SUPPLEMENTARY NOTE 1. Look-up of previously identified loci in our data set

To fully explore the efficacy of accounting for smoking in GWAS of adiposity traits, we conducted a look-up in our data of recently published SNP associations with BMI, WHRadjBMI, and WCadjBMI identified in well-powered GWAS meta-analyses that did not account for SMK status[1,2]. Although our sample size was as little as one third of previously published GWAS[1,2], the majority of these loci (92% for BMI, 97% for WCadjBMI, and 92% for WHRadjBMI) reached Bonferroni corrected significant for at least one of the three Approaches in the current study.

All previously identified 97 BMI-associated SNPs were nominally significant (P<0.05) in Approach 1 (SNPadjSMK) for BMI including the sex-specific loci, 95 of the 97 for Approach 2 (SNPjoint), and seven for Approach 3 (SNPint). A total of 86 loci reached Bonferroni-corrected significance ($P<5.15\times10^{-4}$) for Approach 1, 85 for Approach 2, and none for Approach 3. Finally, 41 loci from Approach 1 and 39 of the 97 from Approach 2 reached genome-wide significance (GWS, $P<5\times10^{-8}$) (44 in total, 45%) (**Supplementary Table 11**). Of the 97 previously identified main effects loci for BMI, 3 of these were genome-wide significant GWS for women-only, 3 for men-only and the remaining in the sex-combined analysis in the previous publication. It is also worth noting that we report results for the All Ancestries meta-analysis, as this was our primary meta-analysis data-set; however, Locke et al. (2015) considered their European-descent only meta-analysis their primary data-set.

Of the 77 previously-identified WCadjBMI loci, 3 of these were GWS for women-only, 3 for men-only and the remaining in the sex-combined analysis as reported in Shungin et al[2]. Of these, 75 were nominally significant for Approachch 1 (SNPadjSMK) and Approach 2 (SNPjoint), and 5 for Approach 3 (SNPint). A total of 73 were Bonferroni-corrected significant ($P<6.49\times10^{-4}$) for Approach 1 and 2; with 41 and 40 reaching GWS, respectively (43 non-overlapping, 56%) (**Supplementary Table 12**).

Eleven of the 68 previously published WHRadjBMI SNPs were associated in the women-only analyses in the previous investigation[2]. Of the 68 variants, 64 were nominally significant for Approach 1 (SNPadjSMK), 59 for Approach 2 (SNPjoint), and 10 for Approach 3 (SNPint). A total of 61 were Bonferroni-corrected significant ($P<6.49\times10^{-4}$) for Approach 1 and 38 for Approach 2; with 36 and 8 reaching GWS, respectively (36 in total, 53%) (**Supplementary Table 13**).

In summary, we replicated all previously-identified BMI loci using one or more of our approaches (P<0.05 and concordant direction of effect), but did not replicate all previously-identified loci for WCadjBMI and WHRadjBMI in our current analyses. It is unclear if the lack of replication of previous findings is due to smaller sample size, patterns of linkage disequilibrium in our all ancestries sample, the adjustment of smoking status in the current discovery analysis, or even a combination of these factors.

SUPPLEMENTARY NOTE 2. Summary of literature search on genes nearest to the 21 novel loci and all GxSMK interaction loci.

We used SNIPPER (http://csg.sph.umich.edu/boehnke/snipper/) to identify potential biological functions of genes ±500kb of our novel association signals and those from Approach 3 (SNPint) for further investigation, and present a summary of those findings in this section (**Online Methods**).

Body Mass Index (BMI)

rs2481665 (*INADL*): There are seven genes within the 500kb region of the lead SNP rs2481665 on chromosome 1. These genes are *INADL, L1TD1, KANK4, USP1, DOCK7, TM2D1,* and *ANGPTL3*. The lead SNP is in intron (#15) of the *INADL* (InaD-Like) gene. *INADL* encodes the protein Palsi1-Associated Tight Junction (PATJ), which helps regulate the formation of tight junctions, and is involved in the processes of cell polarization and directional migration of epithelial cells[3,4]. A GWAS study (n= 815) designed to identify variants associated with childhood obesity in the Hispanic population, found near genome-wide significant associations between the exonic, non-synonymous SNP rs1056513 in *INADL* (204 kb downstream from our lead SNP) and the following fat distribution traits: weight [kg] (EAF[effect allele frequency]: 0.031, p-value: 1.18×10^{-07}); BMI [kg/m^2] (EAF: 0.021, p-value: 8.34×10^{-06}); fat mass [kg] (EAF: 0.035, p-value: 1.59×10^{-07}); trunk fat mass [kg] (EAF: 0.035, p-value: 2.36×10^{-07}); fat free mass [kg] (EAF: 0.034, p-value: 2.80×10^{-07}) and hip circumference (EAF: 0.022, p-value: 2.47×10^{-6}).[5] The SNP rs1056513 accounted for 3% of the variance in body weight and body composition[5]. However, this SNP is not in LD with the lead SNP rs2481665 in this study (R^2<0.2).

Farther away is the *DOCK7* gene, 326 kb downstream from the lead SNP. This gene encodes a guanine nucleotide exchange factor (GEF) protein that is involved in axon formation and neuronal polarization. GWAS studies have reported the association of variants located near the *DOCK7* gene with lipid levels. A GWAS study (n= up to 18,554) conducted with individuals of European ancestry identified the association of rs1213033 with triglycerides (eaf: -0.11, 2×10^{-8})[6]. Another GWAS meta-analysis found a genome-wide significant association between rs1168013 and triglycerides in individuals of European ancestry (n=17,723; eaf: 0.035 (0.007), p-value: 6.4×10^{-8})[7]. However, authors could not replicate this finding in other study samples consisting of 37,774 Europeans and 9,665 individuals of Indian Asian ethnicity. A GWAS replication study assessing the association between 15 SNPs and blood lipid and lipoprotein concentrations in individuals of Asian descent (n=4638), found a marginal association between the variant rs10889353, located in the intronic region of *DOCK7*, and triglycerides (eaf: -0.08, p-value: 6.5×10^{-04})[8]. None of the variants from the different GWAS studies discussed above are in LD with SNP rs2481665 (R^2<0.2).

TM2D1 is another gene in the 500kb area that is 404 kb upstream from rs2481665. This gene encodes a beta-amyloid peptide-binding protein (BBP), which is involved in neural death and in the decrease of cognitive skills that occurs in Alzheimer's disease**.** This protein may be targeted by the beta-amyloid peptide which has been linked to the formation of plaques resulting in neurotoxicity in Alzheimer's disease[9]. The APP, the precursor of beta-amyloid peptide, is expressed in adipose tissue and its expression is up-regulated in obesity[10,11].

ANGPTL3 (Angiopoietin-Like 3) is 469 kb upstream from the lead SNP, and upstream of the *DOCK7* gene. *ANGPTL3* encodes a protein that plays a role in angiogenesis. This protein is expressed mostly in the liver. Mutations in this gene lead to the disease familial hypobetalipoproteinemia type 2 (*FHBL2*), which causes low levels of apolipoprotein B (apoB), total cholesterol, low-density lipoprotein (LDL) cholesterol and high density lipoprotein cholesterol [12]. Several genetic association studies suggest that ANGPTL3 has a role in regulating plasma lipoprotein metabolism[6,8,13,14]. A few single-nucleotide polymorphisms, near the *ANGPTL3* gene, have been associated with lower triglyceride: rs1213033, rs213192, rs12042319[6]. One of these, rs1213033, is also near the *DOCK7* gene[6].

There are several nearby genes with no documented role in adiposity or related cardiometabolic traits. Including, *L1TD1* (Line-1 type transposase domain containing 1) located 66 kb upstream from the lead SNP. *L1TD1* encodes the protein ES Cell-Associated Protein 11, a RNA-binding protein that plays a role in maintaining the pluripotency of stem cells, and in the proliferation of cancer cells[15,16]. Also, *KANK4* (KN

motif and ankyrin repeat domains 4) is a gene located 107 kb downstream from our SNP of interest. It encodes the protein Ankyrin Repeat Domain 38, a member of the Kank family of proteins, which are involved in the control of cytoskeleton microfilaments by regulating the polymerization of actin. The Kank gene is a tumor suppressor in renal cell carcinoma[17]. *USP1*, 307 kb upstream from rs2481665, encodes a protein that cleaves ubiquitin, a peptide that is added to proteins to signal them for degradation, or modification of their cellular location or enzymatic activity.

The intronic rs2481665 variant does not seem to have a functional role (Score 4 in RegulomeDB[18]). Two eQTLs were found for rs2481665 (Gene: L1TD1, p-value: 2.1×10^{-7}, EAF: -0.73, tissue: brain-cerebellum) and (Gene: INALD, p-value: 4.0×10^{-6}, EAF: 0.29, tissue: heart-atrial appendage).

rs10929925 (*LOC400940*): *LOC400940* and *SOX11* are the two genes on Chr2 that are within 500 kb of the lead SNP rs10929925. SNP rs10929925 is downstream of *LOC400940*, the nearest gene, a non-coding RNA gene that remains uncharacterized. The variant is also 314 kb downstream from *SOX11*, a gene without introns that encodes a transcription factor that is part of the SOX (SRY-related HMG-box) family. This family of transcription factors is involved with processes that regulate embryonic development and cell fate[19]. One study has proposed that *SOX11* has a role in brain development after observing that mutations in the gene may lead to microcephaly, developmental delays and other features found in mild Coffin-Siris Syndrome, a genetic disorder that causes developmental delays[20]. A recent GWAS meta-analysis study of fat distribution, which included 224,459 individuals of European and non-European ancestry, identified a genome wide significant association ($p=4.5 \times 10^{-8}$) between rs10929925 and hip circumference unadjusted for BMI [2]. Based on a literature review, the study identified *SOX11* as the best candidate gene for rs10929925.[2]

There is no available information regarding the potential regulatory role of the lead SNP (RegulomeDB[18]). But there is evidence of an eQTL, although it does not reach 5% FDR (Gene: *SOX11*, P-value: 8.7×10^{-6}, Effect size: 0.39, Tissue: thyroid). In brain tissue, the SNP altered the TATA box motif of the DIx3 gene a homeodomain gene (HaploReg[21]).

rs6794880 (*SRRM1P2):* The 500kb region around the lead SNP, rs6794880, does not show the presence of any protein coding genes. The nearest genomic feature to rs6794880 is SRRM1P2, a pseudogene, named the serine/arginine repetitive matrix 1 pseudogene 2. Upstream rs6794880 is *LINC00971*, a long intergenic non-protein coding RNA gene that remains uncharacterized.

There is no evidence that the lead SNP rs6794880 has a functional/regulatory role (Score 6 in RegulomeDB[18]) in the genome. Additionally, there are no reports of eQTLs for this variant.

rs12629427 *(EPHA3)*: There is only one gene found within 500kb of the peak signal, rs12629427. *EPHA3* (EPH receptor A3) is 11kb downstream from rs12629427, and is a member of the ephrin receptor subfamily of the protein-tyrosine kinase family. EPH and EPH-related receptors have been implicated in mediating developmental events, particularly in the nervous system. This gene encodes a protein that binds ephrin-A ligands. *EPHA3* has been implicated in the pathogenesis of lung cancer[22-26]. The SNP rs12629427 has a score of 6 in RegulomeDB[18] (minimal binding evidence). No significant eQTLs were found for rs12629427 and no GWAS hits were identified within the 1MB region of the lead SNP.

rs2173039 (*EPHA3*): There is only one gene found within 500kb of rs2173039, which is 14.5kb upstream from EPHA3 (EPH receptor A3). See rs12629427 above.

rs13069244 (*CCDC39*): A total of 4 genes are found within 500kb of the lead marker, rs13069244. *CCDC39* (coiled-coil domain containing 39) is located 43.88kb downstream from the lead marker and encodes a protein involved in the motility of cilia and flagella. Defects in this gene cause primary ciliary dyskinesia type 14. Lung disease was worse in those with IDA/CA/MTD ultrastructural defects, most of whom had biallelic mutations in *CCDC39*[27]. *FXR1* (fragile X mental retardation, autosomal homolog 1) is located 189kb downstream from rs13069244, and codes for an RNA binding protein that shuttles between the nucleus and cytoplasm, and is associated with polyribosomes, predominantly with the 60S ribosomal subunit. Deregulation of FXR protein 1 by the lipodystrophic lamin A p.R482W mutation elicits a myogenic gene expression program in preadipocytes[28]. *DNAJC19* (DnaJ (Hsp40) homolog, subfamily C, member 19), located 260kb upstream from our lead marker, encodes a protein involved in the ATP-dependent transport of transit peptide-containing proteins from the inner cell membrane to the mitochondrial matrix. Defects in this gene are a cause of 3-methylglutaconic aciduria type 5 (MGA5), also known as dilated cardiomyopathy with ataxia (DCMA)[29-31]. The loss of DNAJC19/PHB complexes affects cardiolipin acylation and leads to the accumulation of cardiolipin species with altered acyl chains[32]. There is no evidence that rs13069244 has a functional/regulatory role (RegulomeDB[18] Score 6: minimal binding evidence) in the genome. No GWAS hits were identified within the 1Mb region of rs13069244 and no report of eQTL for the variant.

rs336396 (*INPP4B*): There are two genes found within 500kb of rs336396. The SNP lies within *INPP4B* (inositol polyphosphate-4-phosphatase, type II, 105kDa), which encodes inositol polyphosphate 4-phosphatase type II, one of the enzymes involved in phosphatidylinositol signaling pathways. INPP4B has been identified as a tumor suppressor by negatively regulating normal and malignant cell proliferation through regulation of the PI3K/Akt signaling pathway[33,34]. Different residues within the catalytic site of INPP4B are responsible for activity with lipid and protein substrates[35]. *IL15* (interleukin 15) is located 407kb upstream of rs336396. *IL15* encodes a cytokine that regulates T and natural killer (NK) cell activation and proliferation. This cytokine may act as an antagonist to IL2, which binds common hematopoietin receptor subunits, and may compete for the same receptor. This cytokine induces the activation of JAK kinases, as well as the phosphorylation and activation of transcription activators STAT3, STAT5, and STAT6. Murine models show that this cytokine may increase expression of apoptosis inhibitor BCL2L1/BCL-x(L), possibly through the transcription activation activity of STAT6, and thus prevent apoptosis. Cigarette smoke compromises IL-15 production – and as a result NK cell function – which could link to the higher incidence of cancers or viral infections observed among smokers[36]. A group of SNPs, upstream from *IL15*, were associated with both smoking status and quantity of cigarette consumption[37]. No data was provided for rs336396 by RegulomeDB[18]. No GWAS hits were identified within the 1Mb region of rs336396 and no report of an eQTL for the variant.

rs12902602 (*CHRNA5-CHRNA3-CHRNB4*): A total of 10 genes are found within 500kb of rs12902602. The SNP is located 33.81kb upstream of *CHRNB4* (cholinergic receptor, nicotinic beta 4). The *CHRNA5-CHRNA3-CHRNB4* gene cluster has consistently been associated with smoking quantity and nicotine dependence[38-40], COPD, lung cancer and peripheral artery disease[39,41,42], and increased risk of death[43]. Variants of *CHRNA5-CHRNA3-CHRNB4* have also been associated with lower birth weight from smoking mothers[44], and with lower BMI in current adult smokers[45,46], but with lower BMI in never smokers[46]. The *CHRNA5-CHRNA3-CHRNB4* genes encode the nicotinic acetylcholine receptor (nAChR) subunits α3, α5 and β4 that are expressed in mammalian brain[47,48]. GWASs have also identified loci at *ADAMTS7* (ADAM metallopeptidase with thrombospondin type 1 motif 7), at 84.14 kb downstream from the leader SNP rs12902602, associated with coronary artery disease and its risk factors[49-52].

Waist Circumference adjusted for BMI (WCADJBMI):

rs17396340 (*KIF1B*). A total of 10 genes are found within 500kb of the lead marker, rs17396340, which is intronic to *KIF1B*. We highlight four genes in the region here. *KIF1B* is involved in synaptic vesicle and mitochondrial transport, and may play a critical role in the development of hepatocellular carcinoma[53]. *6PGD* codes for an oxidative carboxylase responsible for reduction of 6-phosphogluconate. Cells lacking 6PGD appear to metabolize glucose as an inhibitor to induce senescence[54]. *RBP7* is involved in carotenoid metabolism. In avian model organisms, the *RBP7* promoter is important in regulating expression of several genes in adipose tissue at later developmental stages[55]. Nicotinamide mononucleotide adenylyltransferease (*NMNAT*) reversibly catalyzes the important step in the biosynthesis of NAD from ATP and NMN. NAD and NADP are used reversibly in anabolic and catabolic reactions. NAD is necessary for cell survival in oxidative stress and DNA damage. The top SNP, rs17396340, is associated with the expression levels of ARSA (p-value of 6.0e-05) at LCL tissue in *Homo sapiens*. Human adipocytes express functional DAR (Dopamine receptors) and ARSA, suggesting a regulatory role for peripheral dopamine in adipose functions[56]. It is speculated that the propensity of some DAR-activating antipsychotics to increase weight and alter metabolic homeostasis is due to their direct action on adipose tissue. Our lead SNP is also associated with mean platelet volume[57]. From HaploReg[21], the lead SNP, rs17396340, is annotated as KIF1B in GENCODE, and is functionally annotated as intronic. This lead SNP is associated with enhancer histone marks in 9 tissues; associated with regulatory motifs at GATA and Hoxa5; and with cis-eQTLs from various tissues (cells transformed fibroblasts, muscle skeletal, lymphoblastoid EUR exonlevel, lymphoblastoid EUR genelevel, and whole blood). The RegulomeDB[18] score for the lead SNP is 4.

rs6743226 (*HDLBP*). A total of 10 genes are found within 500kb of our lead marker, rs6743226. Three, of biological interest, are mentioned here. Our lead SNP, rs6743226, is intronic to *HDLBP,* which codes for a protein that binds high density lipoprotein (HDL) that functions to regulate excess cholesterol levels in cells.

STK25 codes for a serine/threonine kinase with important functions in the Golgi apparatus. This gene has been associated with severe hypoxia[58] and pseudohypoparathyroidism, symptoms of which include short stature and obesity[59]. Significantly higher serine/threonine kinase 25 (STK25) levels were observed in the skeletal muscle of type 2 diabetic patients, compared with individuals with normal glucose tolerance[60]. The overexpression of STK25 in conditions of excess dietary fuels associates with a shift in the metabolic balance in peripheral tissues from lipid oxidation to storage, leading to a systemic insulin resistance[61].

Expression of PAS domain containing serine/threonine kinase (*PASK*) is regulated by glucose and the encoded protein plays a role in the regulation of insulin gene expression. Down regulation of this gene may play a role in type 2 diabetes[62-64]. Far2 and Stk25 are candidate genes for the HDL cholesterol locus in mice[65]. The top SNP, rs6743226, is associated with the expression of B-cell CLL/lymphoma 10 (BCL10). The protein encoded by the gene *BCL10* contains a caspase recruitment domain (CARD), and induce apoptosis and to activate NF-kappaB MALT1 and this protein are thought to synergize in the activation of NF-kappaB, and the deregulation of either of them may contribute to the same pathogenetic process that leads to the malignancy[66].

There is no GWAS signal nearby the lead SNP rs6743226. This lead SNP is associated with enhancer histone marks in 4 tissues; associated with regulatory motifs changed at Goxa and TCF12; and with eQTL from various tissues including adipose subcutaneous, lung, and muscle tissues. The RegulomeDB[18] score for the lead SNP is 6.

rs4378999 *(DOCK3)*: A total of 4 genes are found near our lead marker, rs4378999, *DOCK3*, *MANF*, *VPRBP*, and *RBM15B*. Our lead variant is intronic to *DOCK3* (dedicator of cytokinesis 3), which is highly expressed in the central nervous system and like previously identified obesity related genes, is involved in neurite outgrowth downstream of BDNF-TrkB[67]. *MANF* (mesencephalic astrocyte-derived neurotrophic factor) is an endoplasmic reticulum protein that acts to protect ER in response to cellular/organismal stress [68], for example, expression is increased in skeletal muscle of the leg in rats in response to exercise [69]. Further, recent evidence shows that *MANF* may be an important factor in the protection of pancreatic beta cells and disruption of *MANF* expression can lead to diabetes [68]. There is very little known about *VPRBP*, and *RBM15B.*

Genome-wide association studies have reported the association within 1MB region of lead SNPs for height (R^2=0.35)[70,71] and melanoma (R^2=0.48)[72]. Our lead SNP is associated with regulatory motifs changed at Cdx2; and with eQTL from various tissues including adipose subcutaneous, and muscle skeletal. The lead SNP is associated eQTL in esophagus muscularis tissue based on GTEx[73] lookup. GWAS studies have report the association within 1Mb of lead SNP for height (R^2=0.38)[71], and fibrinogen (R^2=0.41)[74]. The RegulomeDB[18] does not have data for lead SNP rs4378999.

rs7697556 (*ADAMTS3*): One gene is found within 500kb of our lead marker, rs7697556. ADAM metallopeptidase with thrombospondin type 1 motif, 3 (*ADAMTS3*) is located 80 kb upstream of our variant, rs7697556. While there is no established role for ADAMTS3 in obesity-related traits, there are a number of variants within and near this gene associated with relate anthropometric and cardiometabolic traits, including height[70,71], lipid metabolism[75], and metabolites[76]. From There is no score assigned for our lead SNP in the RegulomeDB[18].

rs10269774 (*CDK6*): A total of 10 genes are found within 500 kb of the lead marker, rs10269774. The SNP is located within an intron in cyclin-dependent kinase 6 (*CDK6*). CDK family members are important regulators of cell cycle progression. GWAS have reported associations between *CDK6* variants with height[70,71,77-81]. The *CDK6*-rs2282978 associated with height is in complete LD with our lead marker (rs10269774: R^2=1, D'=1). Also, GWAS identified associations between *CDK6* variants with white blood cell counts[82] and rheumatoid arthritis[83,84]. *CDK6* rs42041 is associated with juvenile idiopathic arthritis (JIA)[85], and patients with JIA are significantly shorter and more often overweight or obese than controls[86]. Research suggests that the microRNA-103a-3p controls proliferation and osteogenic differentiation of human adipose tissue-derived stromal cells by binding to specific target sequences in the *CDK6* mRNA 3'-untranslated region[87]. Another study in the human placental transcriptome found that *CDK6* mRNA levels correlated with offspring birth weight and birth weight percentiles[88].

rs10269774 is located in enhancer regions (H3K4Me1 and H3K27ac) with histone modification enrichment in mammary epithelial tissue and lymphoblastoid cell lines. rs10269774 was suggested to have cis-acting associations with five gamma-glutamyltransferase (GGT) family gene expression in lymphoblastoid of Yoruba population (p=6E−05[89]). Elevated serum GGT is associated with waist circumference[90,91], BMI[91], visceral fat area[91], triglyceride levels[91], metabolic syndrome[90,92], coronary artery calcification[93] and biomarkers of atherosclerosis[94], arterial stiffness[95,96], incident CVD and death[92]. rs10269774 is located near to several transcription factor binding sites (*CTCF*, *EP300*, *JUN*, *POLR2A*, *FOS, NFIC*, and *RFX5*, among others).

rs9409082 and rs9408815 (*TMEM38B*): A total of 3 genes are found within 500 kb of the lead markers rs9409082 and rs9408815. At 364 kb downstream of rs9409082 is located *TMEM38B* (transmembrane

protein 38B, 9q31.2) gene, which encodes an intracellular monovalent cation channel that functions in maintenance of intracellular calcium release. Deletions in *TMEM38B* are associated with autosomal recessive osteogenesis imperfecta[97-99]. There is evidence of genome-wide association between rs9409082 with height[70]. Also, GWAS have reported several variants in this region associated with age at menarche[100-102], which is a risk factor to develop obesity, type 2 diabetes, cardiovascular disease, breast cancer and all-cause mortality[101]. However, the reported variants for age at menarche are in low-to-moderate LD ($0.005 < R^2 < 0.68$) with our lead marker from Approach 1, rs9409082. Variants on 9q31, in low LD with rs9409082, have shown suggestive association with visceral adipose to subcutaneous adipose ratio in men ($R^2=0.161$)[103] and with a protein quantitative trait locus modulating cellular response to chemotherapy ($R^2=0.002$)[104].

At 497.6 kb downstream of rs9409082 is the *FKTN* (fukutin, 9q31.2) gene that encodes a putative transmembrane protein of the cis-Golgi compartment. *FKTN* protein may be involved in the glycosylation of alpha-dystroglycan in skeletal muscle. Mutations in *FKTN* have shown association with congenital muscular dystrophy[105,106]. No significant eQTLs were found for SNP rs9409082 (GTEx[73], SNIPPER, RegulomeDB[18], and HaploReg[21]).

rs6012558 (*ARFGEF2*): A total of 11 genes are found within 500kb +/- of our lead SNP, rs6012558, which is 6,989 bp upstream of *ARFGEF2* (ADP-ribosylation factor guanine nucleotide-exchange factor 2). *ARFGEF2*'s primary function involves intracellular trafficking. Our lead variant is 86,866 bp upstream of *PREX1* (phosphatidylinositol-3,4,5-trisphosphate-dependent Rac exchange factor 1), a gene which encodes a protein involved in intraceullar signaling, lipid and protein binding, and regulation of GTPase activity [107-109]. *PREX1* is primarily expressed in the blood leukocytes and brain[107]. Recent mouse models indicate that PREX1 may be important for the regulation of thermogenic potential of brown adipose tissue and white preadipocytes, making this gene very important for energy expenditure[110]. Additionally, rs6012558 is a significant (<5% FDR) cis-acting expression quantitative trait locus (cis-eQTL) for *ARFGEF2* (subcutaneous adipose and sigmoid colon tissues), *CSE1L* (artery, thyroid, subcutaneous adipose, esophagus mucosa, and skeletal muscle tissues), and *STAU1* (transformed fibroblast cells) (GTEx[73]). Additional evidence that this variant lies in a potentially important regulatory region includes a RegulomeDB[18] score of 4 [18], it is nearby (<500kb +/- and $R^2>0.7$) other variants that rest in active enhancers for *ARFGEF2*, other cis-eQTLs for *ARFGEF2* (monocytes, whole blood, cerebellum, and temporal cortex), *DDX27* (monocytes), *C2orf199* (monocytes), *CSE1L* (whole blood), and *PREX1* (Cerebellum and Temporal Cortex) (HaploReg[21] and UCSC Browser[111]). Our lead SNP is within 500kb +/- of several previously identified GWAS SNPs for multiple traits, the nearest of which is rs6012564 associated with tendency toward anger (distance=10kb)[112]; however, all of these are in low LD with rs6012558 ($R^2<0.3$).

rs4141488 (*GRIN2A*): There are only two genes within 500 kb +/- of our lead SNP, rs4141488, which lies 218 kb downstream of *GRIN2A* (glutamate receptor, ionotropic, N-methyl D-aspartate 2A). The primary function of *GRIN2A* is to assist in controlling long-term memory and learning through regulation and efficiency of synaptic transmission. These receptors are essentially the gateway for calcium into post-synaptic cells[113]. Variants in this gene have been associated with various forms of epilepsy, sleep patterns, delayed psychomotor development, speech difficulties, seizures, mental retardation, and various mental disorders, including heroin addiction[114-120]. The only other gene within 500 kb of rs4141488 is C16orf72; little is known about the function of this gene. While GTEx[73] revealed no significant eQTLs nearby our lead variant, there is some evidence that this locus may lie within an important regulatory region. RegulomeDB[18] provided a score of 5 (minimal binding evidence) for rs4141488. Additionally, HaploReg[21] and UCSC browser show that our lead SNP and variants in high LD

(R^2>0.7) are within active enhancer regions for several tissues, including liver, fetal leg muscle, smooth stomach and intestinal muscle, cortex, and several embryonic and pluripotent cell types; and within altered binding motifs for EWSR1-FLI1, Elf3, STAT, CDP, HNF1, and SOX. Our lead SNP is within 500kb +/- of several previously identified GWAS SNPs for multiple traits, the nearest of which is rs17550532 associated with sudden cardiac arrest[121]. Other associations in this region include behavioral disinhibition[122], venous thromboembolism[123], and Transforming Growth Factor-β1 [5]; however, all of these are in low LD with rs4141488 (R^2<0.4).

rs1545348 (*RAI14*): Our lead SNP, rs1545348, lies within the intron of *RAI14* (Retinoic Acid Induced 14), although very little is known about the function of this gene in humans. There are four additional genes within 500 kb+/- of rs1545348, including *RAD1* (RAD1 checkpoint DNA exonuclease) 187 kb upstream. *RAD1* encodes a protein involved in stopping the cell cycle in response to DNA damage, as well as recruiting other proteins responsible for DNA repair[124,125], including in response to stress caused by cigarette smoke[126]. There is strong evidence of a regulatory role within the region surrounding our lead variant (RegulomeDB[18] score 4, minimal binding evidence). One significant (beta=-0.28, P=5.3E-6) eQTL between rs1545348 and *TTC23L* was found in sun exposed skin tissue (lower leg) (GTEx[73]). Additionally, HaploReg[21] and the UCSC browser reveal that the region surrounding our lead variant (+/- 500 kb, R^2>0.7) harbors marks of open and active chromatin and DNase hypersensitive regions across multiple tissues, including cancer, pluripotent, and normal tissue, brain and adipose tissue among others. Traits with nearby GWAS associations include several metabolite markers and left ventricular mass, although each of these associations are in low LD with rs1545348[127-131].

rs6470765 (*GSDMC*): There are three genes within 500 kb +/- of our lead SNP, rs6470765, which lies within an intron of *GSDMC* (gasdermin C). There is very little known about the function of *GSDMC*. Our lead SNP also lies 80 kb downstream of *FAM49B* (family with sequence similarity 49, member B). Similar to *CDK6*, a gene nearby another one of our novel variants, rs10269774, *FAM49B* is a target of *BACH1* transcription factor, which is involved in cellular response to oxidative stress and management of the cell cycle[132]. Also, *ASAP1* (ArfGAP With SH3 Domain, Ankyrin Repeat And PH Domain 1), a gene located 328 kb upstream of our association signal, may be involved in the differentiation of fibroblasts into adipocytes[133]. There is moderate evidence for the functional role of lead variant in regulation of gene expression (RegulomeDB[18] score of 6: minimal binding evidence). However, the GTEx[73] database indicates that rs6470765 is a significant eQTL for *GSDMC* in skeletal muscle, sun-exposed skin, and mucous in the esophagus. Furthermore, HaploReg[21] and the UCSC Browser highlight moderate evidence for regulatory elements in high LD >0.9, including DNAse hypersentive regions, and active enhancer and promotor regions in >20 tissue types (e.g. lung, adipose, skeletal muscle, epidermal and esophageal tissues, and many stem/pluripotent cell types). Our lead variant is within several altered binding sites for FOX1, FOX2 and SOX. Last, our lead SNP is in high LD with other potential cis-eQTLs for *GSDMC*. Nearby associations with other traits include height, hip circumference adjusted for BMI, and inflammatory bowel disorder[2,70,71,134].

rs6076699 (*PRNP*): There are seven genes within 500 kb+/- of our lead SNP, rs6076699. The lead SNP is 100kb upstream of *PRNP* (prion protein) is likely a signaling transducer involved in multiple biological processes related to nervous system, immune system, and general cellular functions[135-138]. Mutations in the repeat region as well as elsewhere in this gene have been associated with Creutzfeldt-Jakob disease, fatal familial insomnia, Gerstmann-Straussler disease, Huntington disease-like 1, and kuru [139-145].

Alternate forms of the oligmers have been shown to form in response to oxidative stress caused by copper exposure[146]. Copper is present in cigarette smoke and elevated in serum of smokers, but is not

outside of safe ranges according the U.S. Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, and Office on Smoking and Health[147,148]. Our lead SNP is 136 kb upstream from a related gene, *PRND* (prion protein 2), which is biochemically and structurally similar to *PRNP*[149]. Like PRNP, mutations in this gene may also be involved in neurocognitive disorders, although there are only weak associations[150,151]. A third prion protein (testes specific, *PRNT*) is found 145 kb away from our lead SNP; however no much is known about the function of this gene. Other nearby genes include *SLC23A2* (Solute Carrier Family 23 [Ascorbic Acid Transporter], Member 2), *ADRA1D* (Adrenoceptor Alpha 1D), *SMOX* (Spermine Oxidase), and *RASSF2* (Ras association [RalGDS/AF-6] domain family member 2). *SLC23A2* is essential for the uptake and transport of Vitamin C, which is an important nutrient for DNA and cellular repair in response to oxidative stress both directly and through supporting the repair of Vitamin E after exposure to oxidative agents[152-155]. Furthermore, this region is associated with success in smoking cessation and is implicated in addictive behaviors in general[156,157]. Nearby GWAS-identified associations include preeclampsia, and height[70,71,158]. There is little evidence that our association signal is involved in regulation of gene expression (RegulomeDB[18] score-5: minimal binding evidence) [18]. While our tag SNP is located within an active enhancer region (open chromatin marks, DNAse hypersentivity, and several transcription factor binding motifs), this activity appears tissue specific (sex-specific tissues and lungs)[21,111]. There are no other significant regulatory elements in high LD with rs6076699[21,73].

Waist-to-Hip Ratio adjusted for BMI (WHRadjBMI)

rs670752 (*BBX*): There are only three genes within 500 kb+/- of our lead SNP, rs670752, which lies within an intron of *BBX* (Bobby Sox Homolog [Drosophila]). While there is little known about the function of *BBX*, another nearby intronic variant, rs6437740, has been associated with smoking behavior in a previous GWAS[159]. Other nearby genes include *CCDC54* (coiled-coil domain containing 54) and *CD47* (CD47 molecule). Much is known about the function of *CD47* due to mouse models. *CD47* encodes a cell surface antigen involved in immune response to bacteria, cell adhesion, inflammatory response, and cell to cell signaling[160-162]. *CD47* expression is significantly decreased in obese individuals and negatively correlated with BMI, WC, and HIP in RBC [163].

Conversely, in mouse models, *CD47* deficient mice show decreased weight gain on high fat diets, increased energy expenditure, improved glucose profile, and decreased inflammation[164]. Our lead SNP, rs670752, has a score of 6 (very little binding evidence) in RegulomeDB[18] and no significant eQTLs were identified in GTEx[73]. However, our tag SNP was identified as a significant eQTL for *BBX* in brain tissue in HaploReg[21], Additionally, multiple SNPs in high LD with rs670752 provide several lines of evidence for nearby regulatory elements (e.g. active promoters, transcription factor binding motifs, strong and poised enhancers), mostly in pluripotent and embryonic cell lines, but also blood cell lines and brain tissue[21,111].

rs589428 (*EHMT2*). A total of seventy-seven genes are found near our lead SNP, rs589428, which is intronic within *EHMT2* (Euchromatic Histone-Lysine N-Methyltransferase 2). *EHMT2* encodes a histone methyltransferase, a group of genes involved in repression of transcription through the regulation of chromatin state [165]. The lead SNP is 302kb downstream of *TNF*. In patients with end-stage renal disease (ESRD) on long-term hemodialysis (HD), the SNP in the promoter region of the *IL-6* and *TNF-alpha*, and *IL-10*, show a strong association with indices of comorbidity and function, and biological and nutritional markers[166]. TNF-alpha promotes bone loss and inhibits bone formation and has an important role as a mediator of skeletal damage in inflammatory arthritis[167-170]. *TNF* is the master regulator of other inflammatory cytokines and the major cytokine in the pathogenesis of chronic inflammatory disease[171]. TNF-alpha exerts an important influence on adipose tissue metabolism and function. It inhibits the

expression of two major adipose tissue differentiation regulators: CCAAT and PPARγ-2 [172]. TNF-alpha promoter methylation levels could be involved in the susceptibility to stroke[173] and correlates with increased risk of coronary artery disease[174]. The risk of early childhood wheeze associated with early maternal smoking may be modified by TNF[175]. The lead SNP is also 287kb upstream of *NCR3*, which is associated with pulmonary function[176].

The top SNP is 17.5kb upstream of *NEU1* (Sialidase 1 (Lysosomal Sialidase)). The activity of *NEU1* is higher in epididymal fat and lower in the livers of two strains of obese and diabetic mice. Fluctuations in *NEU1* activity might be associated with the pathological status of these tissues in obesity[177]. The lead SNP is 50kb downstream of *HSPA1B*. Functional *HSPA1B* variants are associated with lung cancer risk and survival[178]. The top SNP is 65kb upstream of *CFB*. Increased concentrations of circulating binding factors fH and fB in subjects with altered glucose tolerance could reflect increased SVC-induced activation of the alternative pathway of the complement in omental adipose tissue linked to insulin resistance and metabolic disturbances[179]. The top SNP is 91kb upstream of *STK19*, which has been reported to be a pleiotropic gene for metabolic syndrome and inflammation and is associated with TG, BMI, WAIST, SBP and inflammatory markers including plasminogen activator inhibitor 1 (PAI-1) and white blood cell count (WBCC)[180]. Our top snp is 102kb upstream of *C4A*, which was identified as novel potential adipokine candidate regulator of obesity and adipose regions [181] between visceral and subcutaneous adipose tissue. The Top SNP is 102kb upstream of *C4B*. The carriers of C4B*Q0 (silent allele for the C4B gene) have a substantially increased risk to suffer from myocardial infarction or stroke. Compared to controls, C4B*Q0 carrier frequency was significantly higher at diagnosis in Icelandic smokers with angina pectoris (AP) or acute myocardial infarction (AMI) and Hungarian smokers with severe coronary artery disease, while no such difference was seen in nonsmokers. These findings indicate that C4B*Q0 genotype can be considered as a major covariate of smoking in precipitating the risk for AMI and associated mortality[182]. The top SNP is 150kb upstream of *DDAH2* in which SNP rs9267551 may confer increased risk for type 2 diabetes by affecting insulin sensitivity through increased asymmetric dimethylarginine (ADMA) levels [183,184].

Our top SNP is 222kb downstream of *APOM*. The PCSK9 pathway contributes to plasma apoM regulation in humans and the influence of PCSK9 on circulating apoM appears to be modified by adiposity [185]. In addition, APOM expression is related to FEV1/FVC (forced expiratory volume 1/ forced vital capacity) ratio and per cent emphysema [186]. The top SNP is 261kb downstream of *AGER/RAGE*. The lower level of soluble RAGE/AGER is associated with a number of components of metabolic syndrome (central obesity, hypertension, and hyperglycemia) [187]. Soluble RAGE is inversely associated with pancreatic cancer risk among Finnish male smokers [188]. The RAGE(2) haplotype is associated with diabetic nephropathy (DN) in type 2 diabetics and with earlier DN onset and, thus, can be regarded a marker for DN [189]. RAGE, via its interaction with ligands, serves as a cofactor exacerbating diabetic vascular disease [190]. Serum endogenous secretory RAGE (esRAGE) levels were inversely correlated with BMI and serum HDL-cholesterol[191]. In healthy subjects plasma levels of sRAGE were negatively correlated with BMI and waist/hip ratio supporting a possible protective role for these proteins before any evidence of diabetic or vascular complications[192].

The top SNP is 263 downstream of *AIF1*. The serum AIF-1 concentrations were positively correlated with levels of fasting plasma glucose, hemoglobin A1c, triglycerides, and uric acid, and with WC and BMI, and were inversely correlated with HDL cholesterol levels[193]. Also, the variants in AIF1 show evidence of association with adult obesity in the Greek population[194]. The top SNP is 306 downstream of *LTA*. SNPs in LTA are associated with chronic kidney disease in Type 2 diabetes[195]. The variability of LT-alpha

genotypes may have potential implications for individual susceptibility to asthma in atopic or in ever-smoking Chinese adults in Hong Kong[196].

The genome-wide association studies have reported the associations within 1Mb of region for age at menopause (R^2=0.32)[197], telomere length (R^2=0.22)[198], idiopathic membranous nephropathy[199] (R^2=0.45), chronic hepatitis B infection[200] (R^2= 0.45) and phospholipid levels (plasma) (R^2=0.23)[201]. This lead SNP is associated with regulatory motifs changed at Bcl6b, NF-kappaB, Pou5f1; associated with enhancer histone marks in stomach mucosa, HSMM cell derived skeletal muscle myotubes cell tissue; and in eQTL in various tissues including subcutaneous adipose, visceral omentum, lung and skeletal muscle tissues. The lead SNP is associated with eQTL in tibial artery and blood tissues from GTEx[73] analysis. The RegulomeDB[18] score for the lead SNP is 1f.

rs1856293 *(EYA4)*: A total of nine genes are found near our lead SNP, rs1856293. The lead SNP is 342kb downstream of *RPS12*. *RPS12* is a potential target gene of microRNA-377, which has been consistently upregulated in *in vitro* diabetic nephropathy (DN) models and in *in vivo* DN mouse models[202]. If *RPS12* is also upregulated in the diabetic milieu, it may contribute to the progression of DN. *RPS12* has been reported to be a strong candidate for diabetic nephropathy[203]. In addition, in the study of E3 rats, there were significant positive correlations between TG and the expression of *RPS12* gene[204]. The lead SNP is 83kb upstream of *EYA4*. Serum methylation levels of *EYA4* were significant discriminants between stage I colorectal cancer and healthy controls [205] and high methylation of the EYA4 gene is associated with ulcerative colitis with colorectal cancer[206]. The lead SNP is 446kb upstream of *VNN1*. Alternative splicing in *VNN1* is associated with colorectal cancer[207]. The combination of VNN1 and MMP9 may be used as a blood biomarker panel for the discrimination of pancreatic cancer-associated diabetes from type II diabetes[208]. There is no reported GWAS signal in high LD with the lead SNP. This lead SNP is associated with regulatory motifs changed at Esr2, LRH1, Myf_3, Sin3Ak-20_disc3 and T3R; and associated with enhancer histone marks in ESDR, SKIN and brain tissue. The RegulomeDB[18] score for the lead SNP is 6.

rs2001945 (*TRIB1*): There are five protein coding genes within 500 kb+/- of our lead SNP, rs2001945, which lies 27 kb downstream from *TRIB1*. *TRIB1* (tribbles pseudokinase 1) encodes a protein involved in ATP binding and the MAPK/ERK1/2 pathway[209]. Very little is known about the function of the other nearby genes, including *NSMCE2* (non-SMC element 2, *MMS21* homolog), *KIAA0196* (strumpellin), *SQLE* (qualene epoxidase), and *ZNF572* (Zinc Finger Protein 572). GTEx[73] indentified no significant eQTLs for our lead SNP; however, RegulomeDB[18] provided a score of 4 (minimal binding evidence [Transcription Factor binding + DNase peak]). Further, HaploReg[21]/UCSC Genome Browser reveal multiple lines of evidence across multiple tissues, including cis-eQTLs between rs2001945 for *TRIB1* and *NSMCE2* in brain tissue, strong DNAse hypersensitivity clusters both at the association peak and across SNPs in high LD with our lead SNP, transcription factor binding motifs, and open chromatin marks primarily in Human Umbilical Vein Endothelial Cells (HUVEC). There are several nearby previously-identified GWAS signals for related cardiometabolic and digestion-related traits, including lipids (e.g. triglycerides, LDL, HDL)[6,8,13,14,210-217], adiponectin[218], liver enzyme levels[219], gestational age[5], inflammatory bowel disease[134], Crohn's disease[220,221], and metabolite levels[222].

rs17065323 (*SMIM2*): A total of 6 genes are found within 500 kb of the lead marker, rs17065323. The SNP rs17065323, which is located 23.19 kb downstream of the long intergenic non-protein coding RNA 284 (*LINC00284*, 13q14.11), showed suggestive association with uric acid levels (p=8.7E-6, [223]). Variants of the *LACC1* (laccase (multicopper oxidoreductase) domain containing 1), at 159.72 downstream of rs17065323, were genome-wide associated with Crohn's disease [134,221], and a *LACC1* mutant showed evidence of association with systemic juvenile idiopathic arthritis [224]. In addition, GWASs have suggested

associations between variants on 13q14 with response to tocilizumab in rheumatoid arthritis (p=2E-7[225]), antineutrophil cytoplasmic antibody-associated vasculitis (p=3E-6[226]), and myotrophic lateral sclerosis (p=4E-6, [227]), as well as *SERP2* genotype-carbohydrate interaction influencing fasting insulin and homeostasis model assessment of insulin resistance (p=7E-6 and p=5E-6 , respectively [228]). The nearest protein-coding gene to our tag SNP is *SMIM2* (Small Integral Membrane Protein 2), located 89.5 kb upstream; however, very little is known about the function of *SMIM2*.

rs1049281 (*HLA-C*): Eighty-six genes are found within 500kb of rs1049281, which lies within the *HLA-C* gene at 6p21.3. *HLA-C*encodes an HLA class I heavy chain paralogue found in nearly all cells and important in the function of the immune system. There is strong evidence that our SNP is in a region likely to affect binding activity and gene expression in adipose tissue (RegulomeDB[18] score 1f). Over 100 alleles of the *HLA-C* gene have been described, and *HLA-C* has been associated with risk of various autoimmune diseases which can influence adiposity, including Type I diabetes, celiac disease, and psoriatic arthritis [229,230]. Our lead SNP is 314569 bp downstream of *DPCR1,* a gene associated with diffuse panbronchiolitis, a chronic inflammatory lung disease [231]. A variant near this gene (rs9368649), has been suggestively associated with smoking status (ever somker) and pack years (P~1.3E-07) [232], but not at GWS. This SNP is not in high LD with our lead SNP (R^2=0.152, D'=0.902). Our lead SNP is 190789 bp upstream of *HCP5*, a lncRNA. A variant (rs12175489) near this gene was suggestively associated (p=2.13E-06) with visceral adipose tissue (VAT) in men [103], but this variant is also not in high LD with our lead SNP (R^2=0.022, D'=0.478). Our lead SNP is 336394bp upstream of *AIF1*, 310030bp downstream of *NCR3*, and 341847 upstream of *BAT2*. Three variants in this region [rs2260000 (R^2=0.122, D'=0.526), rs1077393 (R^2=0.114, D'=0.434), and rs2844479 (R^2=0.100, D'=0.523) have been previously associated with variation in weight [233]. Another variant near *NCR3* (rs2070600) has been previously associated with ever-smoking and lung function, but is not in high LD with our lead SNP (R^2=0.137, D'=0.642) [176,232]. Our lead SNP is 340905bp downstream of *VARS2*, and a variant near this gene (rs7751505) has been suggestively associated with height change ($P<4.05 \times 10^{-6}$), though it is not in LD with our top SNP (R^2=0.054, D'=0.569). Two other variants in the region have been previously associated with extremes of height (p<5E-08), one of which is in strong LD with our lead SNP (rs2247056, 28923bp from rs1049281: R^2=0.814, D'=1.000; rs7741091: R^2=0.093, D'=0.652) [77].

SUPPLEMENTARY NOTE 3. **Detailed summary of eQTL methods and results.**

eQTL Methods

We used two approaches to systematically explore the role of novel loci in regulating gene expression. First, to gain a general overview of the regulatory role of newly identified GWAS regions, we conducted an eQTL lookup using >50 eQTL studies [234], with specific citations for >100 datasets included in the current query: 1) Blood cell related eQTL studies included fresh lymphocytes [235], fresh leukocytes [236], leukocyte samples in individuals with Celiac disease [237], whole blood samples [73,238-256], lymphoblastoid cell lines (LCL) derived from asthmatic children [257,258], HapMap LCL from 3 populations [259], a separate study on HapMap CEU LCL [260], additional LCL population samples [261-267],neutrophils [268,269],CD19+ B cells [270], primary PHA-stimulated T cells [261,264], CD4+ T cells [271], peripheral blood monocytes [267,270,272-275], long non-coding RNAs in monocytes [276] and CD14+ monocytes before and after stimulation with LPS or interferon-gamma [277], CD11+ dendritic cells before and after *Mycobacterium tuberculosis* infection [278] and a separate study of dendritic cells before or after stimulation with LPS, influenza or interferon-beta [279]. Micro-RNA QTLs [280,281], DNase-I QTLs [282], histone acetylation QTLs [283], and ribosomal occupancy QTLs [284] were also queried for LCL. Splicing QTLs [285] and micro-RNA QTLs [286] were queried in whole blood. 2) Non-blood cell tissue eQTLs searched included omental and subcutaneous adipose tissues[73,238,256,263,287], visceral adipose tissue [256], stomach [287], endometrial carcinomas [288], ER+ and ER- breast cancer tumor

cells [289], liver [256,287,290-293], osteoblasts [294], intestine [295] and normal and cancerous colon [296,297], skeletal muscle [256,298], breast tissue (normal and cancer)[299,300], lung [73,301-304], skin [73,263,267,305], primary fibroblasts [261,264,306], sputum [307], pancreatic islet cells [308], prostate [309], rectal mucosa [310], arterial wall [256] and heart tissue from left ventricles [73,311] and left and right atria [312]. Micro-RNA QTLs were also queried for gluteal and abdominal adipose [313] and liver [314]. Methylation QTLs were queried in pancreatic islet cells [315]. Further mRNA and micro-RNA QTLs were queried from ER+ invasive breast cancer samples, colon-, kidney renal clear-, lung- and prostate-adenocarcinoma samples [316]; 2 Brain eQTL studies included brain cortex [252,272,317-319], cerebellar cortex [320], cerebellum [289,318,321-323], frontal cortex [320,321,323], gliomas [324], hippocampus [320,323], inferior olivary nucleus (from medulla) [320], intralobular white matter [320], occiptal cortex [320], parietal lobe [322], pons [321], pre-frontal cortex [289,323,325,326], putamen (at the level of anterior commussure) [320], substantia nigra [320], temporal cortex [318,320,321,323], thalamus [323] and visual cortex [289].

Additional eQTL data was integrated from online sources including ScanDB (http://www.scandb.org/newinterface/about.html), the Broad Institute GTEx[73] Portal, and the Pritchard Lab (eqtl.uchicago.edu). Cerebellum, parietal lobe and liver eQTL data were downloaded from ScanDB. Cis-eQTLs were limited to those with P<1.0E-6 and trans-eQTLs with P<5.0E-8. Results for GTEx[73] Analysis V4 for 13 tissues were downloaded from the GTEx[73] Portal and then additionally filtered as described below [www. GTExportal.org: thyroid, leg skin (sun exposed), tibial nerve, aortic artery, tibial artery, skeletal muscle, esophagus mucosa, esophagus muscularis, lung, heart (left ventricle), stomach, whole blood, and subcutaneous adipose tissue [73]]. Splicing QTL (sQTL) results generated with sQTLseeker with false discovery rate P≤0.05 were retained. For all gene-level eQTLs, if at least 1 SNP passed the tissue-specific empirical threshold in GTEx[73], the best SNP for that eQTL was always retained. All gene-level eQTL SNPs with P<1.67E-11 were also retained, reflecting a global threshold correction of P=0.05/(30,000 genes X 1,000,000 tests).

Second, since public databases with eQTL data do not have information available on current smoking status, we also conducted an eQTL association analysis using expression results derived from fasting peripheral whole blood collected. Total RNA was isolated from frozen PAXgene blood tubes (PreAnalytiX, Hombrechtikon, Switzerland) and amplified using the WT-Ovation Pico RNA Amplification System (NuGEN, San Carlos, CA) according to the manufacturers' standard operating procedures. The obtained cDNA was hybridized to the Human Exon 1.0 ST Array (Affymetrix, Inc., Santa Clara, CA). The raw data were quantile-normalized, log2 transformed, followed by summarization using Robust Multi-array Average [327]and further adjusted for technical covariates, including the first principal component of the expression data, batch effect, and the all-probeset-mean residual. Study specific covariates in the association model included blood cell counts and cohort membership.
We evaluated all transcripts +/- 1MB around each novel variant in the Framingham Heart Study while accounting for current smoking status, using the following four approaches similar to those used in our primary analyses of our traits:

Model 1 (adjusted main effect of eQTL): Expression ~***SNP*** + SMK + age + age-squared + sex + study specific covariates

Model 2 (main effect of eQTL stratified by smoking status): Expression ~ ***SNP*** + age + age-squared + sex + study specific covariates

Model 3 (Interaction effect of eQTL): Expression ~ SNP + SMK + ***SNP*SMK*** + age + age-squared + sex + study specific covariates

Model 4 (Joint effect of eQTL): Expression ~ ***SNP*** + SMK + ***SNP*SMK*** + age + age-squared + sex + study specific covariates

Significance level was evaluated by FDR < 5% per eQTL analysis and across all loci identified for that model in the primary meta-analysis.

eQTL Results by Trait

Only significant cis-eQTLS in high LD with our novel lead SNPs (r^2>0.9, calculated in the CEU+YRI+CHB+JPT 1000 Genomes reference panel), or proxy SNPs, were retained for consideration.

For BMI, three of our seven novel SNPs across six loci that had at least one variant in high LD (r^2>0.9) with the tag SNP that is significantly (**Online Methods**) associated with expression of a gene transcript in the cerebellum and prefrontal cortex, or blood cell types, including *EPHA3*, *TTC14*, and *INADL*. Notably, our lead SNP, rs2481665, is a significant cis-eQTL for *INADL*, in prefrontal cortex tissue, and for *INADL* and *LITD1* in whole blood after adjusting for SMK (false discovery rate, FDR<5%). For the joint main + interaction effect eQTL analysis, we identified one significant eQTL for a BMI associated variant (rs12902602) for three gene transcripts (*PSMA4, CHRNA5*, and *CTSH*).

For WCadjBMI, five of our 12 novel SNPs were in high LD with a cis-eQTL for gene transcripts in the cerebellum, temporal cortex, prefrontal cortex, lymphoblastoid cells, liver, lung, lymph, omental adipose, subcutaneous adipose, Primary PHA-stimulated T cells, skin, and blood cell tissues in publicly available databases. In our cis-eQTL analyses adjusting for SMK, four of our nine novel lead SNPs were significant cis-eQTLs for 14 gene transcripts in 12 genes. Additionally, for the joint main + interaction effect eQTL analysis, we identified that two variants that were associated with the expression of *SEPT2, FARP2, PASK*, and *HDLBP* (rs6743226) and *KIF1B* (rs17396340).

For WHRadjBMI, three of out six novel SNPs were in high LD with a nearby cis-eQTL for gene transcripts in subcutaneous adipose tissue and blood cell types. We identified five novel WHRadjBMI variants near significant cis-eQTLs for 49 gene transcripts after adjusting for SMK, the most significant of which was between our tag SNP rs1049281 and *MSH5*. Additionally, for the joint main and interaction effect eQTL analysis, we identified two novel WHRadjBMI variants (rs1049281, rs1856293) were associated with 19 gene transcripts.

Across all of our three obesity-related traits, the majority of significant cis-eQTLs from public databases are found in blood cell lines (63% of unique SNP-transcript associations) (**Supplementary Table 16**). However, as in previous eQTL analyses of obesity-associated variants, we identify cis-eQTLs in brain and adipose tissue. Further analyses are needed to determine if these tissue-specific eQTLs remain significant after accounting for SMK, but our de-novo analysis in whole blood samples from the Framingham Heart Study using models to account for SMK indicate that gene expression may underlie our association signals in some instances and smoking exposure may play a role in influencing these associations (**Supplementary Tables 16-18**).

SUPPLEMENTARY NOTE 4. Full list of acknowledgments, including study-specific acknowledgements.

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AGES: The Reykjavik Study cohort 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 attended, resulting in 71% recruitment rate. 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. [Harris, T. B. et al. (2007). American Journal of Epidemiology, 165(9), 1076-1087. doi:10.1093/aje/kwk115]. This study has been funded by NIH contract N01-AG-1-2100, the NIA Intramural Research Program, 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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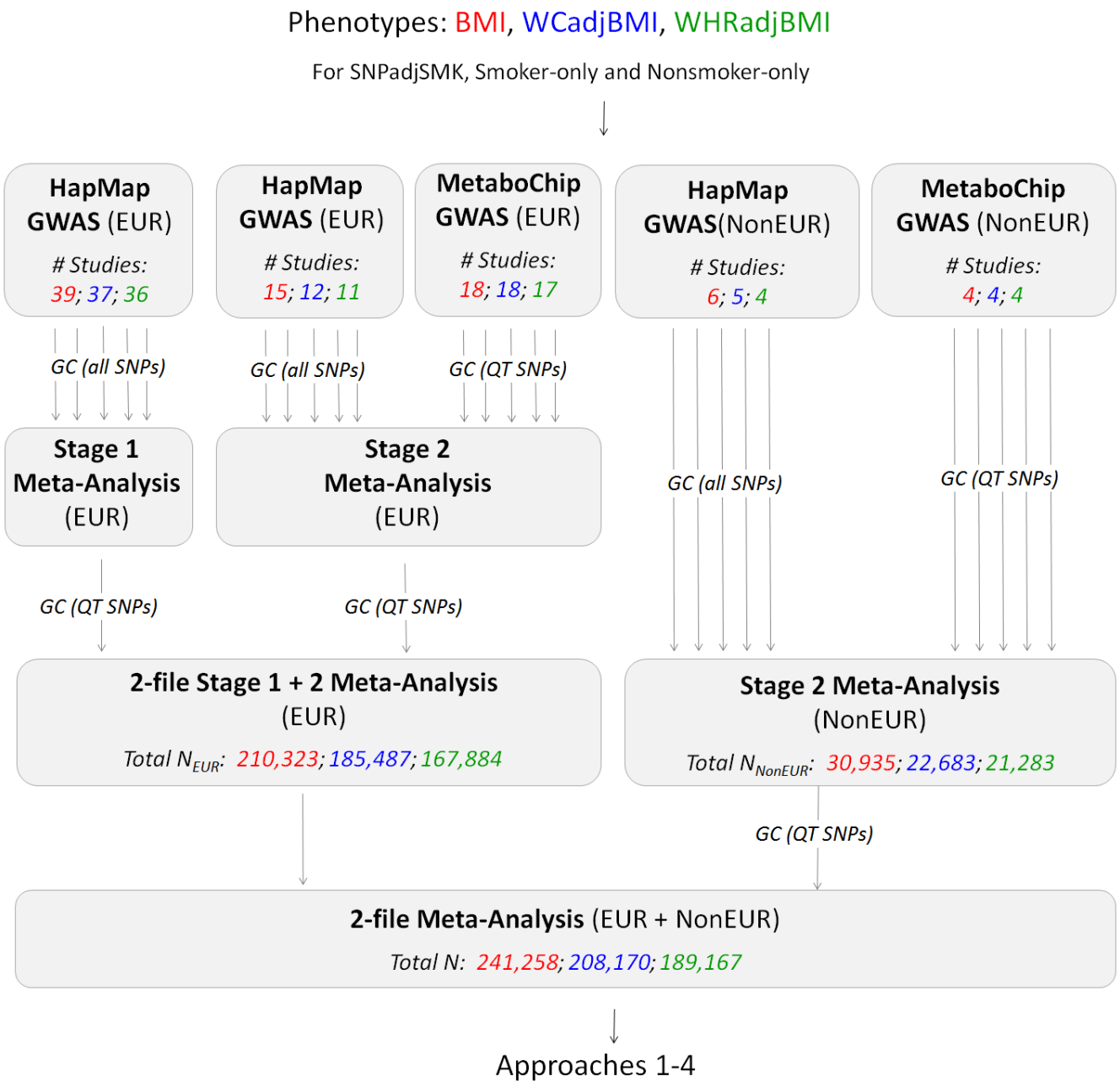
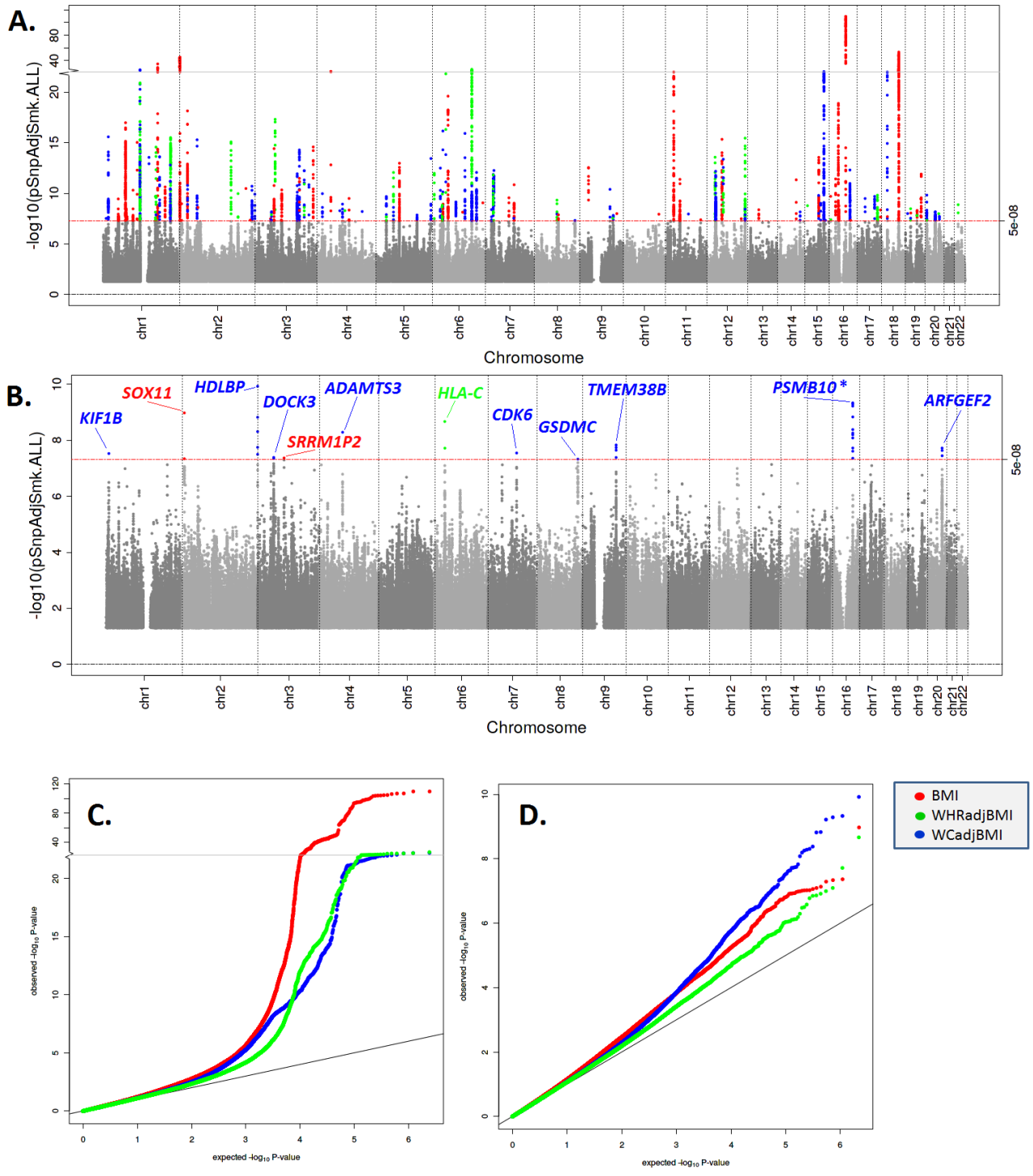
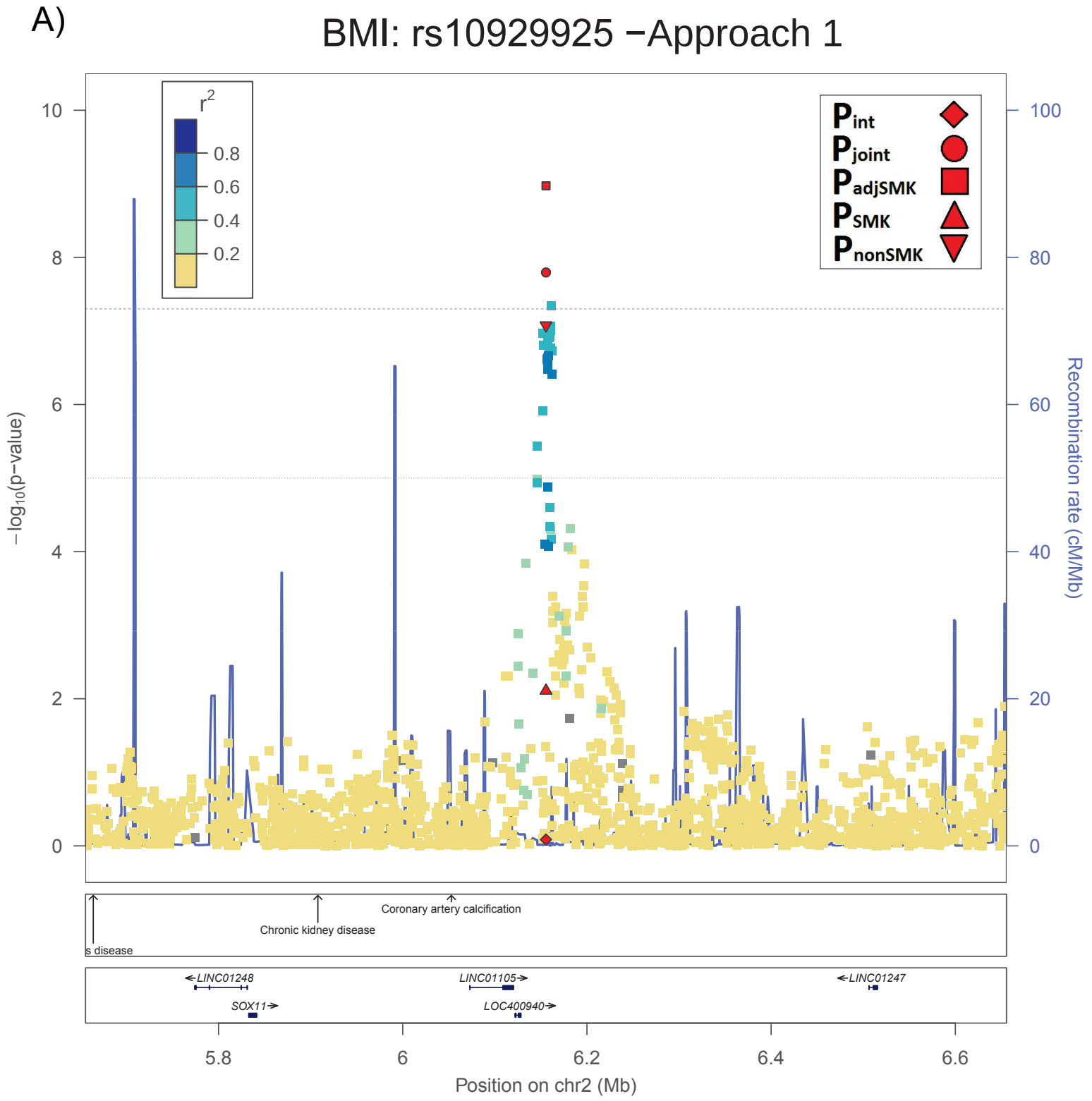
Supplementary Figure 1. Summary of overall study design and workflow for meta-analyses. All numbers provided represent the maximum number specific for that trait (BMI-red, WCadjBMI-blue, and WHRadjBMI-green) and strata (EUR-European descent participants, nonEUR-excluding European descent participants). Three studies provided GWAS data for EUR and nonEUR participants.

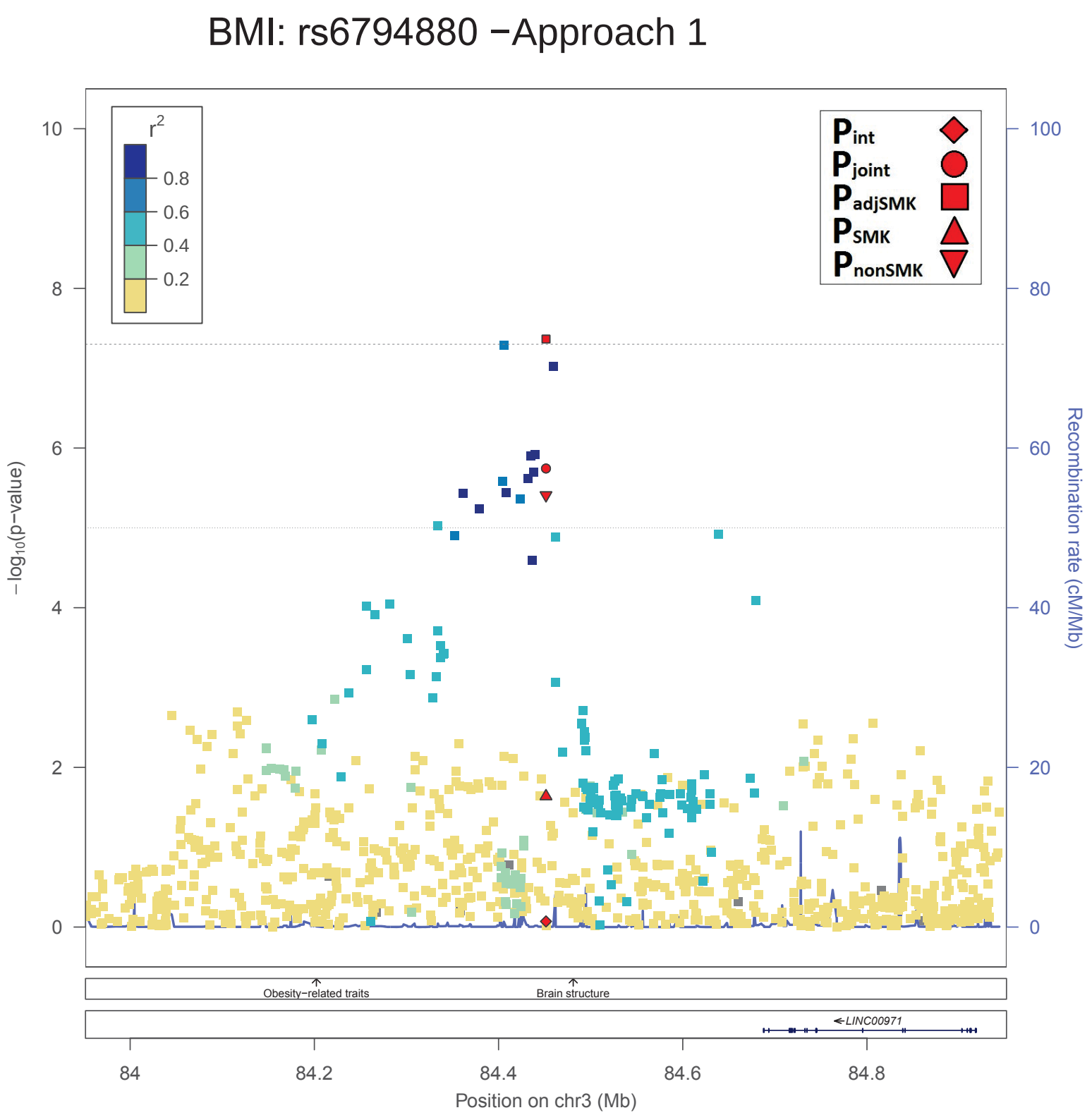


Supplementary Figure 2. Summary plots of discovery meta-analysis for Approach 1 primary meta-analyses. (A) Manhattan plot showing the loci identified in Approach 1 in primary meta-analyses, used to identify significant main effects loci (SNPadjSMK), in the primary meta-analyses association –log10P-values for BMI-red, WCadjBMI-blue, and WHRadjBMI-green; (B) Manhattan plot showing the loci identified in Approach 1 excluding known regions +/- 500 kb and labeled with the nearest gene to the index SNP; (C) QQ-plot showing the Approach 1 P-values as observed against those expected under the null for each phenotypes separately (colored); (D) QQ-plot for Approach 1 after excluding known association regions. **PSMB10* locus is >500 +/- kb from previously identified index SNPs, but is not independent of known GWAS signals.

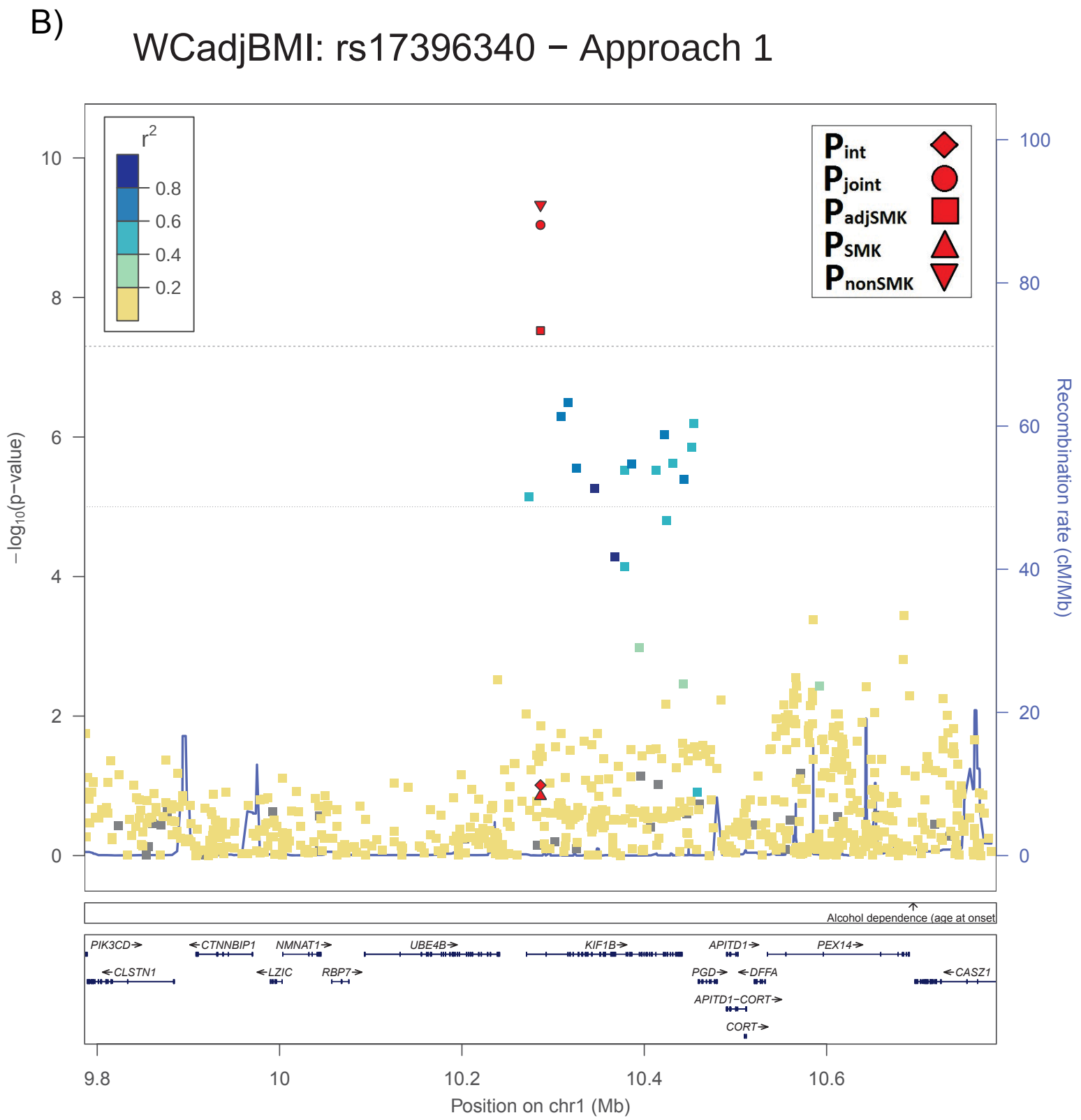


Supplementary Figure 3. Regional association plot for all loci identified in Approach 1 in primary meta-analyses, used to identify significant interaction (SNPadjSMK), in the primary meta-analyses for A) BMI, B) WCadjBMI, and C) WHRadjBMI, and ordered as they appear in Table 1. LD has been calculated using the combined ancestries from the 1000 Genomes Phase 1 reference panel. For comparison, each plot highlights the p-value for the tag SNP in Approach 1 (P_{adjSMK}), Approach 2 (P_{joint}), Approach 3 (P_{int}), current smokers (P_{SMK}), and in nonsmokers (P_{nonSMK}). EUR-European-only meta-analysis.

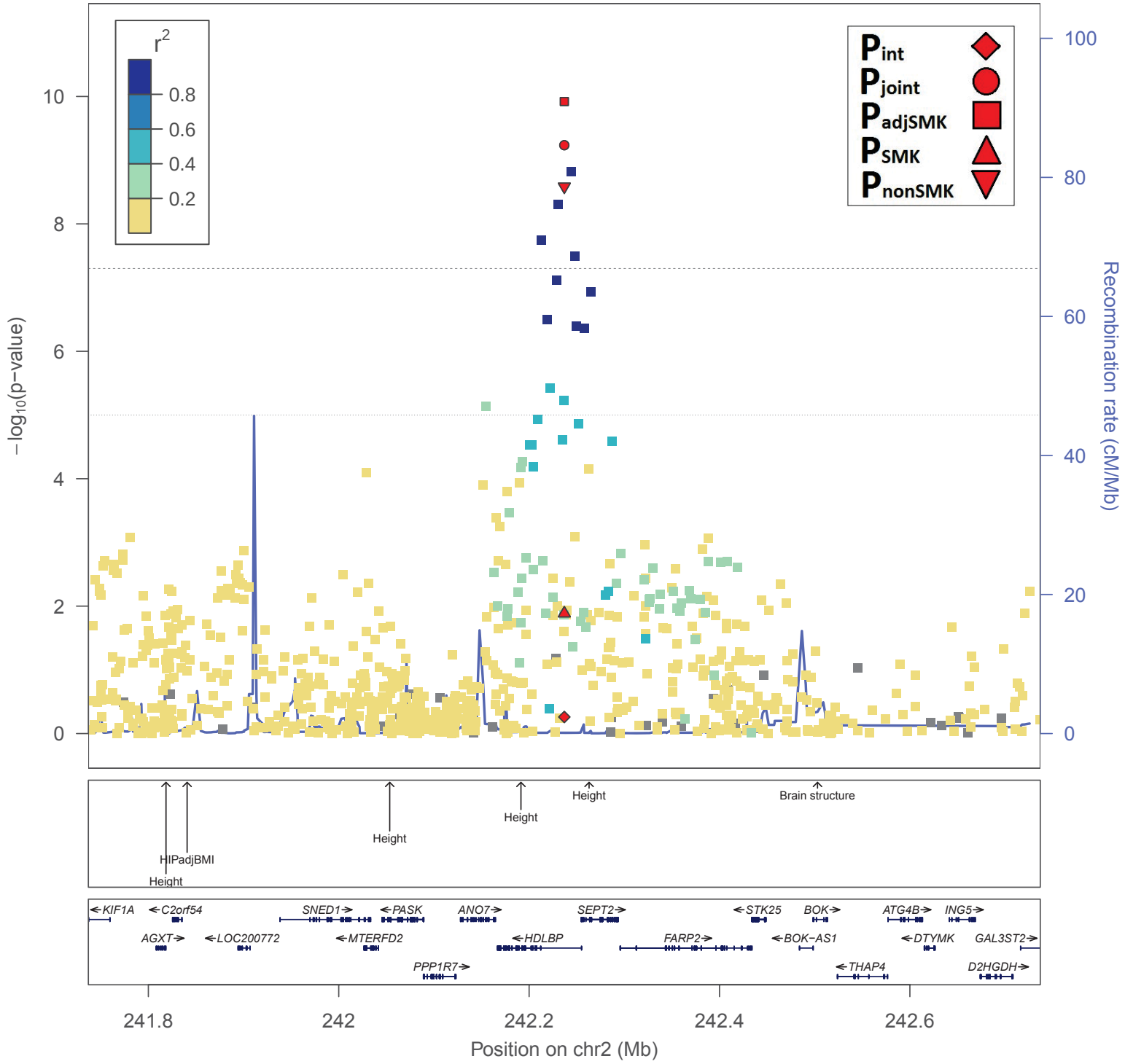

A)
BMI: rs10929925 −Approach 1
r2
0.8
0.6
0.4
0.2
Pint
Pjoint
PadjSMK
PSMK
PnonSMK
−log10(p−value)
Recombination rate (cM/Mb)
Coronary artery calcification
Chronic kidney disease
s disease
LINC01248
LINC01105
LINC01247
SOX11
LOC400940
Position on chr2 (Mb)


BMI: rs6794880 −Approach 1
r2
0.8
0.6
0.4
0.2
Pint
Pjoint
PadjSMK
PSMK
PnonSMK
−log10(p−value)
Recombination rate (cM/Mb)
Obesity−related traits
Brain structure
LINC00971
Position on chr3 (Mb)

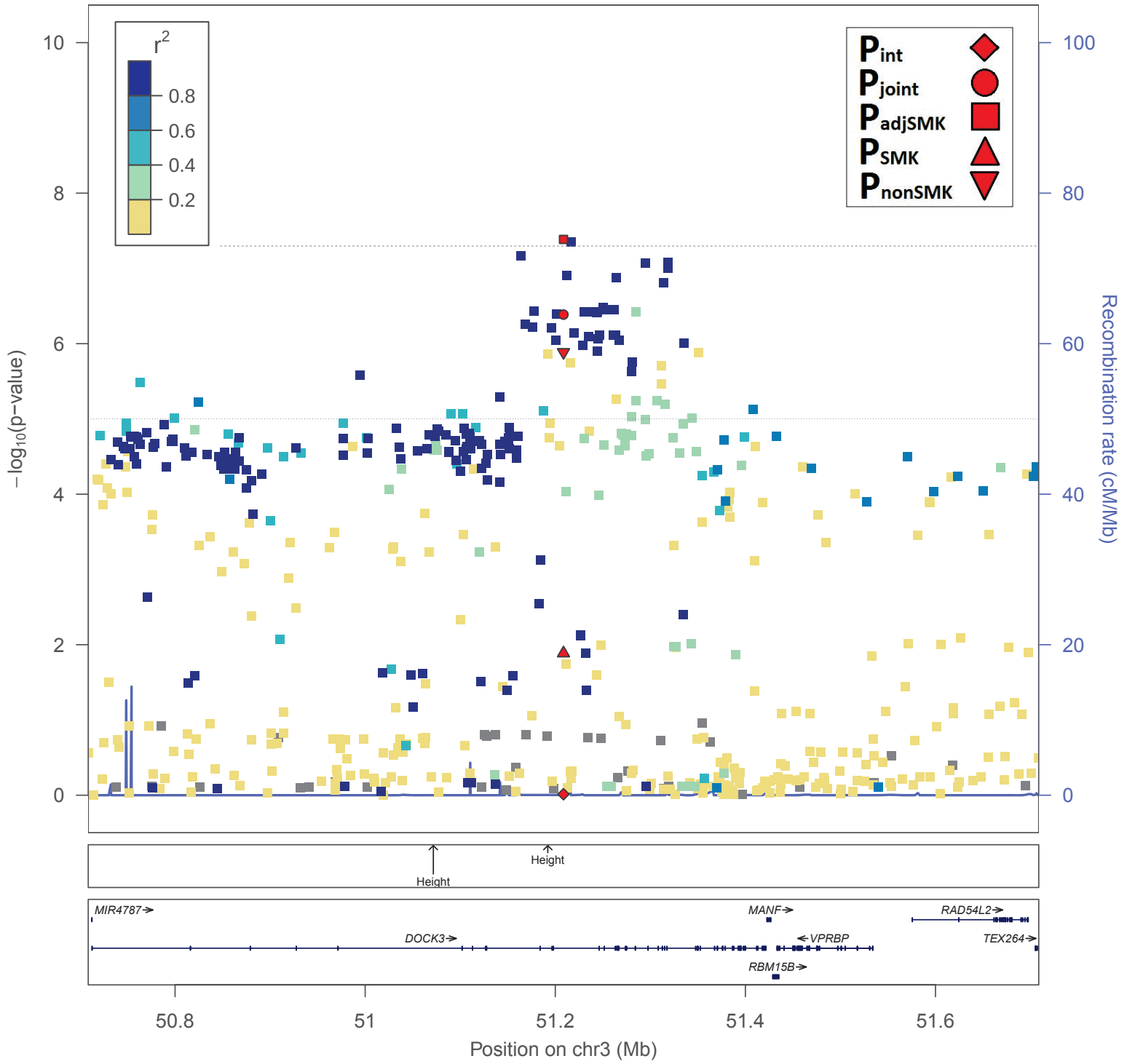
B)


WCadjBMI: rs17396340 − Approach 1
r2
0.8
0.6
0.4
0.2
Pint
Pjoint
PadjSMK
PSMK
PnonSMK
−log10(p−value)
Recombination rate (cM/Mb)
Alcohol dependence (age at onset
PIK3CD
CTNNBIP1
NMNAT1
UBE4B
KIF1B
APITD1
PEX14
CLSTN1
LZIC
RBP7
PGD
DFFA
CASZ1
APITD1−CORT
CORT
Position on chr1 (Mb)

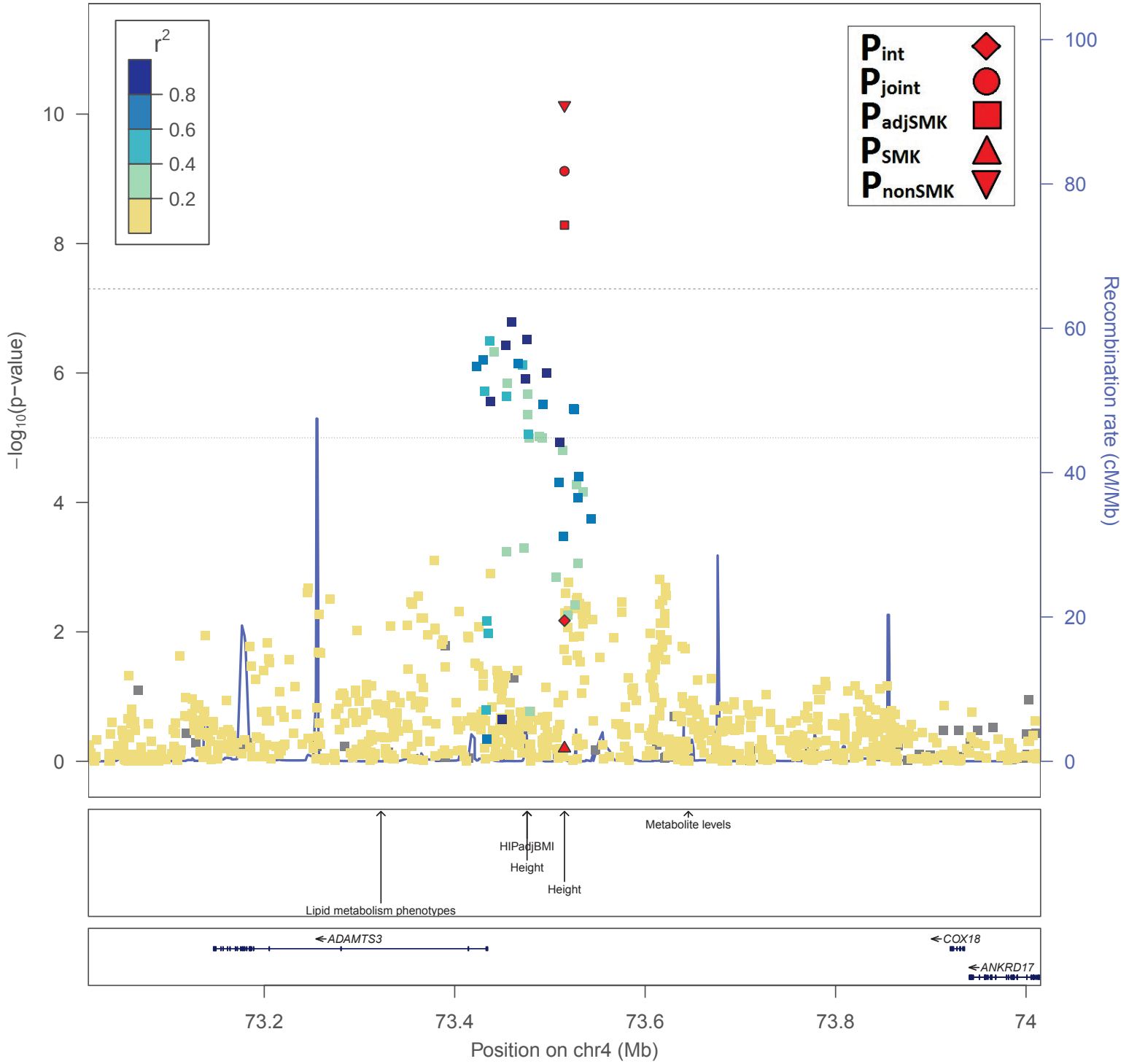
WCadjBMI: rs6743226 − Approach 1



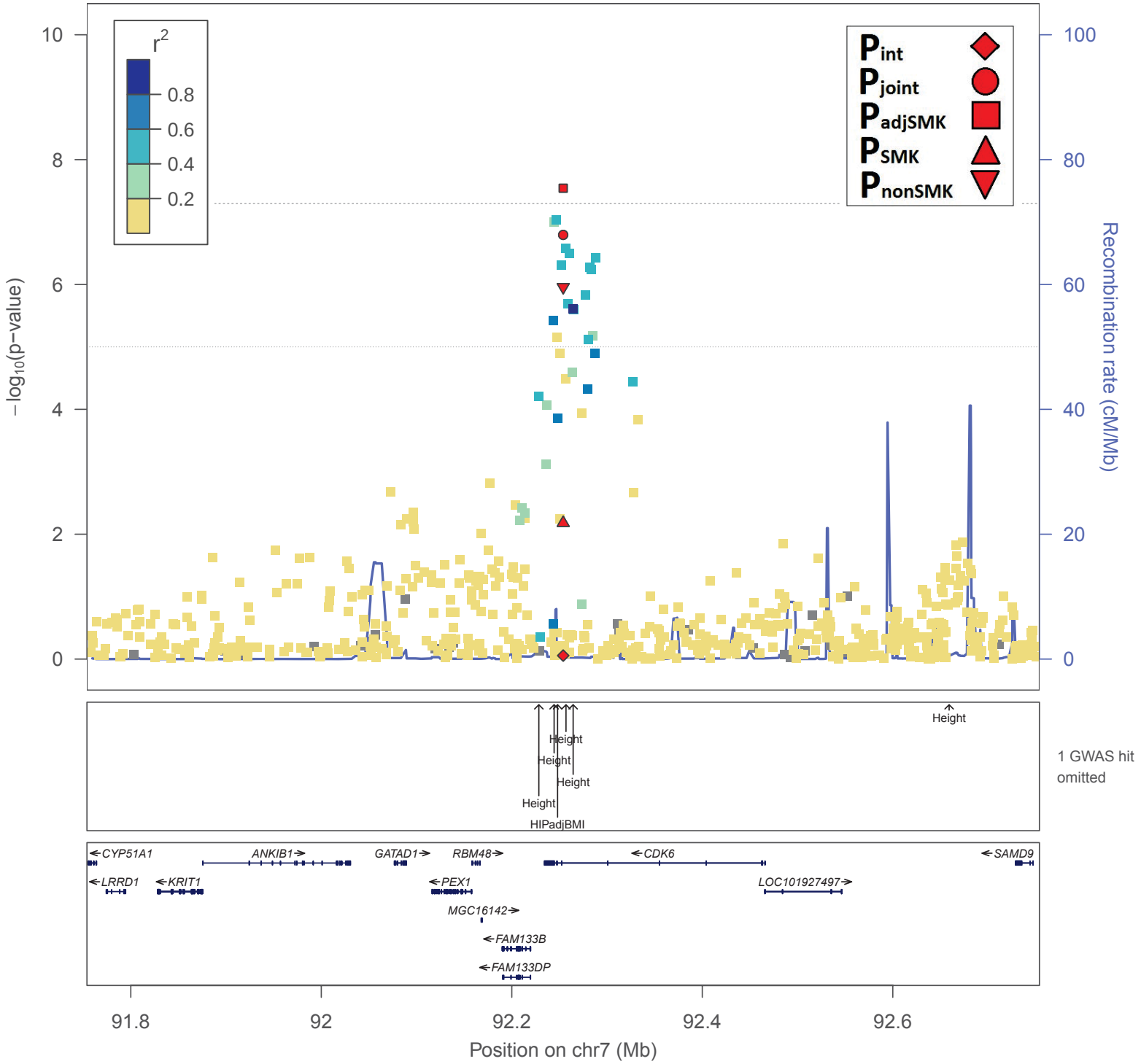
WCadjBMI: rs4378999 − Approach 1



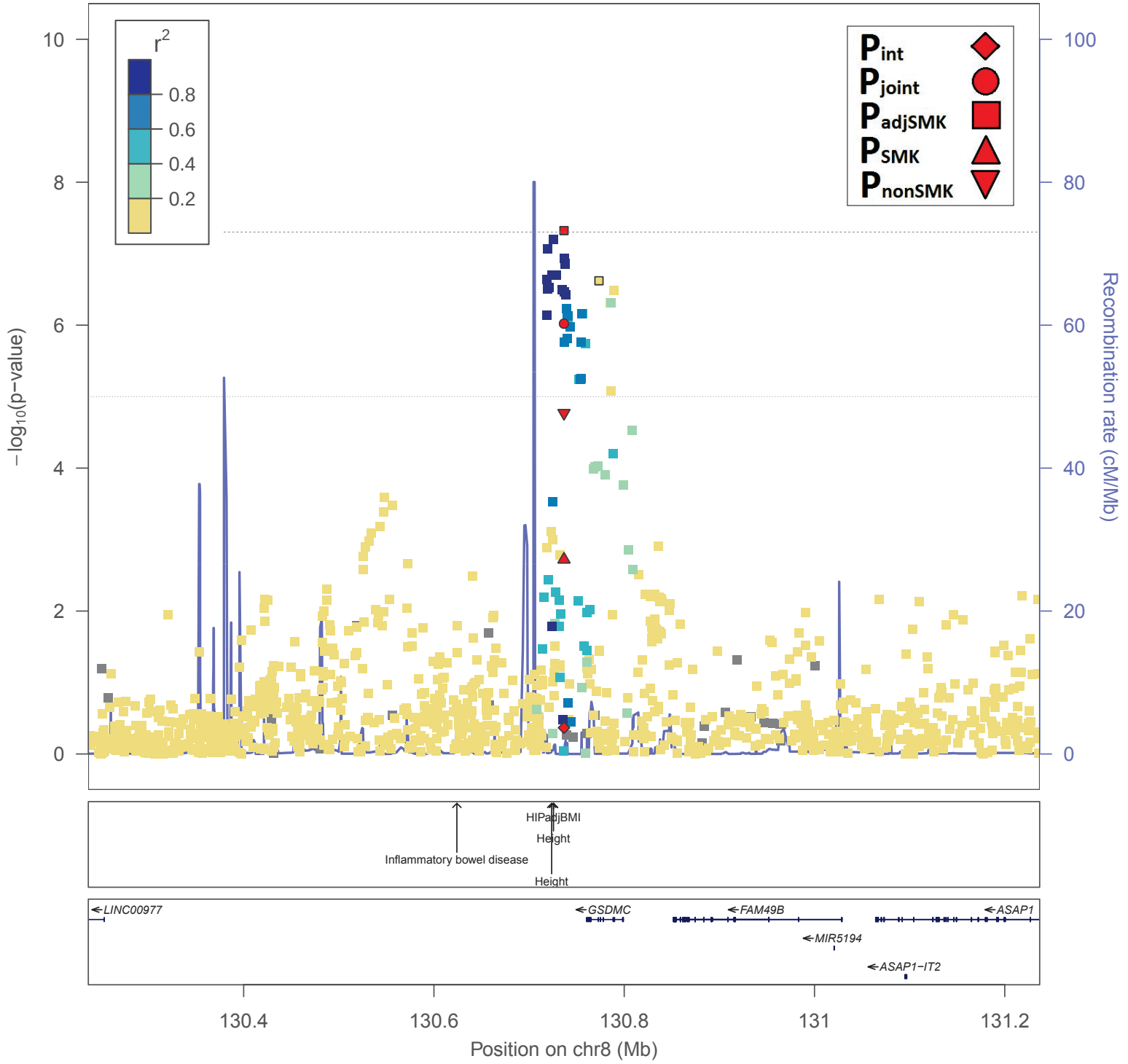
WCadjBMI: rs7697556 − Approach 1



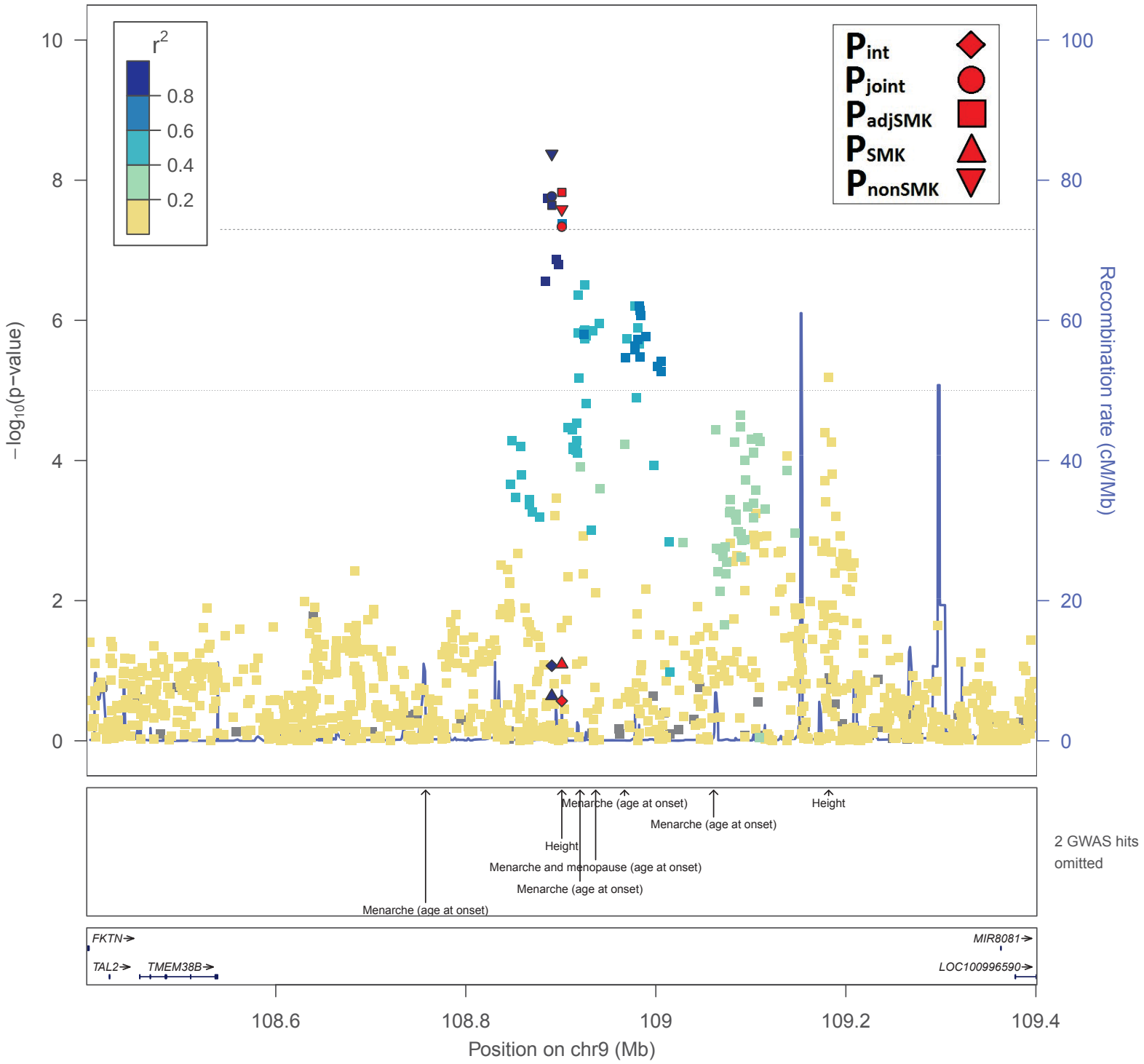
WCadjBMI: rs10269774 − Approach 1



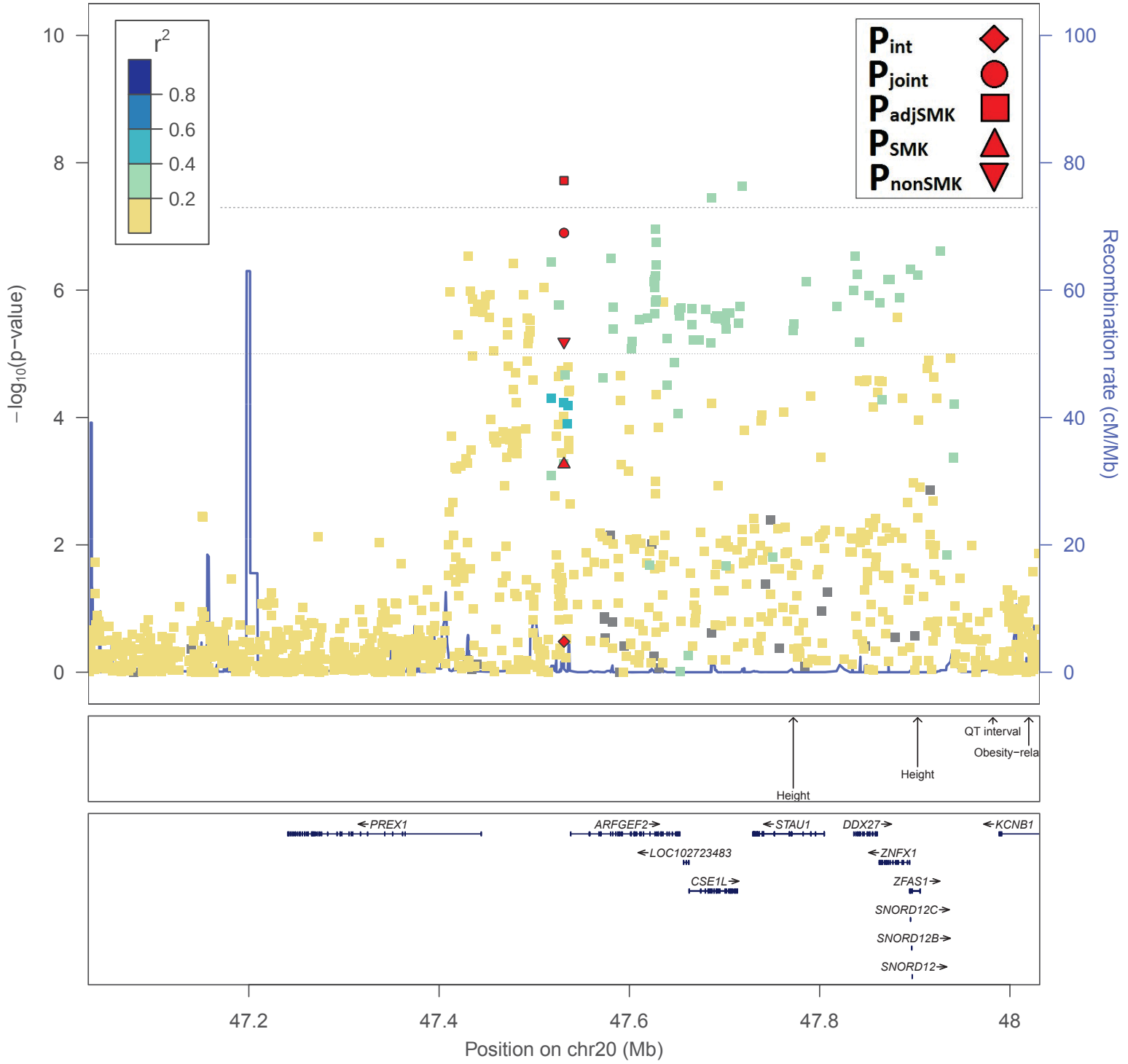
WCadjBMI: rs6470765 − Approach 1



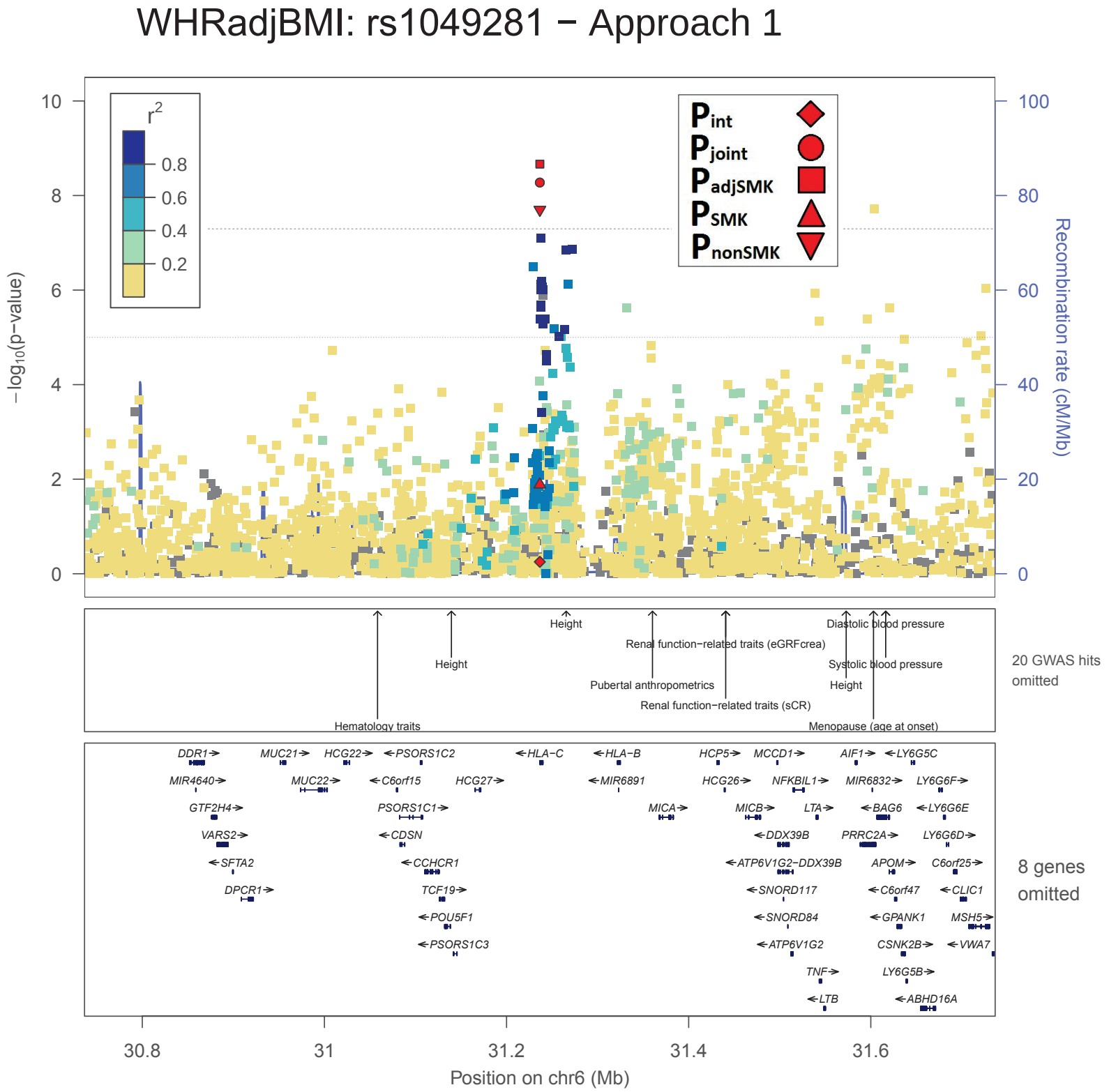
WCadjBMI: rs9409082 − Approach 1



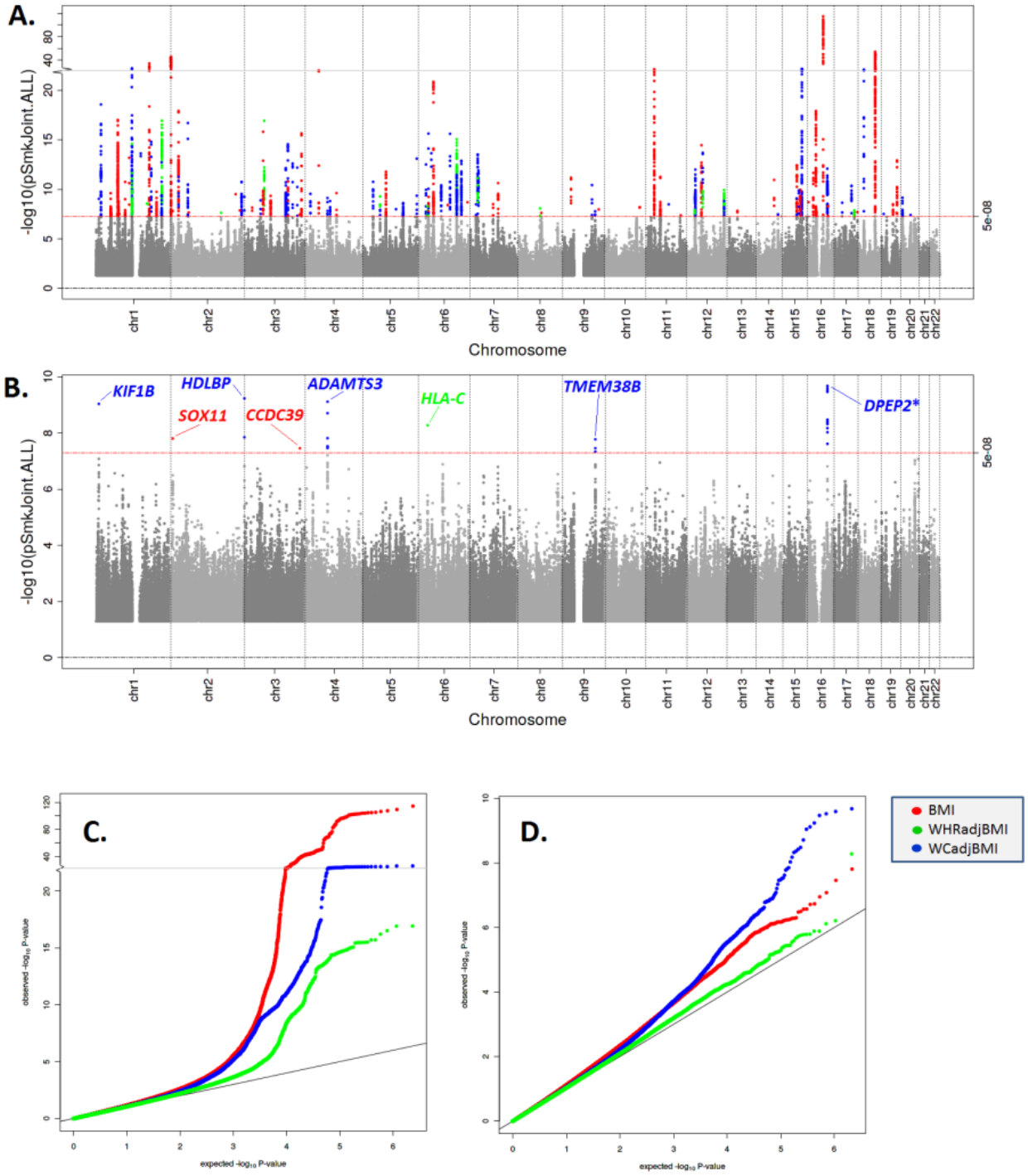
WCadjBMI: rs6012558 − Approach 1



C)

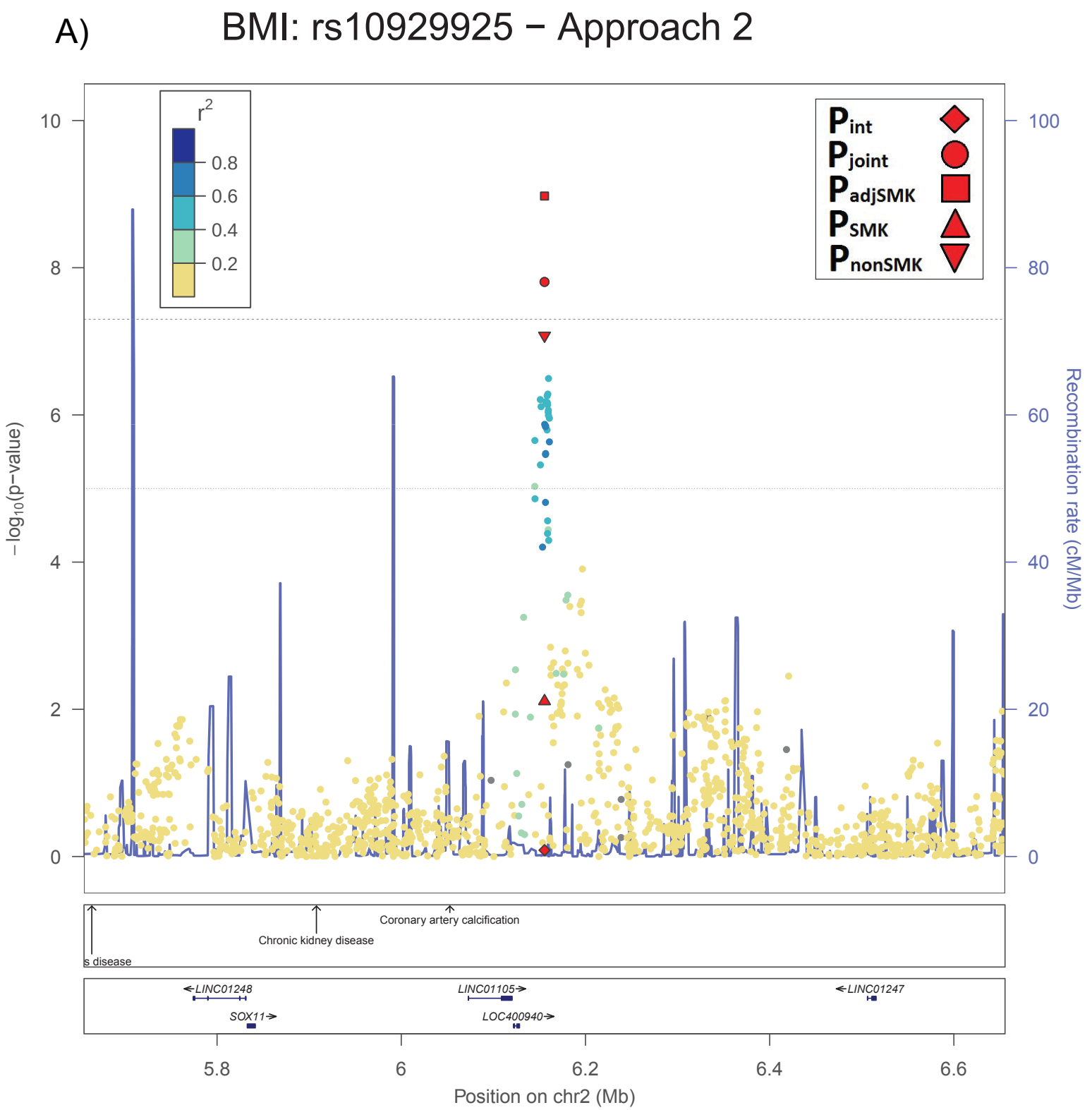

WHRadjBMI: rs1049281 − Approach 1
r2
0.8
0.6
0.4
0.2
Pint
Pjoint
PadjSMK
PSMK
PnonSMK
−log10(p−value)
Recombination rate (cM/Mb)
Hematology traits
Height
Height
Pubertal anthropometrics
Renal function−related traits (eGRFcrea)
Renal function−related traits (sCR)
Diastolic blood pressure
Systolic blood pressure
Height
Menopause (age at onset)
20 GWAS hits omitted
8 genes omitted
Position on chr6 (Mb)

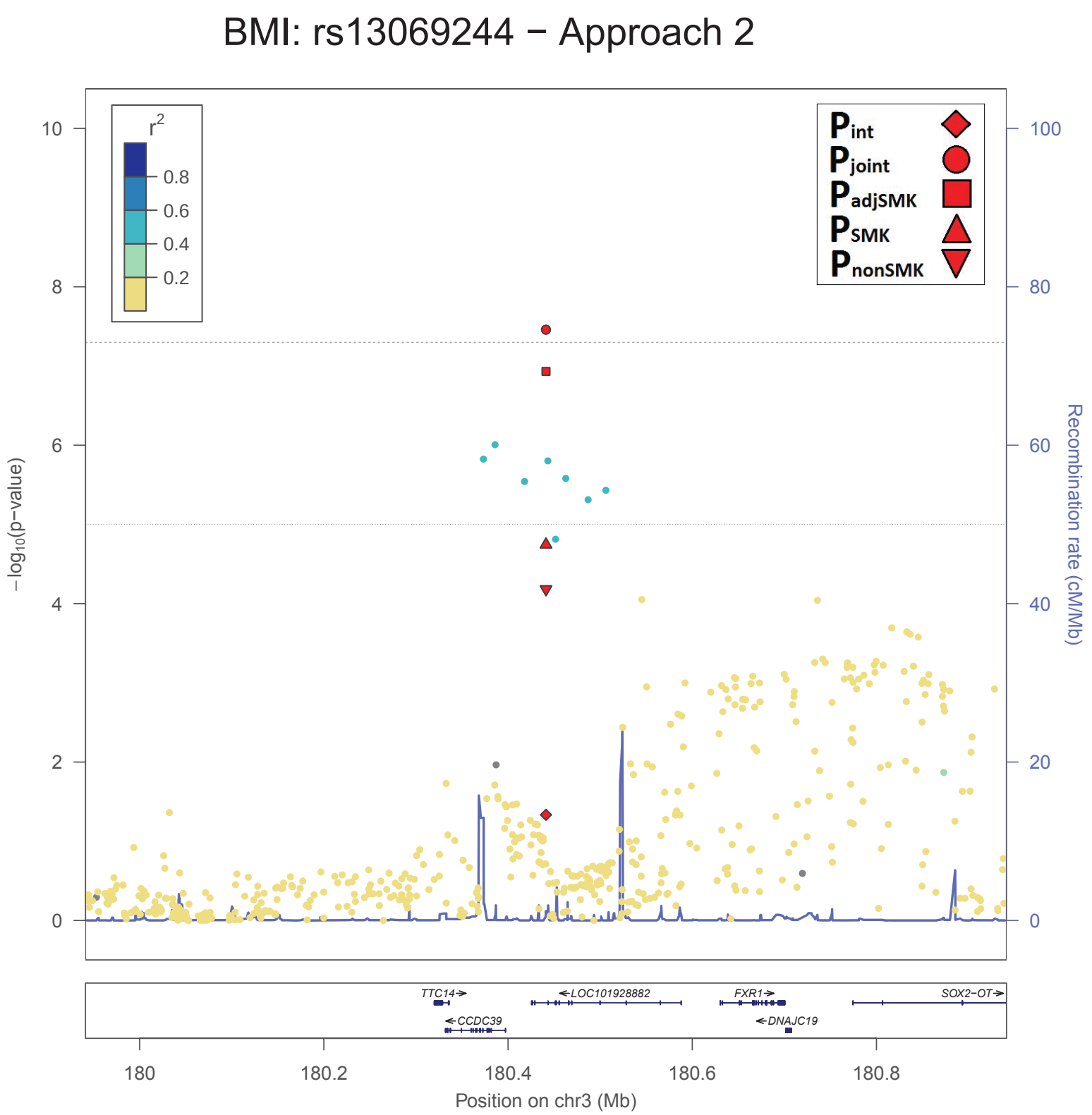
Supplementary Figure 4. Summary plots of discovery meta-analysis for Approach 2 primary meta-analyses. (A) Manhattan plot showing the loci identified in Approach 2 in primary meta-analyses, used to identify significant joint main+interaction effects loci (SNPjoint), in the primary meta-analyses association –log10P-values for BMI-red, WCadjBMI-blue, and WHRadjBMI-green; (B) Manhattan plot showing the loci identified in Approach 2 excluding known regions +/- 500 kb and labeled with the nearest gene to the index SNP; (C) QQ-plot showing the Approach 2 P-values as observed against those expected under the null for each phenotypes separately (colored); (D) QQ-plot for Approach 2 after excluding known association regions.



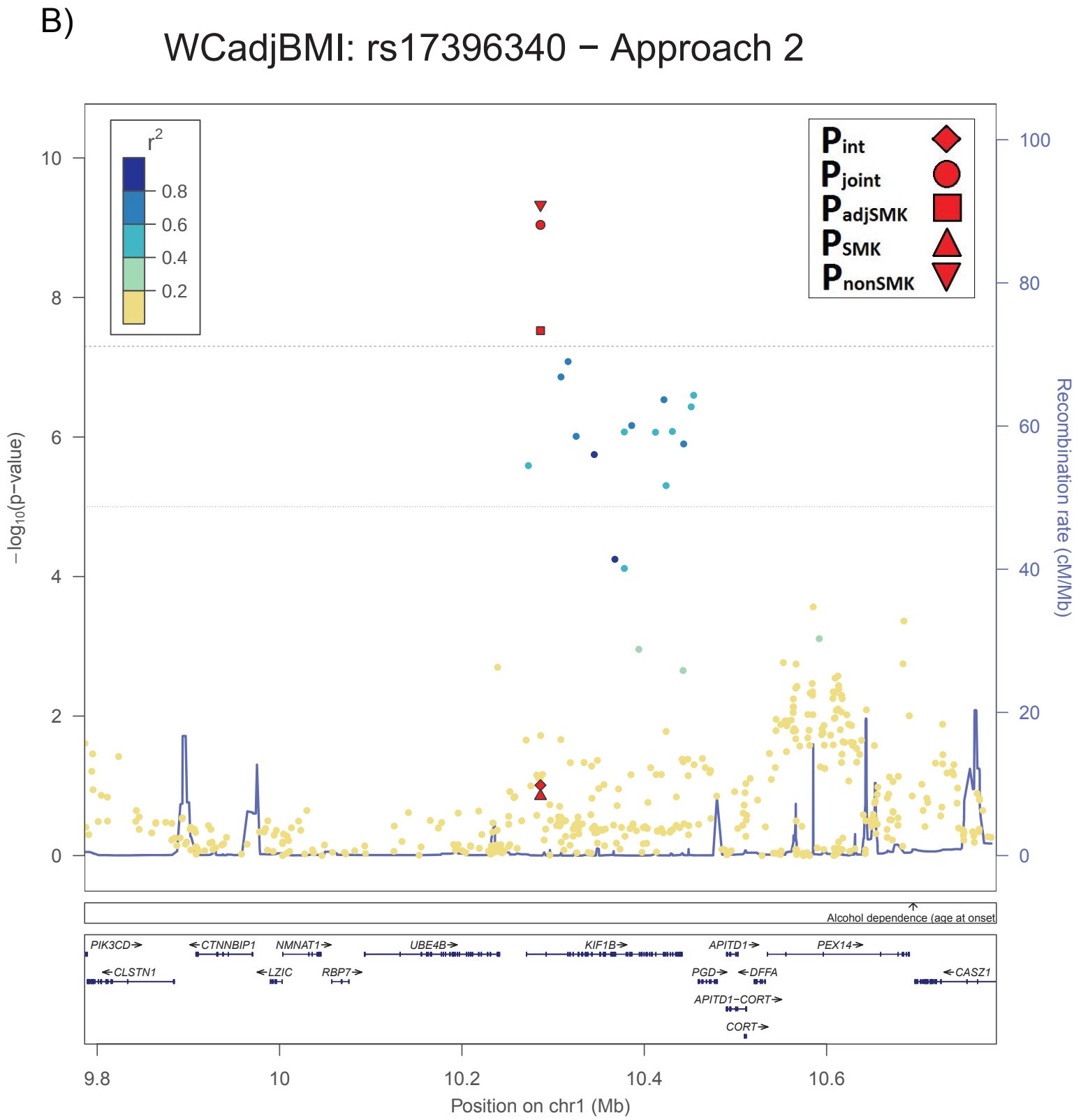
Supplementary Figure 5. Regional association plot for all loci identified in Approach 2 in primary meta-analyses, used to identify significant interaction (SNPint), in the primary meta-analyses for A) BMI and B) WCadjBMI, and ordered as they appear in Table 1. LD has been calculated using the combined ancestries from the 1000 Genomes Phase 1 reference panel. For comparison, each plot highlights the p-value for the tag SNP in Approach 1 (P_{adjSMK}), Approach 2 (P_{joint}), Approach 3 (P_{int}), current smokers (P_{SMK}), and in nonsmokers (P_{nonSMK}). EUR-European-only meta-analysis.

A)

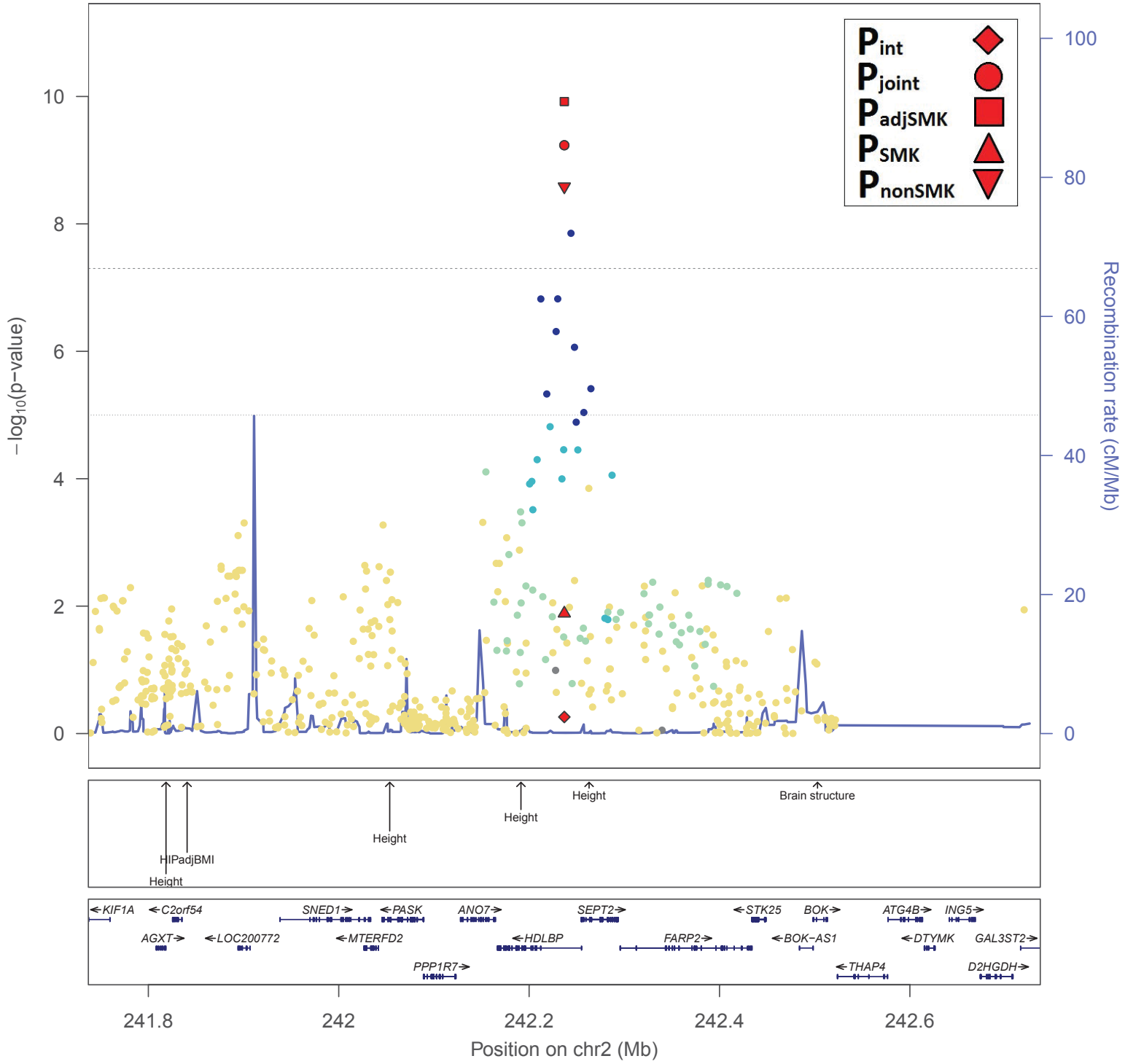

BMI: rs10929925 − Approach 2
r2
0.8
0.6
0.4
0.2
Pint
Pjoint
PadjSMK
PSMK
PnonSMK
−log10(p−value)
Recombination rate (cM/Mb)
Coronary artery calcification
Chronic kidney disease
s disease
LINC01248
LINC01105
LINC01247
SOX11
LOC400940
Position on chr2 (Mb)


BMI: rs13069244 − Approach 2
r2
0.8
0.6
0.4
0.2
Pint
Pjoint
PadjSMK
PSMK
PnonSMK
10
8
6
4
2
0
100
80
60
40
20
0
−log10(p−value)
Recombination rate (cM/Mb)
TTC14
LOC101928882
FXR1
SOX2−OT
CCDC39
DNAJC19
180
180.2
180.4
180.6
180.8
Position on chr3 (Mb)

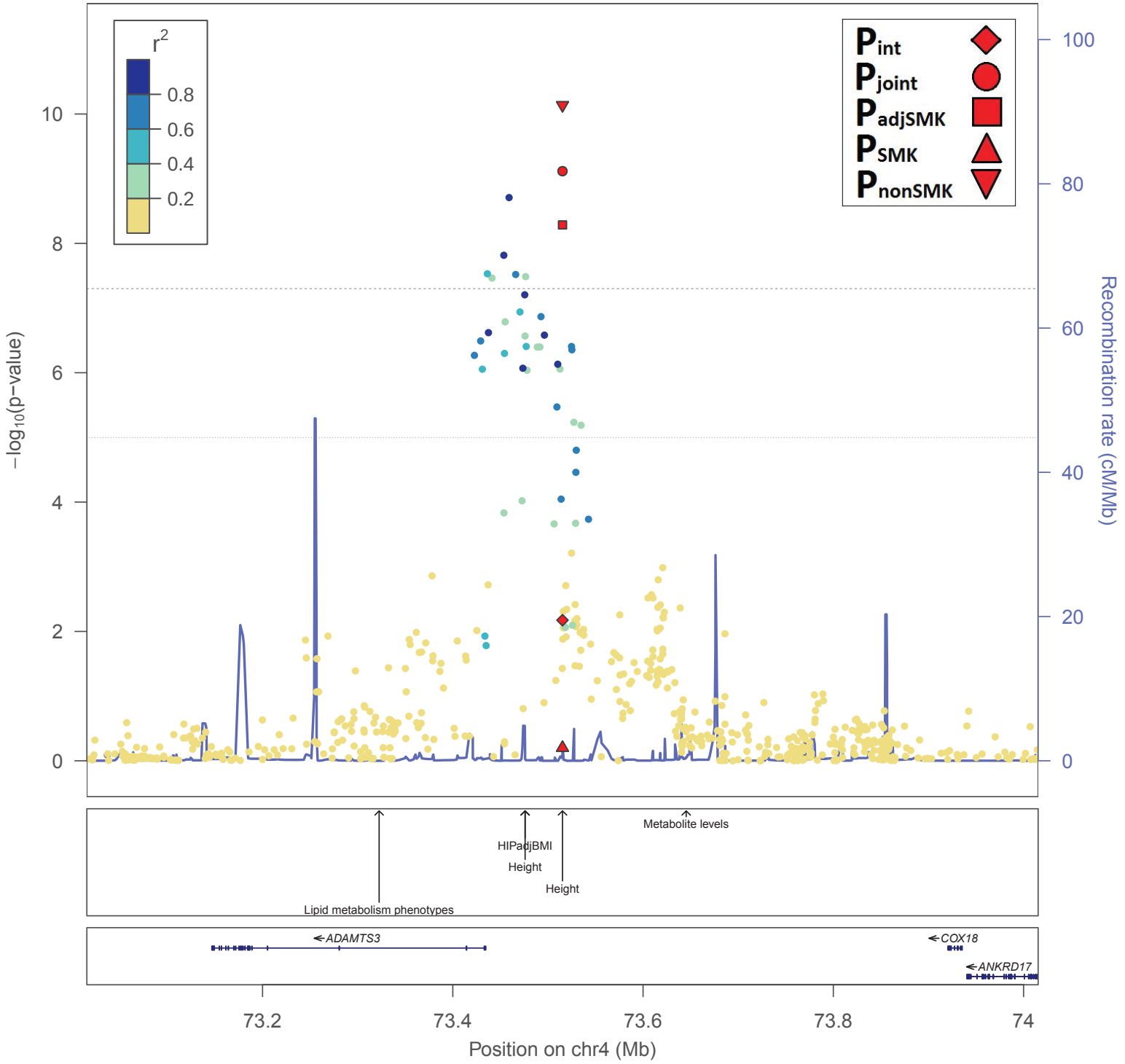
B)


WCadjBMI: rs17396340 − Approach 2
r2
0.8
0.6
0.4
0.2
Pint
Pjoint
PadjSMK
PSMK
PnonSMK
−log10(p−value)
Recombination rate (cM/Mb)
Alcohol dependence (age at onset
PIK3CD
CTNNBIP1
NMNAT1
UBE4B
KIF1B
APITD1
PEX14
CLSTN1
LZIC
RBP7
PGD
DFFA
CASZ1
APITD1−CORT
CORT
Position on chr1 (Mb)

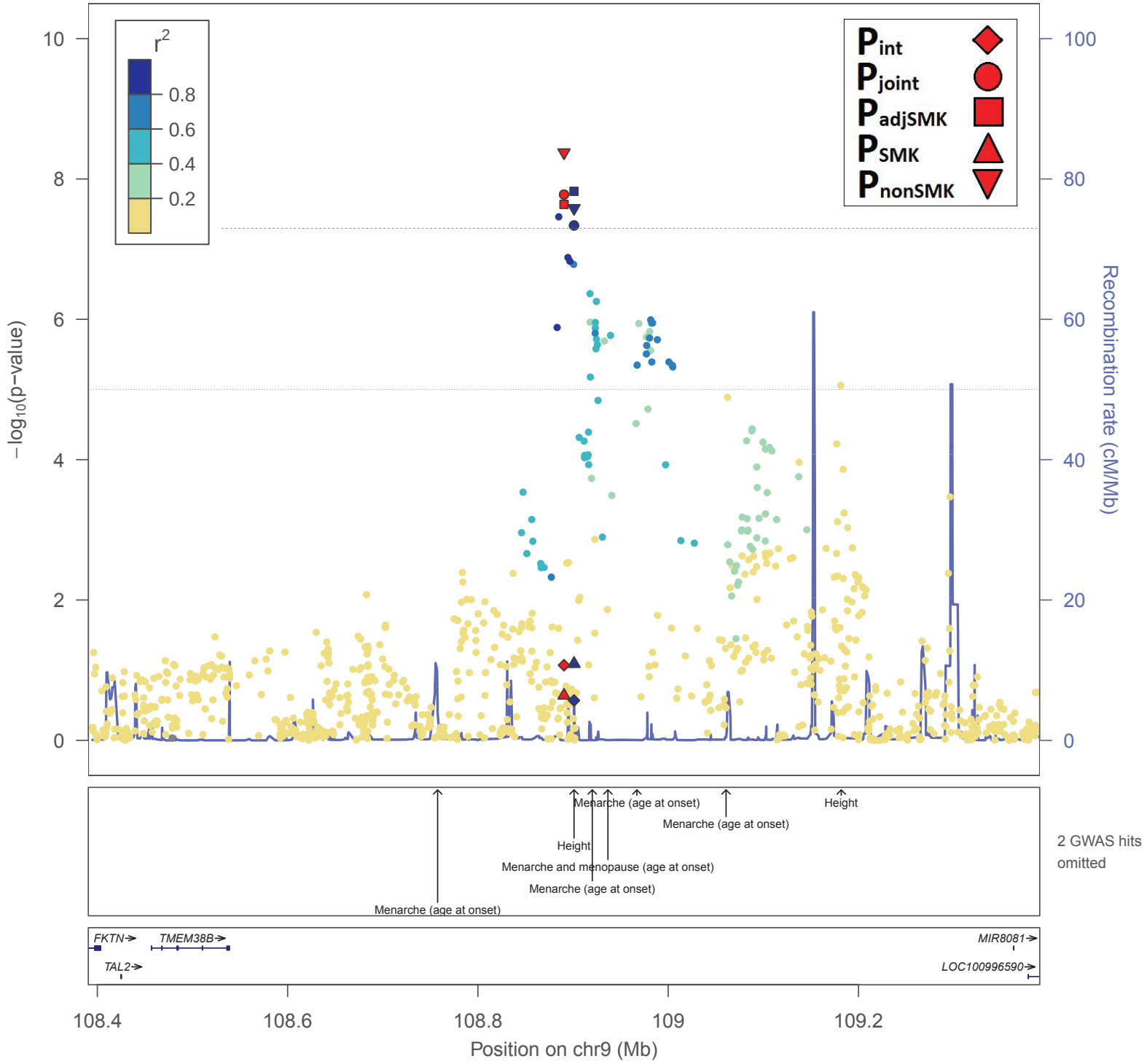
WCadjBMI: rs6743226 − Approach 2



WCadjBMI: rs7697556 − Approach 2

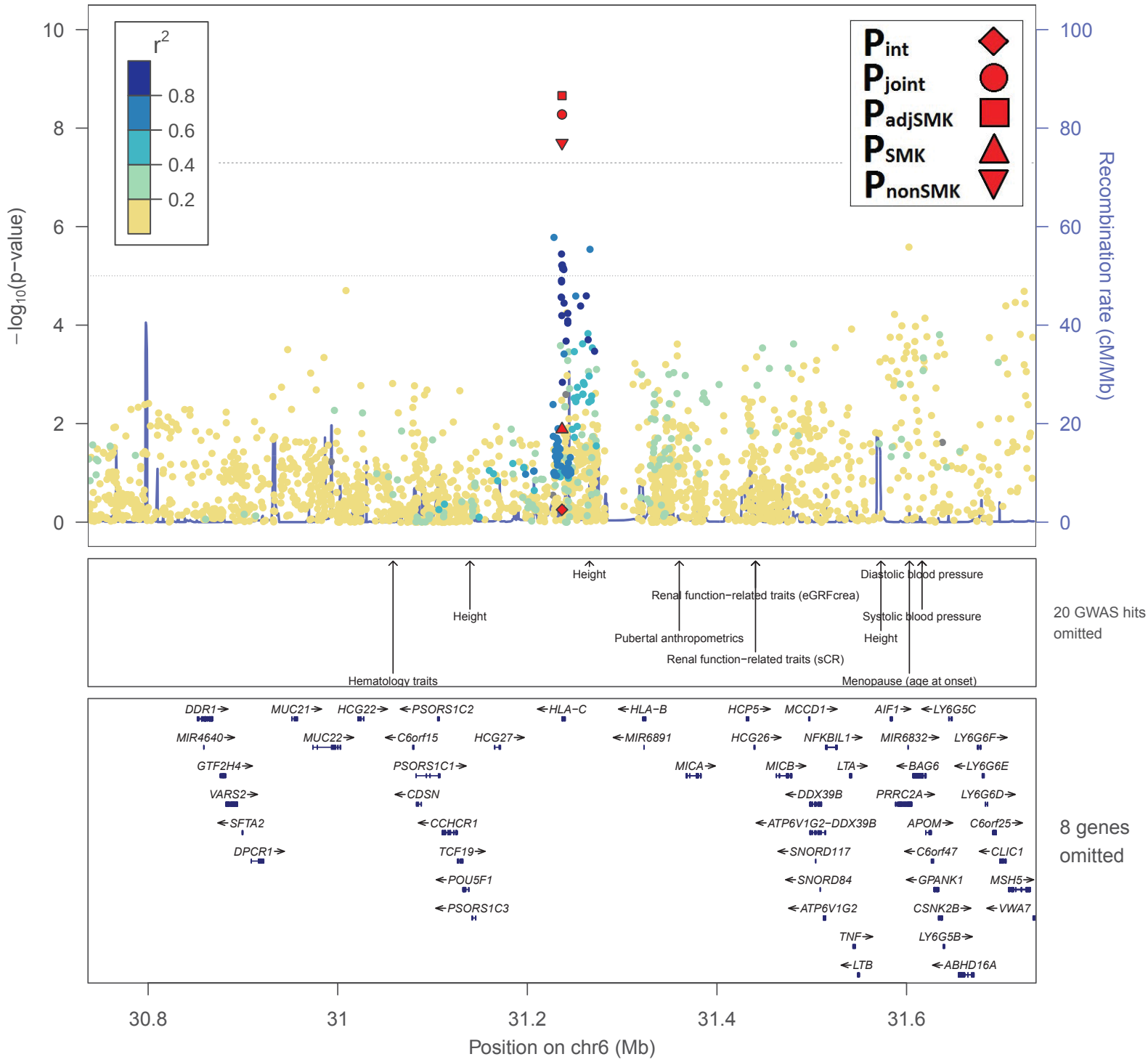


WCadjBMI: rs9408815 − Approach 2



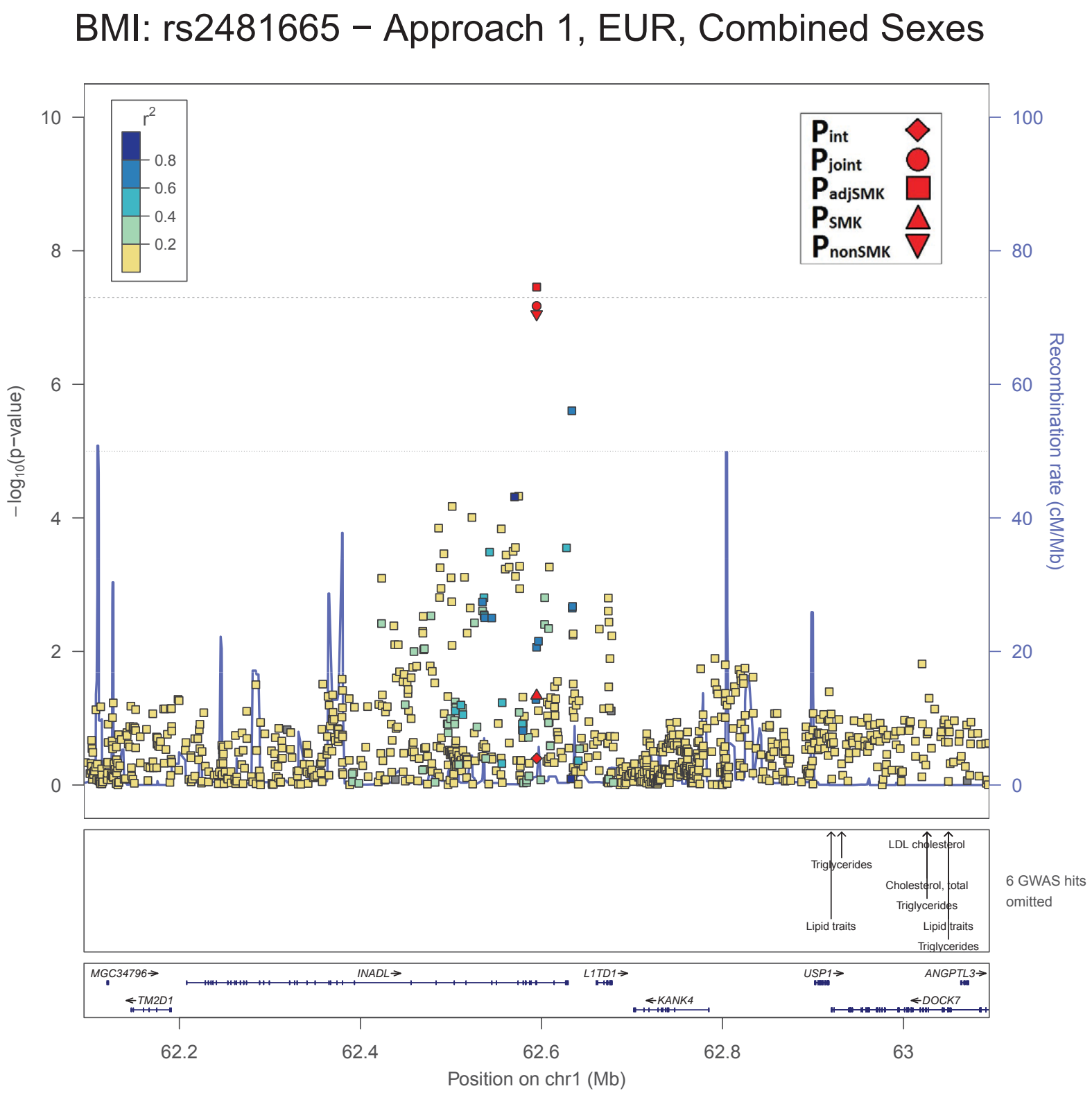
C)

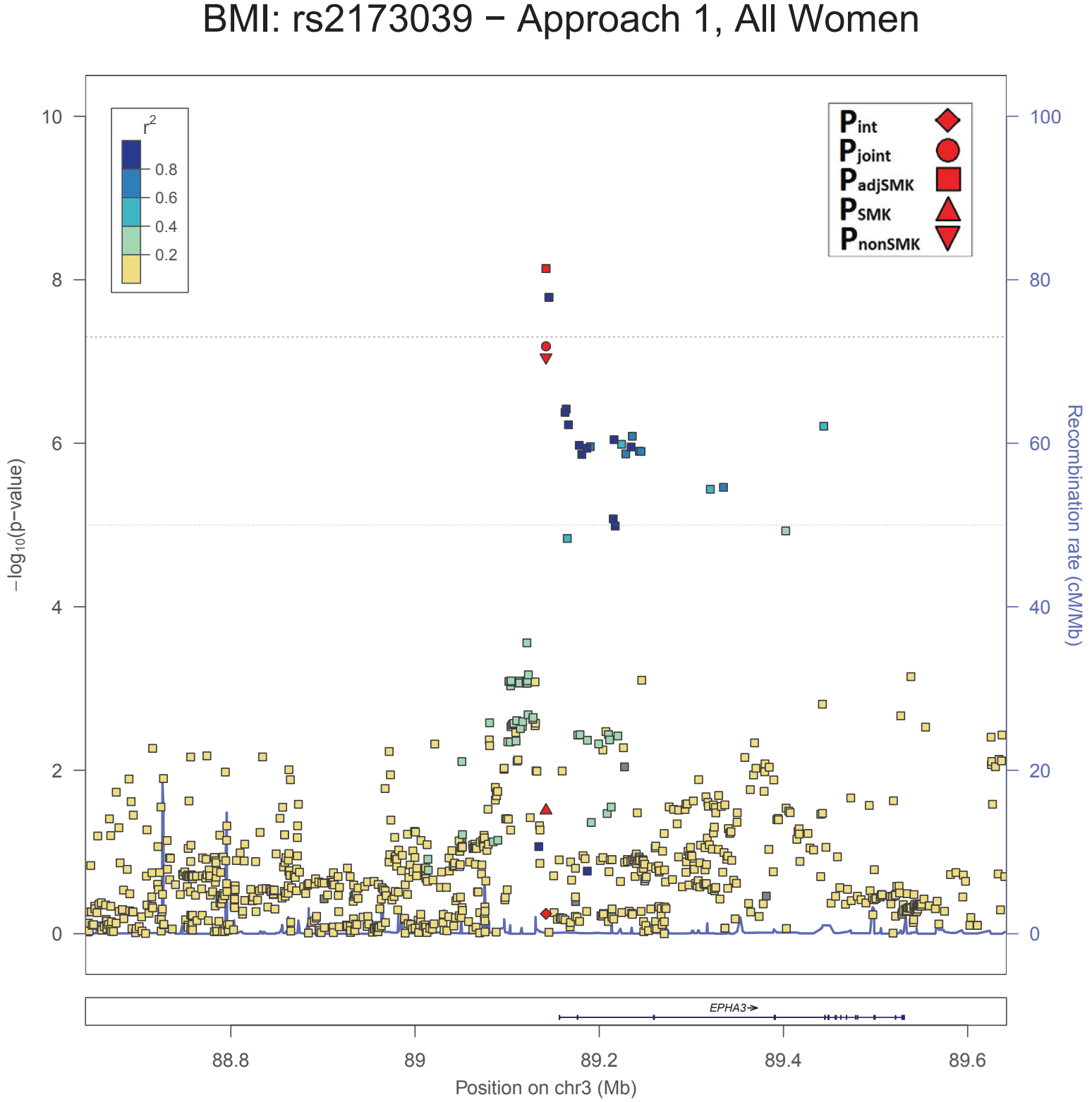
WHRadjBMI: rs1049281 − Approach 2



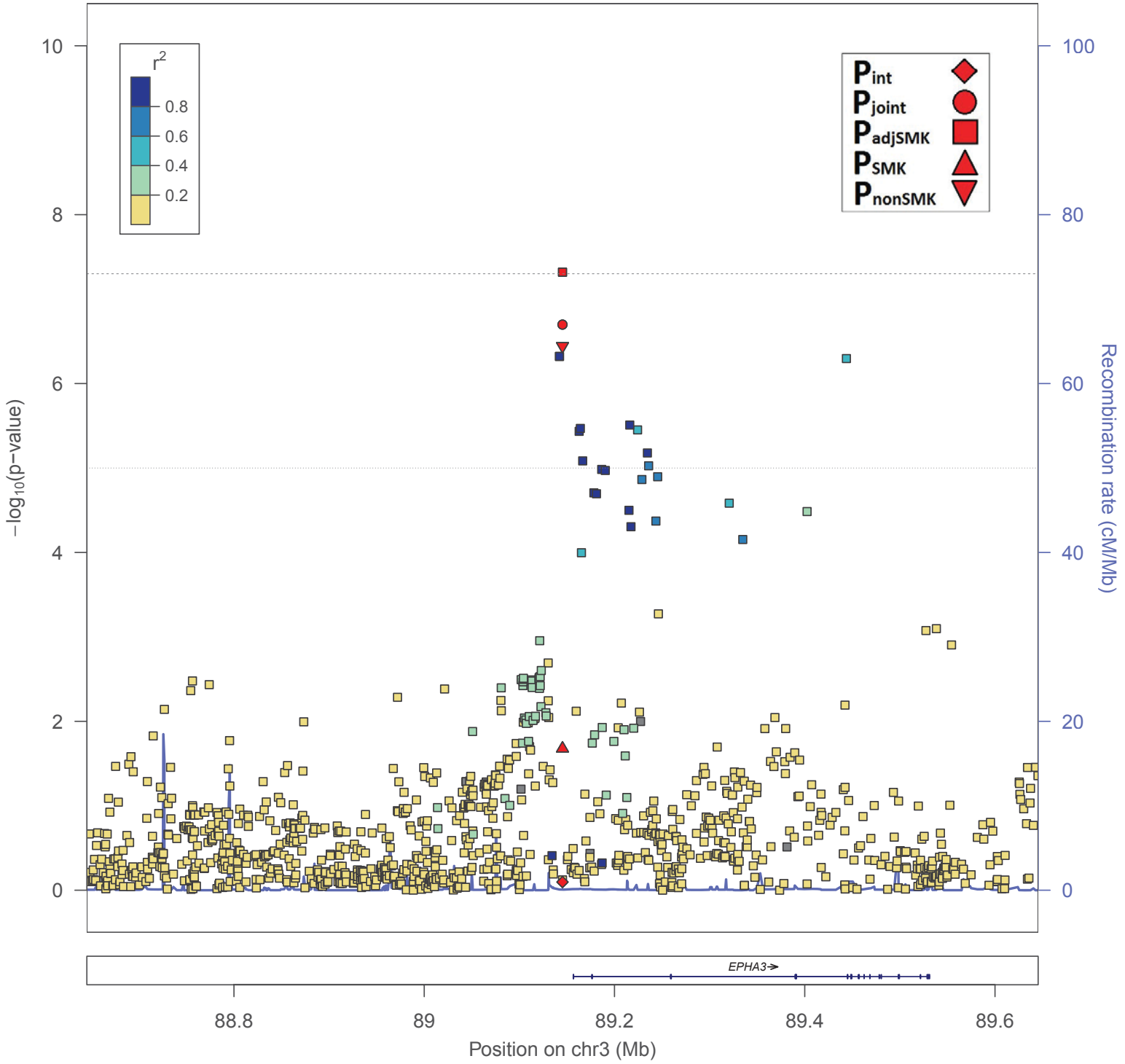
Supplementary Figure 6. Regional association plot for all loci identified in Secondary meta-analyses, and ordered as they appear in Tables 2. LD has been calculated using the combined ancestries from the 1000 Genomes Phase 1 reference panel. For comparison, each plot highlights the p-value for the tag SNP in Approach 1 (P_{adjSMK}), Approach 2 (P_{joint}), Approach 3 (P_{int}), current smokers (P_{SMK}), and in nonsmokers (P_{nonSMK}). P-values are shown from the strata in which the signal was identified (e.g. European-only women).

A.

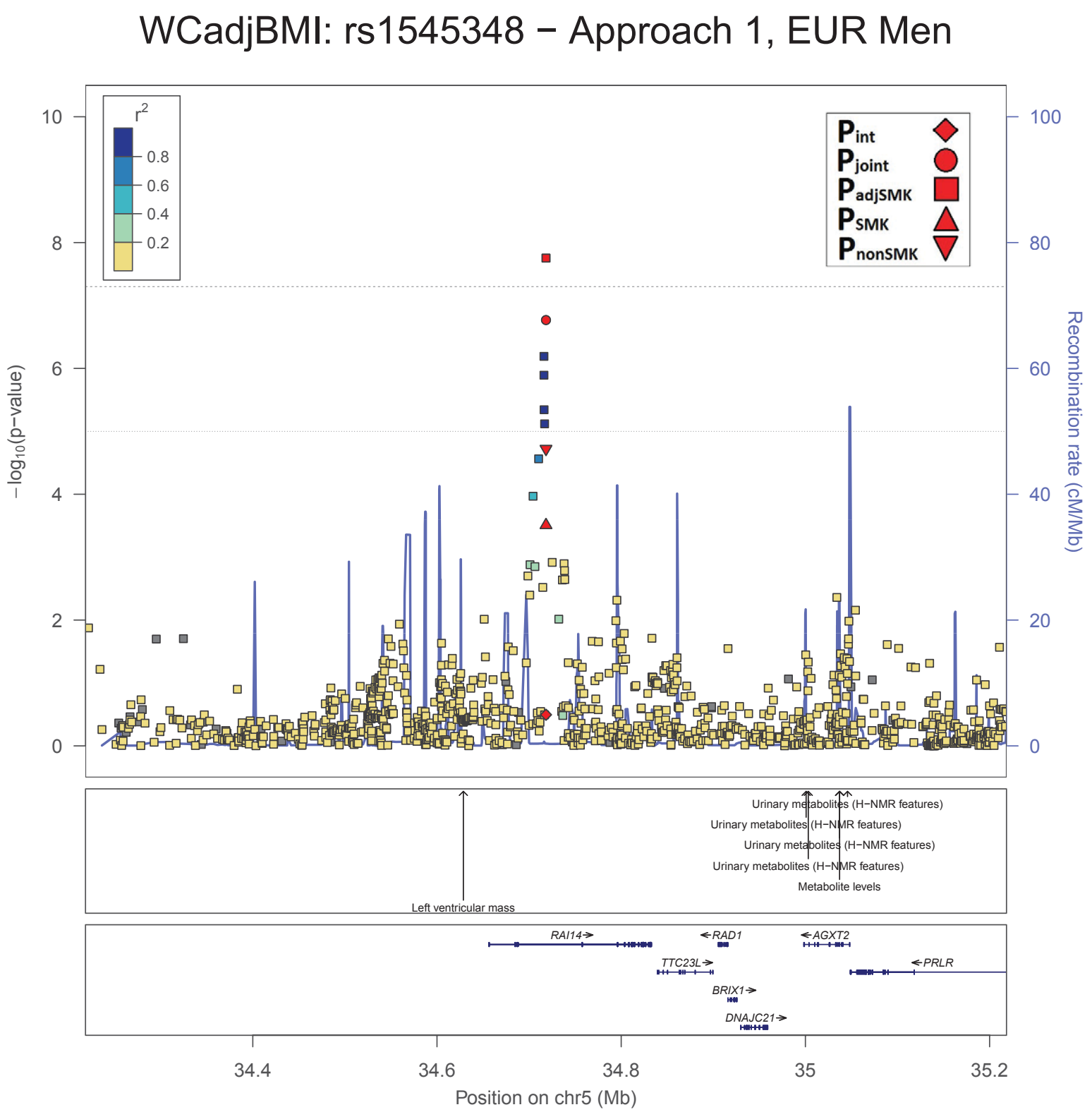

BMI: rs2481665 − Approach 1, EUR, Combined Sexes
r2
0.8
0.6
0.4
0.2
Pint
Pjoint
PadjSMK
PSMK
PnonSMK
−log10(p−value)
Recombination rate (cM/Mb)
Triglycerides
Lipid traits
LDL cholesterol
Cholesterol, total
Triglycerides
Lipid traits
Triglycerides
6 GWAS hits omitted
MGC34796
INADL
L1TD1
USP1
ANGPTL3
TM2D1
KANK4
DOCK7
Position on chr1 (Mb)


BMI: rs2173039 − Approach 1, All Women
r2
0.8
0.6
0.4
0.2
Pint
Pjoint
PadjSMK
PSMK
PnonSMK
−log10(p−value)
Recombination rate (cM/Mb)
EPHA3
Position on chr3 (Mb)
88.8
89
89.2
89.4
89.6

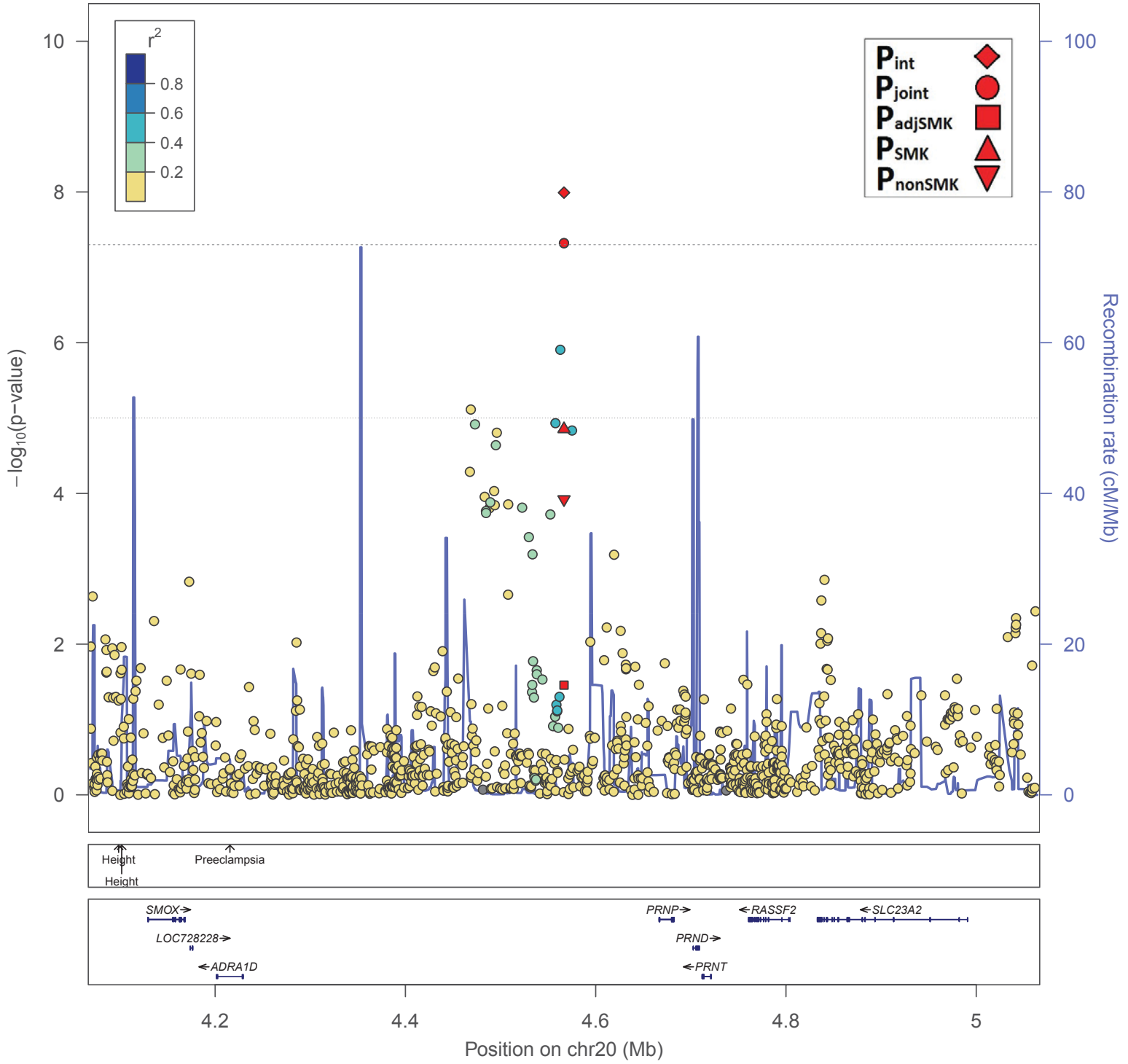
BMI: rs12629427 − Approach 1, EUR Women



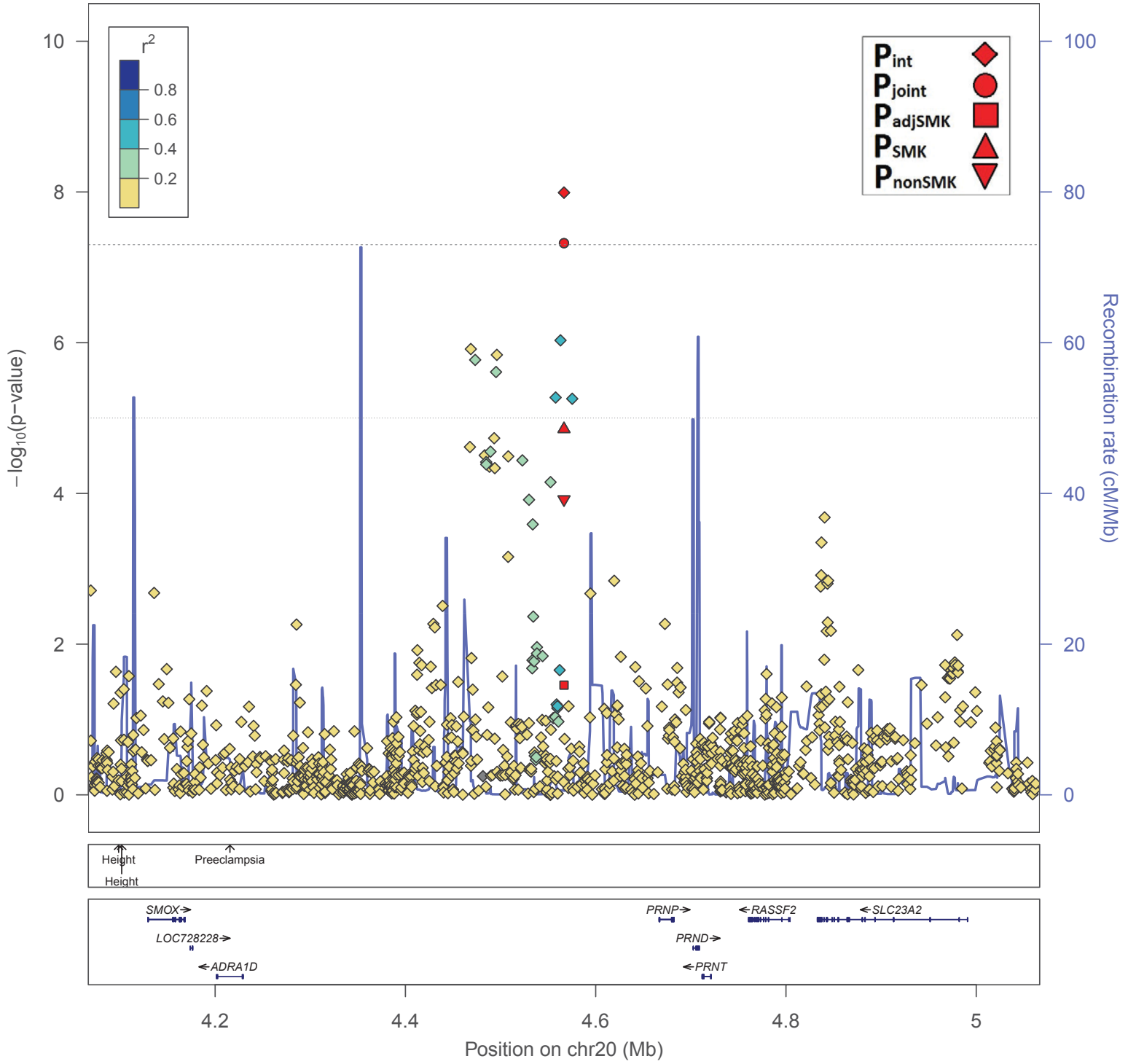
B.


WCadjBMI: rs1545348 − Approach 1, EUR Men
r2
0.8
0.6
0.4
0.2
Pint
Pjoint
PadjSMK
PSMK
PnonSMK
−log10(p−value)
Recombination rate (cM/Mb)
Urinary metabolites (H−NMR features)
Urinary metabolites (H−NMR features)
Urinary metabolites (H−NMR features)
Urinary metabolites (H−NMR features)
Metabolite levels
Left ventricular mass
RAI14
RAD1
AGXT2
TTC23L
PRLR
BRIX1
DNAJC21
Position on chr5 (Mb)

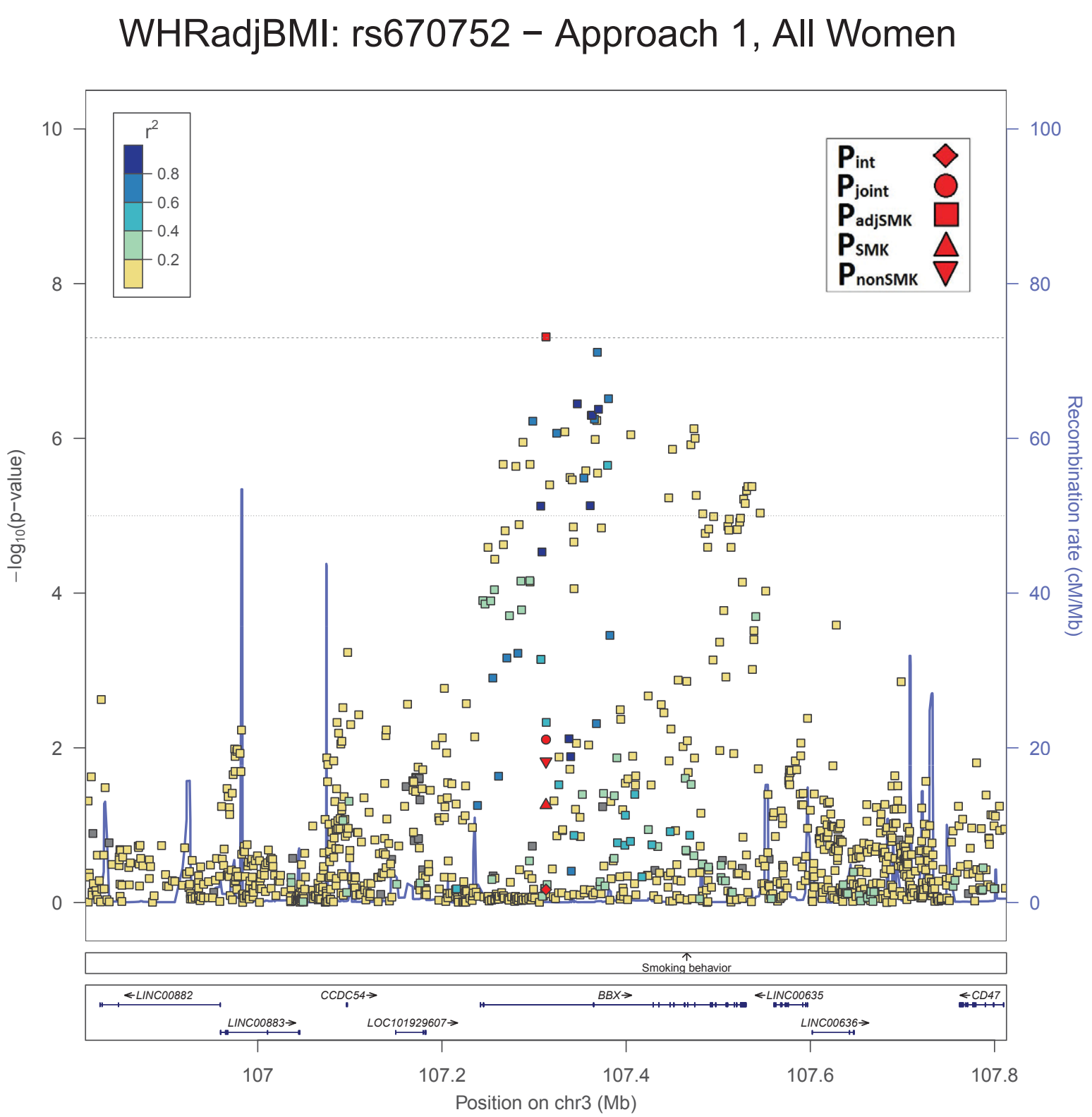
WCadjBMI: rs6076699 − Approach 2, EUR Women



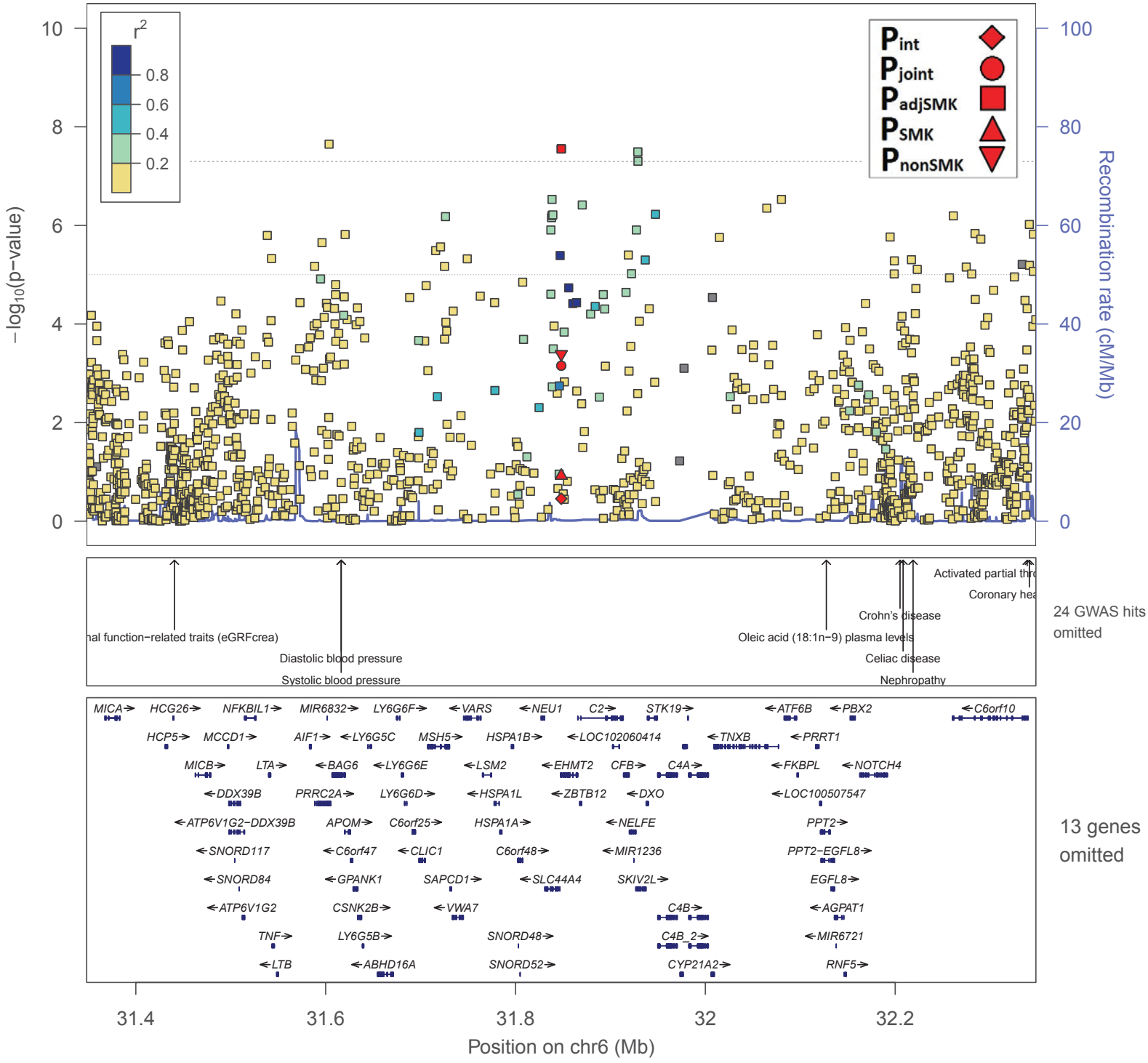
WCadjBMI: rs6076699 − Approach 3, EUR Women



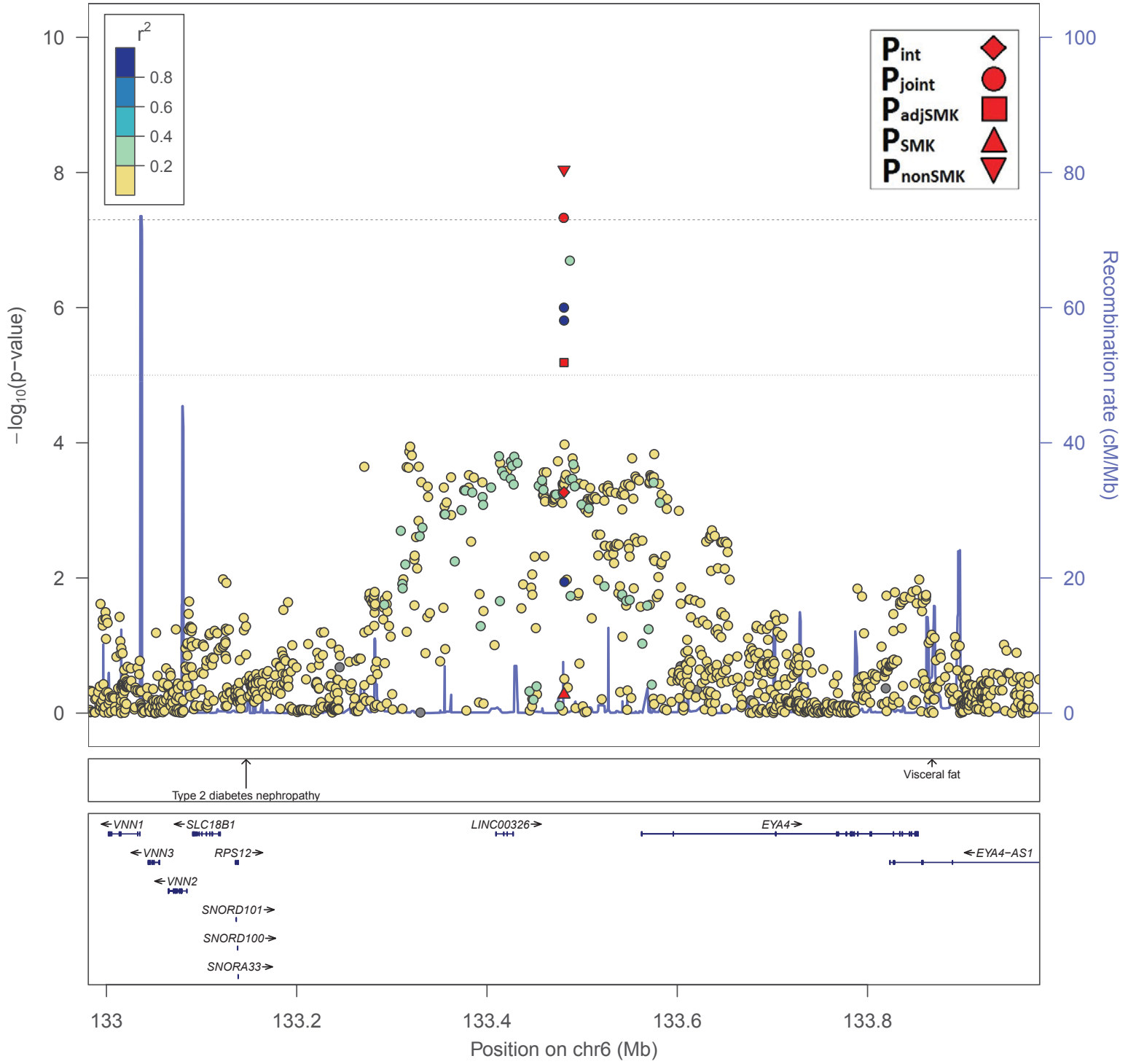
C.


WHRadjBMI: rs670752 − Approach 1, All Women
r2
0.8
0.6
0.4
0.2
Pint
Pjoint
PadjSMK
PSMK
PnonSMK
−log10(p−value)
Recombination rate (cM/Mb)
Smoking behavior
LINC00882
CCDC54
BBX
LINC00635
CD47
LINC00883
LOC101929607
LINC00636
Position on chr3 (Mb)

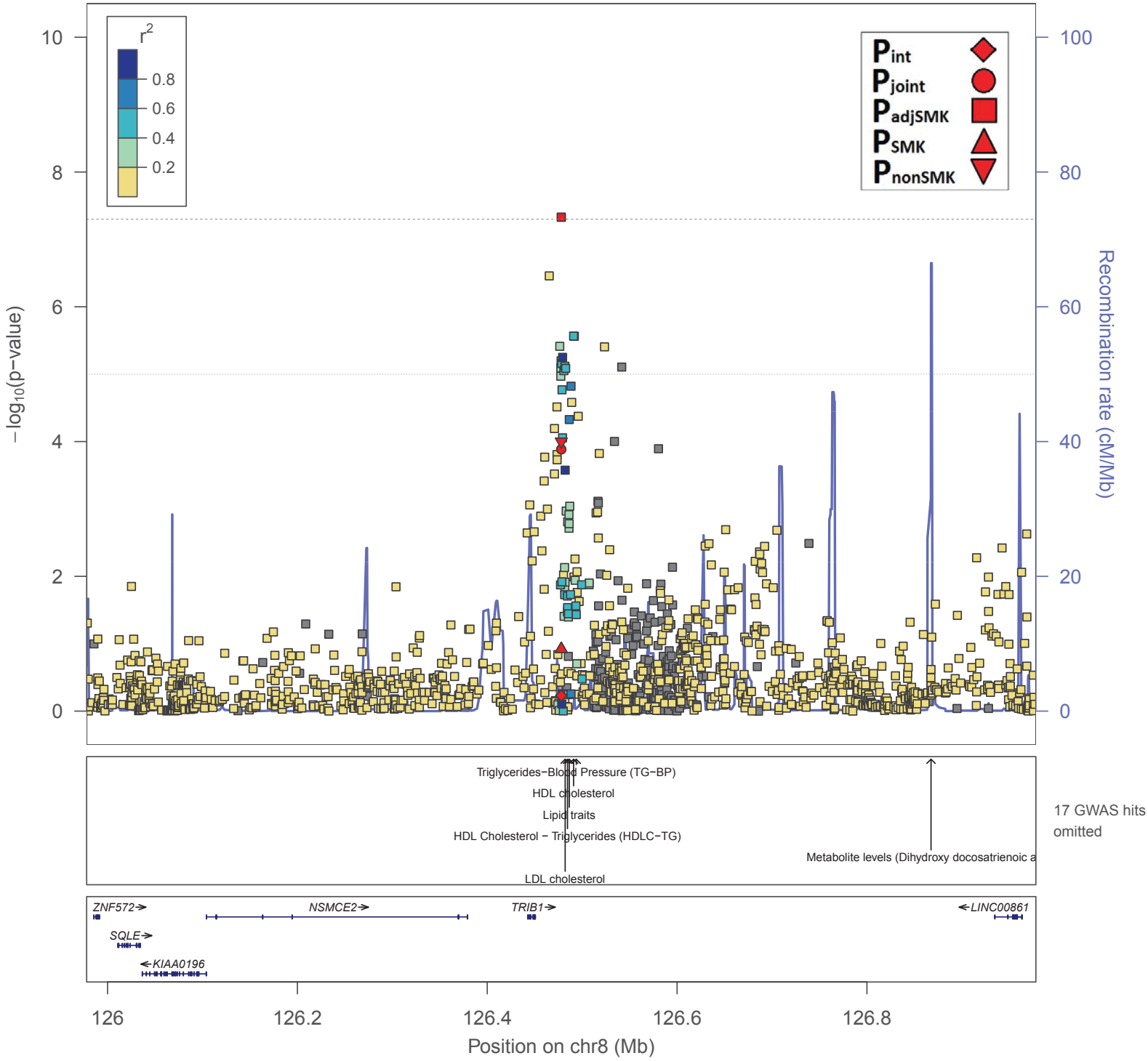
WHRadjBMI: rs589428 − Approach 1, EUR Combined Sexes



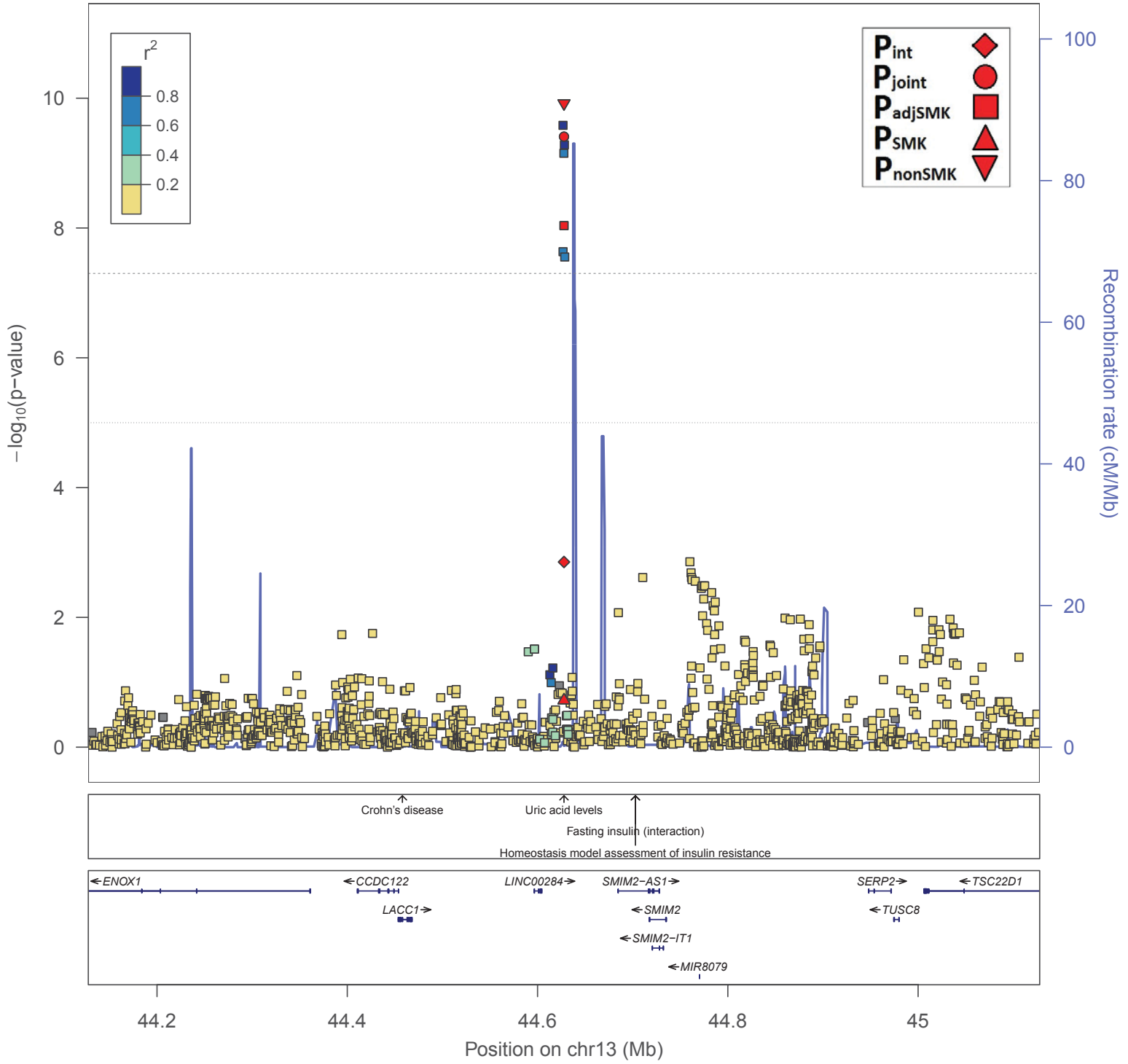
WHRadjBMI: rs1856293 − Approach 2 EUR Combined Sexes



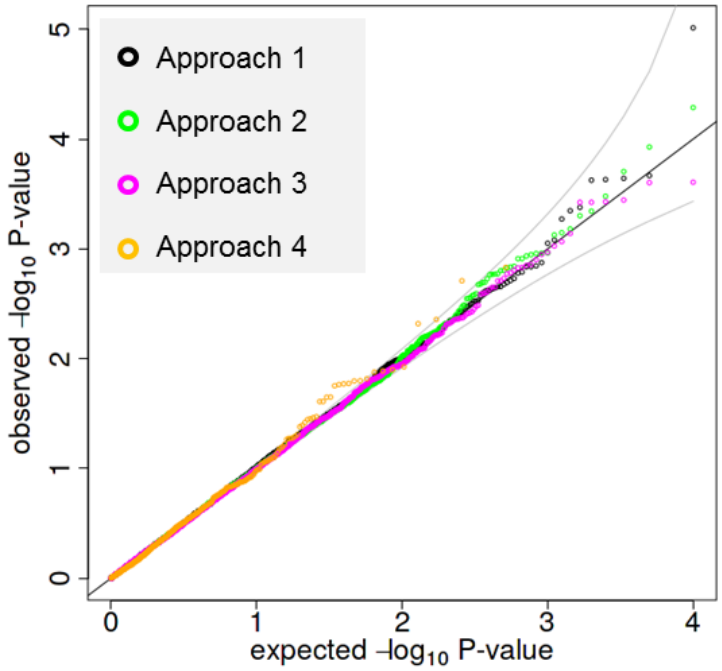
WHRadjBMI: rs2001945 − Approach 1, All Women



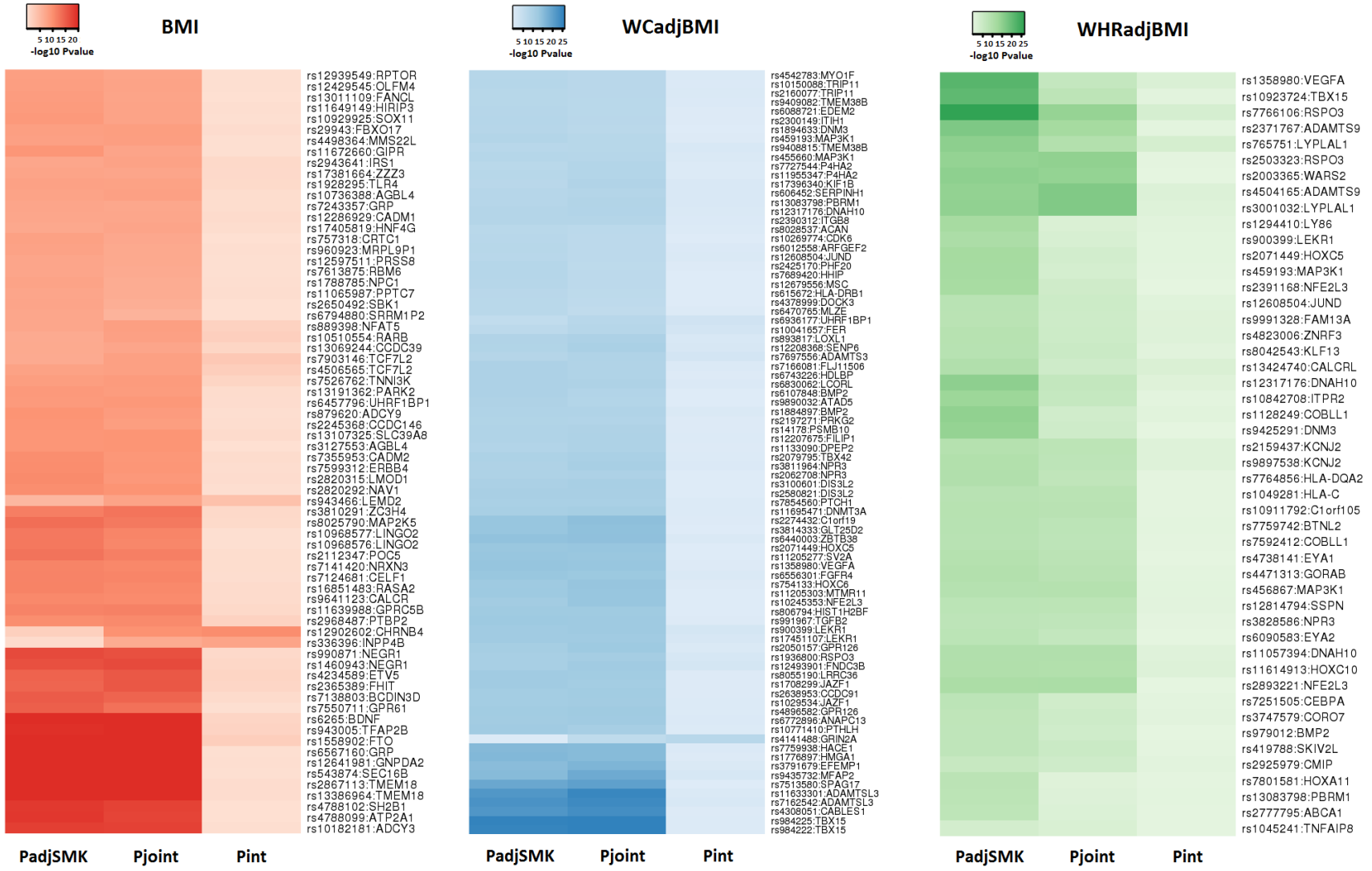
WHRadjBMI: rs17065323 − Approach 1, EUR Combined Sexes



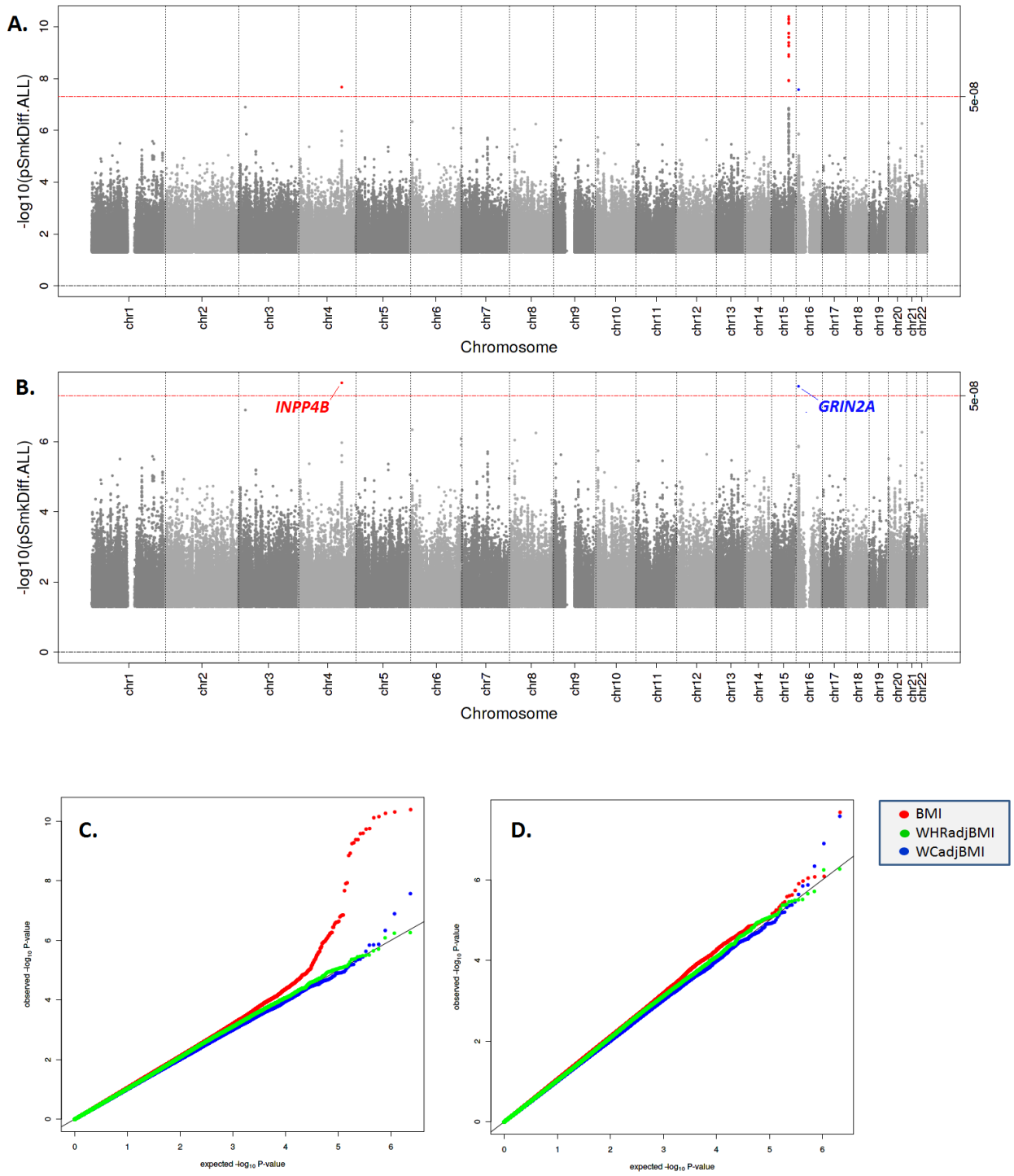
Supplementary Figure 7. Simulation-based estimation of type 1 error using QQ plots. Shown are the QQ plots of simulation results for Approach 1 (adjusted effect), Approach 2 (joint effect), Approach 3 and 4 (interaction effects). The simulation was based on MAF=0.05, 50,000 smokers and 180,000 nonsmokers.



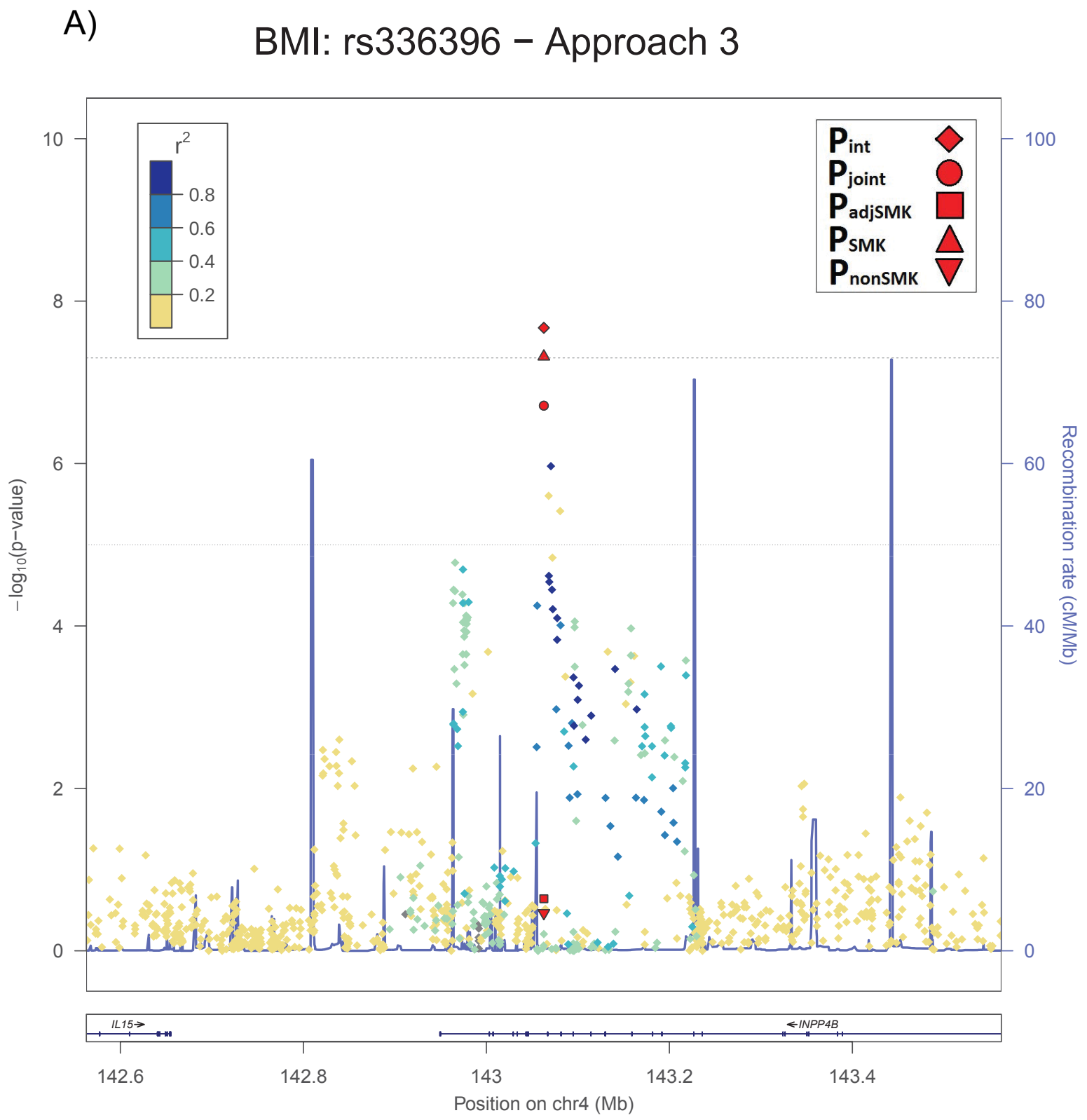
Supplementary Fig. 8. Heatmap of –log10P-values for SNPadjSMK, SNPjoint, and SNPint models. We have included each variant identified in the all ancestries analysis which was significant for Approaches 1-3. Strength of color represents the –log10 P-value from the all ancestries, combined sexes meta-analysis.



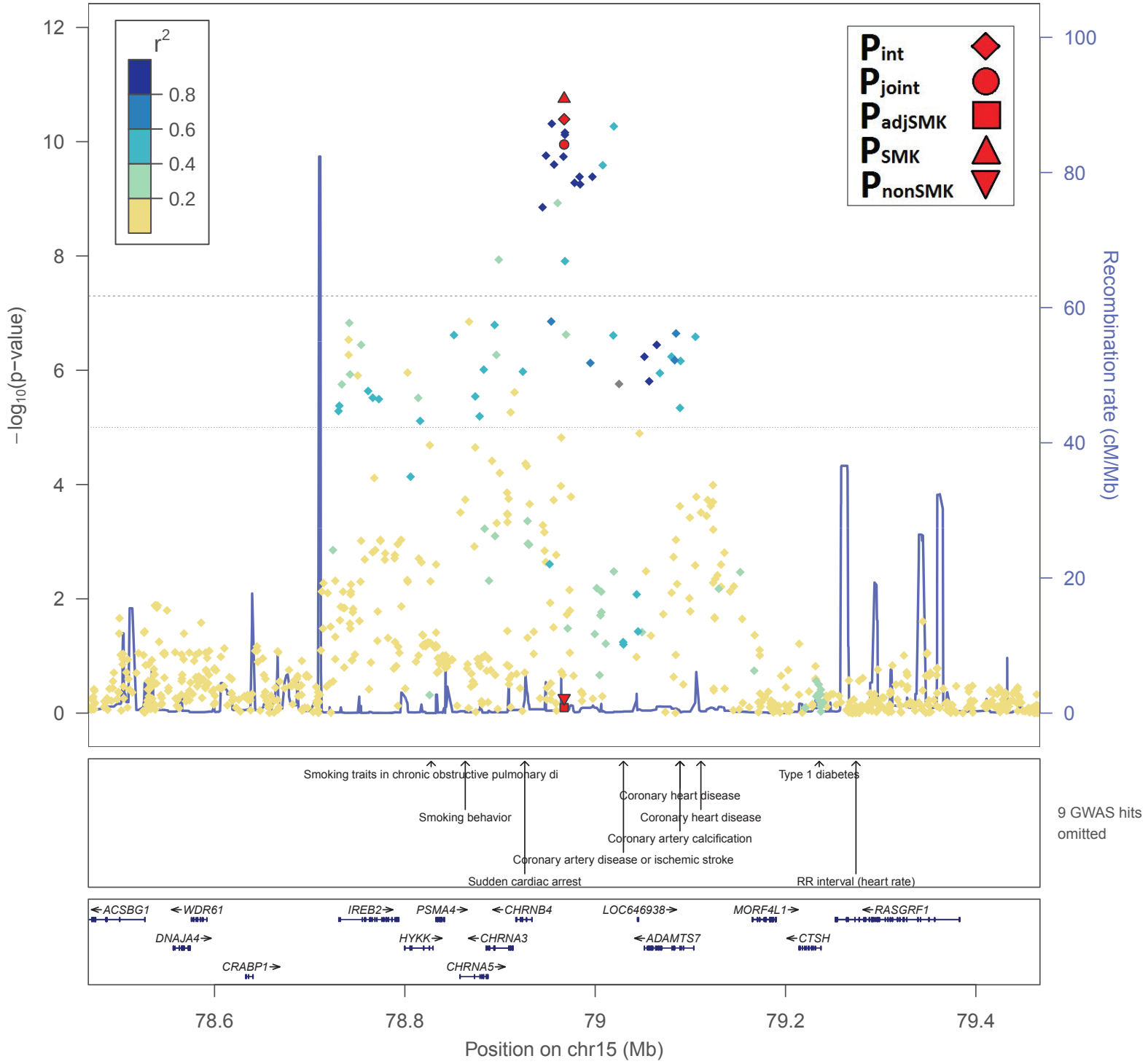
Supplementary Figure ϕ. Summary plots of discovery meta-analysis for Approach 3 primary meta-analyses. (A) Manhattan plot showing the loci identified in Approach 2 in primary meta-analyses, used to identify significant interaction effects loci (SNPint), in the primary meta-analyses association –log10P-values for BMI-red, WCadjBMI-blue, and WHRadjBMI-green; (B) Manhattan plot showing the loci identified in Approach 2 excluding known regions +/- 500 kb and labeled with the nearest gene to the index SNP; (C) QQ-plot showing the Approach 2 P-values as observed against those expected under the null for each phenotypes separately (colored); (D) QQ-plot for Approach 2 after excluding known association regions.



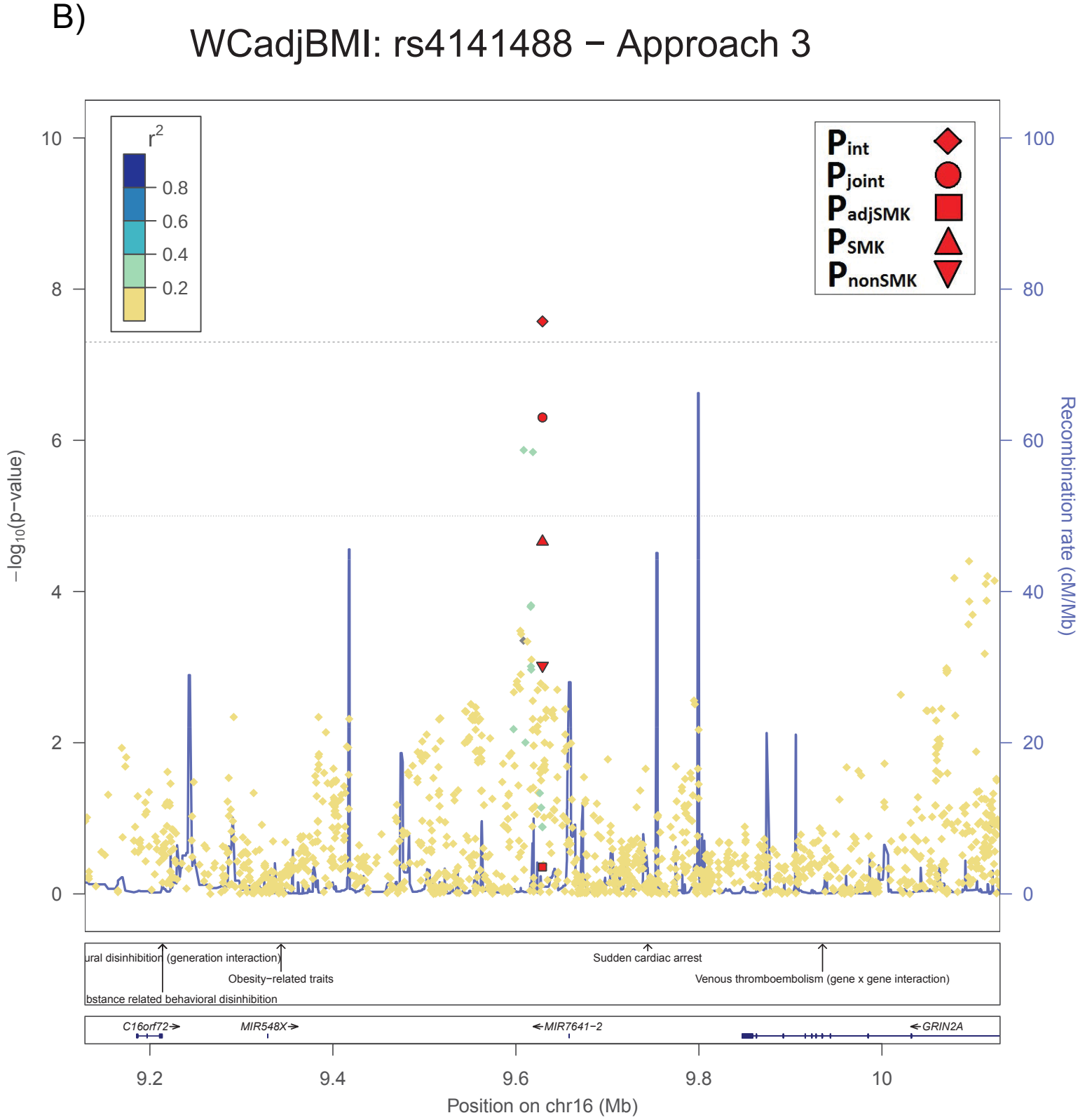
Supplementary Figure мл. Regional association plot for all loci identified in Approach 3 in primary meta-analyses, used to identify significant interaction (SNPint), in the primary meta-analyses for A) BMI and B) WCadjBMI, and ordered as they appear in Table 3. LD has been calculated using the combined ancestries from the 1000 Genomes Phase 1 reference panel. For comparison, each plot highlights the p-value for the tag SNP in Approach 1 (P_{adjSMK}), Approach 2 (P_{joint}), Approach 3 (P_{int}), current smokers (P_{SMK}), and in nonsmokers (P_{nonSMK}). EUR-European-only meta-analysis.


A)
BMI: rs336396 − Approach 3
r2
0.8
0.6
0.4
0.2
Pint
Pjoint
PadjSMK
PSMK
PnonSMK
−log10(p−value)
Recombination rate (cM/Mb)
IL15
INPP4B
142.6
142.8
143
143.2
143.4
Position on chr4 (Mb)

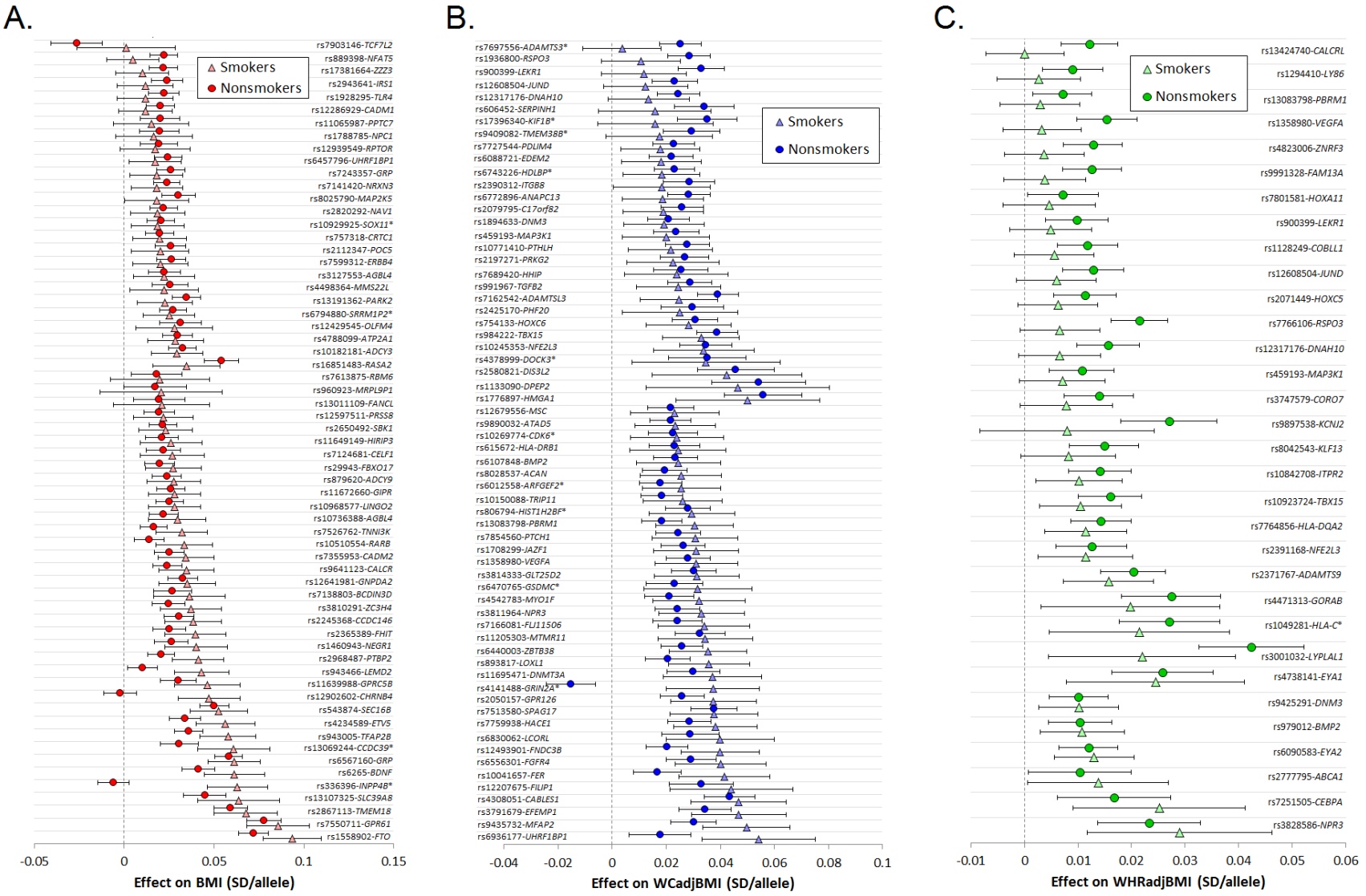
BMI: rs12902602 − Approach 3



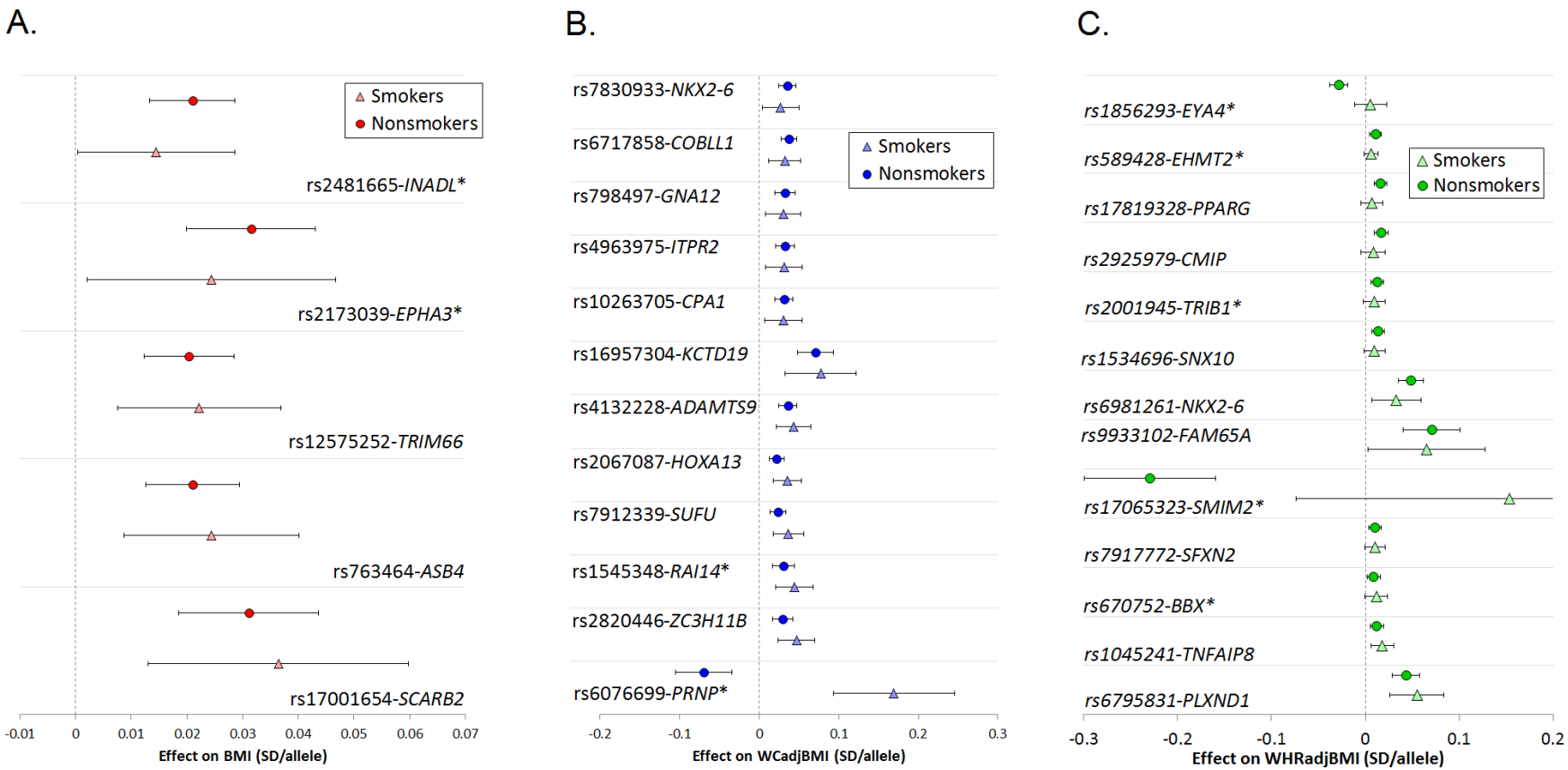
B)


WCadjBMI: rs4141488 − Approach 3
r2
0.8
0.6
0.4
0.2
Pint
Pjoint
PadjSMK
PSMK
PnonSMK
−log10(p−value)
Recombination rate (cM/Mb)
ural disinhibition (generation interaction)
Obesity−related traits
bstance related behavioral disinhibition
Sudden cardiac arrest
Venous thromboembolism (gene x gene interaction)
C16orf72
MIR548X
MIR7641−2
GRIN2A
Position on chr16 (Mb)

Supplementary Figure MM. Estimated effects (β ± 95% CI) per risk allele for A) BMI, B) WCadjBMI, and C) WHRadjBMI for the most significant variant for each locus identified in the primary meta-analyses (combined ancestries and combined sexes) for Approaches 1 (SNPadjSMK), 2 (SNPjoint) and 3 (SNPint). Loci are ordered by greater magnitude of effect in smokers compared to nonsmokers and labeled with the nearest gene.



Supplementary Figure 1H. Estimated effect estimates (β ± 95% CI) per risk allele for A) BMI, B) WCadjBMI, and C) WHRadjBMI for the most significant variant for each locus identified in the secondary meta-analyses (sex-stratified and European-only analyses) for Approaches 1 (SNPadjSMK), 2 (SNPjoint) and 3 (SNPint). Loci are ordered by greater magnitude of effect in smokers compared to nonsmokers and labeled with the nearest gene.



Supplementary Figure 13. Comparison of estimated effect estimates (SE) per risk allele in GIANT only and UKBiobank validation analysis for A) BMI stratified by smoking status, B) BMI adjusted for smoking status, C) WCadjBMI stratified by smoking status, D) WCadjBMI adjusted for smoking status, E) WHRadjBMI stratified by smoking status, and F) WHRadjBMI adjusted for smoking status for each novel and GxSMK SNP in Tables 1-4.