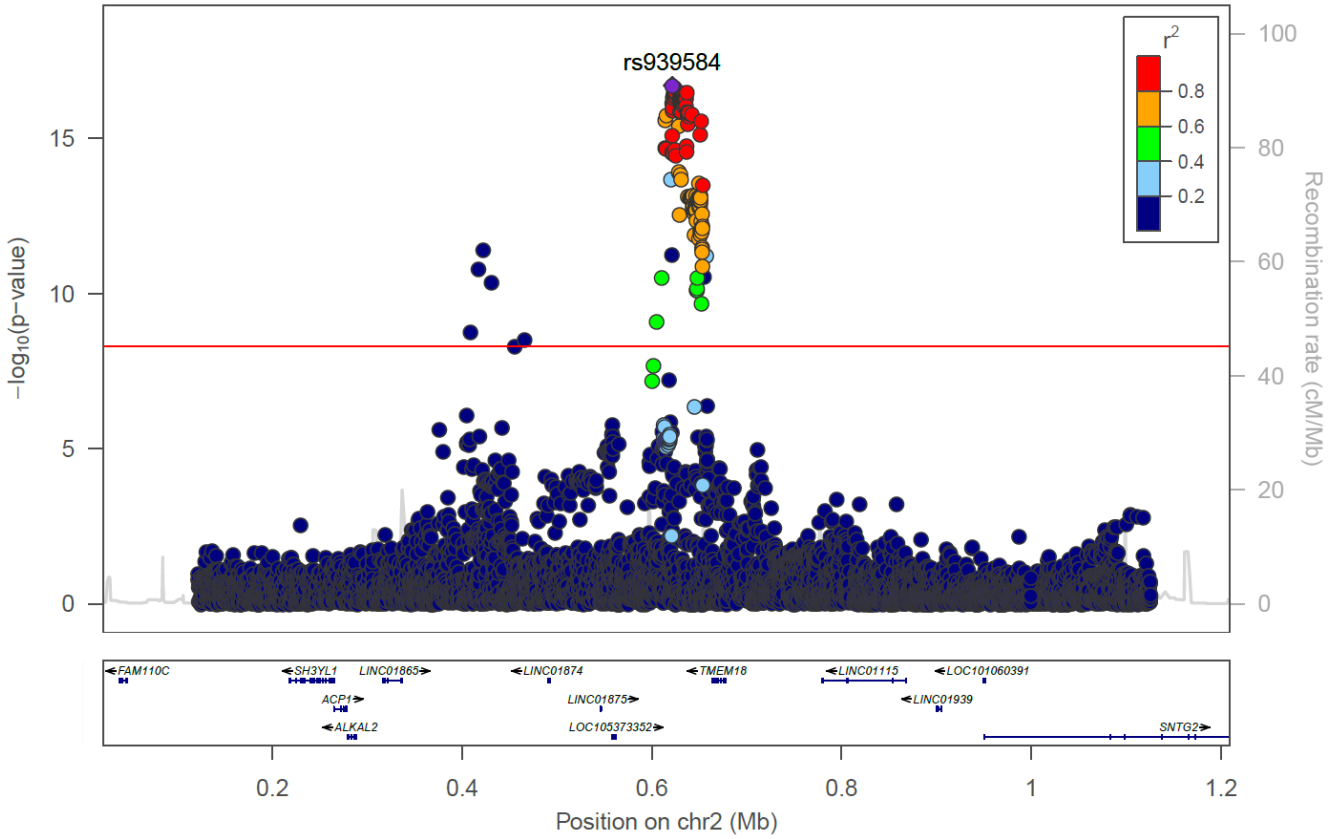
Supplementary Figure 3. Regional association plots

Regional association plots for each significant locus in the multi-population analysis, including all variants ± 500 kb from index variant. The plots appear in order of chromosomal location. TOPMed study populations were used to calculate linkage disequilibrium (LD). The red line indicates genome-wide significance threshold $P = 5 \times 10^{-9}$.

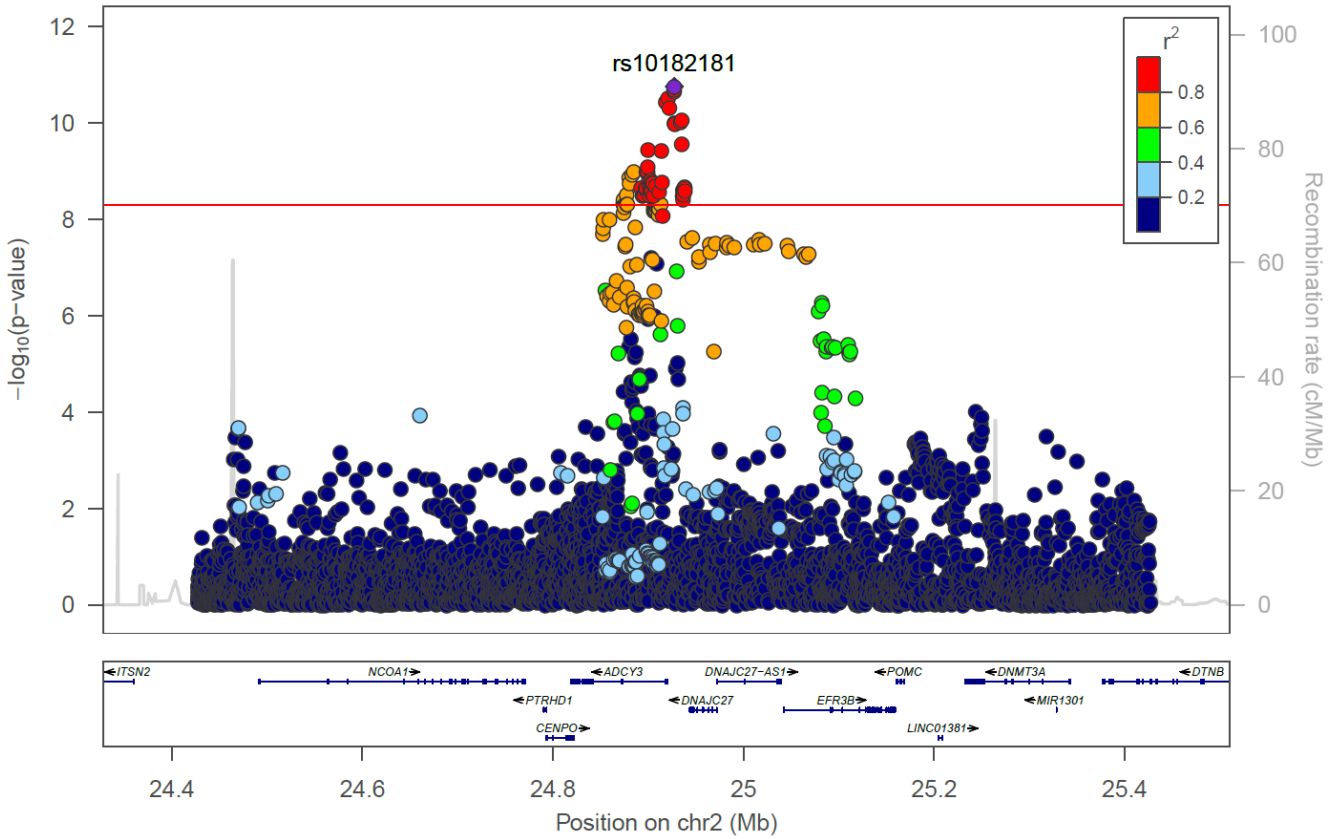
A) *SEC16B*, rs543874; B) *TMEM18*, rs939584; C) *ADCY3*, rs10182181; D) *ETV5*, rs869400; E) *GNPDA2*, rs12507026; F) *POC5*, rs2307111; G) *TFAP2B*, rs2206277; H) *HNF4G*, rs830463; I) *BDNF*, rs3838785; J) *BCDIN3D*, rs7138803; K) *OLFM4*, rs9568868; L) *FTO*, rs1421085; M) *MC4R*, rs6567160; N) *ZC3H4*, rs28590228; O) *MTMR3*, rs111490516; P) *DMD*, rs1379871.



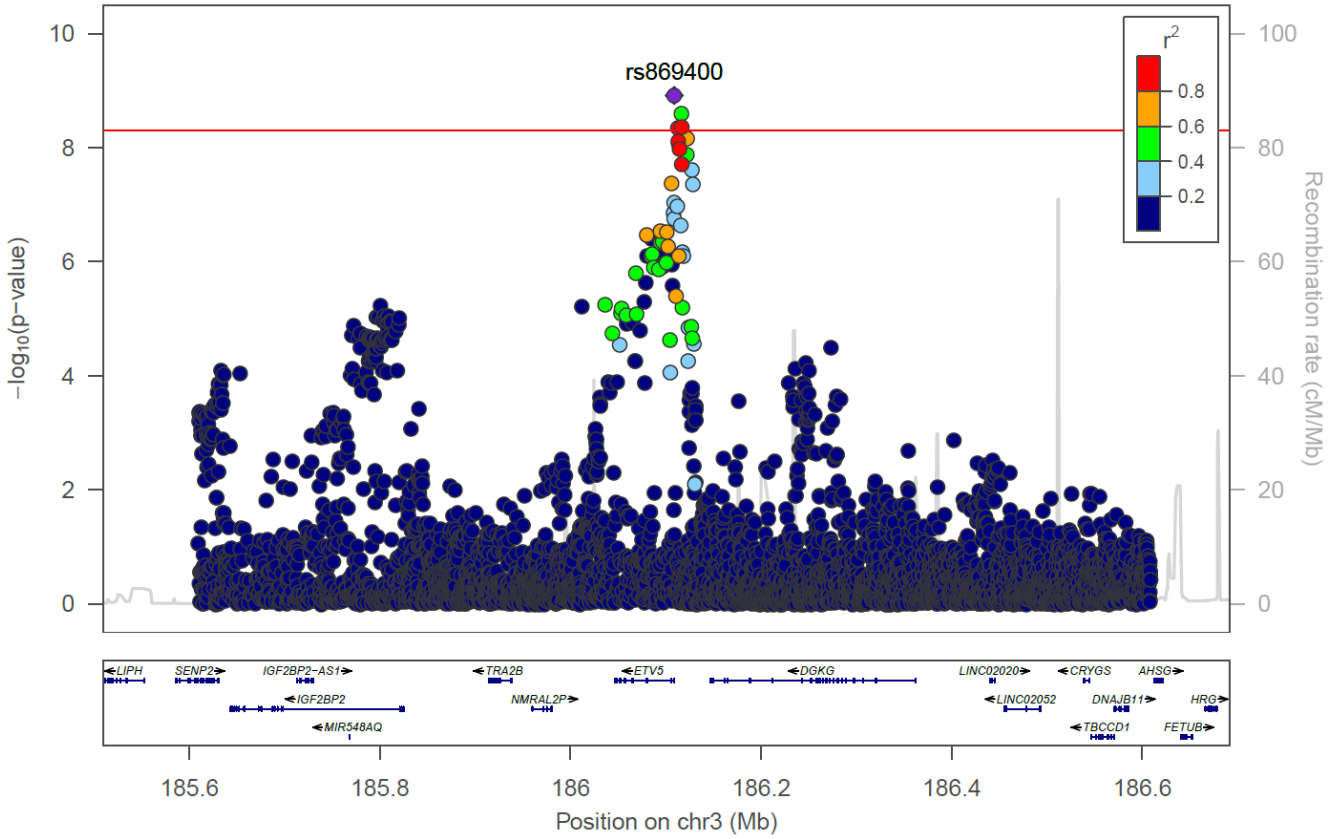
B) *TMEM18*, rs939584



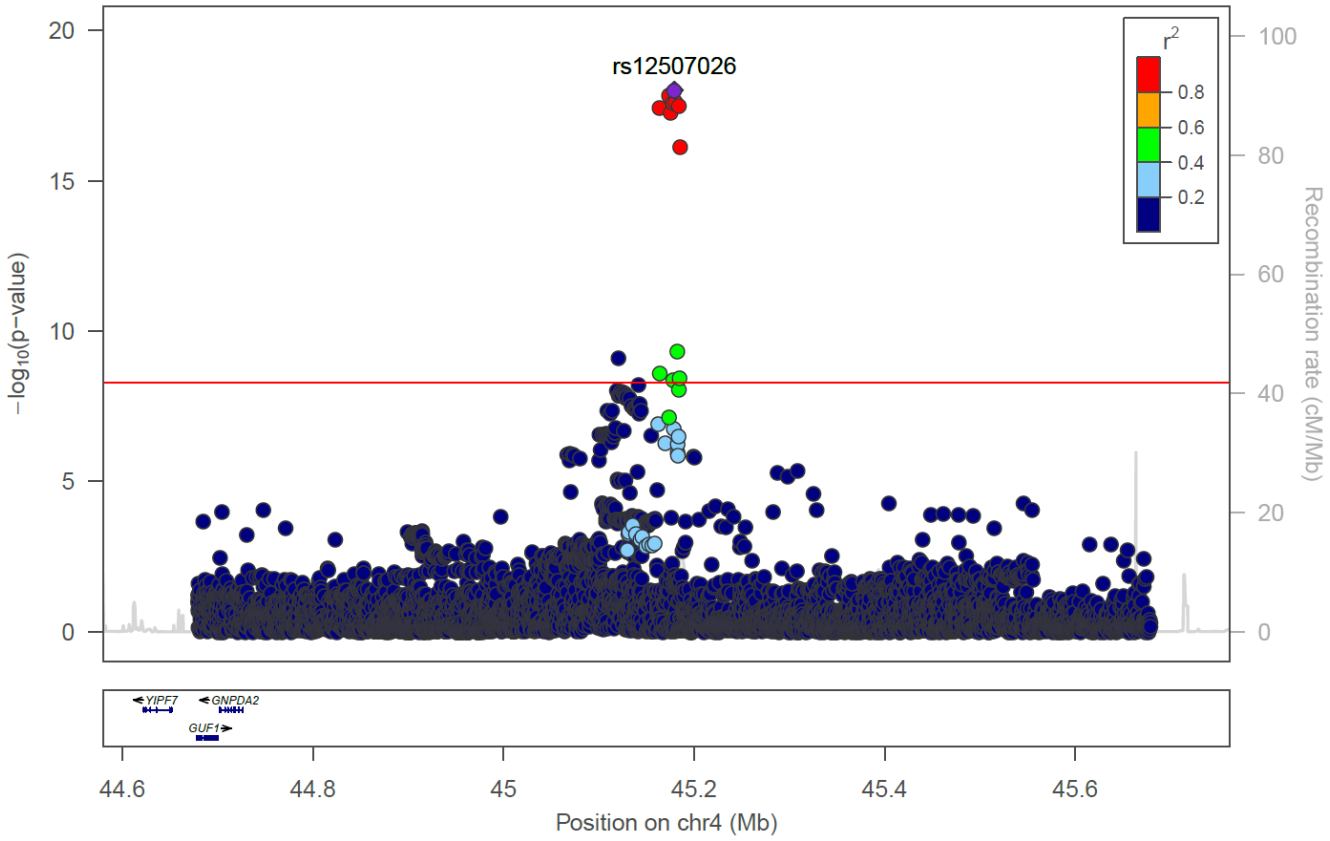
C) *ADCY3*, rs10182181



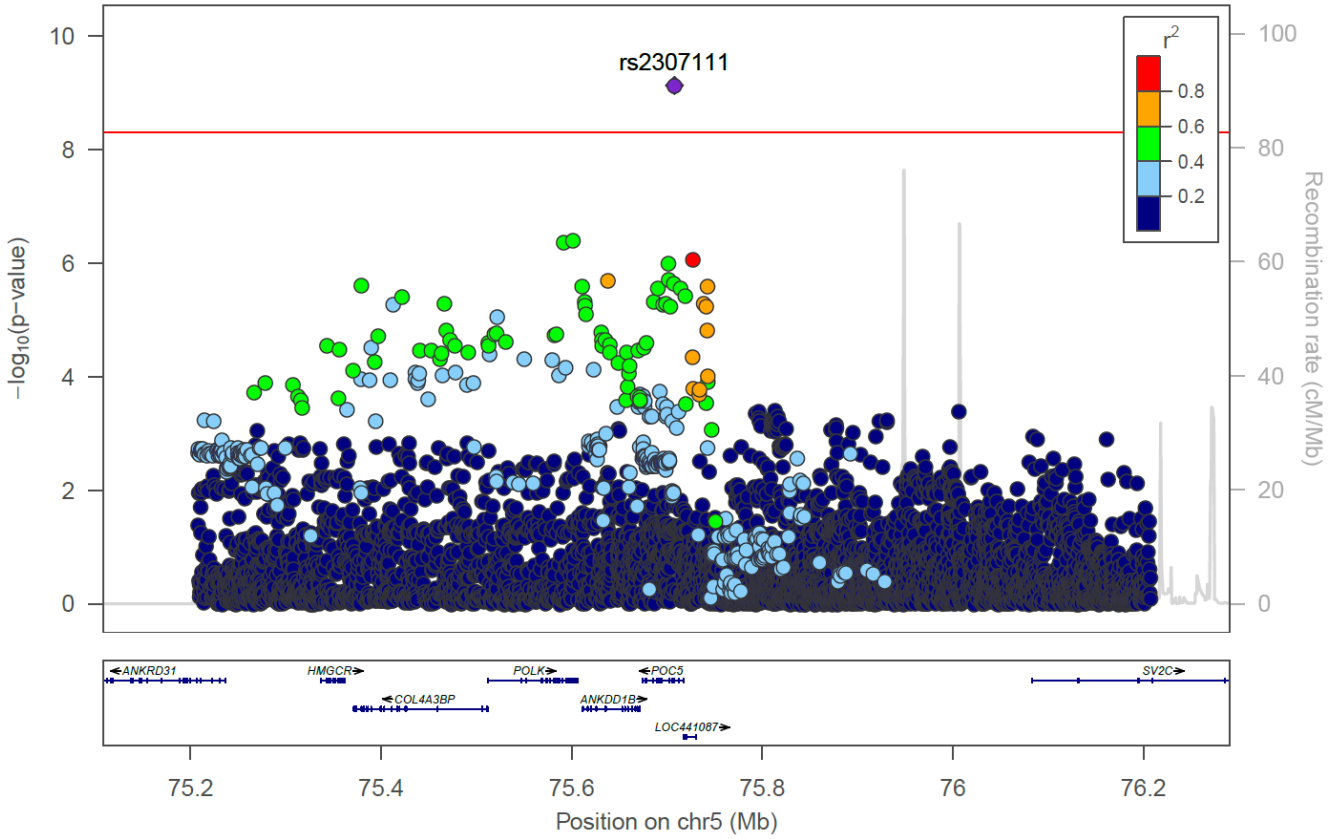
D) *ETV5*, rs869400



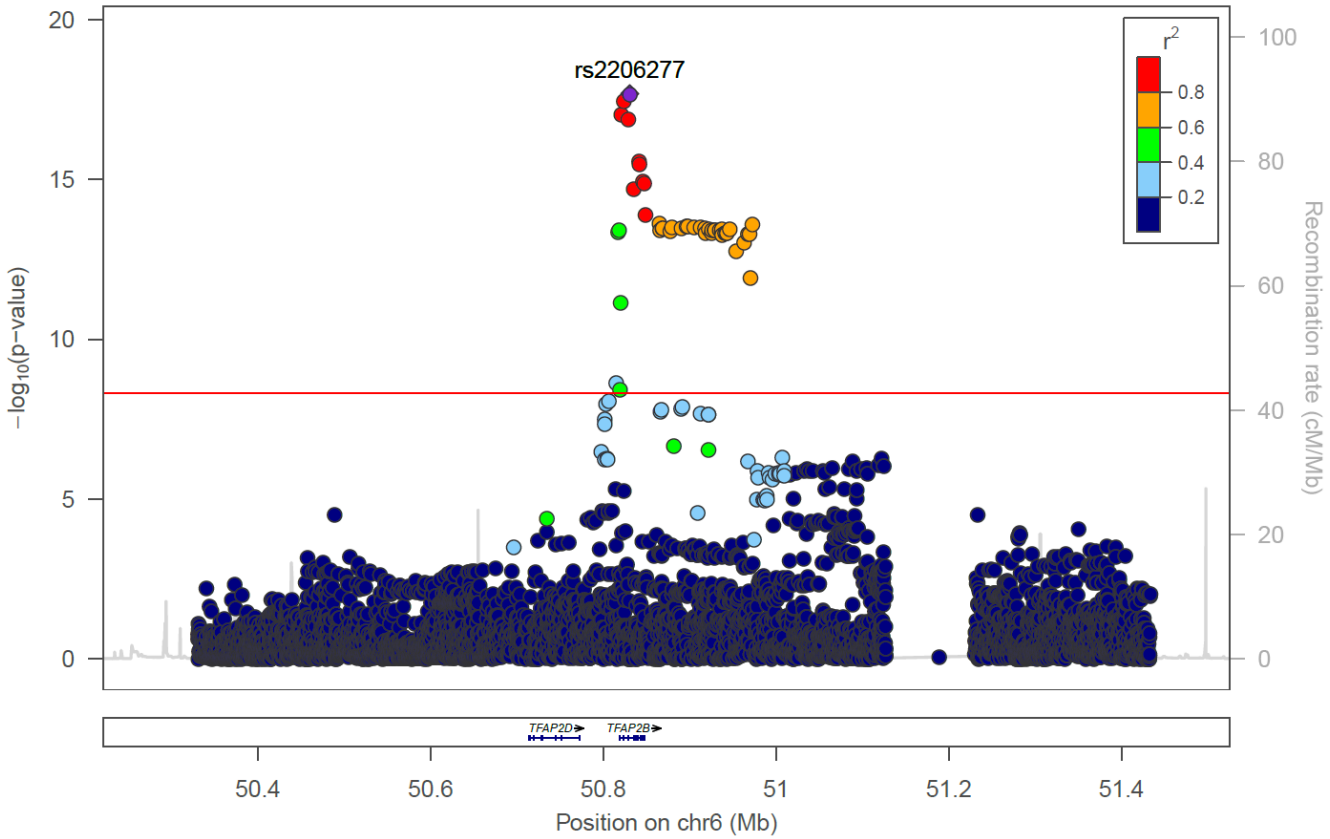
E) *GNPDA2*, rs12507026



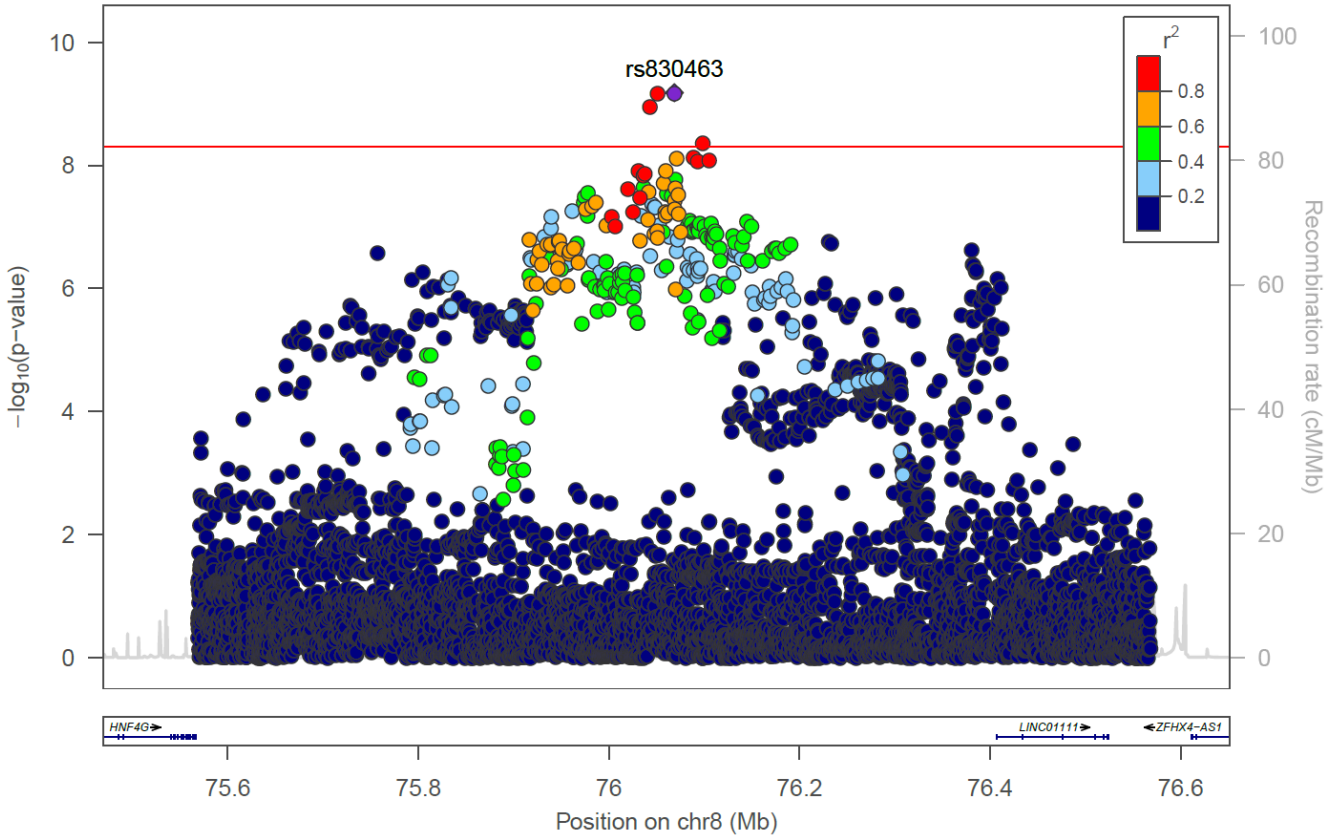
F) *POC5*, rs2307111



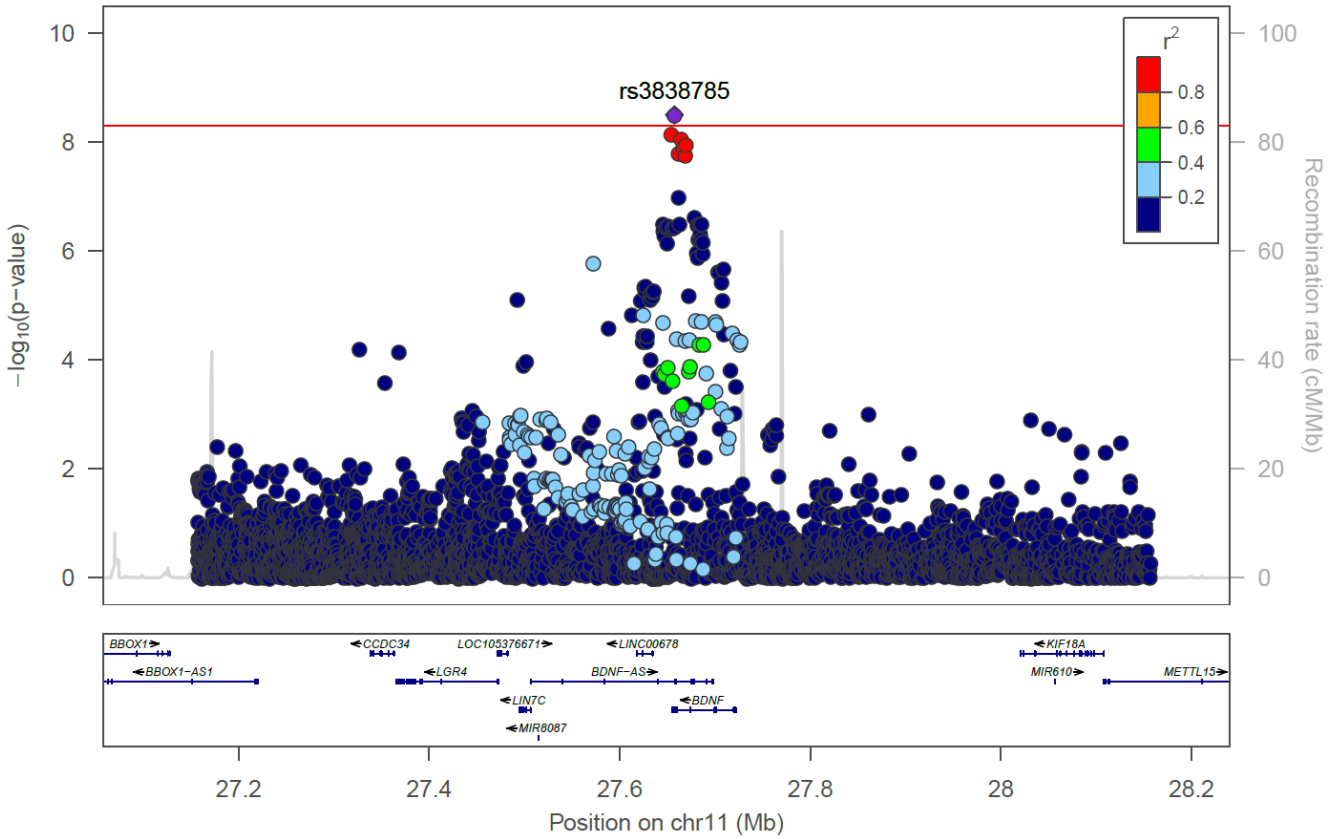
G) *TFAP2B*, rs2206277



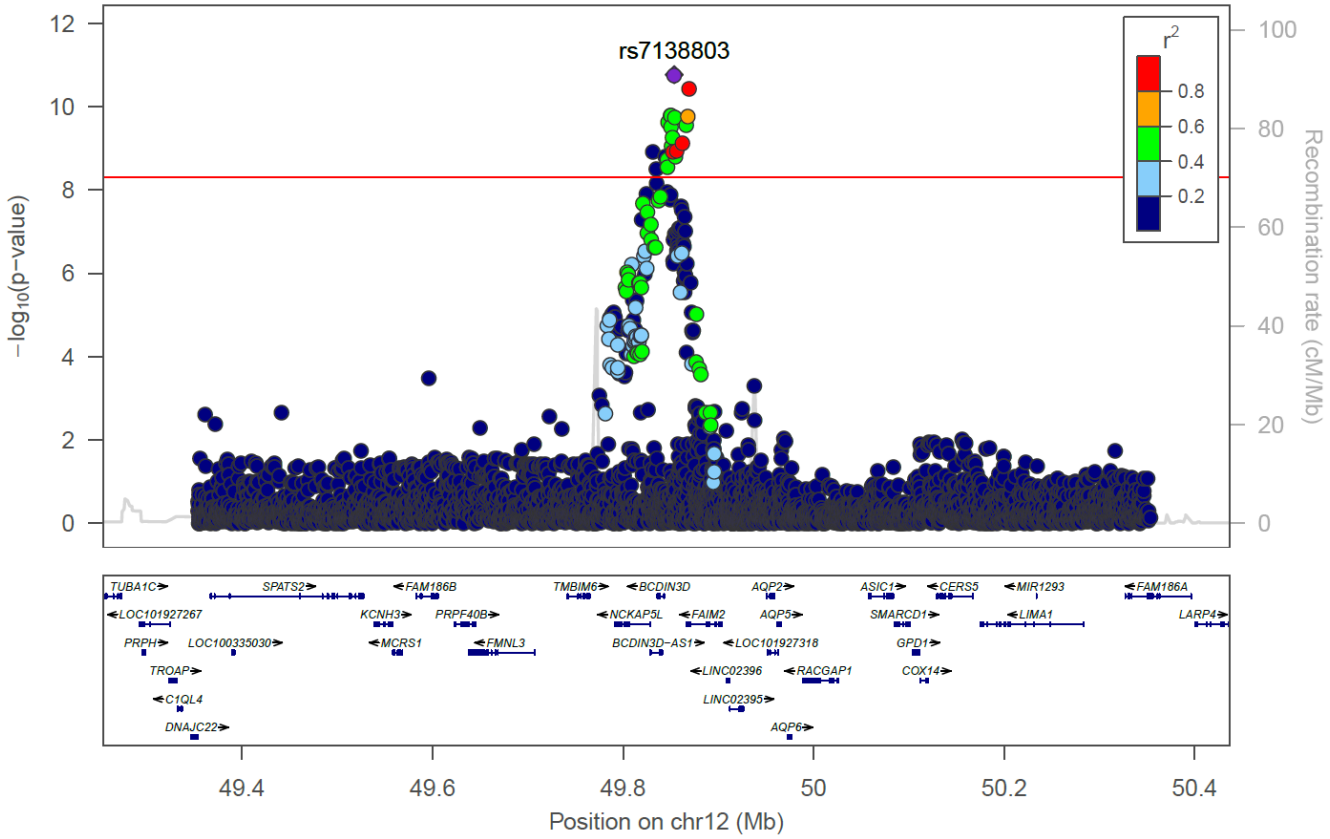
H) *HNF4G*, rs830463



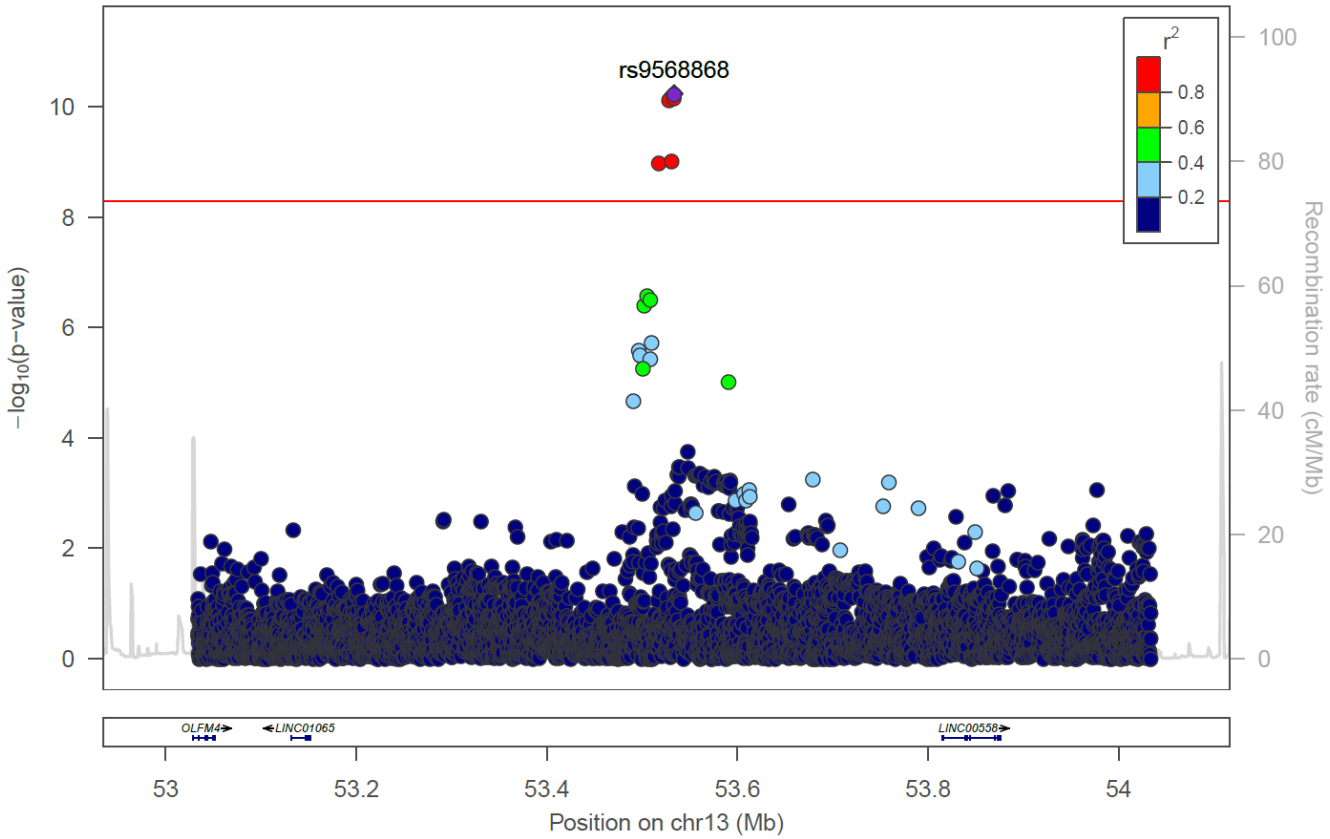
I) *BDNF*, rs3838785



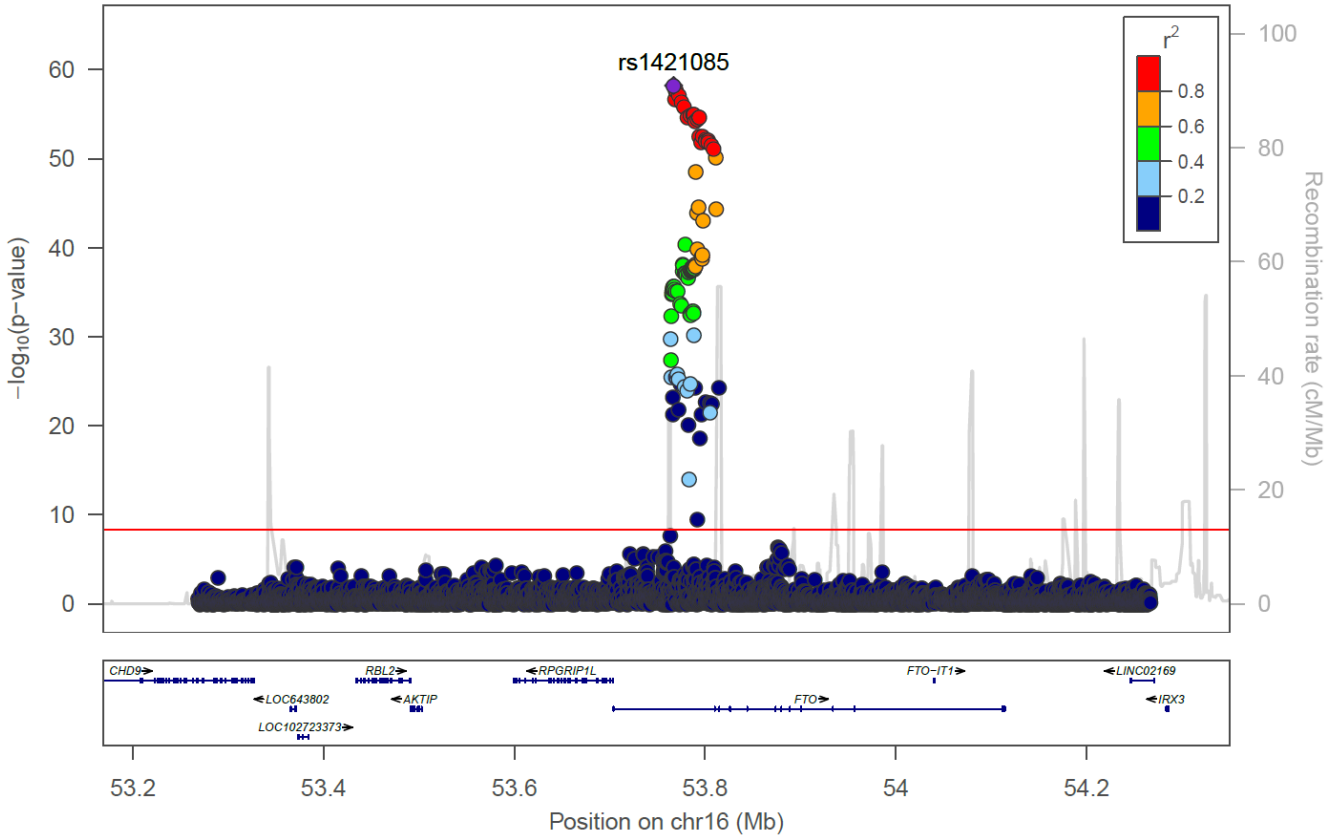
J) *BCDIN3D*, rs7138803



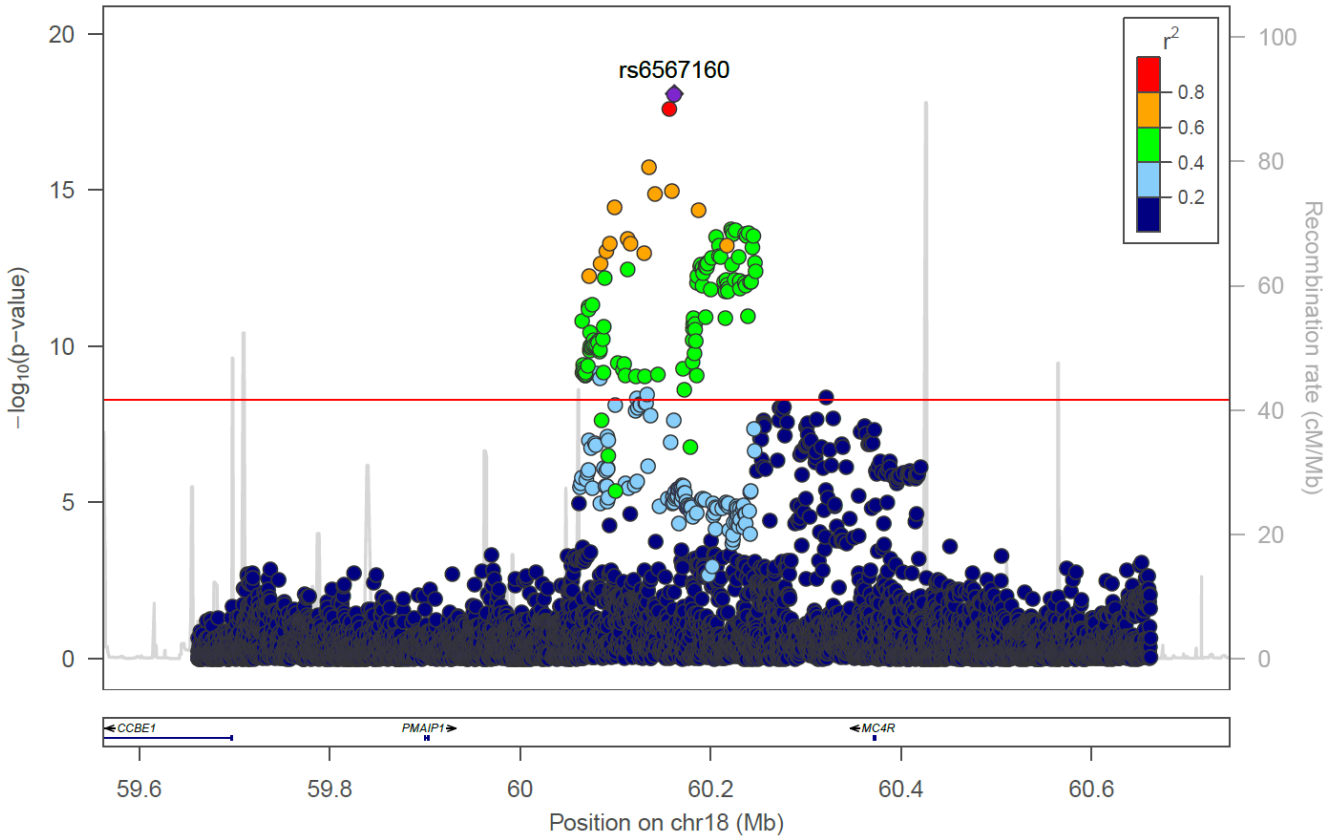
K) *OLFM4*, rs9568868



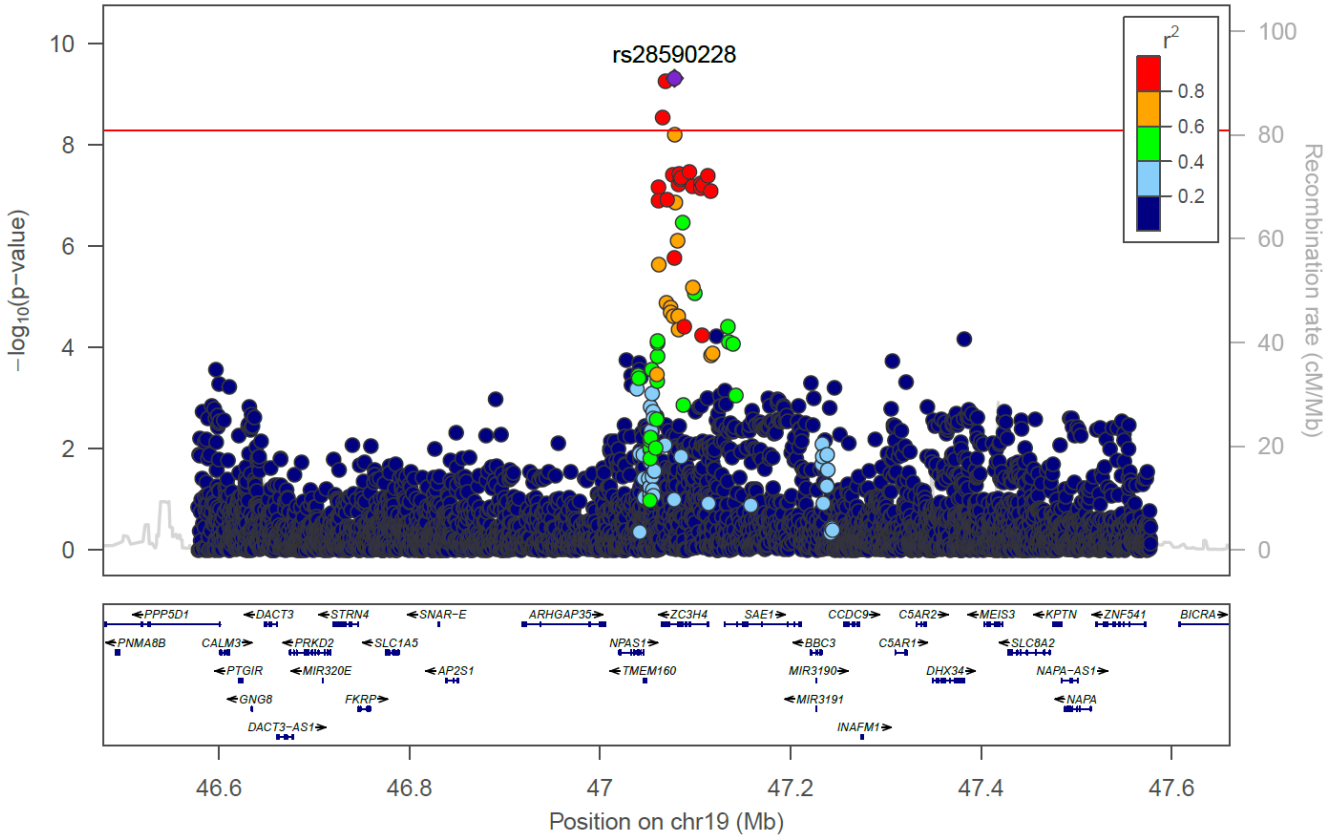
L) *FTO*, rs1421085



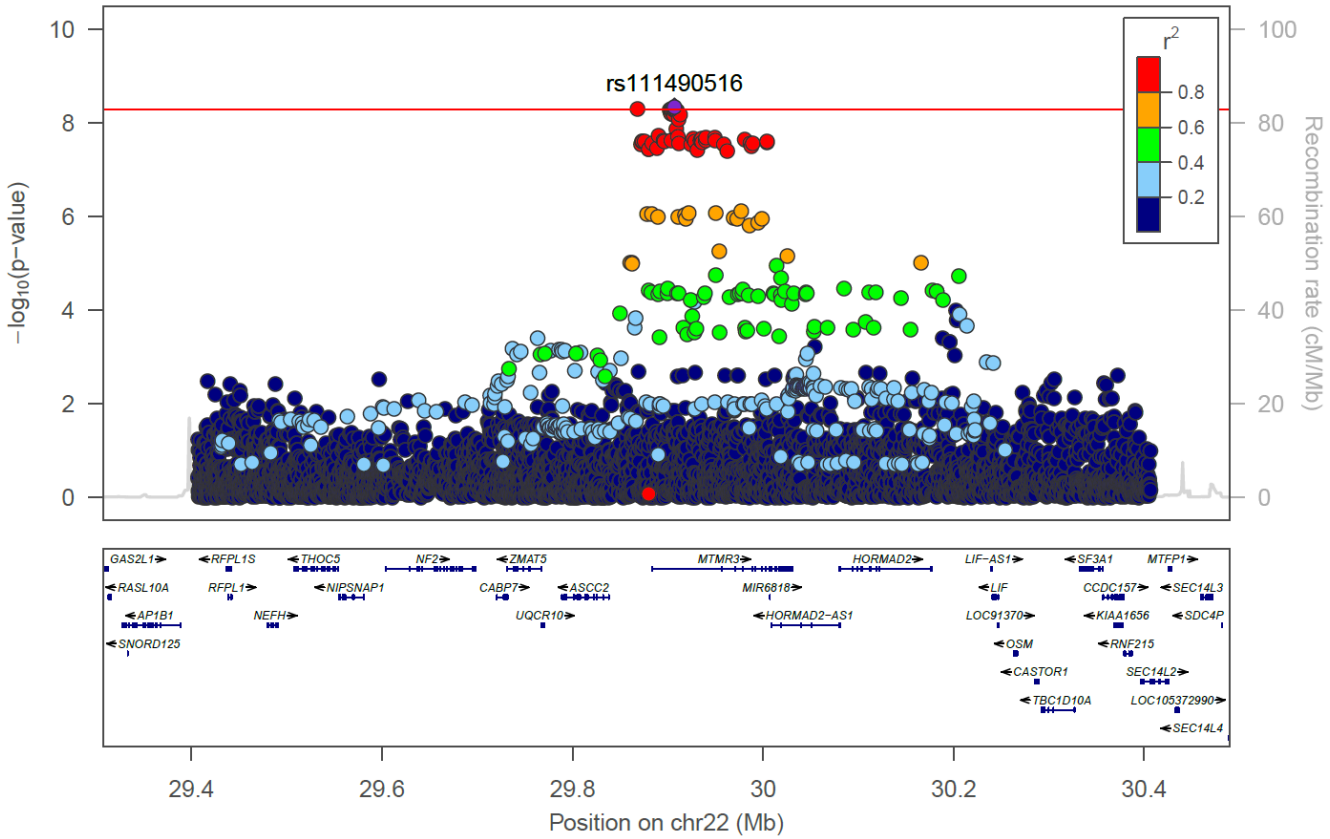
M) *MC4R*, rs6567160



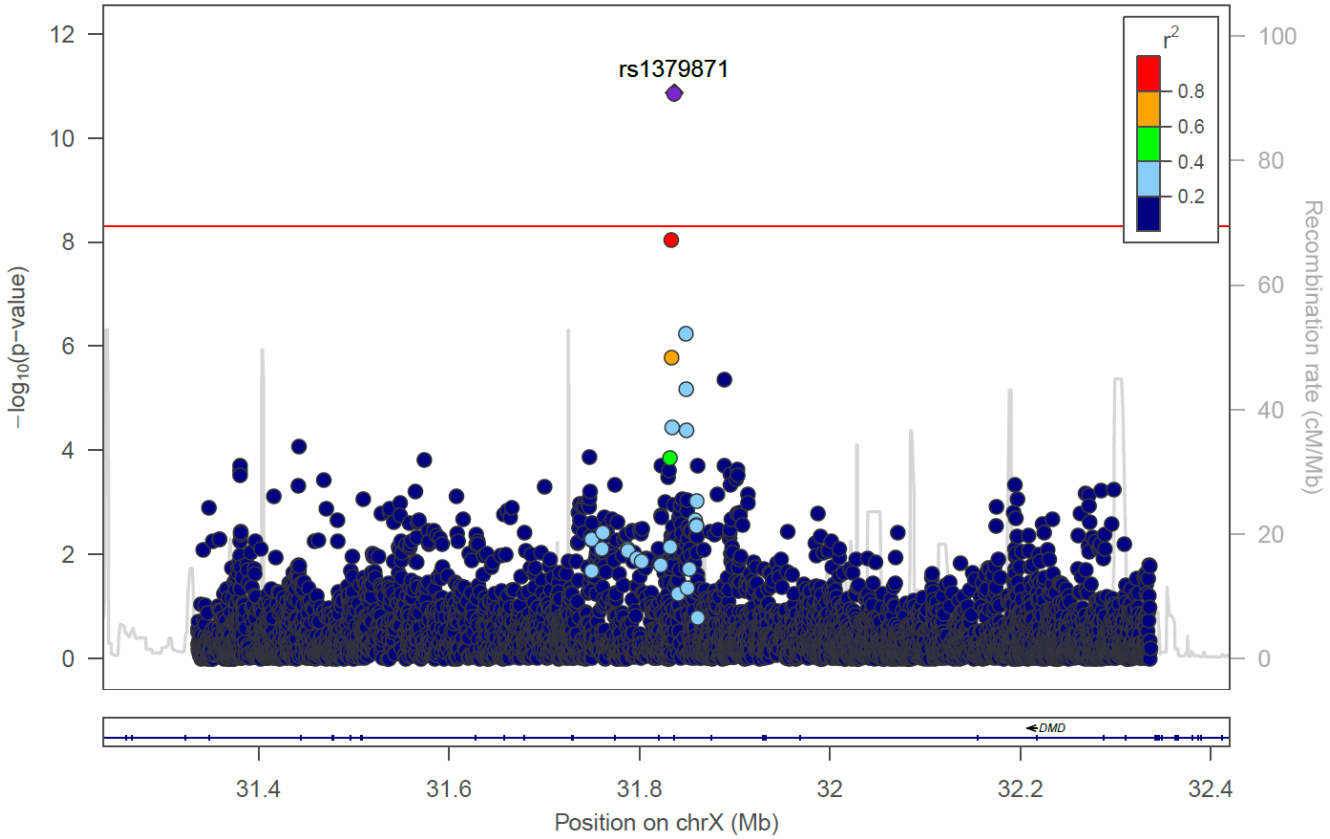
N) *ZC3H4*, rs28590228



O) *MTMR3*, rs111490516

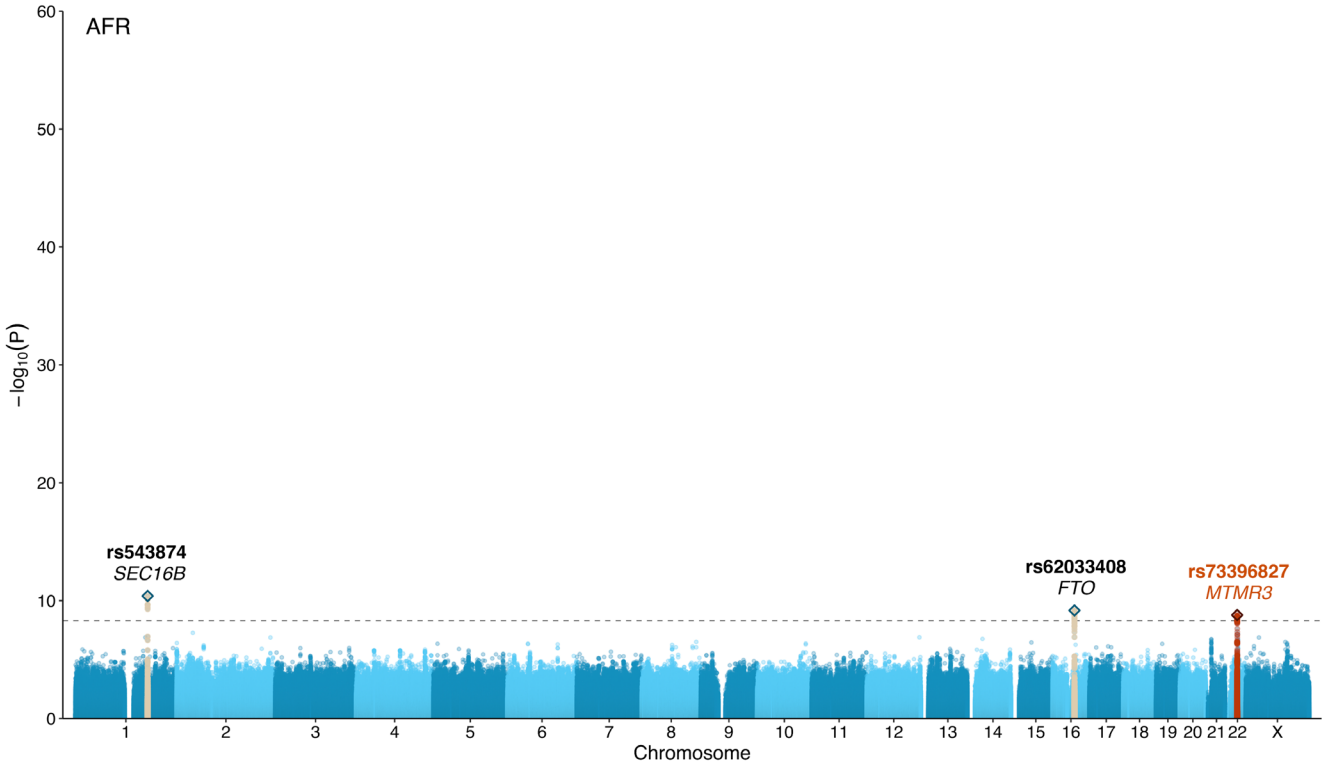


P) *DMD*, rs1379871



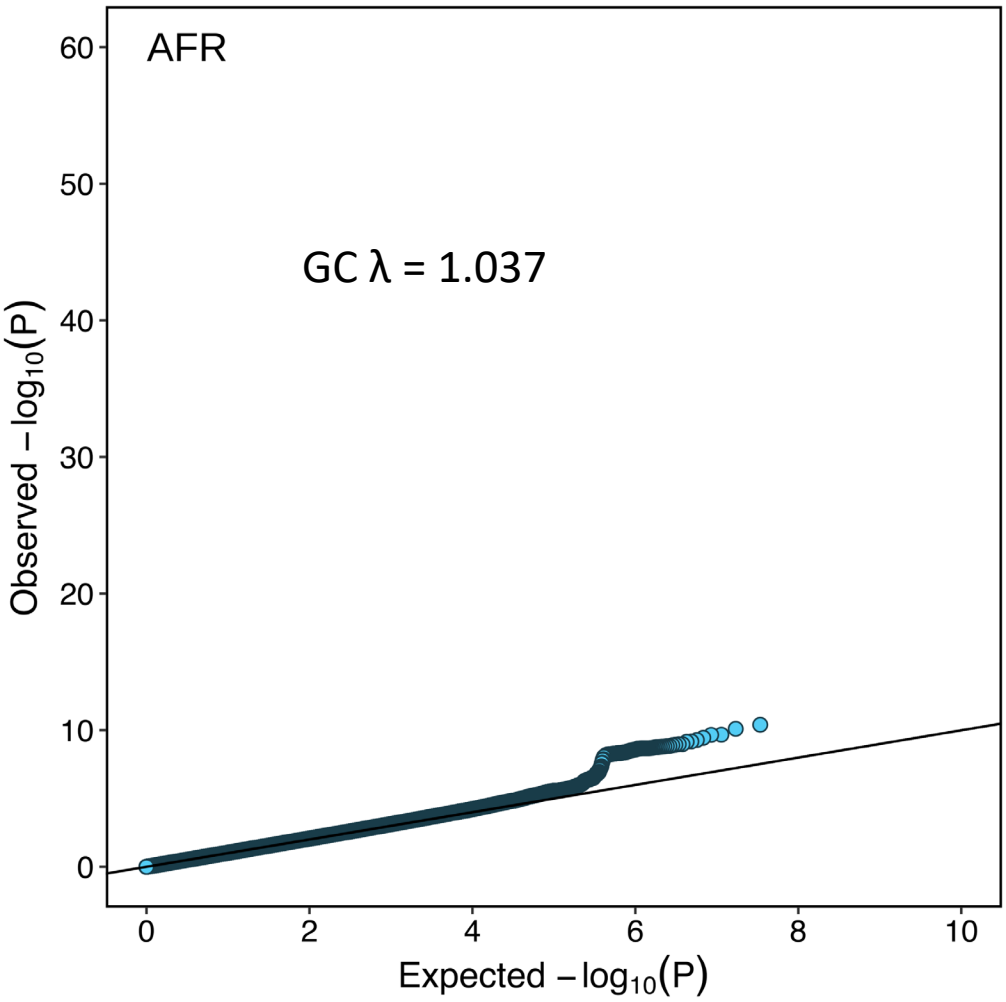
Supplementary Figure 4. Manhattan plot of African population group BMI GWAS

Manhattan plot of African population group, single variant analysis (N = 22,488 individuals). The novel locus *(MTMR3)* is highlighted in red. Previously reported BMI loci are in dark beige. The horizontal dashed line indicates genome-wide significant threshold $P = 5 \times 10^{-9}$.



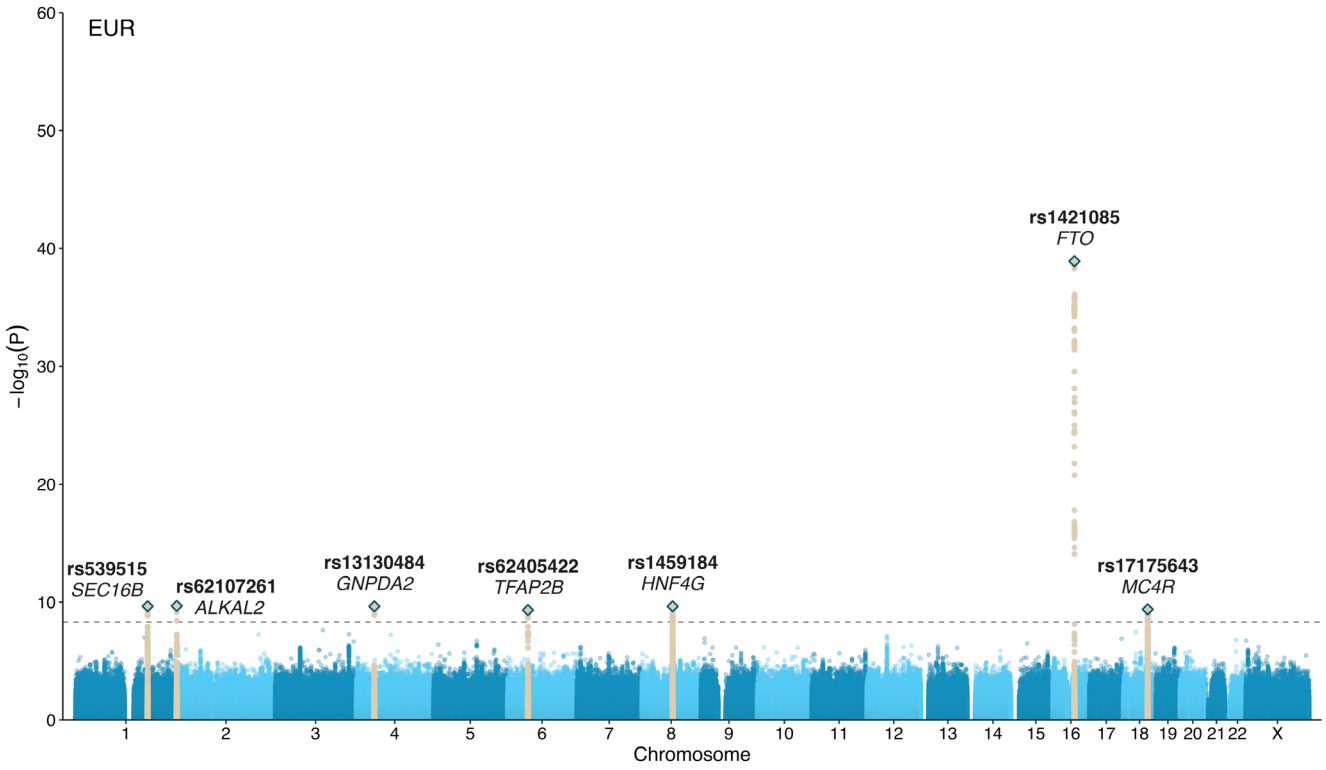
Supplementary Figure 5. QQ plot of African population group BMI GWAS

Quantile-quantile plot of African population group, single variant analysis (N = 22,488 individuals).



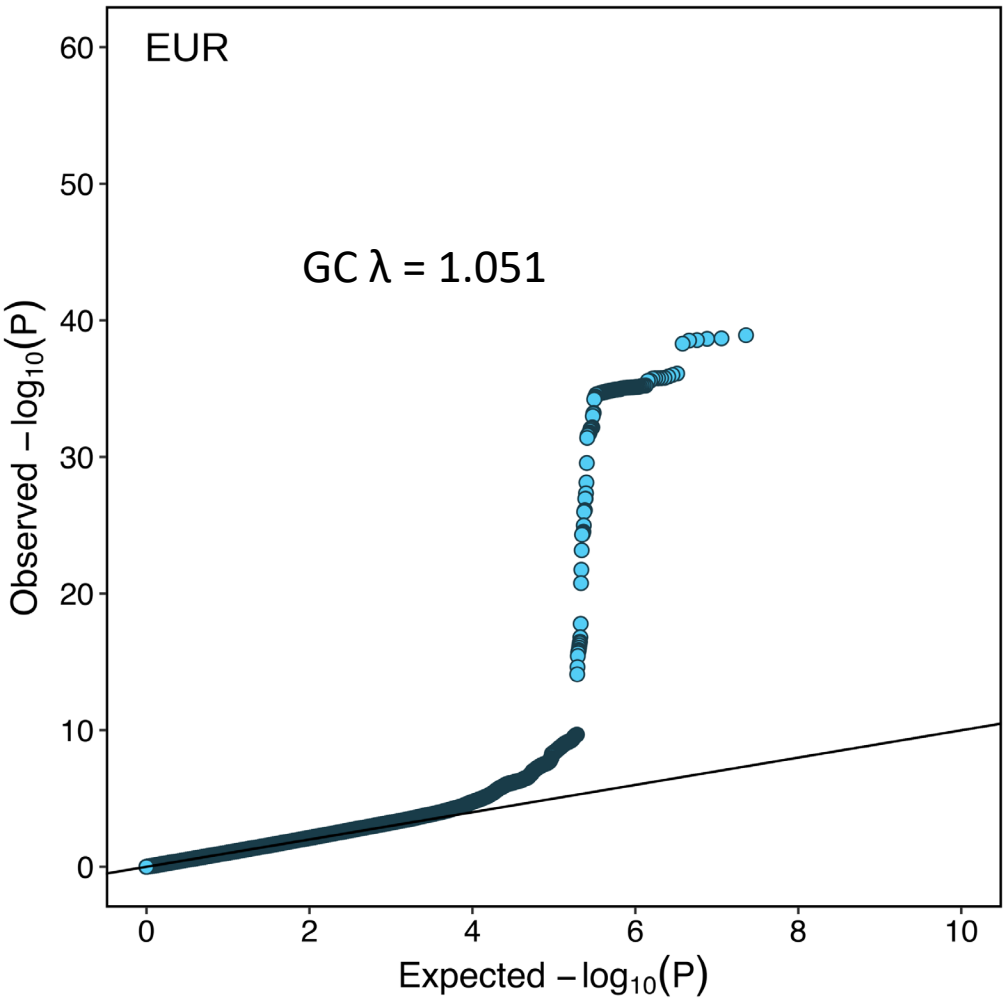
Supplementary Figure 6. Manhattan plot of European population group BMI GWAS

Manhattan plot of European population group, single variant analysis (N = 43,434 individuals). Previously reported BMI loci are in dark beige. The horizontal dashed line indicates genome-wide significant threshold $P = 5 \times 10^{-9}$.



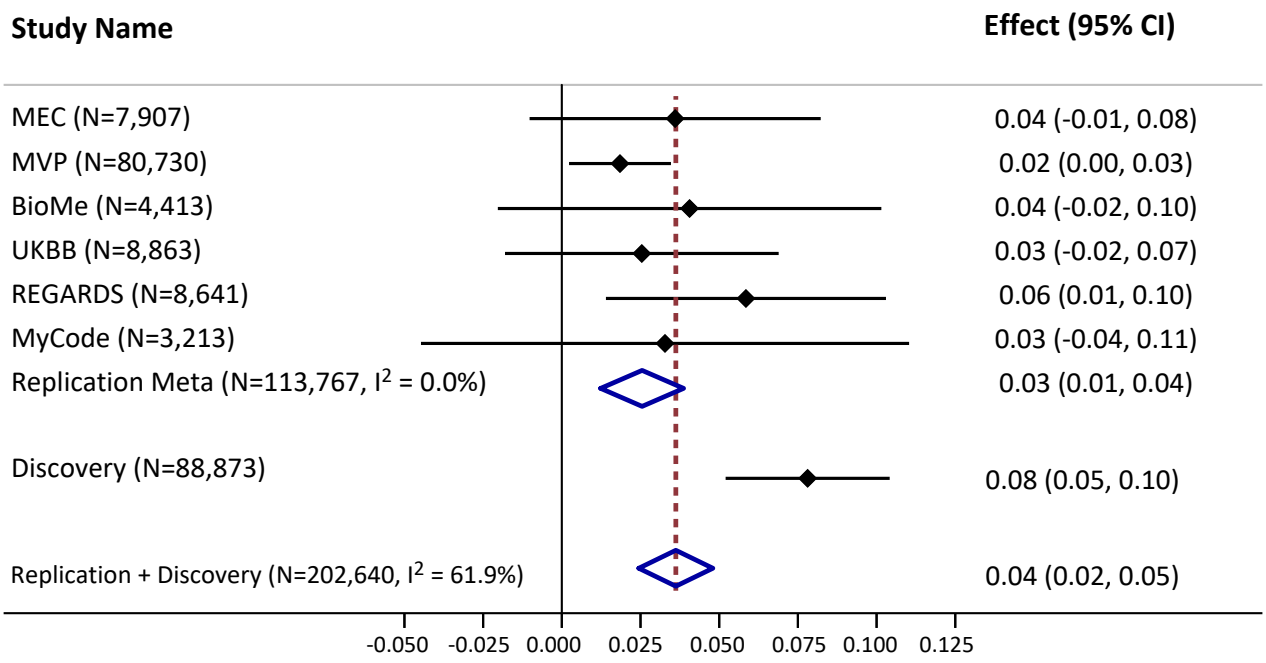
Supplementary Figure 7. QQ plot of European population group BMI GWAS

Quantile-quantile plot of European population group, single variant analysis (N = 43,434 individuals).



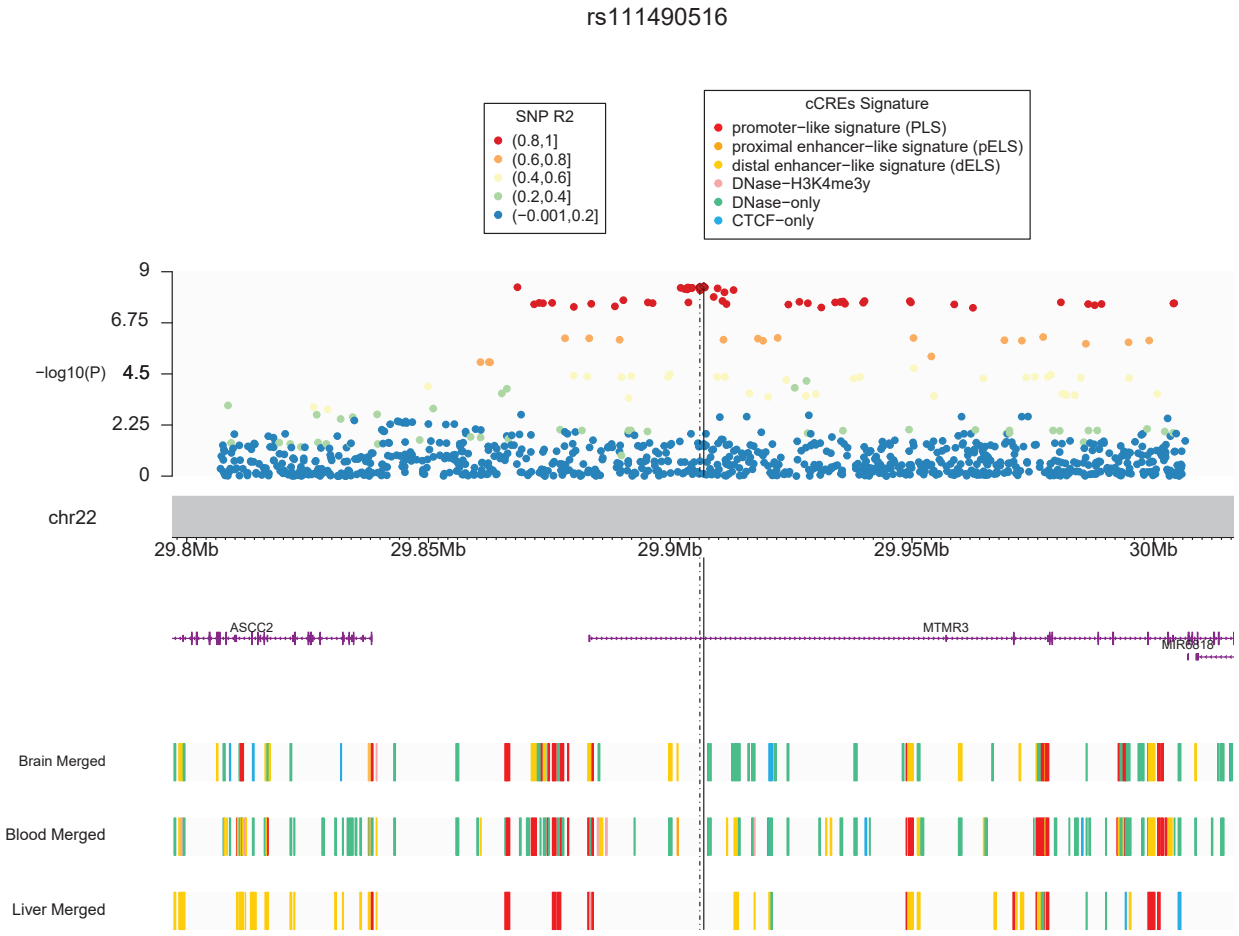
Supplementary Figure 8. Forest plot of rs73396827 replication.

All effect estimates (95% confidence interval) are oriented on the BMI increasing allele and are provided as standard deviation per allele. Actual beta values and P-values are in Supplementary Data 8.



Supplementary Figure 9. Regional association plot for novel locus with ENCODE annotations.

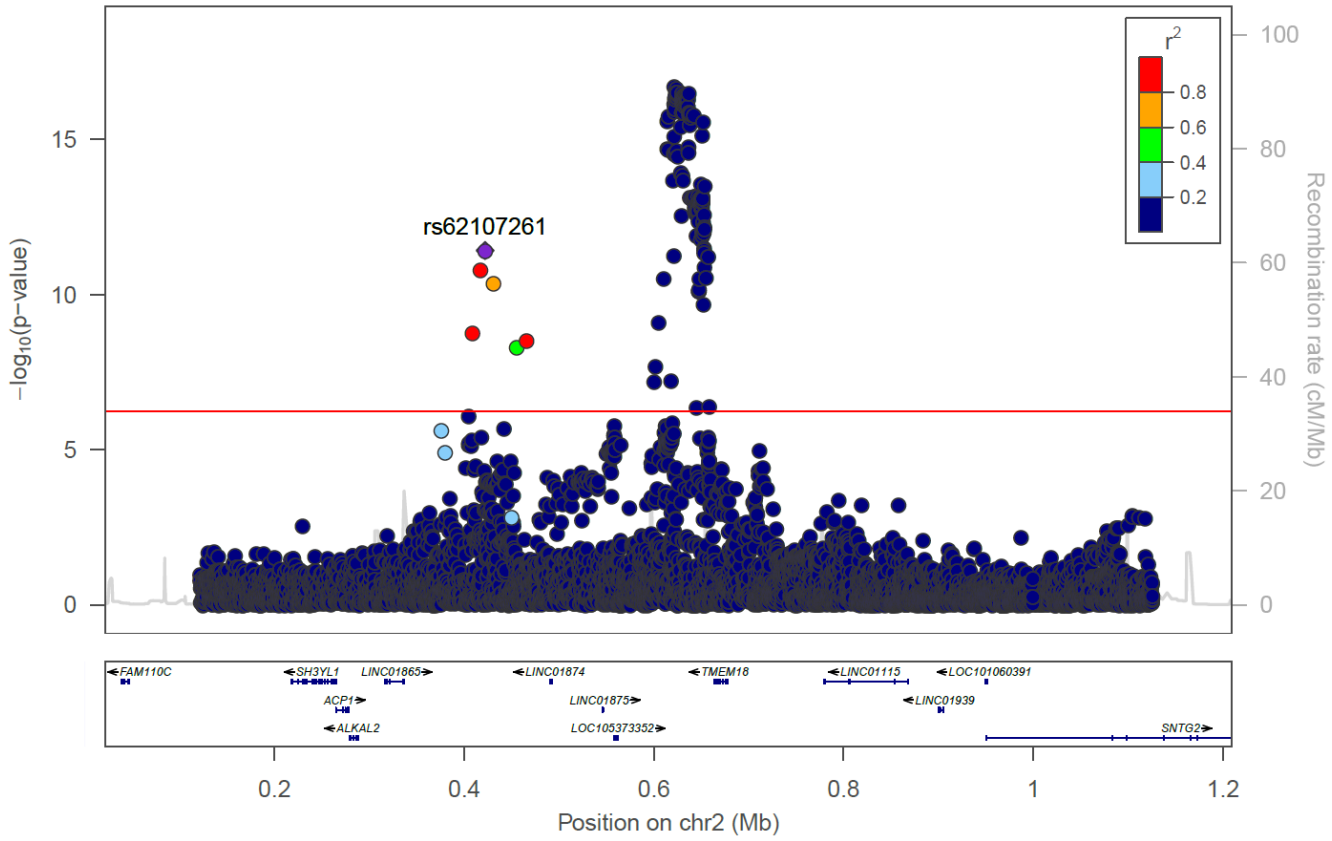
Regional association plot including association results and LD from the pooled analysis for rs111490516. Annotation for potential candidate cis-regulatory elements from ENCODE are included for each reported SNP in the region.



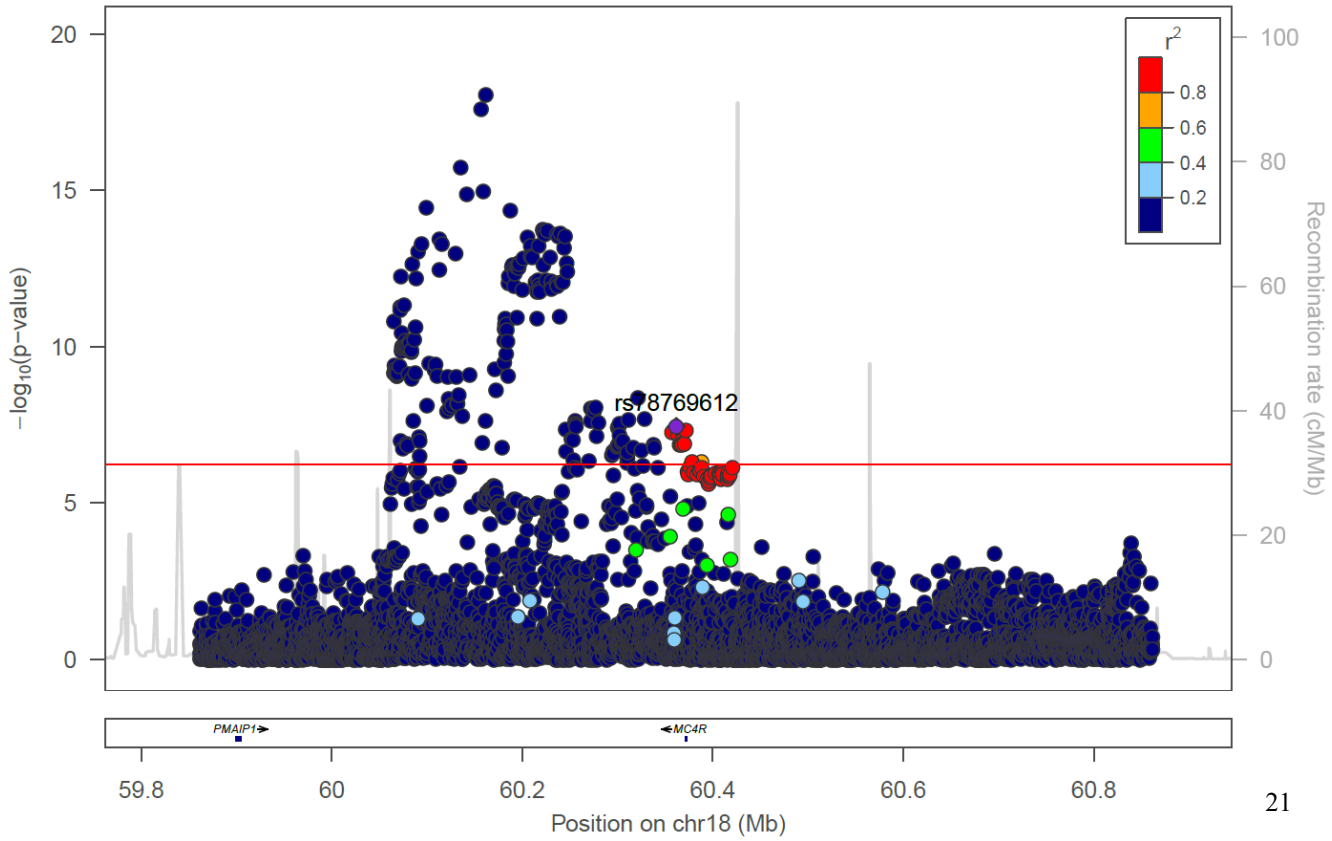
Supplementary Figure 10. Regional association plots of secondary signals

Regional association plots for each significant secondary signal in the multi-population analysis following conditional analysis on top variant, including all variants ± 500 kb from index variant. TOPMed study populations were used to calculate LD. The red line indicates $P = 5.67 \times 10^{-7}$. A) *ALKAL2*, rs62107261; B) *MC4R*, rs78769612.

A) *ALKAL2*, rs62107261

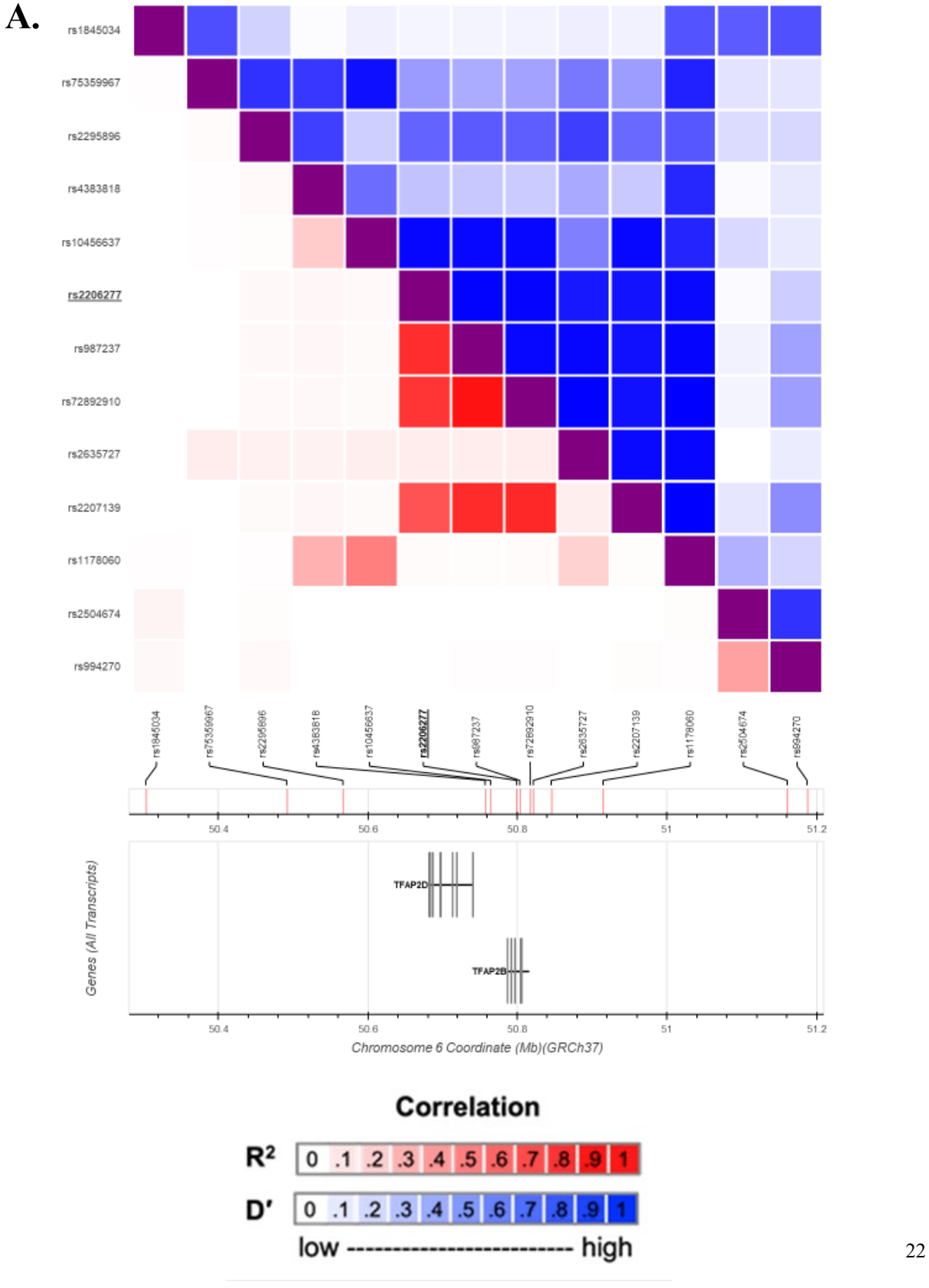


B) *MC4R*, rs78769612



Supplementary Figure 11. LD matrix heatmap for conditionally independent SNPs in known BMI-risk loci

Pairwise LD matrix heatmap for lead index SNP in discovery analyses (bold and underlined) and published BMI GWAS SNPs within 500 kb (+/-) of index SNPs. A) rs2206277 index SNP in *TFAP2B* locus; B) rs3838785 in *BDNF* locus.



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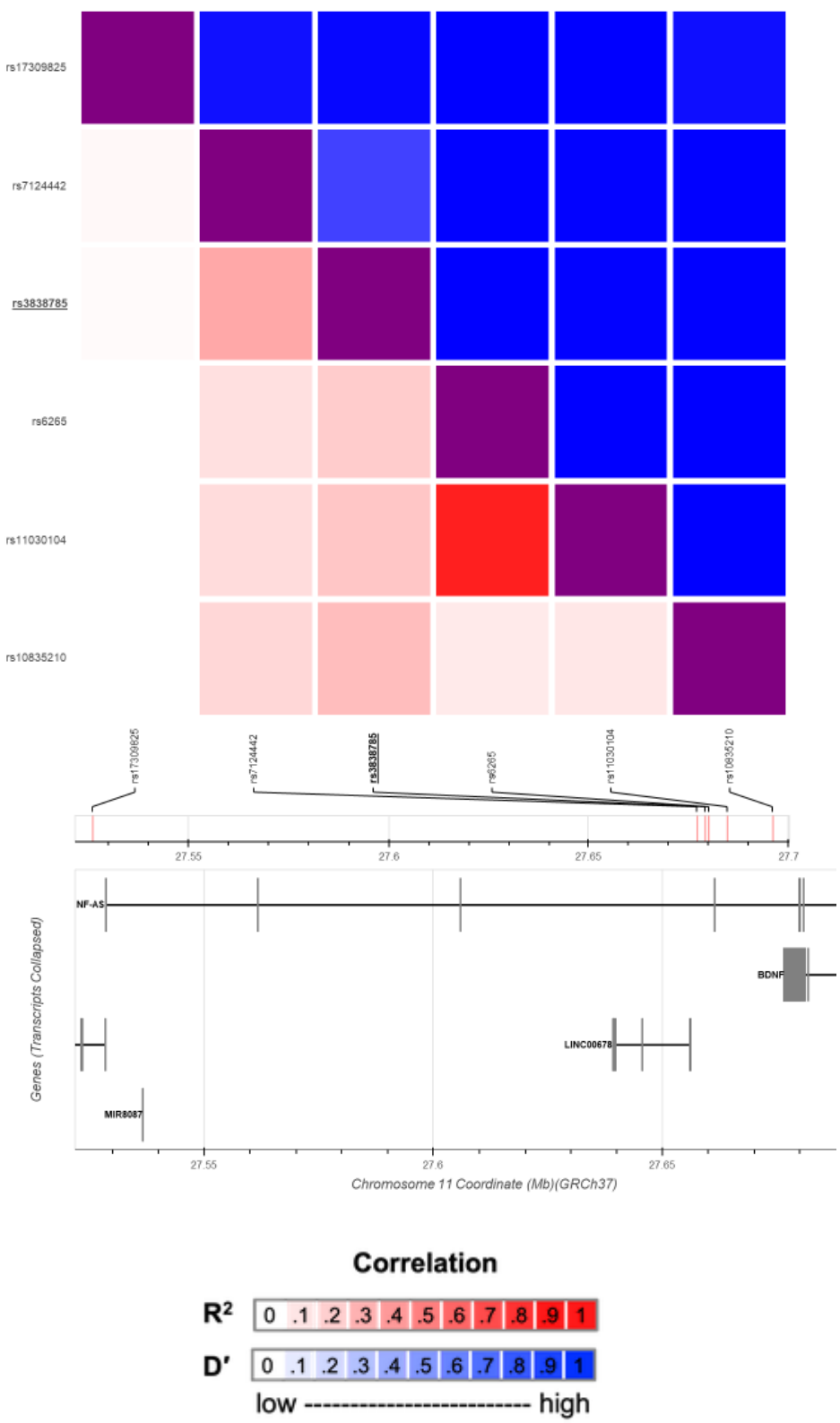
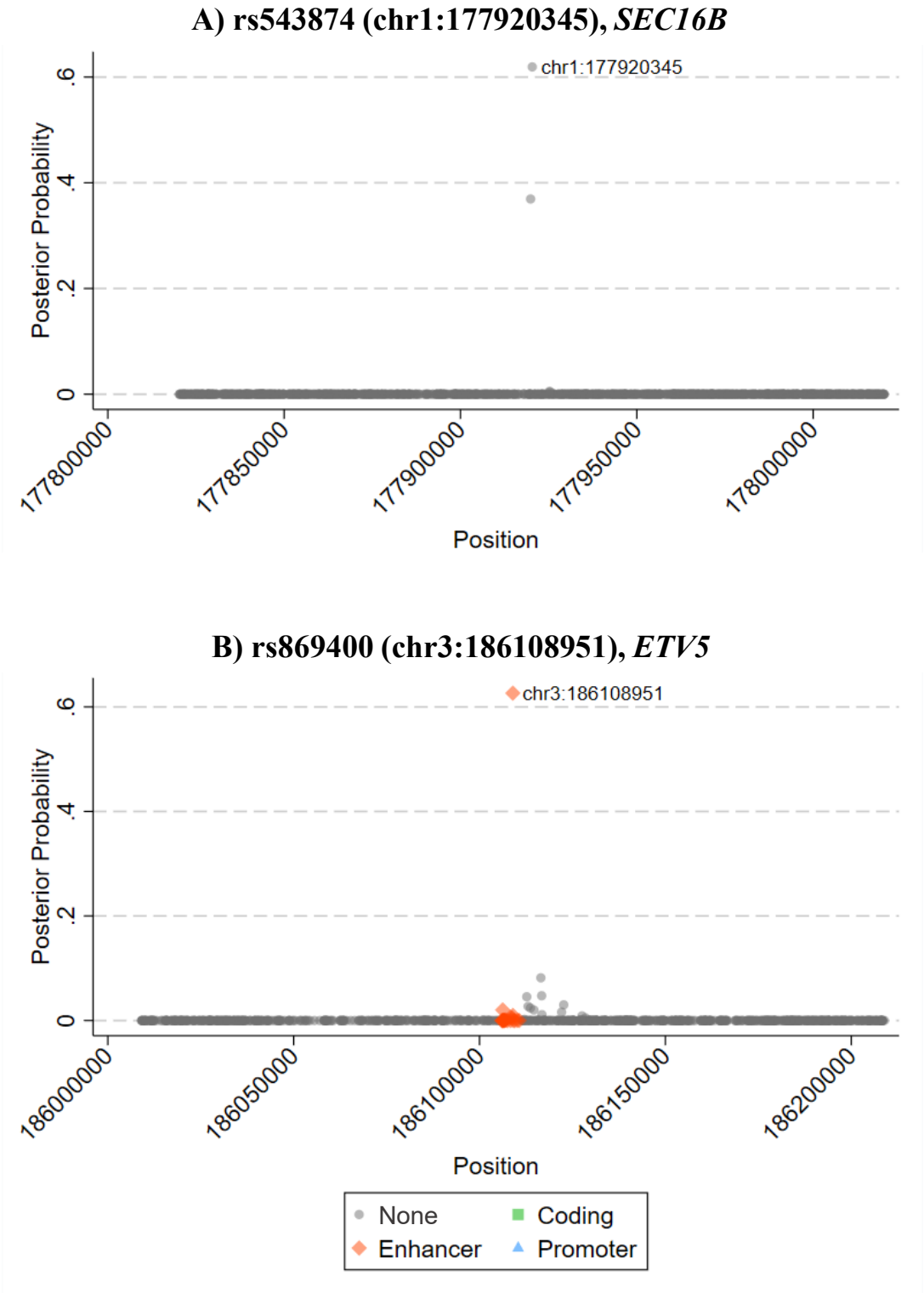
B.



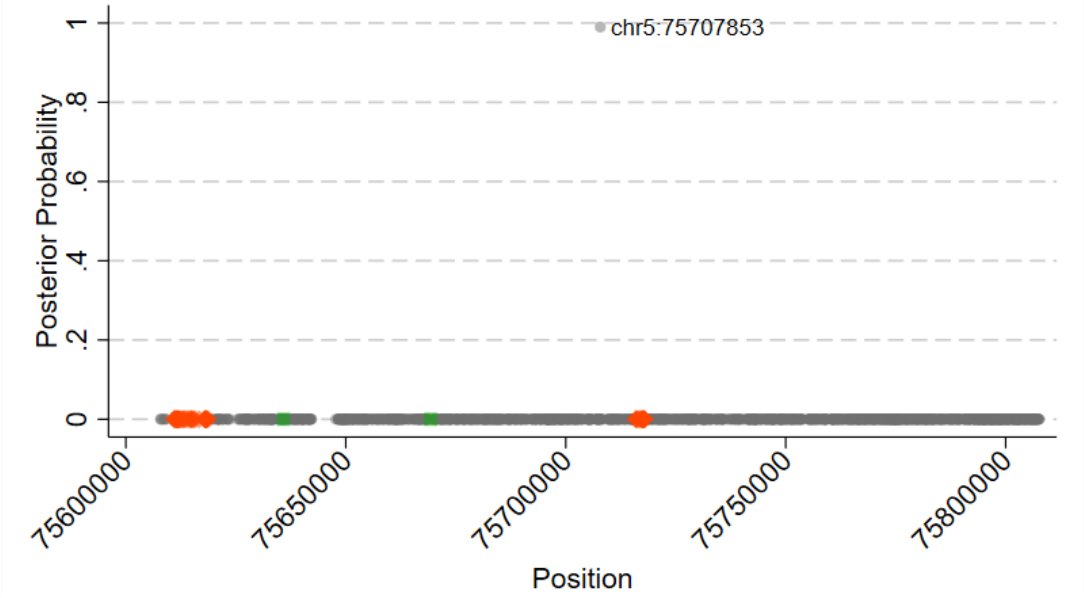
Supplementary Figure 12. Fine-mapping regional plots

Regional plots of posterior probability (PP) from fine-mapping analysis in PAINTOR, including all variants ± 100 kb from index variant for each locus with any variant exhibiting a moderate PP > 0.5. The plots appear in order of chromosomal location. TOPMed study populations were used to calculate LD. Shape and color indicate potential functional consequence of each variant as reported in Variant Effect Prediction (VEP) tool or GeneHancer (see methods for details).

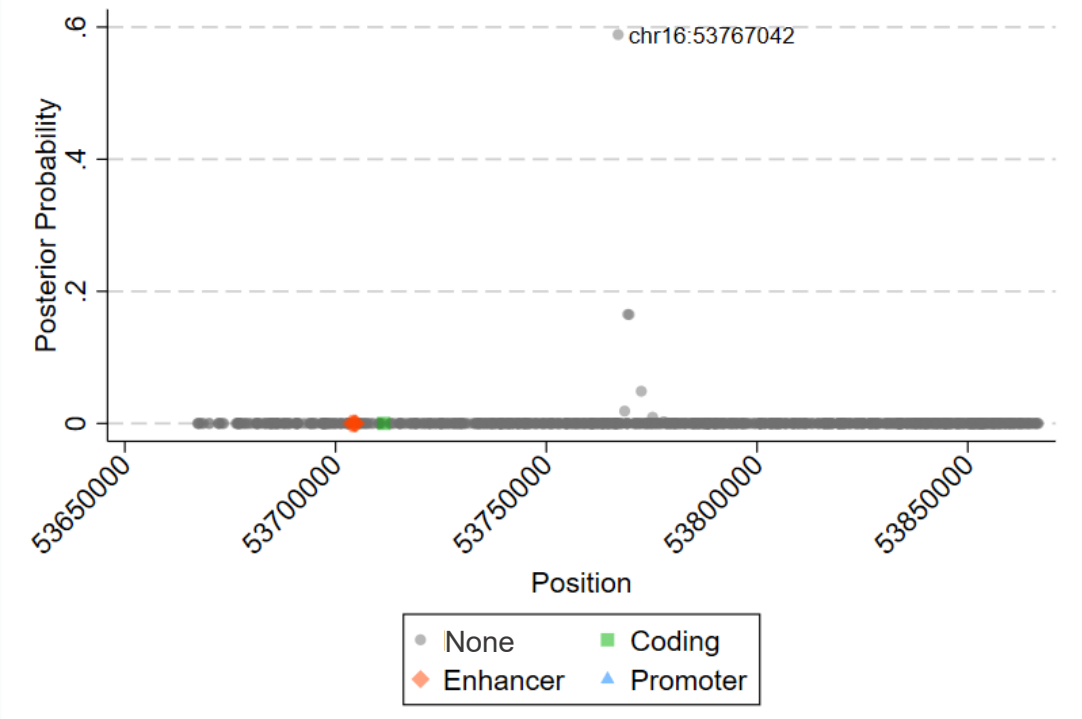
A) rs543874, *SEC16B;* B) rs869400, *ETV5*; C) rs2307111, *POC5*; D) rs1421085, *FTO*; E) rs6567160, *MC4R*; F) rs55731973, *ZC3H4*; G) rs1379871, *DMD*.



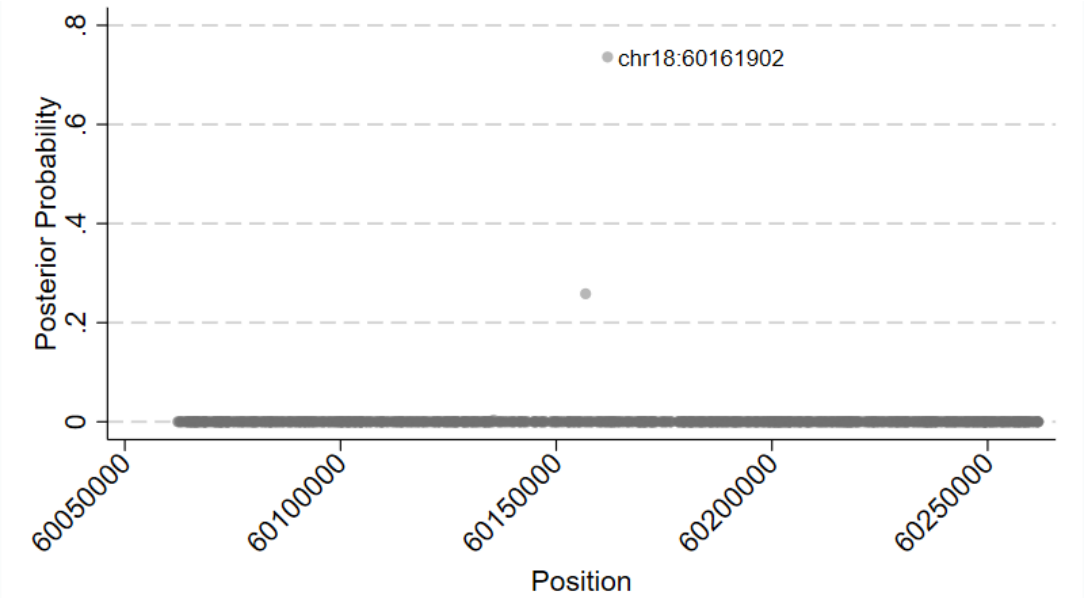
C) rs2307111 (chr5: 75707853), *POC5*



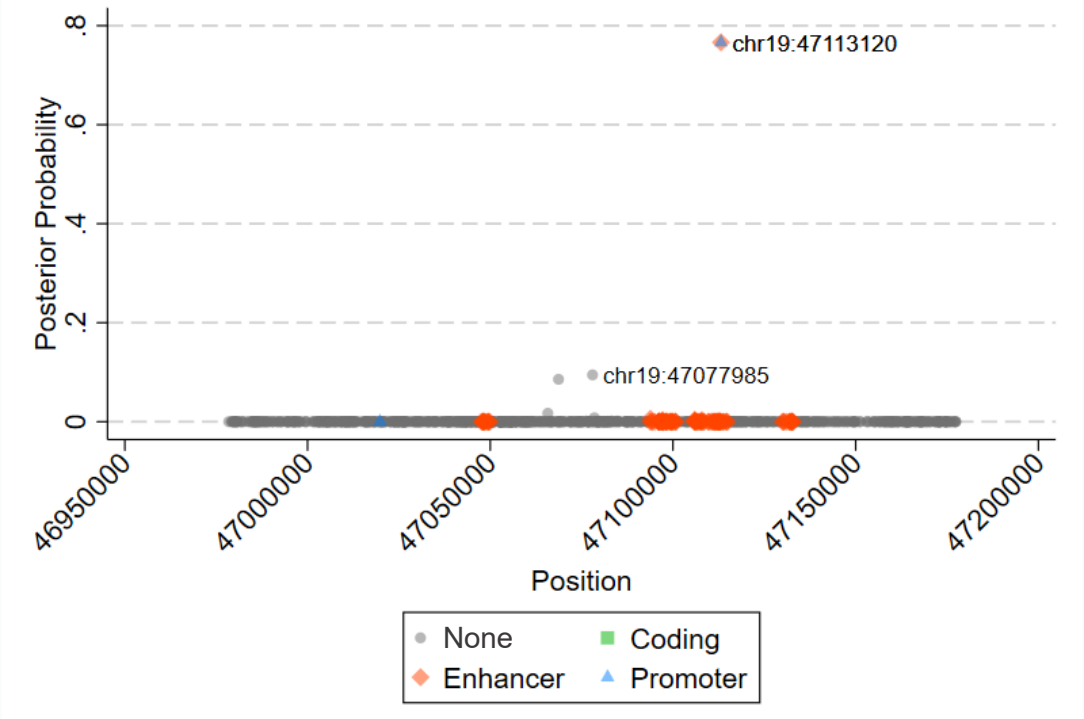
D) rs1421085 (chr16:53767042), *FTO*



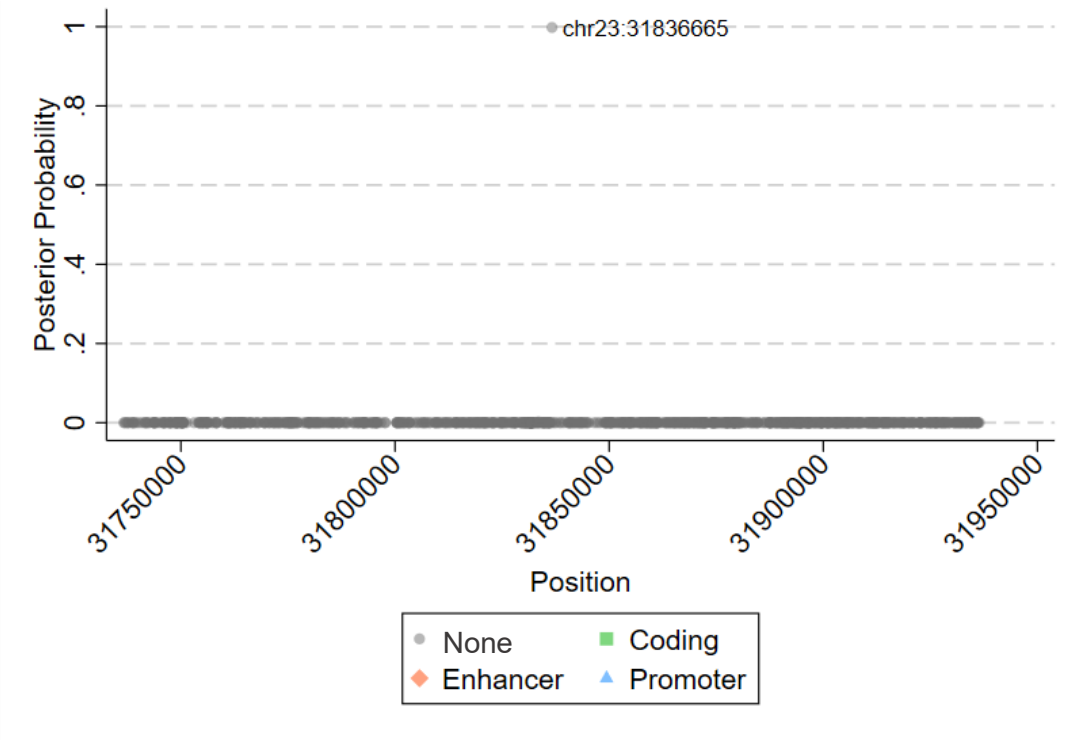
E) rs6567160 (chr18:60161902), *MC4R*



F) rs55731973 (chr19:47113120), *ZC3H4*

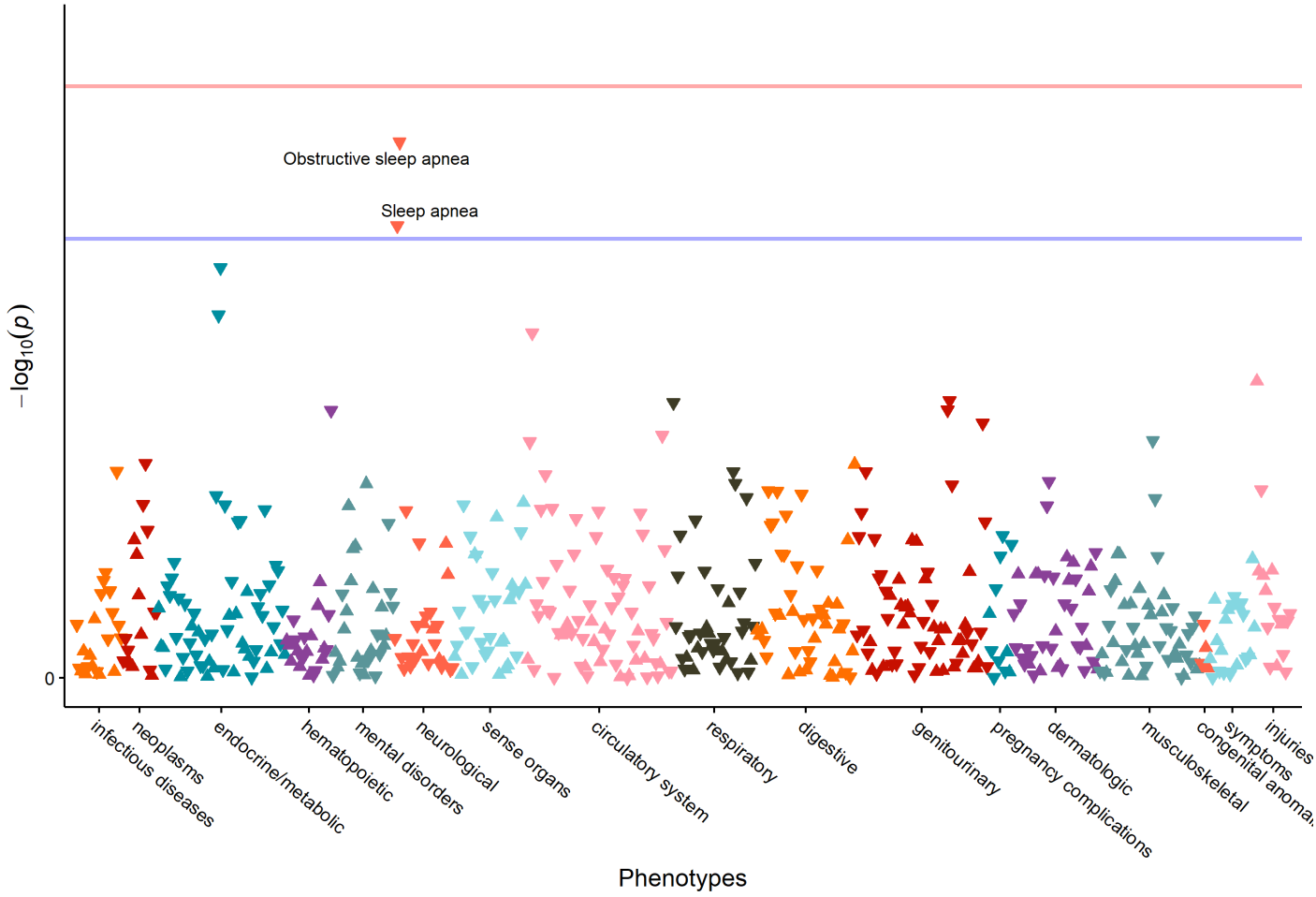


G) rs1379871 (chrX:31836665), *DMD*



Supplementary Figure 13. PheWAS meta-analysis Manhattan plot

Manhattan plot of the PheWAS meta-analysis results. The red line indicates phenome-wide significance threshold ($P < 0.05/538$ PheCodes $= 9.3 \times 10^{-5}$), and the blue line indicates suggestive significance ($P < 0.001$). Only suggestively significant PheCodes are annotate with their phenotype. Arrow indicates direction of effect.



SUPPLEMENTARY NOTE

I. REPLICATION COHORTS DESCRIPTIONS

MEC (Multiethnic Cohort) is a population-based prospective cohort study including approximately 215,000 men and women from Hawaii and California [Kolonel, L. N. et al. A multiethnic cohort in Hawaii and Los Angeles: baseline characteristics. Am. J. 869 Epidemiol. 151, 346–357 (2000)]. All participants were 45-75 years of age at baseline, and primarily of five ancestries: Japanese Americans, African Americans, European Americans, Hispanic/Latinos, and Native Hawaiians. MEC was funded by the National Cancer Institute in 1993 to examine lifestyle risk factors and genetic susceptibility to cancer. All eligible cohort members completed baseline and follow-up questionnaires. Participants from the MEC sample in the current analyses included 3,825 women and 3,281 men who self-reported African American background, had measured height and weight available, and had genetic data available. Of these, 4,593 were genotyped on the MEGA chip and 2,513 were genotyped on the Illumina Human1M-Duo chip.

MVP (Million Veteran Program) participants were recruited from over 60 Veterans Health Administration medical centers nationwide since 2011. The design of MVP has been previously described [1]. A unique feature of MVP is the linkage of a large biobank to an extensive, national, database from 2003 onward that integrates multiple elements such as diagnosis codes, procedure codes, laboratory values, and imaging reports, which permits detailed phenotyping of this large cohort. MVP has received ethical and study protocol approval by the Veterans Affairs Central Institutional Review Board in accordance with the principles outlined in the Declaration of Helsinki. DNA extracted from participants' blood was genotyped using a customized Affymetrix Axiom® biobank array, the MVP 1.0 Genotyping Array. The array was enriched for both common and rare genetic variants of clinical significance in different ethnic backgrounds. Quality-control procedures used to assign ancestry, remove low-quality samples and variants, and perform genotype imputation were previously described [2]. We excluded: duplicate samples, samples with more heterozygosity than expected an excess (>2.5%) of missing genotype calls, or discordance between genetically inferred sex and phenotypic gender. In addition, one individual from each pair of related individuals (more than second degree relatedness as measured by the KING software) were removed. The MVP participants were assigned to mutually exclusive racial/ethnic groups using HARE (Harmonized Ancestry and Race/Ethnicity), a machine learning algorithm that integrates genetically inferred ancestry with self-identified race/ethnicity [3]. The present study included non-Hispanic African Americans with both genotypic and phenotypic data for genetic association analyses. The phenotyping and analytical details of body mass index in the MVP were previously described [4]. SNP rs111490516 was imputed with quality score of 0.7083.

The UK Biobank is a prospective cohort study with genetic and phenotypic data on more than 500,000 individuals, aged between 39–69 years. Study design, protocols, sample handling and quality control have been described in detail elsewhere (PMID: 25826379 and PMID: 30305743). African ancestry was determined using k-means clustering (PMID: 32692746). Briefly, clustering was performed by projecting the 1000 genomes reference panel dataset based on the PCA loadings from the UK Biobank. We performed k-means clustering with a pre-specified number of 4 clusters. Individuals from the UK Biobank that clustered with the AFR 1000G cluster were assigned African ancestry.

REGARDS (The Reasons for Geographic and Racial Differences in Stroke project), sponsored by the National Institutes of Health (NIH), is a national study focusing on learning more about the factors that increase a person's risk of having a stroke. REGARDS is an observational study of risk factors for stroke in unrelated adults 45 years or older. 30,239 African American and European American participants were recruited between January 2003 and October 2007. The study design and objectives have been previously described [5]. MEGAEX genotype data is available for 8,837 African American and 1,716 European

American REGARDS participants. The study is ongoing and will follow participants for many years.

BioMe is an ongoing electronic medical record-linked biobank with more than 60,000 patients enrolled through the Mount Sinai Health System in New York. BioMe is a multiethnic biobank comprising individuals of African, Hispanic, European, Asian, and other ancestries [6]. Genotyping data is available on 32,595 individuals and was done using the Global Screening Array (GSA-24v1-0_A1). The data was cleaned for duplicate samples, discordant sex, heterozygosity rate that exceeded 6 SD from the population mean, call rate<95% at the site and individual level, and deviation from Hardy Weinberg equilibrium. Replication was conducted within self-reported African ancestry.

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NHLBI TOPMed: The Genetic Epidemiology of Asthma in Costa Rica - Asthma in Costa Rica cohort (CRA)

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NHLBI TOPMed: Samoan Adiposity Study (Samoan)

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NHLBI TOPMed: Taiwan Study of Hypertension using Rare Variants (THRV)
The Rare Variants for Hypertension in Taiwan Chinese (THRV) is supported by the National Heart, Lung, and Blood Institute (NHLBI) grant (R01HL111249) and its participation in TOPMed is supported by an NHLBI supplement (R01HL111249-04S1). THRV is a collaborative study between Washington University in St. Louis, LA BioMed at Harbor UCLA, University of Texas in Houston, Taichung Veterans General Hospital, Taipei Veterans General Hospital, Tri-Service General Hospital, National Health Research Institutes, National Taiwan University, and Baylor University. THRV is based (substantially) on the parent SAPPHIRe study, along with additional population-based and hospital-based cohorts. SAPPHIRe was supported by NHLBI grants (U01HL54527, U01HL54498) and Taiwan funds, and the other cohorts were supported by Taiwan funds.

NHLBI TOPMed: Vanderbilt Atrial Fibrillation Ablation Registry (VAFAR)

NHLBI TOPMed: Vanderbilt Genetic Basis of Atrial Fibrillation (VU_AF)

NHLBI TOPMed: Treatment of Pulmonary Hypertension and Sickle Cell Disease with Sildenafil Therapy (walk_PHaSST)
We thank Dr. Mark Gladwin and the investigators of the Walk-PHasst study and the patients who participated in the study. We also thanks the walk-PHaSST clinical site team: Albert Einstein College of Medicine: Jane Little and Verlene Davis; Columbia University: Robyn Barst, Erika Rosenzweig, Margaret Lee and Daniela Brady; UCSF Benioff Children's Hospital Oakland: Claudia Morris, Ward Hagar, Lisa Lavrisha, Howard Rosenfeld, and Elliott Vichinsky; Children's Hospital of Pittsburgh of UPMC: Regina McCollum; Hammersmith Hospital, London: Sally Davies, Gaia Mahalingam, Sharon Meehan, Ofelia Lebanto, and Ines Cabrita; Howard University: Victor Gordeuk, Oswaldo Castro, Onyinye Onyekwere, Vandana Sachdev, Alvin Thomas, Gladys Onojobi, Sharmin Diaz, Margaret Fadojutimi-Akinsiku, and Randa Aladdin; Johns Hopkins University: Reda Girgis, Sophie Lanzkron and Durrant Barasa; NHLBI: Mark Gladwin, Greg Kato, James Taylor, Wynona Coles, Catherine Seamon, Mary Hall, Amy Chi, Cynthia Brenneman, Wen Li, and Erin Smith; University of Colorado: Kathryn Hassell, David Badesch, Deb McCollister and Julie McAfee; University of Illinois at Chicago: Dean Schraufnagel, Robert Molokie, George Kondos, Patricia Cole-Saffold, and Lani Krauz; National Heart & Lung Institute, Imperial College London: Simon Gibbs. Thanks also to the data coordination center team from Rho, Inc.: Nancy Yovetich, Rob Woolson, Jamie Spencer, Christopher Woods, Karen Kesler, Vickie Coble, and Ronald W. Helms. We also thank Dr. Yingze Zhang for directing the Walk-PHasst repository and Dr. Mehdi Nouraie for maintaining the Walk-PHasst database and Dr. Jonathan Goldsmith as a NIH program director for this study. Special thanks to the volunteers who participated in the Walk-PHaSST study. This project was funded with federal funds from the NHLBI, NIH, Department of Health and Human Services, under contract HHSN268200617182C. This study is registered at www.clinicaltrials.gov as NCT00492531. Detail description of the study was published in Blood, 2011

118:855-864, Machado et al "Hospitalization for pain in patients with sickle cell disease treated with sildenafil for elevated TRV and low exercise capacity".

NHLBI TOPMed: Women's Genome Health Study (WGHS)
The WGHS is supported by the National Heart, Lung, and Blood Institute (HL043851 and HL080467) and the National Cancer Institute (CA047988 and UM1CA182913). The most recent cardiovascular endpoints were supported by ARRA funding HL099355.

NHLBI TOPMed: Women's Health Initiative (WHI)
The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts 75N92021D00001, 75N92021D00002, 75N92021D00003, 75N92021D00004, 75N92021D00005.

The Multiethnic Cohort (MEC) is a population-based prospective cohort study including approximately 215,000 men and women from Hawaii and California. All participants were 45-75 years of age at baseline, and primarily of 5 ancestries: Japanese Americans, African Americans, European Americans, Hispanic/Latinos, and Native Hawaiians. (PMIDs: 10695593; 23449381) MEC was funded by the National Cancer Institute in 1993 to examine lifestyle risk factors and genetic susceptibility to cancer. All eligible cohort members completed baseline and follow-up questionnaires. Within the PAGE II investigation, MEC proposes to study: 1) diseases for which we have DNA available for large numbers of cases and controls (breast, prostate, and colorectal cancer, diabetes, and obesity); 2) common traits that are risk factors for these diseases (e.g., body mass index / weight, waist-to-hip ratio, height), and 3) relevant disease-associated biomarkers (e.g., fasting insulin and lipids, steroid hormones). The specific aims are: 1) to determine the population-based epidemiologic profile (allele frequency, main effect, heterogeneity by disease characteristics) of putative causal variants in the five racial/ethnic groups in MEC; 2) for variants displaying effect heterogeneity across ethnic/racial groups, we will utilize differences in LD to identify a more complete spectrum of associated variants at these loci; 3) investigate gene x gene and gene x environment interactions to identify modifiers; 4) examine the associations of putative causal variants with already measured intermediate phenotypes (e.g., plasma insulin, lipids, steroid hormones); and 5) for variants that do not fall within known genes, start to investigate their relationships with gene expression and epigenetic patterns in small genomic studies. The studies listed here are individuals of African and Latino American ancestry/ethnicity who were part of the breast cancer or prostate cancer case/controls substuides. (dbGaP study accession number: phs000220).

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