SUPPLEMENTAL MATERIAL

Discovery Sample

Familial Intracranial Aneurysm Study (FIA Study): Families with at least 2 members who had intracranial aneurysm(s) (IA) were ascertained through 26 clinical centers (41 sites) in North America, New Zealand, and Australia. Exclusion criteria included (i) a fusiform-shaped unruptured IA of a major intracranial trunk artery; (ii) an IA that is part of an arteriovenous malformation; (iii) a family or personal history of polycystic kidney disease, Ehlers Danlos syndrome, Marfan's syndrome, fibromuscular dysplasia, or Moya-Moya disease; or (iv) failure to obtain informed consent from the patient or family members. All medical records and relevant accompanying data were reviewed by a Verification Committee. The FIA study was approved by the Institutional Review Boards/Ethics Committees at all clinical and analytical centers and recruitment sites.

For the present analysis, only individuals having an IA based on an intra-arterial angiogram, operative report, autopsy, or size ≥7 mm on non-invasive imaging (MRA, CTA) were considered "definite" cases. A set of independent unrelated cases obtained by selecting one individual with definite IA from each FIA family self-reported as Caucasian (n=388) was included in Discovery Sample 1. Samples from an additional 30 Caucasian cases were included in Discovery Sample 3, and 1 case was included in Discovery Sample 4. Results from Discovery Sample 1 were previously published.[1]

Further recruitment was undertaken as part of the FIA Study and the requirement for family history of IA was removed and both familial and sporadic IA cases were enrolled. The same exclusion criteria were in place and all cases underwent the same rigorous review from the Verification Committee. A set of 829 Caucasian IA cases was selected for genotyping in Discovery Sample 2. An additional 607 Caucasian IA cases were included in Discovery Sample 3, and 42 were included in Discovery Sample 4

Australasian Cooperative Research on Subarachnoid Hemorrhage Study (ACROSS): Caucasian cases and controls identified from other studies, including those from the Australasian Cooperative Research on Subarachnoid hemorrhage Study (ACROSS), which was a prospective, population-based, case-control study of SAH undertaken in three cities in Australia and one city in New Zealand during the mid-1990s.[2] ACROSS included incidence cases of SAH secondary to documented or presumed ruptured IA who were frequency-matched (by sex, 10-year age strata, and city of residence) to controls selected from electoral rolls in each city. Detailed information about key exposures, such as smoking, hypertension, family history of stroke/IA, was obtained by standardized interviews with subjects (or proxies) and where possible, blood samples were obtained for storage and future DNA extraction. Samples from a total of 135 cases and 168 controls were available for genotyping in Discovery Sample 2. This study was approved by the institutional review committees at 10 sites. This sample has been has been included in a previous report.[1]

UCSF: The University of California, San Francisco recruited a prospective cohort of adult patients with spontaneous SAH due to IA who were admitted to a tertiary-care referral center in San Francisco during 2003 to 2008. Cases were confirmed by non-contrast CT and cerebral

angiogram. After excluding subjects based on FIA exclusion criteria, 184 samples from Caucasian subjects with detailed medical histories and blood banked for DNA were available for genotyping in Discovery Sample 2. This study was approved by the institutional review committee at University of California, San Francisco. This sample has been has been included in a previous report.[1]

ARIC: Genotypic data from a set of 1148 white controls, included in Discovery Sample 2, were obtained through a collaborative agreement with the Atherosclerosis Risk in Communities (ARIC) study. In the ARIC sample, a subset of subjects who never had a stroke or TIA was matched to the cases in Discovery Sample 2 cases by sex and, where possible, by age (±5 years). However, because the age of the ARIC controls was limited to 44–66, cases younger than 39 or older than 71 at onset were matched to controls outside of the 5-year criterion. Genotyping had been performed previously using the Affymetrix **SNP array** 6.0.[3] This sample has been has been included in a previous report.[1]

Cincinnati Control Cohort and Genetic and Environmental Risk Factors for Hemorrhage Stroke: Controls were obtained from two population-based studies. The first was the NINDS-funded case-control Genetic and Environmental Risk Factors for Hemorrhage Stroke (GERFHS) study, which was designed to identify the important environmental and genetic risk factors for IA-related SAH as well as for spontaneous intracerebral hemorrhage. Controls identified by random-digit telephone dialing from the Greater Cincinnati/Northern Kentucky community and matched to enrolled cases by age (±5 years), gender, and race, had the same interview questions regarding environmental risk factors as FIA study participants. Another set of controls free of stroke and IA were selected from the Cincinnati Control Cohort (CCC). The subjects in this cohort were identified by random-digit dialing from the Greater Cincinnati region during 2006. These subjects had blood drawn for DNA extraction as well as extensive interviews including detailed environmental exposures as well as detailed medical history of every major disease. Both studies were approved by the Institutional Review Boards of the University of Cincinnati and all participating hospitals. 113 GERFHS and 290 CCC controls have been included in a previous report.[1] 375 GERFHS and 7 CCC controls were not previously analyzed.

Krakow, Poland: IA cases were recruited from patients of the Department of Neurology and the Department of Neurosurgery and Neurotraumatology of the Jagiellonian University in Krakow. Both subjects with ruptured IAs and with unruptured IA were recruited. Presence of IA was confirmed by intra-arterial angiogram, CTA, MRA or intraoperatively. A total of 504 IA patients were included. The control group included 514 unrelated subjects taken from the population of southern Poland. Control subjects had no apparent neurological disease based on the findings in a structured questionnaire and a neurological examination. All subjects were of European descent. Information about key demographics, family history and risk factors were obtained using a standardized questionnaire. The study was approved by the institutional review board of the Jagiellonian University. All Polish samples were included in Discovery Sample 4.

Genotyping and Quality Review

Genotyping of all samples except ARIC was performed using the Axiom array at the Affymetrix core labs. Genotyping was performed in four batches using similar methods and quality control.

Forty-eight internal samples were genotyped twice for quality control. This yielded a total of 4,323 samples sent for genotyping. However, only 4,249 samples with a QC (dQC) value ≥0.82 and an initial call rate of 97% were released. All released genotypes underwent a common quality review pipeline which included identification of sample duplicates, related individuals, and gender discrepancies, which resulted in the removal of 118 samples. Prior to performing imputation, SNPs were excluded if there were: (i) improper mapping to Genome Reference Consortium GRCh37; (ii) a minor allele frequency (MAF) <0.03; (ii) a SNP call <95%; (iv) a Hardy Weinberg Equilibrium (HWE) p-value $<10^{-4}$ **in control samples**. MAF **and** call rates were calculated by combing all 4 batches together. From the 597,320 SNPs on the Axiom array, 464,632 were retained following this quality review.

Genotypic data for the ARIC samples was obtained from the **Affymetric SNP array** 6.0.[3] These data also underwent quality review and SNPs were removed based on the same criteria listed above. From the 793,799 autosome SNPs on the **Affymetric SNP array** 6.0 that were provided by ARIC following their initial data review, a total of 626,645 were retained for imputation in this study.

A principal component analysis (PCA) was performed using Eigenstrat[4] and data from 11 HapMap phase III populations to identify clusters using the first two eigenvectors computed using the SNPs typed on both platforms. Samples clustering with the European American (CEU **and TSI**) reference set were retained, and those outside this cluster which were likely to contain African, Asian, or Hispanic admixture were removed from further analysis (n=61 of the Axiom-genotyped samples); 16 non-European American samples from the ARIC set were also removed (**Supplemental Figure 1**).

Imputation

Imputation was performed for all autosomes using IMPUTE2 (https://mathgen.stats.ox.ac.uk/impute/impute_v2.html). **We have employed the recommendation of Howie et al[5] to include diverse reference panels to optimize imputation.** All distinct samples genotyped on the Axiom array (n=4060) were imputed together using the 1000Genomes haplotypes (n=1092; data freeze from Nov. 2010, May. 2011, March 2012 phased haplotype release) as the phased reference panel. Only variants with more than one minor copy across all 1000Genome populations were imputed. Original genotypes were not overwritten. ARIC sample (n=1132) were imputed separately using the same reference panel. Only SNPs genotyped on at least one of the arrays (1,195,878 SNPs) were used in the analysis.

Statistical Analysis

The discovery sample consists of samples recruited through multiple studies, some providing both cases and controls and others providing only cases or controls. As a result, we could not analyze each study separately and combine results using meta-analysis. Rather, we have combined all data available from our discovery sample and performed detailed quality review to reduce sources of false positive results due to population stratification and inter-study differences.

Because our sample was genotyped on two platforms, with all samples genotyped in **Affymetric SNP array** 6.0 being controls, extensive and detailed quality review was performed to ensure that spurious association was not detected based on platform effects. As suggested by Sinnott and Kraft[6] we reviewed several SNP metrics, including imputation quality (information) and differences in SNP minor allele frequency in controls genotyped on the Axiom platform, and the ARIC controls genotyped on the **Affymetric SNP array** 6.0. We removed all SNPs with low imputation quality (information score <0.30) as well as SNPs with a significant difference in minor allele frequency between the two sources of control samples ($p<0.1$). To further reduce the influence of rare SNPs, which would typically have less accurate imputation, we removed all SNPs with a minor allele frequency less than 5%. Using this aggressive filtering approach, we retained 672,210 SNPs for analysis. Remaining uncertainty in the imputed genotypes after application of the aggressive information score and minor allele frequency filters was modeled using the "-method score" option in SNPTEST V2. We would expect a slight loss of power in the association tests due to the uncertainty in genotypes; however, previous studies indicate this power loss is minimal, on the order of 7% of the effective sample size on average.[7] All samples were analyzed together with genomic control applied to correct for inflation.

Replication Sample

Two independent samples were used to replicate the primary findings from this study.

Dutch sample: IA patients (n=786) were admitted to the Utrecht University Medical Center (the Netherlands) between 1997 and 2007. The population consisted of 247 men and 539 women and included both patients with ruptured (727) and patients with only unruptured (59) IA. Ruptured IA were defined by symptoms suggestive of subarachnoid hemorrhage (SAH) combined with subarachnoid blood on a computed tomography (CT) scan and a proven aneurysm at angiography (conventional angiogram, CT- or magnetic resonance (MR)-angiogram). Unruptured IA were identified by CT or MR angiography or conventional angiography in the absence of clinical or radiological signs of SAH.[8-11] Patients with fusiform IA, possible traumatic SAH, and polycystic kidney disease were excluded. As controls, we included 3110 Dutch subjects, who were recruited as part of the Nijmegen Biomedical Study (n=1832) and the Nijmegen Bladder Cancer Study (n=1278).[12, 13]

Finnish sample: The Finnish cohort consisted of 880 IA patients treated at the Helsinki and Kuopio University Hospitals, and included both patients with ruptured and unruptured IA.[11] The patients were collected from the registries of Neurosurgery, Kuopio University Hospital, and Neurosurgery, Helsinki University Hospital, solely serving their catchment populations in Eastern and Southern Finland, respectively. The sporadic IAs (sIAs) were angiographically verified and the cases of subarachnoid hemorrhage from ruptured with computed tomography (CT). Patients with fusiform IA (n=5), (not verifiable) traumatic SAH (n=81), and polycystic kidney disease (n=4) were removed. Controls were genetically matched to cases from thee sample sets: anonymous donors from Kuopio University Hospital and Helsinki, the Helsionki Birth Cohort Study (HBCS) and the Health 2000 study (H2000). Anonymous donors were individuals who were Finnish patients at the same hospitals as Finnish cases and gave blood samples for unrelated causes in consecutive days.[11] The Helsinki Birth Cohort Study (HBCS) includes 8,760 individuals born in the Helsinki Central Hospital between 1934 and 1944.[14] A

subset of 1676 Illumina genotyped individuals were available for the present study. The Health 2000 Cohort (H2000) includes 2,402 Finns, and of those 2,138 Illumina genotyped individuals were available for the present study[15, 16]

Replication sample genotyping and quality review

First, a sliding window approach was used to thin the set of SNPs to be approximately independent of each other. A sliding window of 1500 SNPs was shifted by 150 SNPs at a time along chromosomes, and in each step SNPs were filtered if any pairwise r2 was > 0.2, resulting in 79596 independent SNPs. Pairwise IBS distances of these SNPs were used in multidimensional scaling and four first dimensions were used in matching. Plink v. 1.07[17] was used for thinning and MDS analysis. R package optmatch was used to pair each case to three controls. After 1:3 matching, additionally all Eastern Finnish controls from the previous sIA study were included.[17]

All case and control subjects from the Dutch samples were genotyped on the Illumina CNV370 Duo BeadChips in previous GWAS.[8, 11] Some of the Finnish samples had also been previously genotyped. PLINK version 1.07 was used for quality control of both subjects and SNPs. After removal of SNPs with A/T or C/G alleles and SNPs that were not called in any individual, we performed sample QC and SNP QC.

We performed sample QC after merging cases and controls, using a subset of common, high-quality SNPs (as defined by SNPs without deviation from Hardy-Weinberg equilibrium (HWE) ($p > 0.001$), with high minor allele frequency (> 20%) and with low missingness (<1%)), and performed pruning based on linkage disequilibrium ($r^2 > 0.5$). Subjects were removed based on the following three criteria: genotype missingness (subjects with a call rate below 95% were removed), heterozygosity (subjects were excluded if the inbreeding coefficient deviated more than 3 standard deviations from the mean) and cryptic relatedness (by calculating identity-by-descent (IBD) for each pair of individuals). In each pair with an IBD proportion of at least 20%, a subject was excluded, if it exhibited distant relatedness with multiple individuals. For case-control pairs, we removed the control subject. In the remaining pairs, the subject with the lowest call rate was excluded.

We performed principal component analysis (PCA) using EIGENSTRAT on the study subjects and HapMap-CEU subjects. We excluded SNPs from three regions with known long-distance linkage disequilibrium (LD): the major histocompatibility (MHC) region (chr6: 25.8-36 Mbp), the chromosome 8 inversion (chr8: 6-16 Mbp) and a chromosome 17 region (chr17: 40-45 Mbp). We created multi-dimensional scaling plots with the first 4 principal components (PCs), using R version 2.11.[13, 18] Based on visual inspection of these plots, we excluded subjects that appeared to be outliers with respect to the CEU or the study population. After outlier removal, we recomputed principal components to include as covariates for logistic regression.

After sample QC, we excluded SNPs with more than 2% missing genotypes, a minor allele frequency < 1%, genotype missingness higher than the minor allele frequency and HWE deviation ($p < 0.001$). We performed these QC steps in each study cohort separately and again

after merging cases and controls. We also removed SNPs with a differential degree of missingness between cases and controls ($p < 1x10^{-5}$; chi-squared test).

The final sample included 717 Dutch cases, 3004 Dutch controls, 799 Finnish cases, 2317 Finnish controls.

Imputation, association analysis

Genotype imputation was performed using the prephasing/imputation stepwise approach implemented in IMPUTE2 and SHAPEIT (chunk size of 3 Mb and default parameters).[5, 19] The imputation reference set consisted of 2,184 phased haplotypes from the full 1000 Genomes Project data set (February 2012; 40,318,253 variants). All genomic locations are given in NCBI Build 37/UCSC hg19 coordinates. Association testing was carried out in PLINK using imputed SNP dosages and the principal components described above as covariates.

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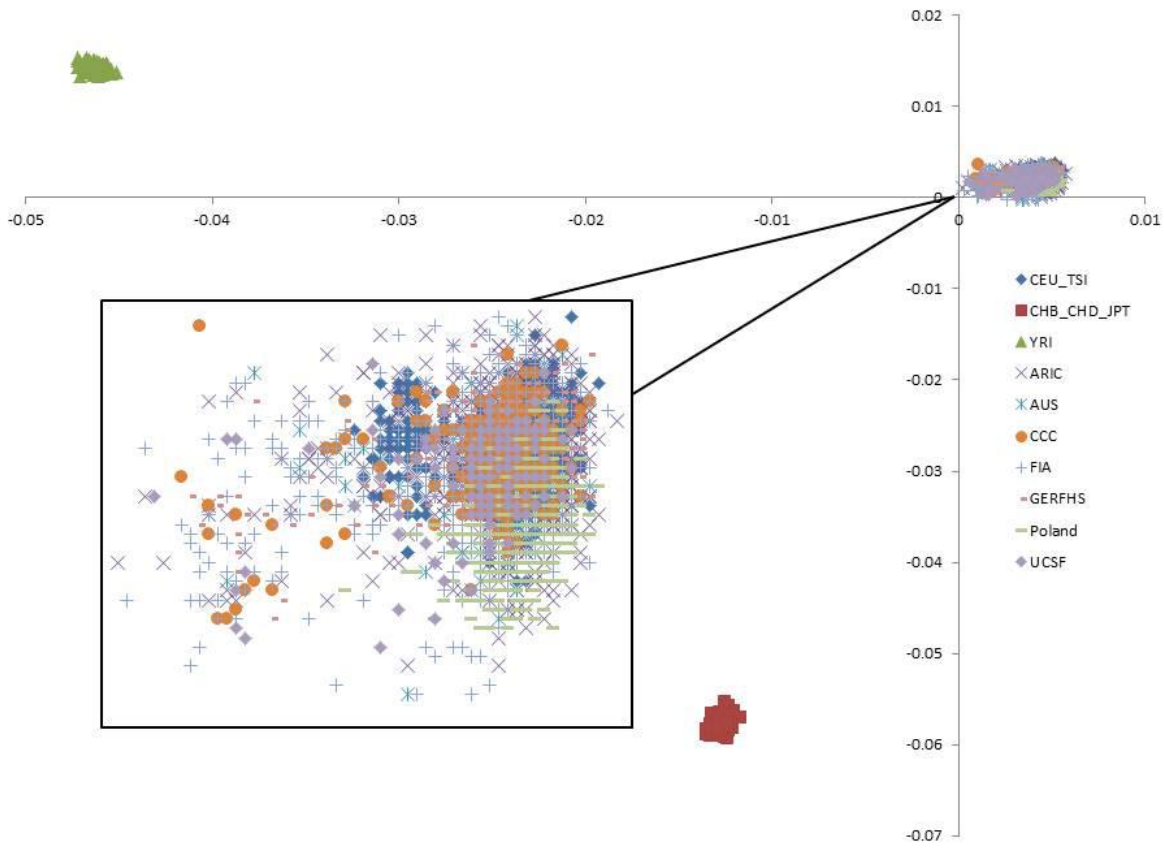
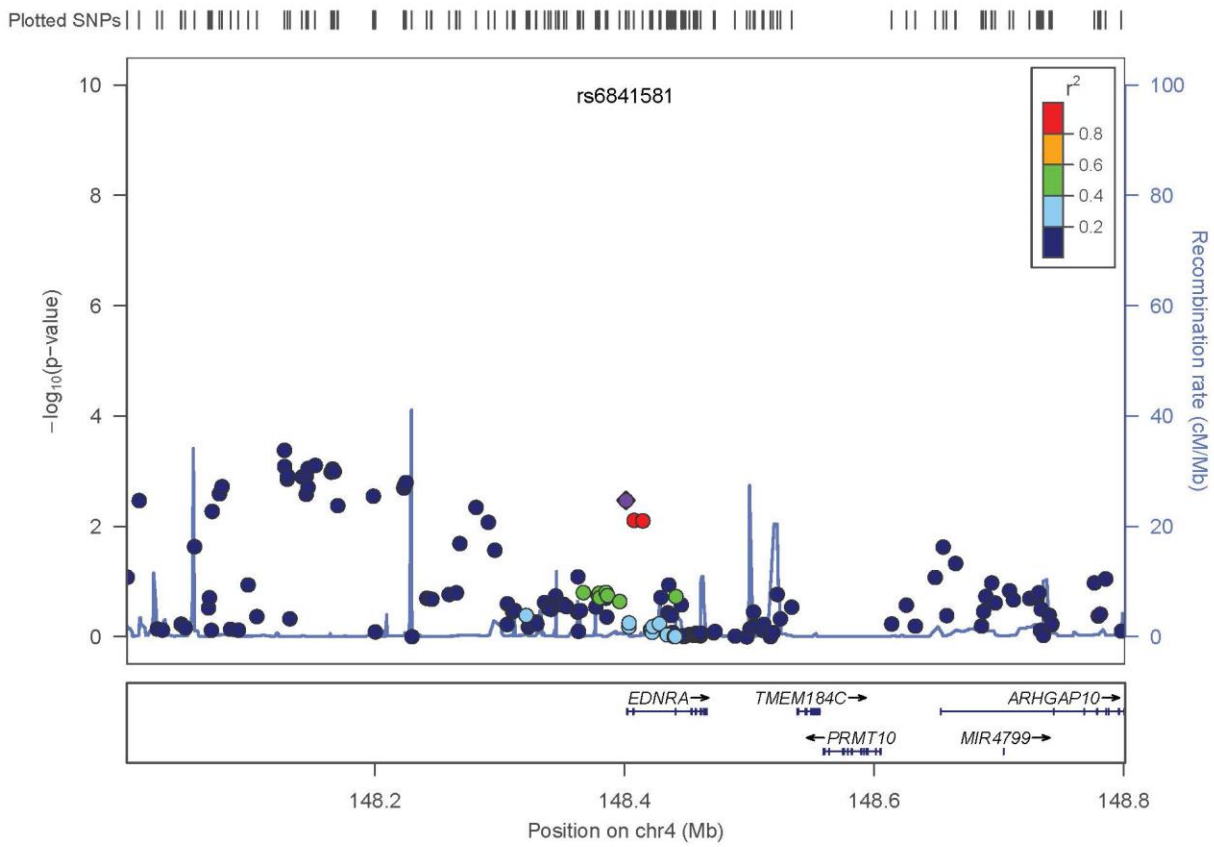


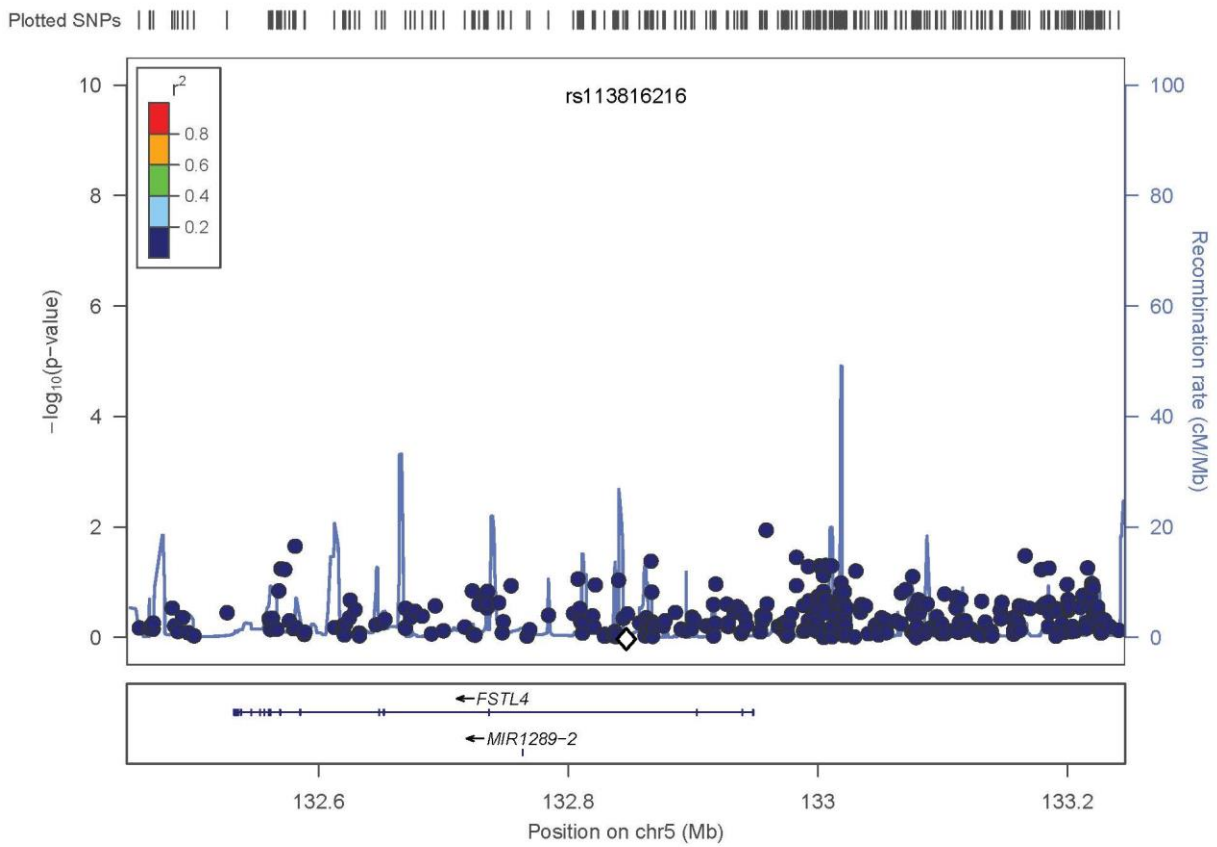
Supplemental Figure I: Principal component clustering plot for genotyped study subjects. Genotyped individuals are shown for PC1 (x-axis) and PC2 (y-axis). Reference populations are: CEU_TSI (Utah residents with Northern and Western European ancestry from the CEPH collection; Tuscans in Italy); CHB_CHD_JPT (Han Chinese in Beijing, China; Chinese in Metropolitan Denver, Colorado; Japanese in Tokyo, Japan); YRI (Yoruba in Ibadan, Nigeria). Study samples clustering

outside the area defined by the CEU and TSI reference samples were excluded from association analyses.

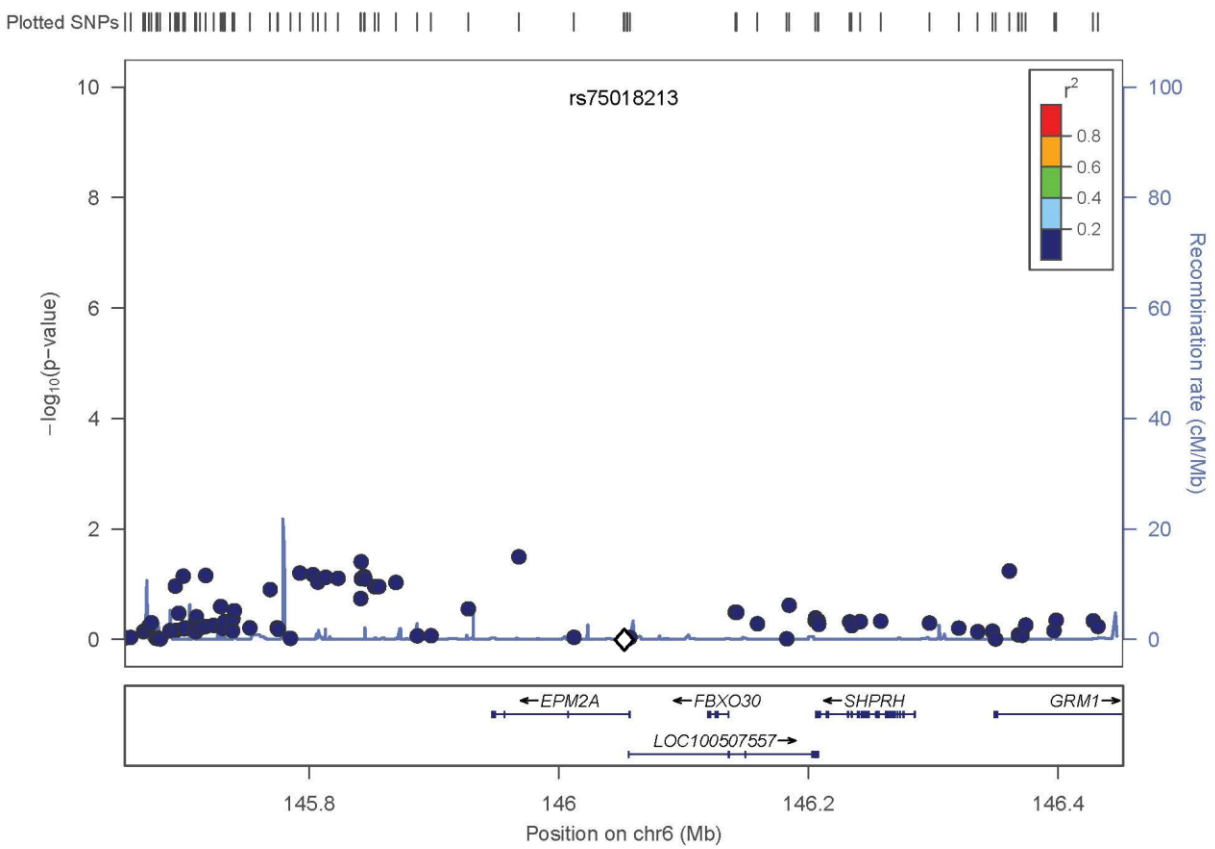
Supplemental Figure II: Comparison with previously reported results from genomewide association studies. (A) Chromosome 4q31.23; (B) Chromosome 5q31.3; (C) Chromosome 6q24.2; (D) Chromosome 8q12.1; (E) Chromosome 10q24.32; (F) Chromosome 12q22; (G) Chromosome 13q13.1; (H) Chromosome 18q11.2; (I) Chromosome 20p12.1. *X*-axis is the physical position on the chromosome (Mb). *Y*-axis denotes the $-\log_{10}$(p-value) for association. The most significant SNP from the initial report is shown at the top of each panel. The extent of LD (as measured by r^2) between each SNP and the most significant SNP from the initial report is indicated by the color scale at top right. Larger values of r^2 indicate greater LD. If the SNP was available in our sample as either a genotyped or imputed SNP, the associated p-value is shown as a purple diamond. If the SNP was not available in our sample, the position of the SNP is shown a white diamond along the X axis.



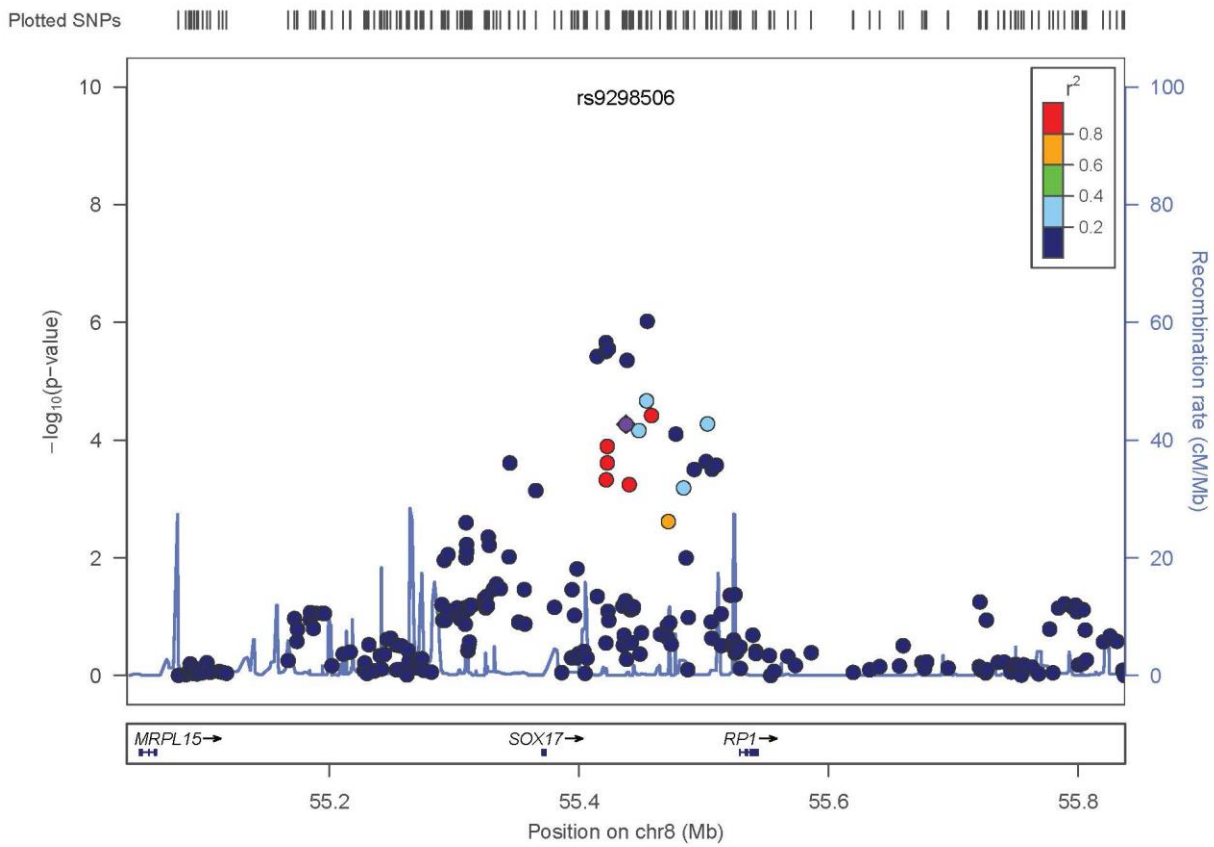
Supplemental Figure II-A: Chromosome 4q31.23



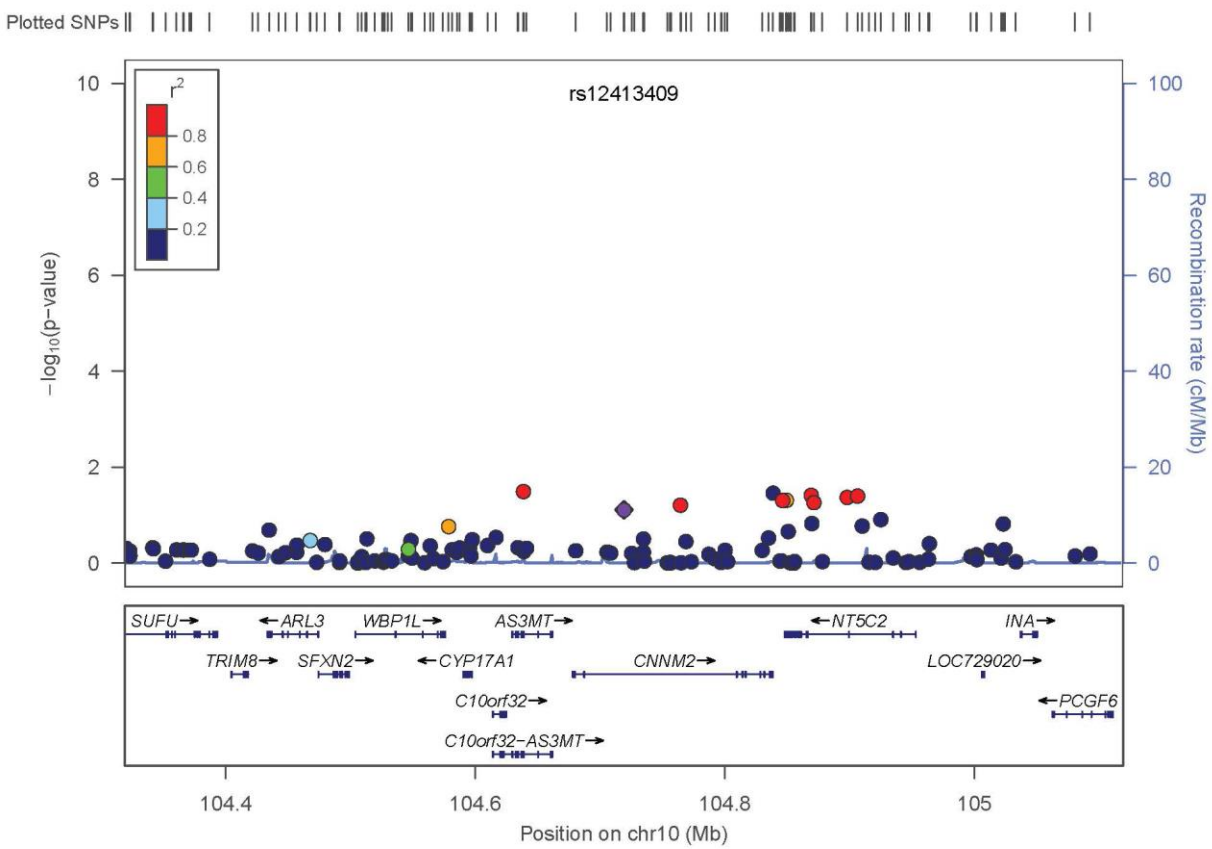
Supplemental Figure II-B: Chromosome 5q31.3



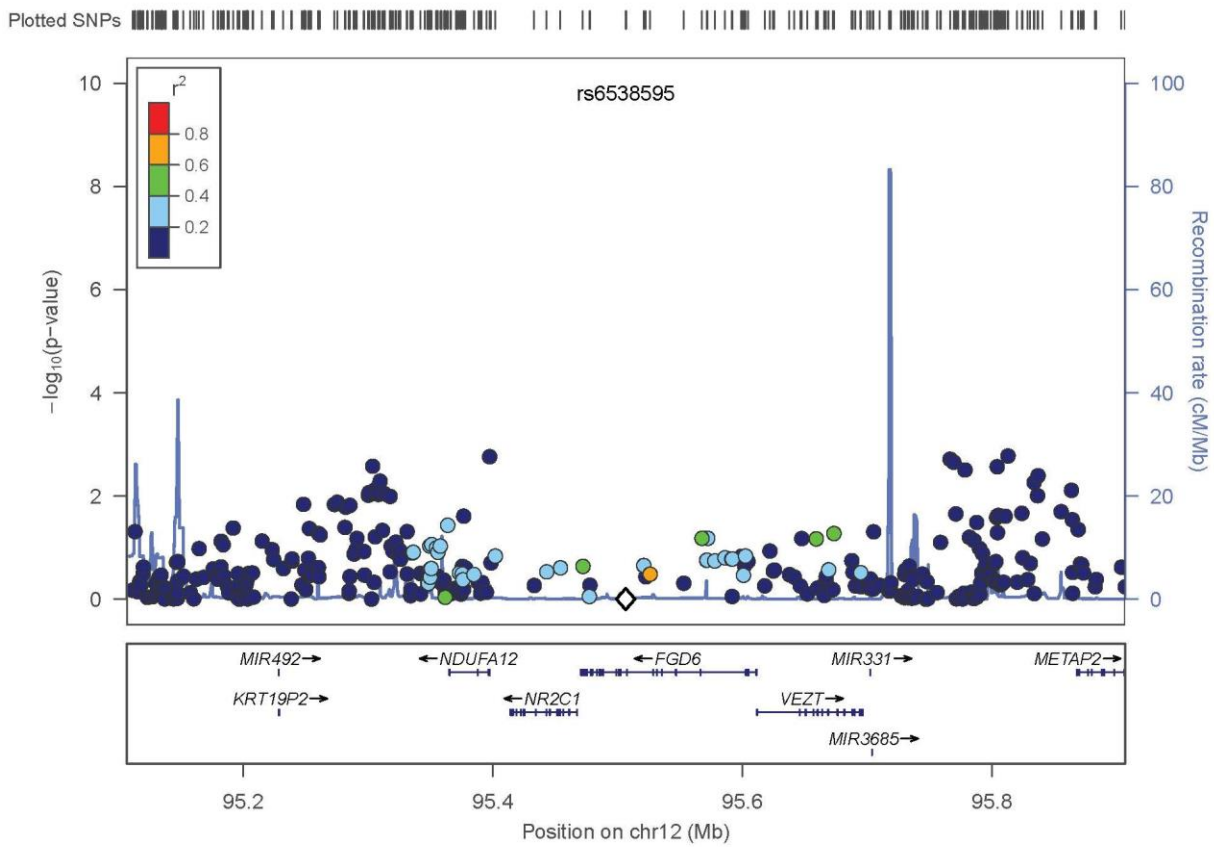
Supplemental Figure II-C: Chromosome 6q24.2



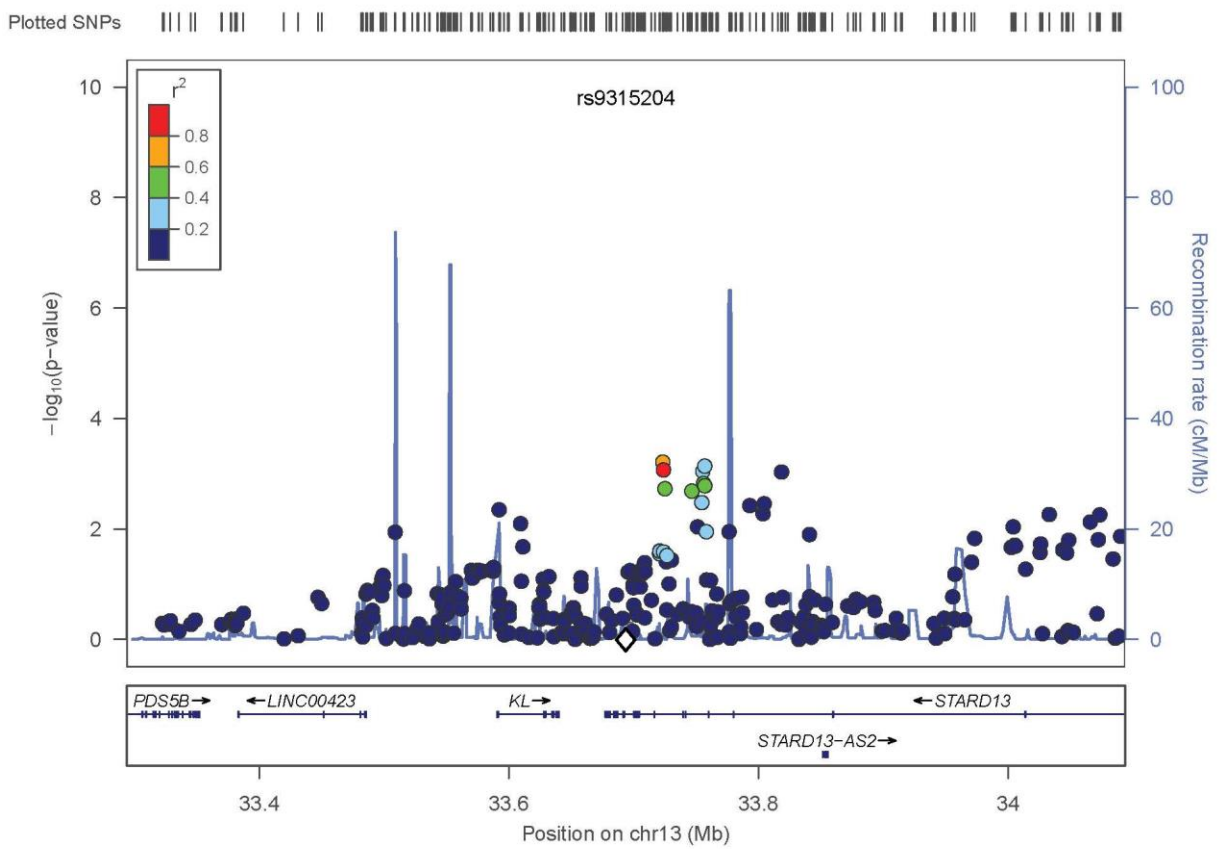
Supplemental Figure II-D: Chromosome 8q12.1



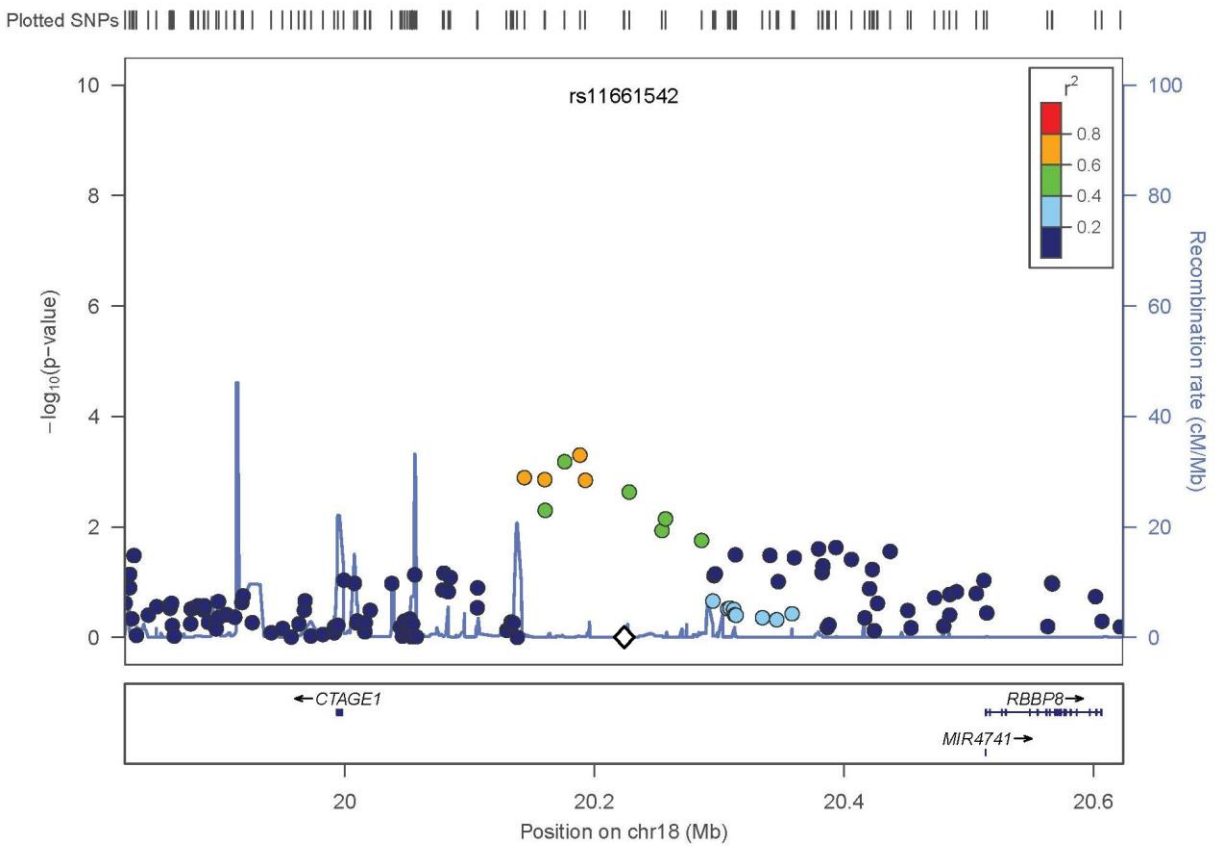
Supplemental Figure II-E: Chromosome 10q24.32



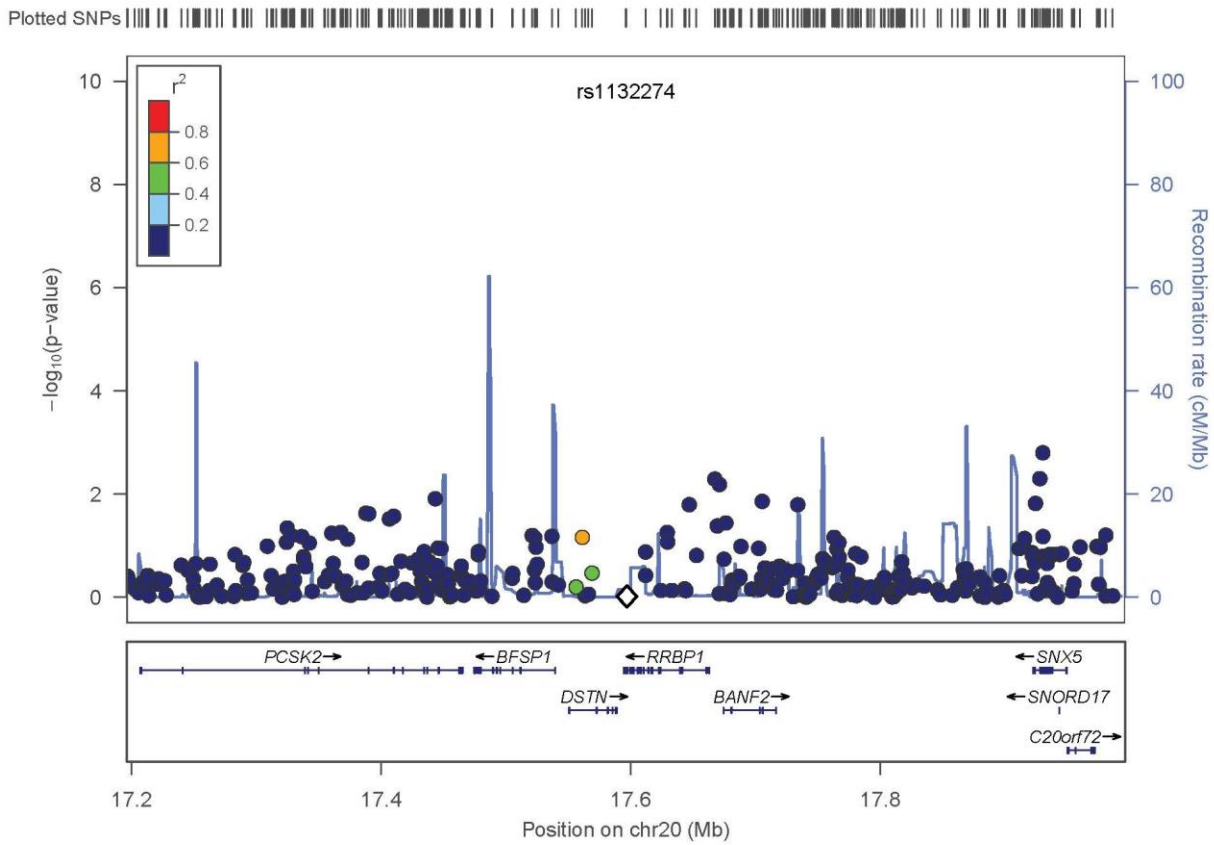
Supplemental Figure II-F: Chromosome 12q22



Supplemental Figure II-G: Chromosome 13q13.1



Supplemental Figure II-H: Chromosome 18q11.2



Supplemental Figure II-I: Chromosome 20p12.1