Supplementary figures 1-15 for the manuscript *Multi-trait Genetic* Association Analysis identifies 50 new risk loci for gastroesophageal reflux, seven new loci for Barrett's esophagus and provides insights into clinical heterogeneity in reflux diagnosis

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Supplementary Figure captions

Supplementary Figure 1. The Quantile-to-Quantile plot for the MTAG GERD GWAS. The red dotted line represents the line at y=x under the null. The x- and y-axis refers to the expected and the observed negative log10 p-value of the association between each individual SNP and GERD susceptibility.

Supplementary Figure 2. Regional LocusZoom plot for all genome-wide GERD loci (n=88) identified in the GERD MTAG analysis

Supplementary Figure 3. Regional LocusZoom plot for the seven novel BE loci identified in the BE MTAG analysis with strong evidence of replication in the independent 23andMe cohort.

Supplementary Figure 4. Comparison of MTAG GERD genome-wide significant loci effect sizes using alternative case definitions for GERD.

Supplementary Figure 5. Comparison of MTAG BE genome-wide significant loci effect sizes between ICD-10 defined BE and pathologically verified BE cases.

Supplementary Figure 6. Venn diagram illustrating the number of genes identified to be associated with GERD and BE susceptibility using multiXcan

Supplementary Figure 7. Regulation of differential gene expression for complete MTAG GERD genes (n=267 input genes) identified in FUMA on 53 human tissues evaluated via MAGMA.

Supplementary Figure 8. GWAS catalog lookup on GERD-associated genes in FUMA.

The enrichment p-value are coded in -log10(p-value) where larger values infer stronger evidence for a significant association. For each gene entry along the x-axis, a yellow block is present if the gene have been previously reported to be associated with the relevant disease/trait of interest (in the y-axis).

Supplementary Figure 9. PheWAS plot illustrating the association between each of the seven novel BE loci identified in the BE MTAG analysis against a range of complex traits from the OpenTarget platform. Each point represent the -log10 p-value of the association between the putative trait of interest and the BE-associated variant.

Supplementary Figure 10. Regulation of differential gene expression for obesity-driven GERD genes on 53 human tissues evaluated via MAGMA. Tissue expression data extracted from the GTEx v8 database.

Supplementary Figure 11. Regulation of differential gene expression for depressiondriven GERD genes on 53 human tissues evaluated via MAGMA. Tissue expression data extracted from the GTEx v8 database.

Supplementary Figure 12. Gene expression heatmap showing the average expression per label (log2 transformed) across 53 human tissues for obesity-driven GERD genes. Tissue expression data extracted from the GTEx v8 database.

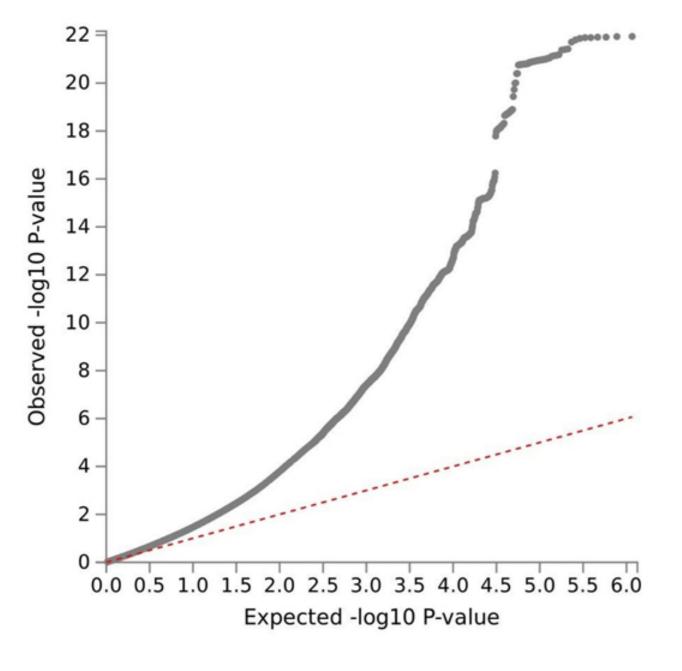
Supplementary Figure 13. Gene expression heatmap showing the average expression per label (log2 transformed) across 53 human tissues for depression-driven GERD genes. Tissue expression data extracted from the GTEx v8 database.

Supplementary Figure 14. Estimation of the genetic association between GERD and risk of Barrett's Esophagus only, stratified by genetic GERD subtypes. Each of the slopes represent the estimated magnitude of association between per unit increase in log(OR) of GERD on log(OR) of BE, for all GERD loci (in blue; with the 95% confidence interval bound shaded), all functional GERD loci (in green), all non-functional GERD loci (in orange) using an inverse variance weighted regression model. Points labelled unclear are those in the indeterminate subset.

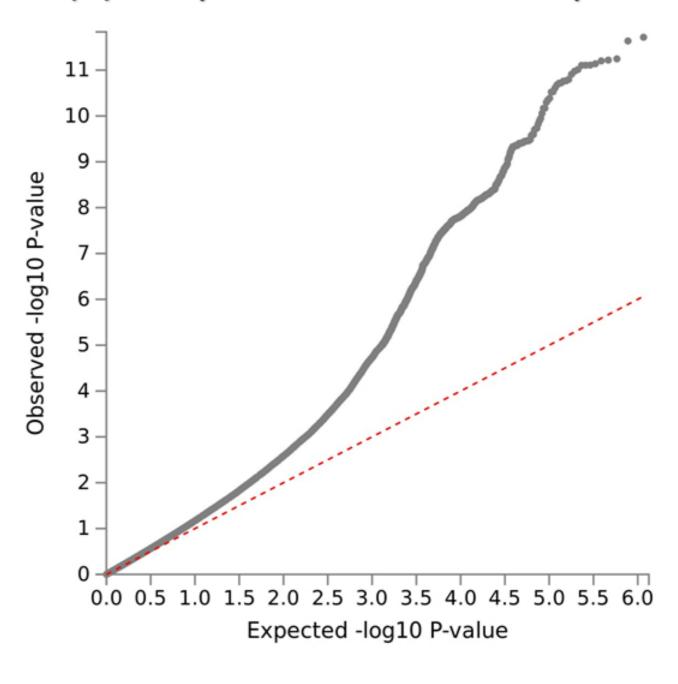
Supplementary Figure 15. Estimation of the genetic association between GERD and risk of Esophageal Adenocarcinoma only, stratified by genetic GERD subtypes. Each of the slopes represent the estimated magnitude of association between per unit increase in log(OR) of GERD on log(OR) of EA, for all GERD loci (in blue; with the 95% confidence interval bound shaded), all functional GERD loci (in green), all non-functional GERD loci (in orange) using an inverse variance weighted regression model. Points labelled unclear are those in the indeterminate subset.

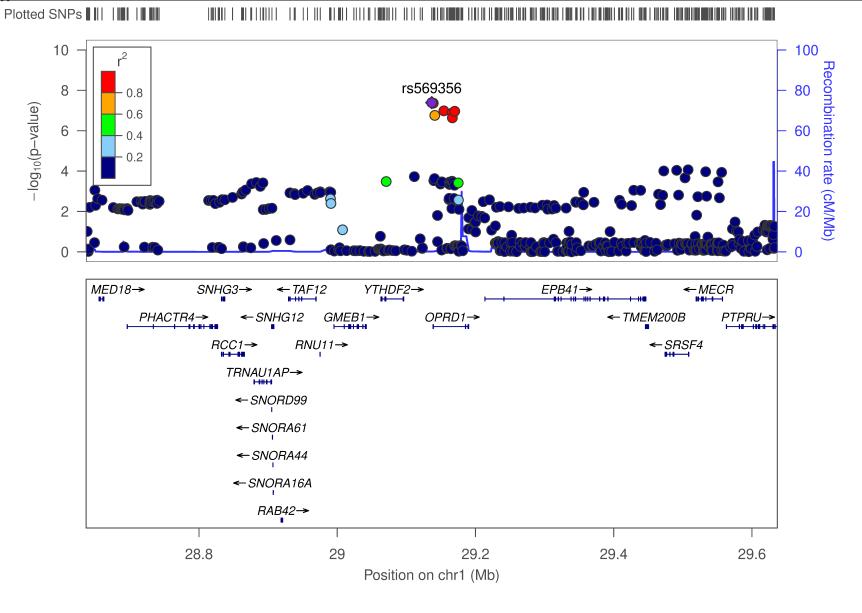
(A) QQ plot for MTAG GERD output

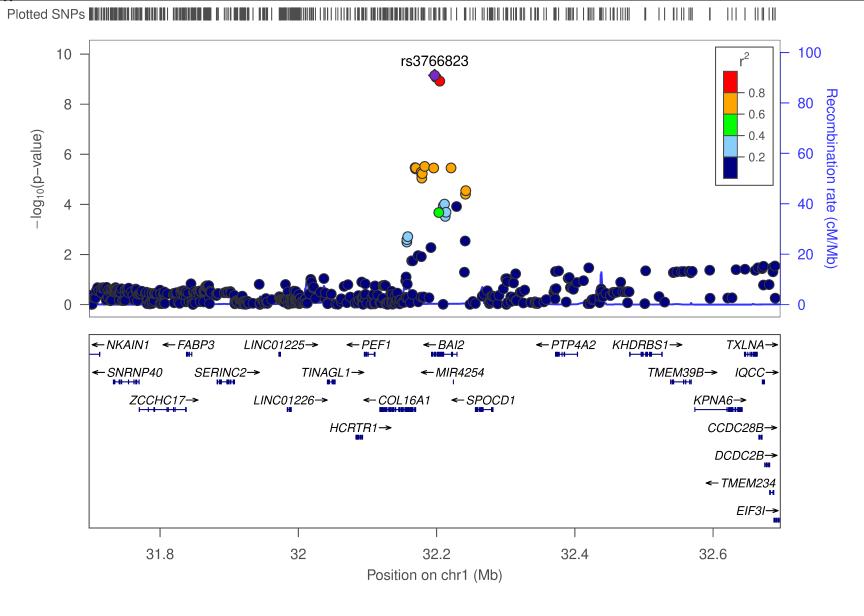
Supplemental material

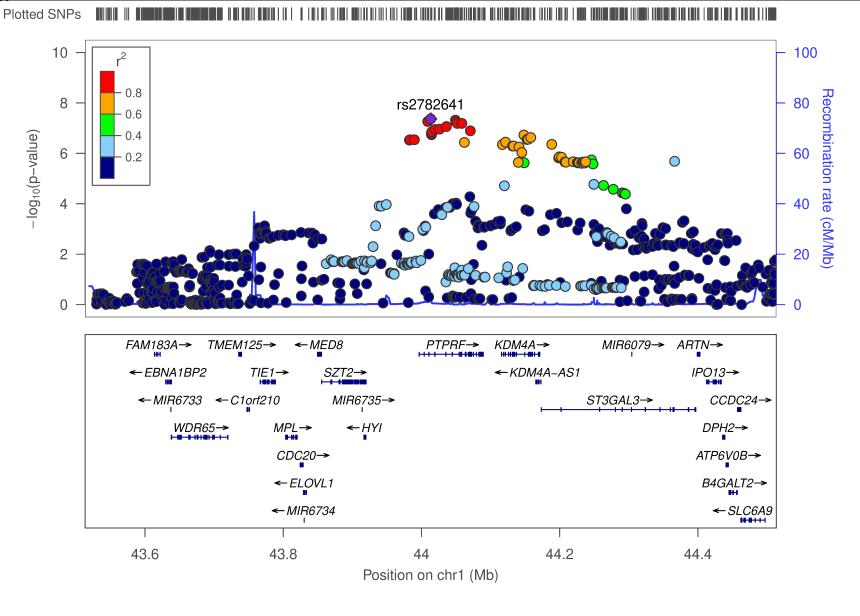


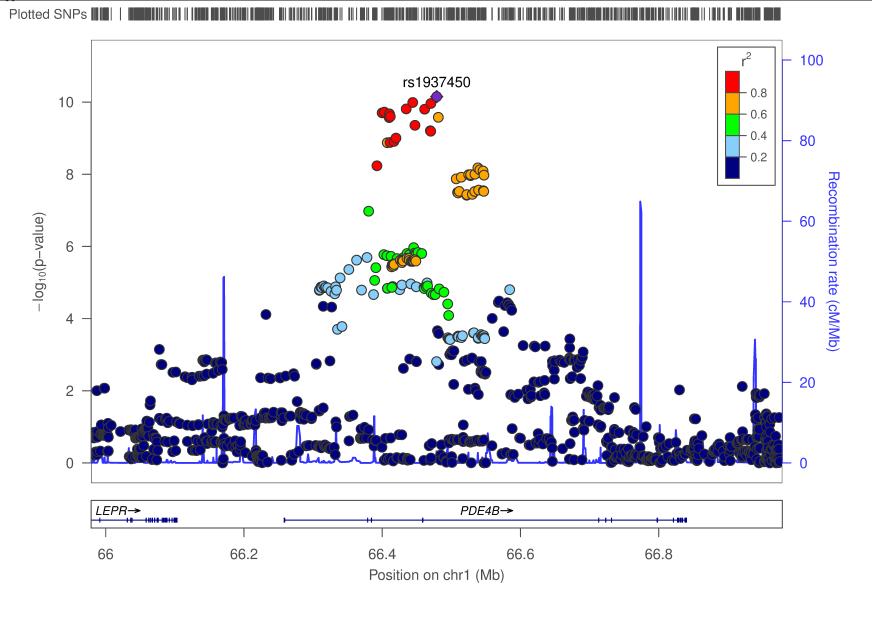
(B) QQ plot for BE GERD output

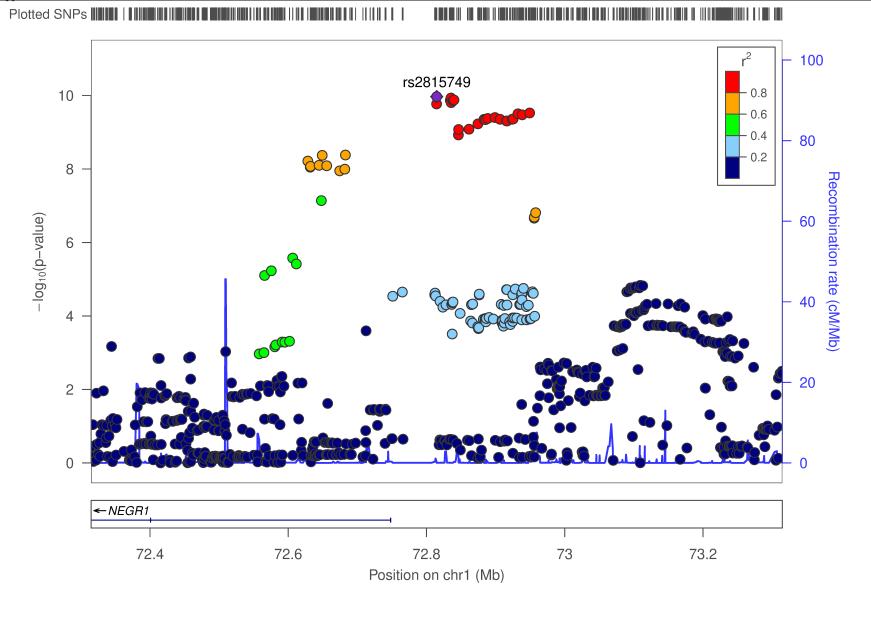


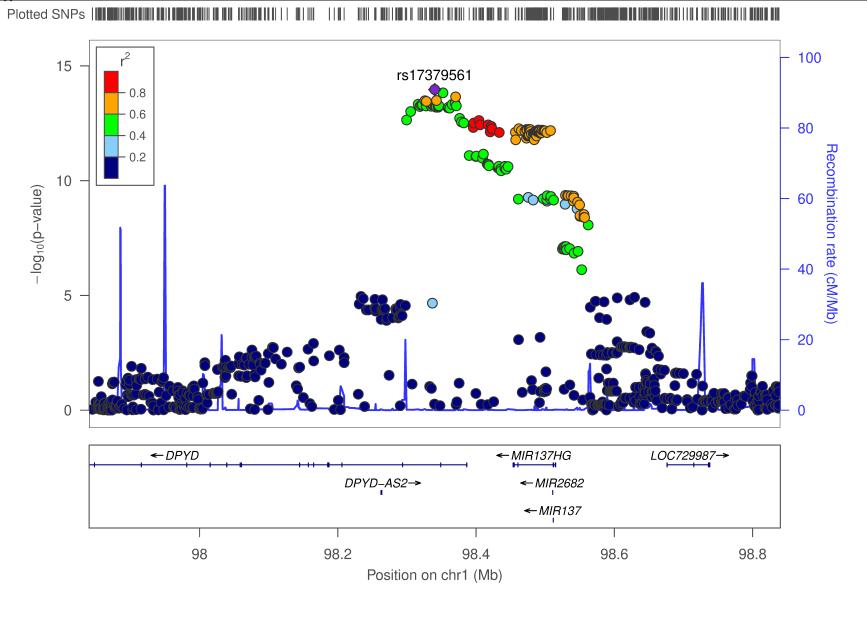


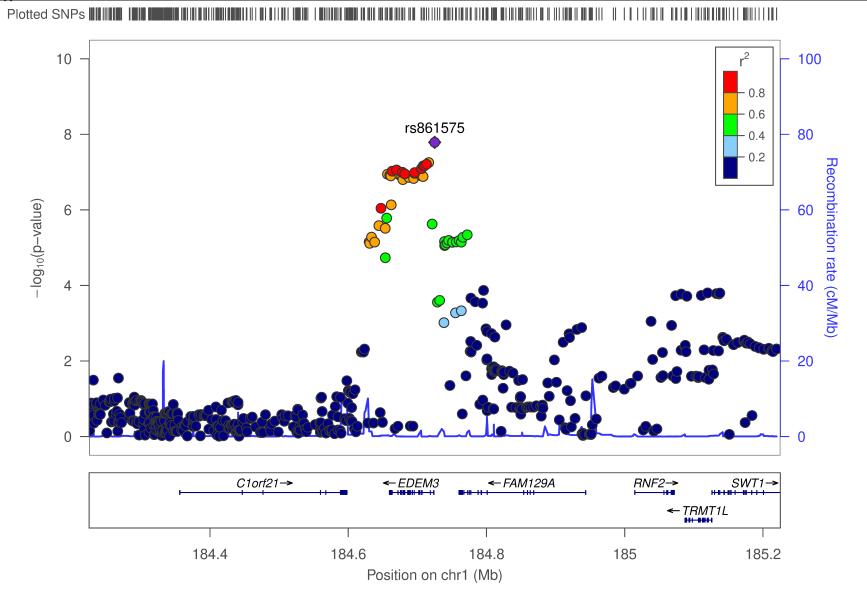




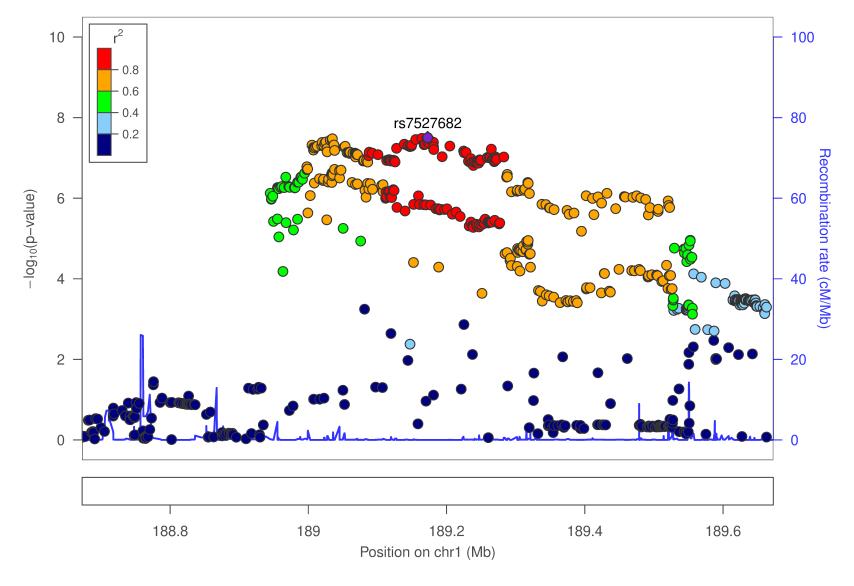


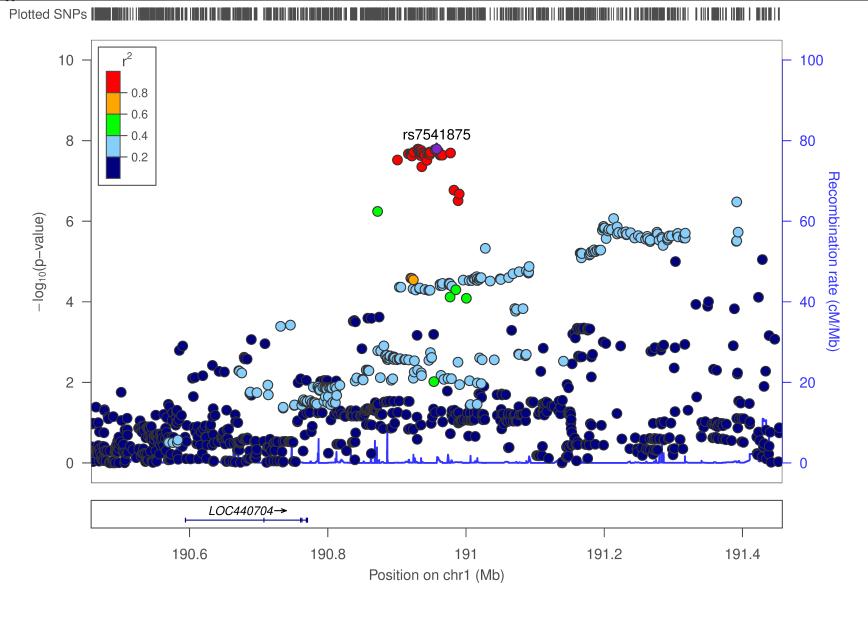


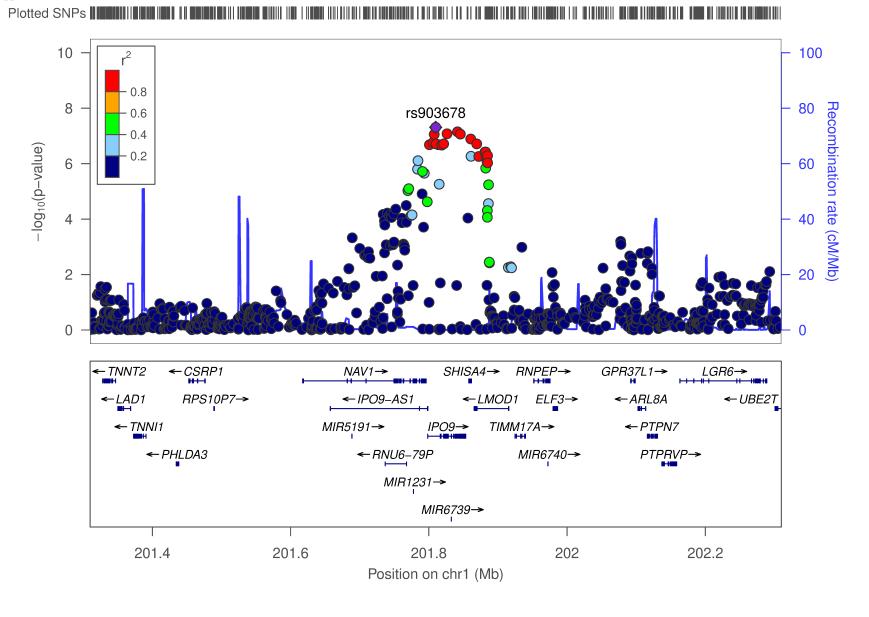


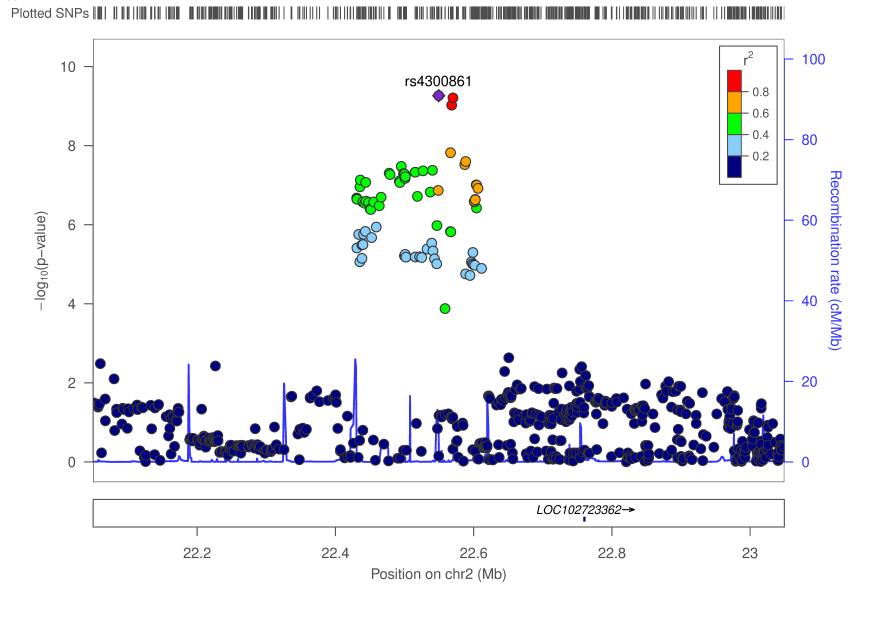


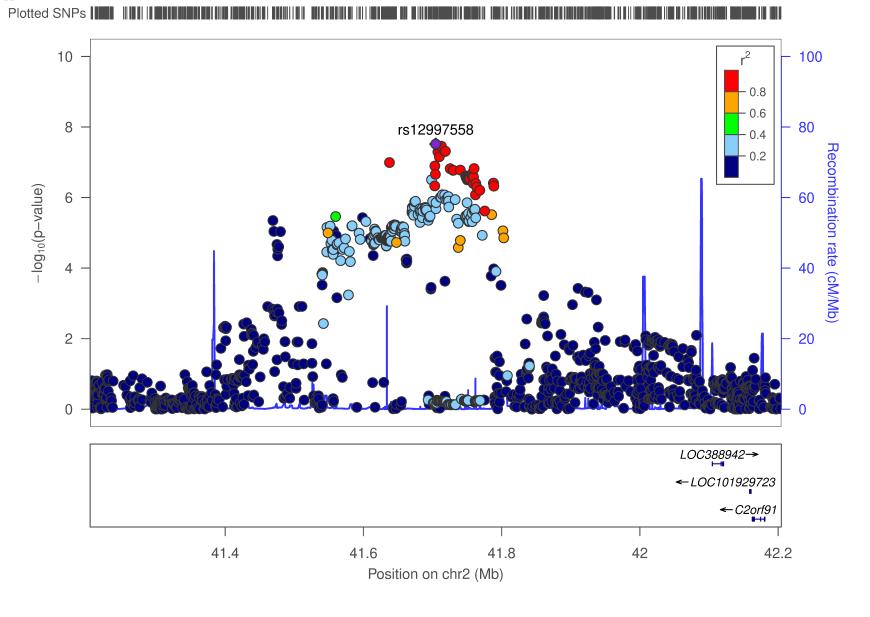


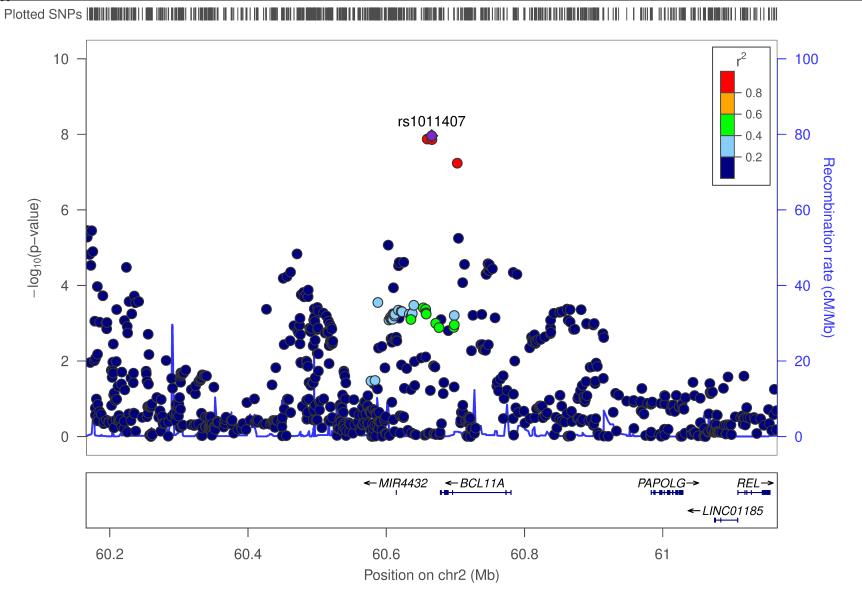


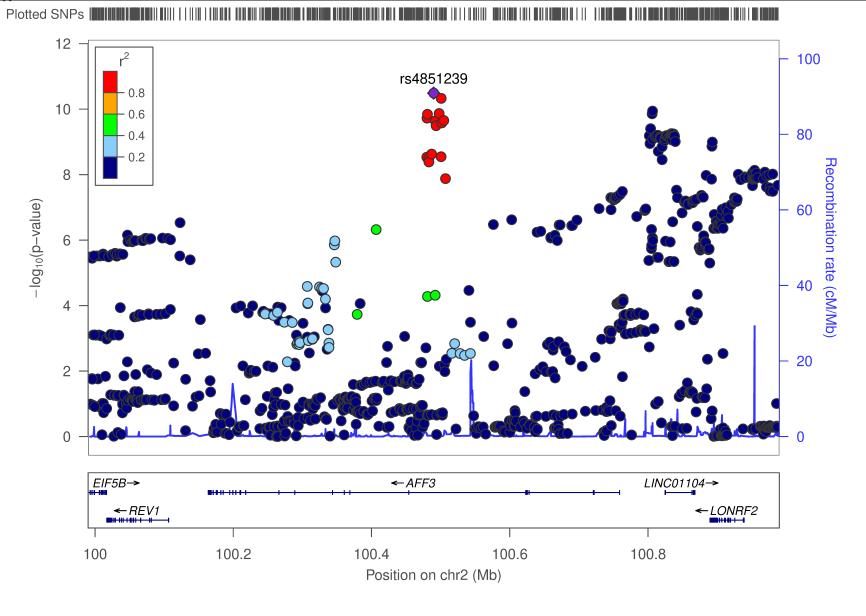




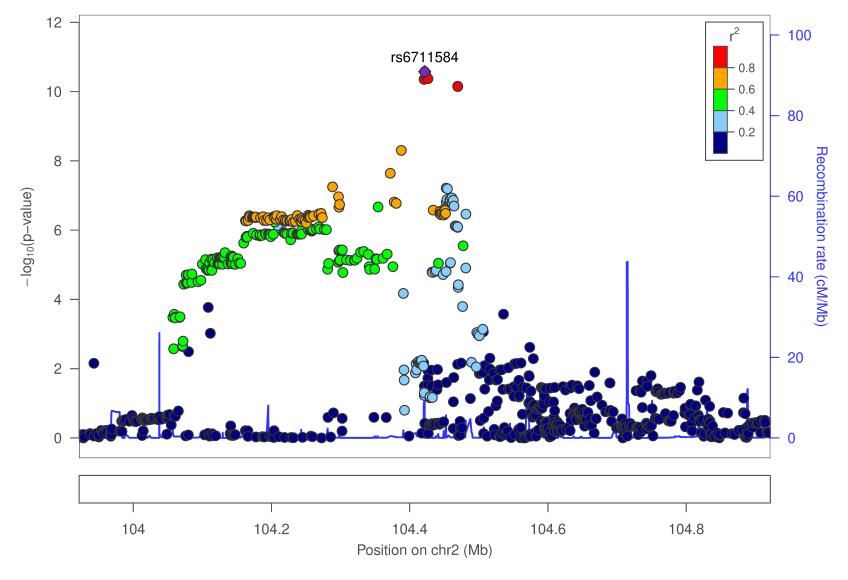




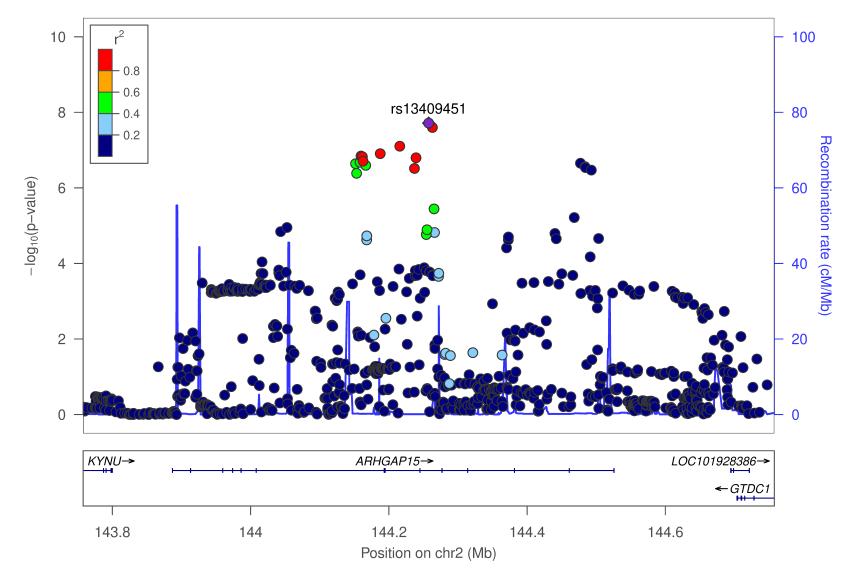


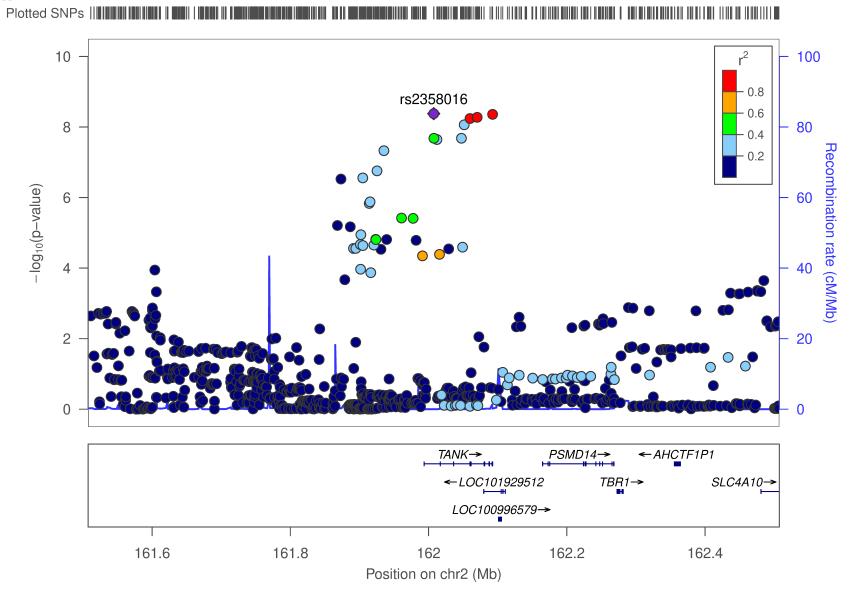


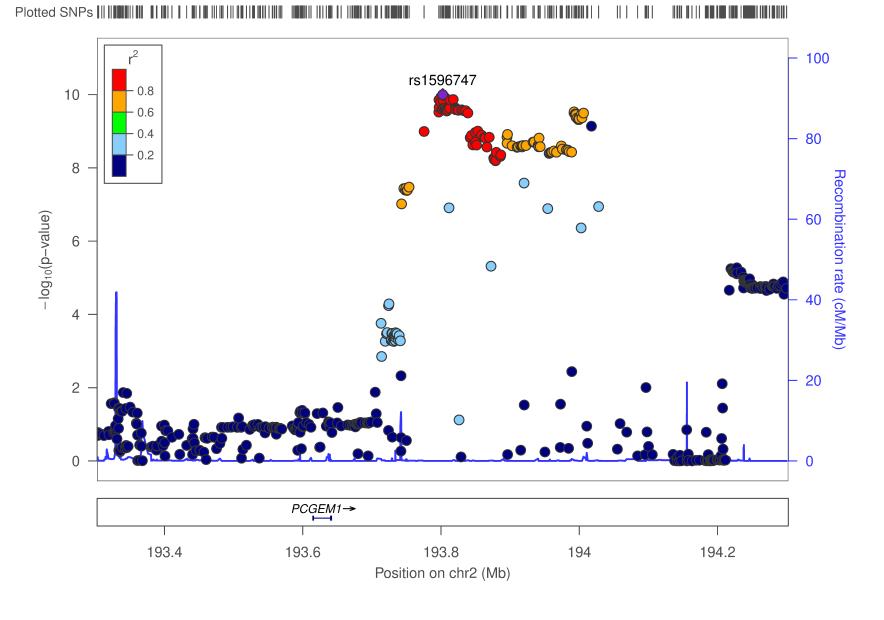


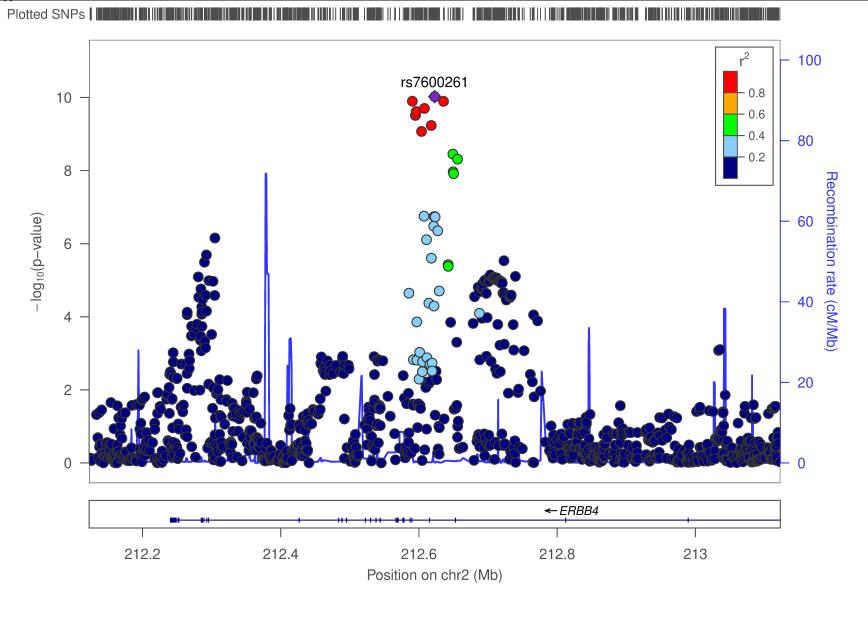


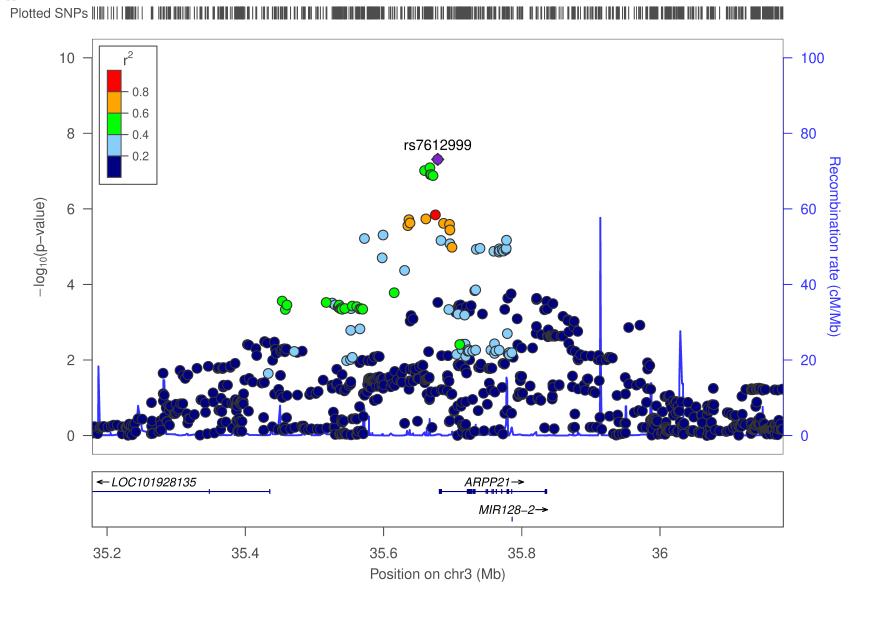




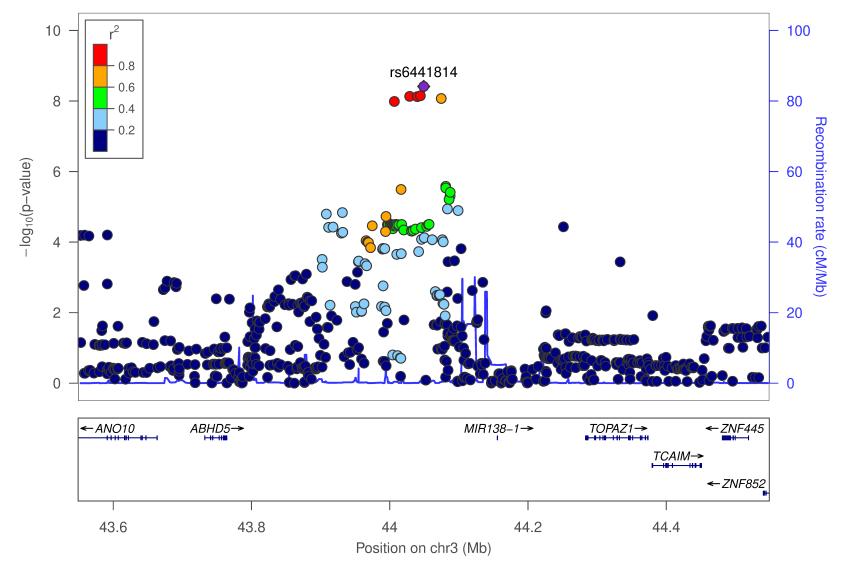


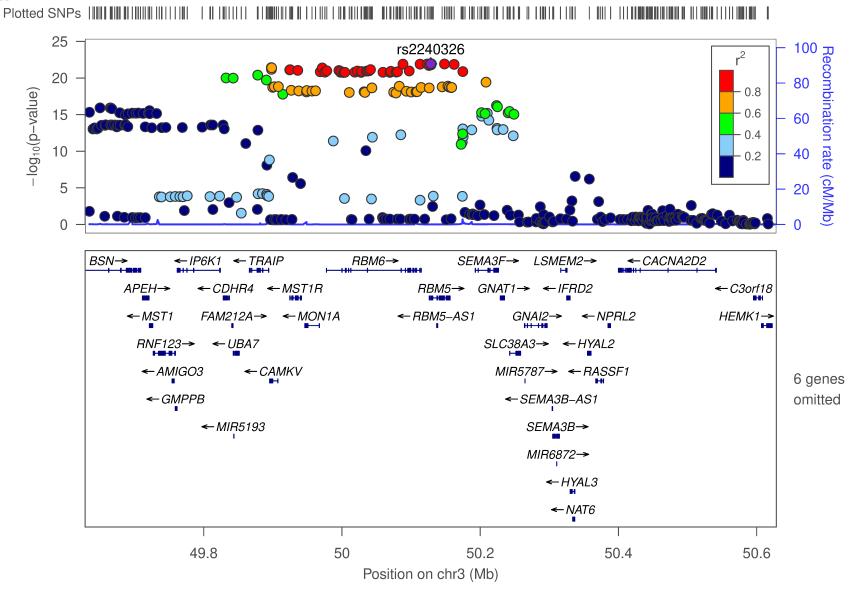


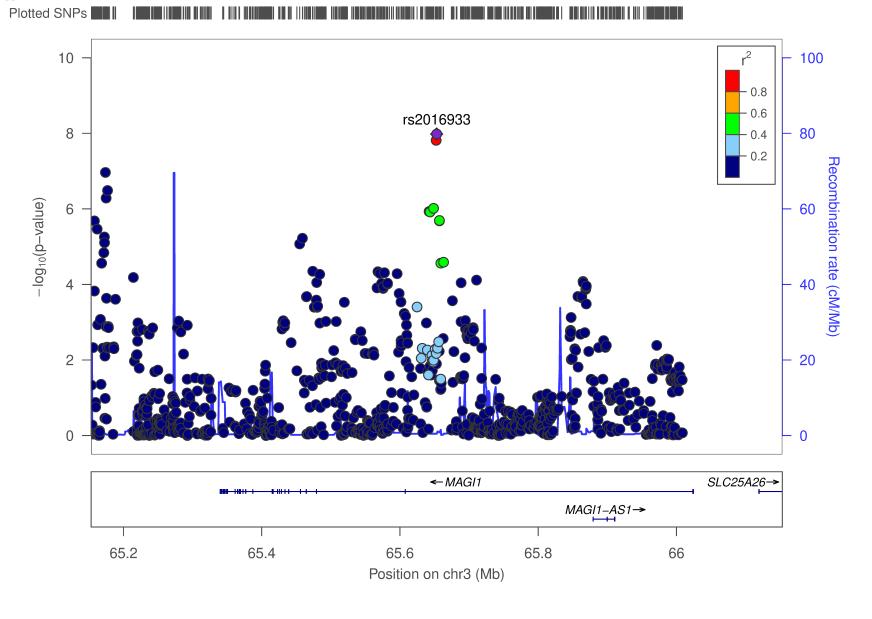


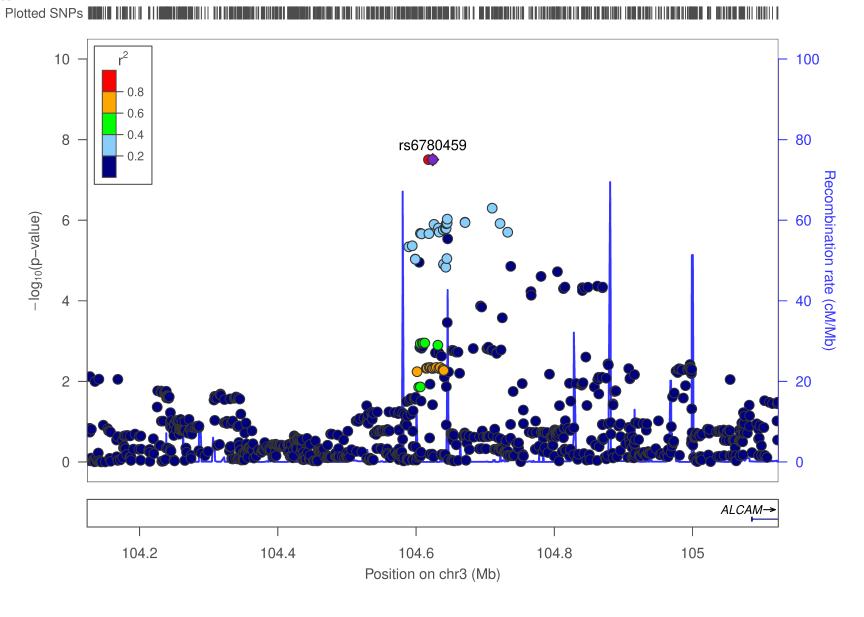


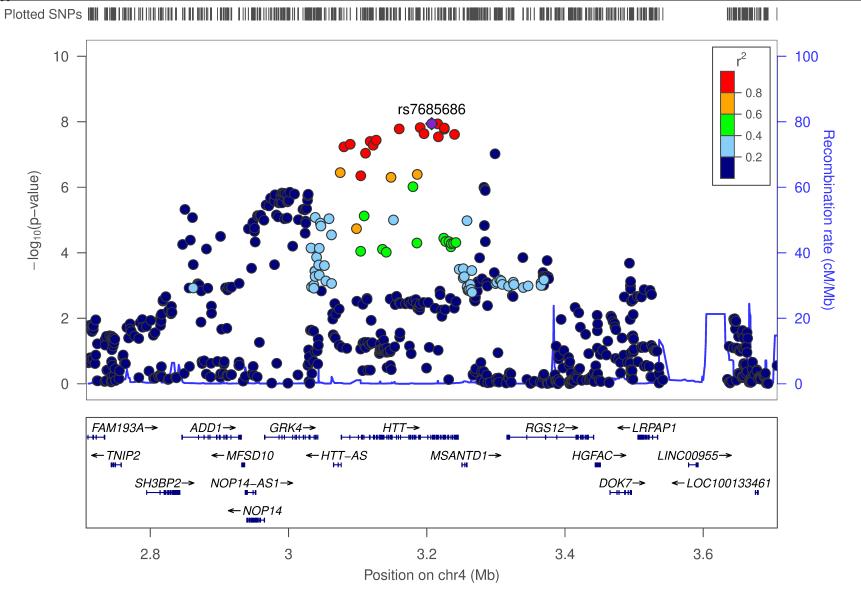


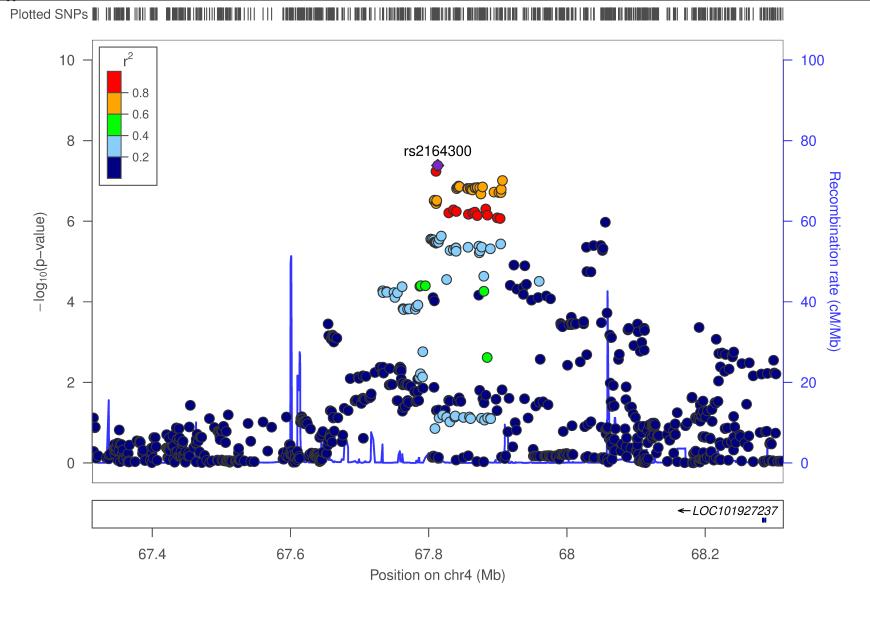


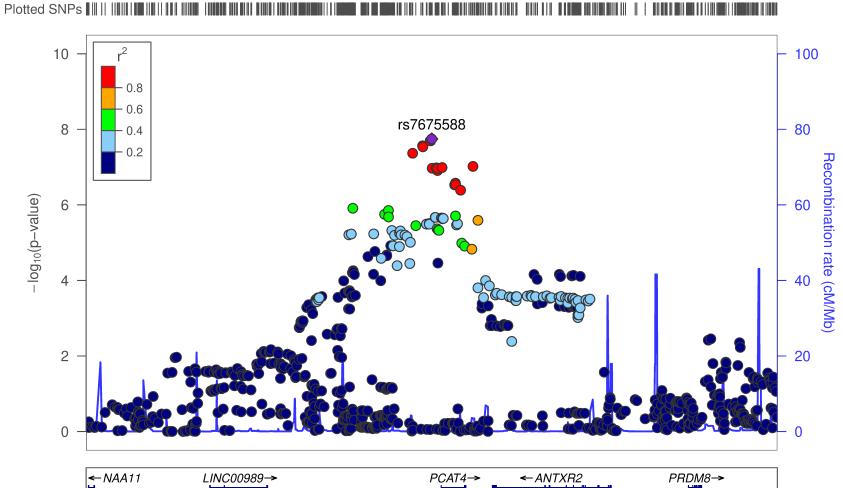


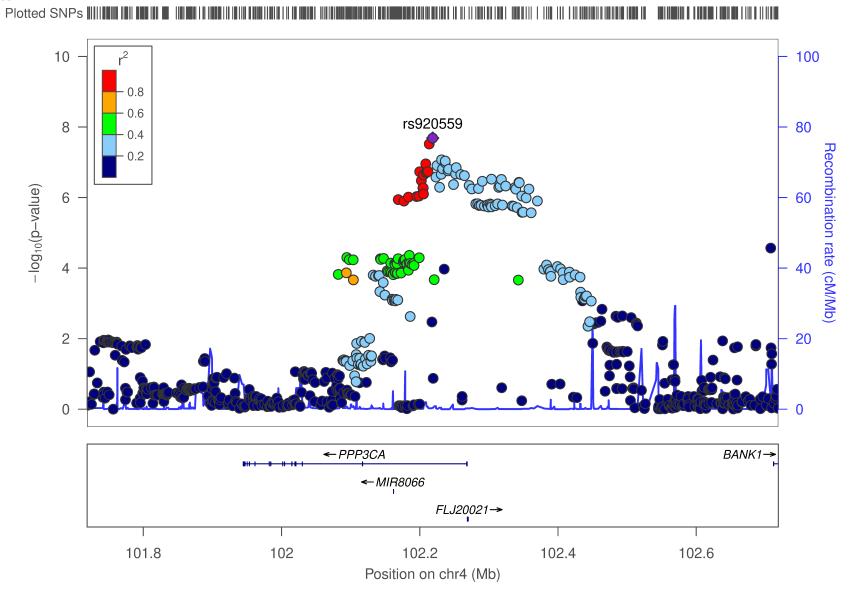


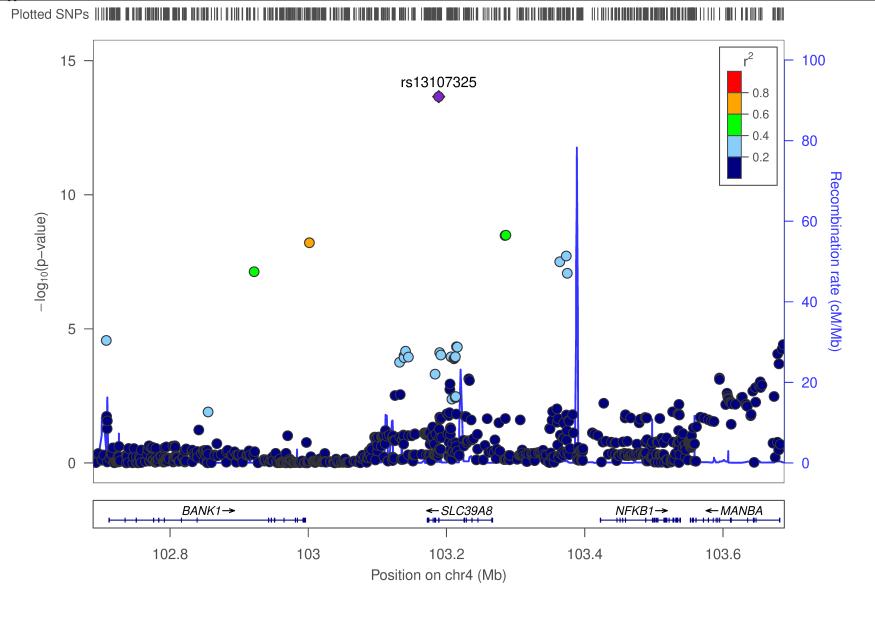


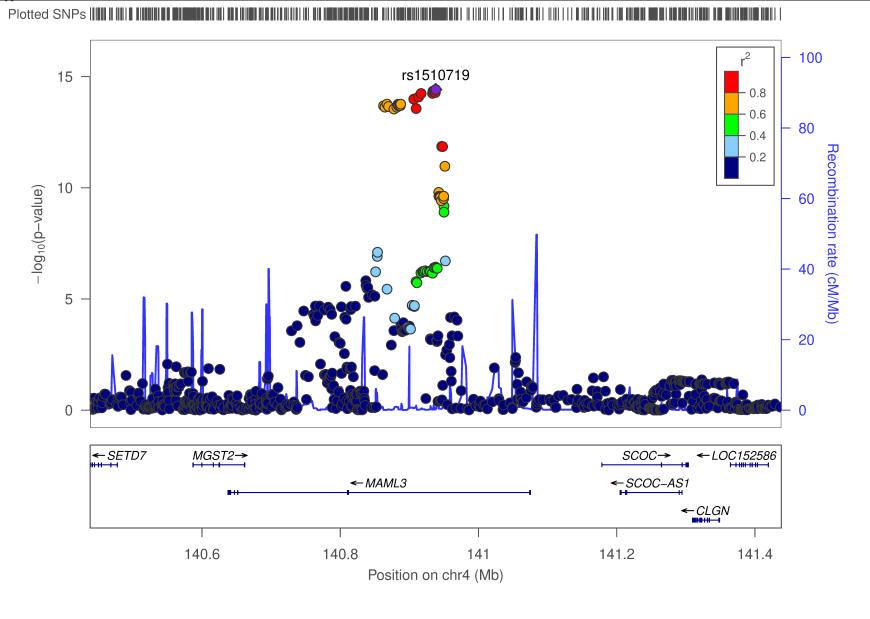


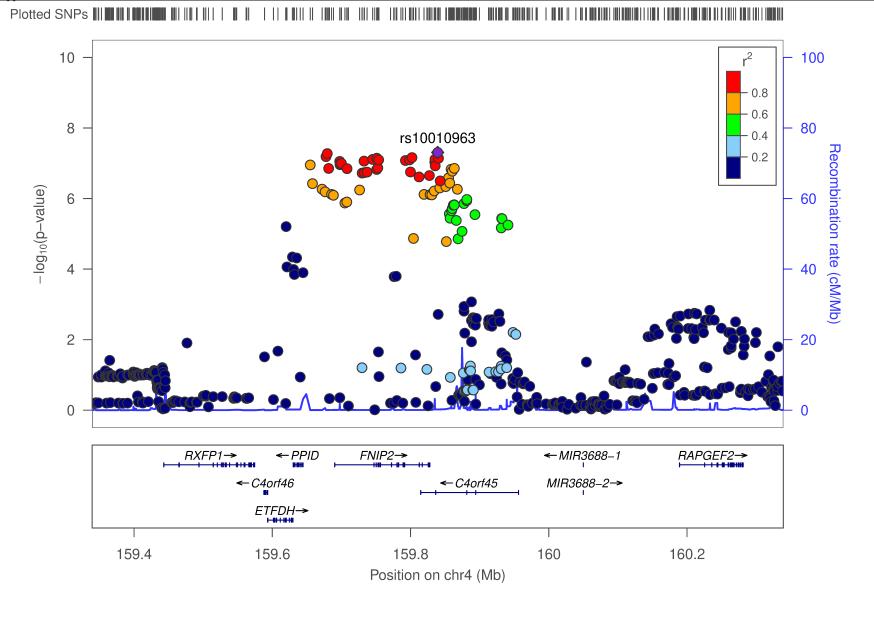


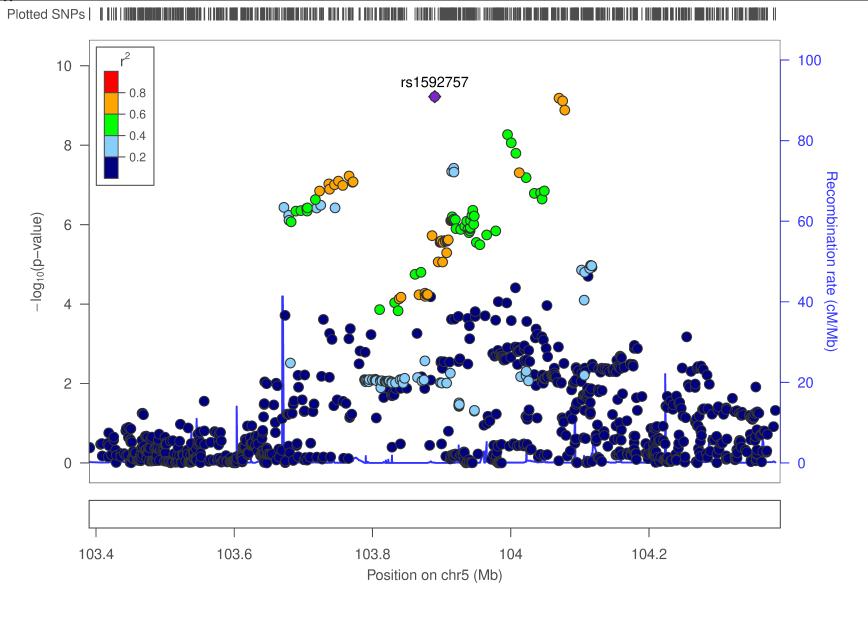


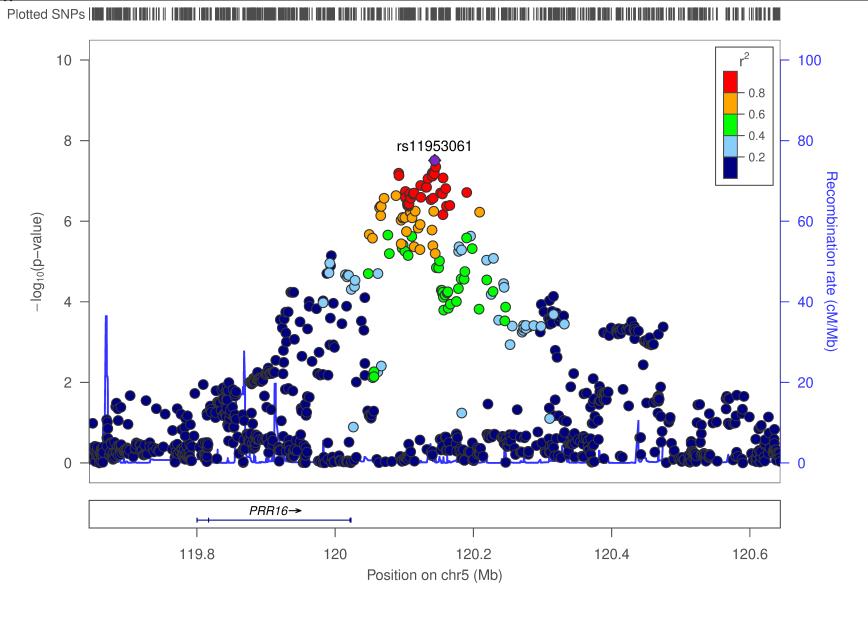


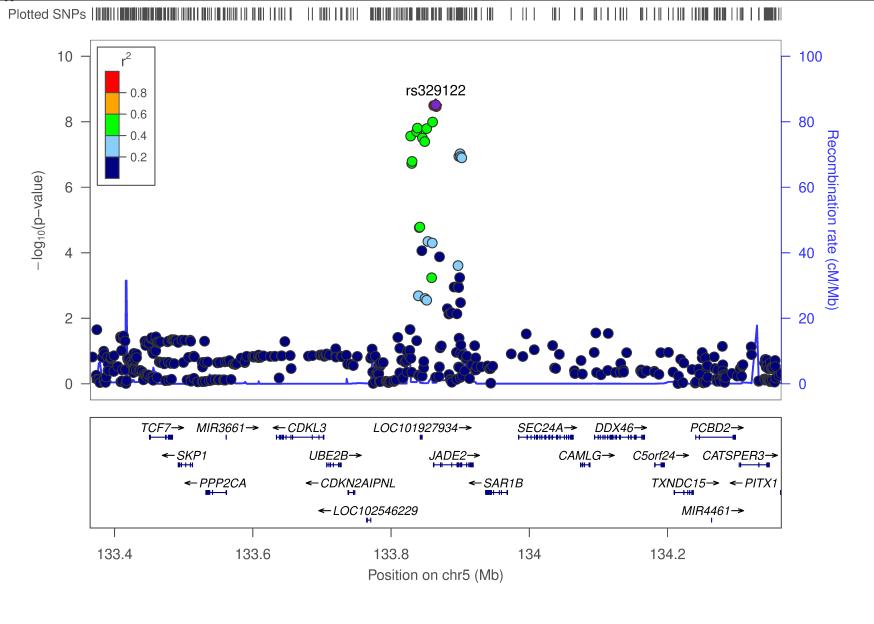


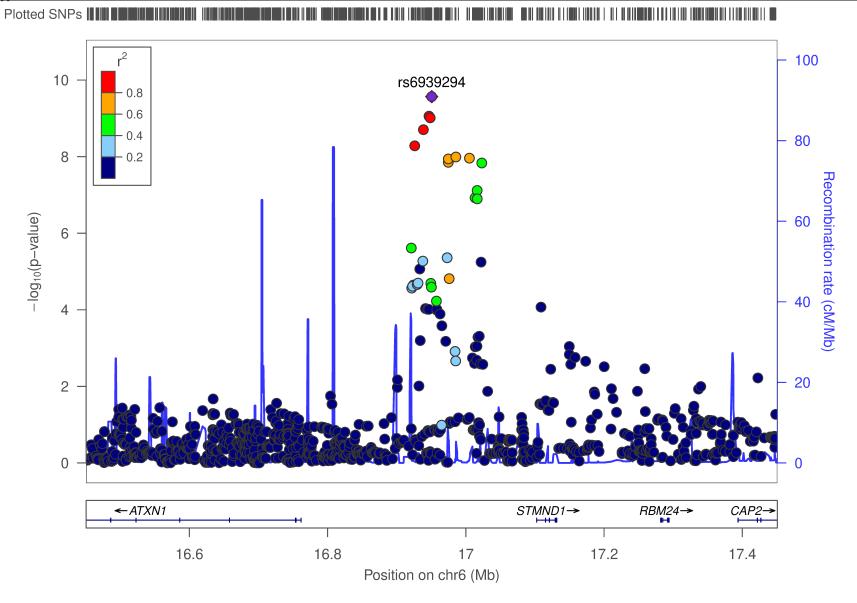


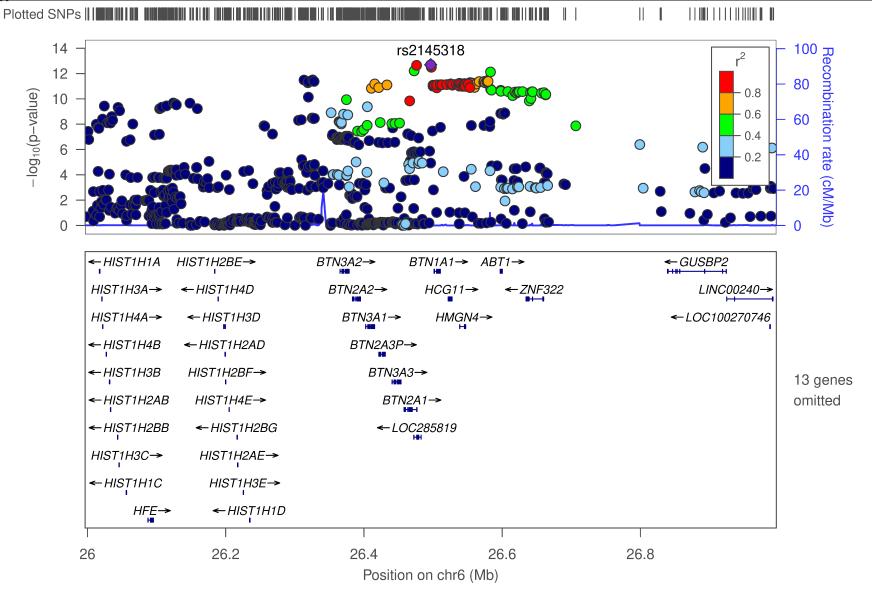


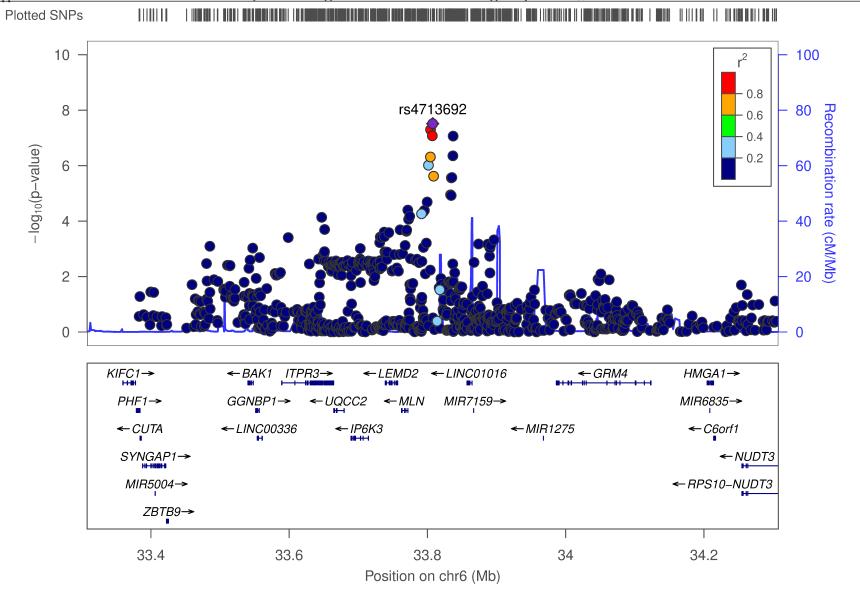


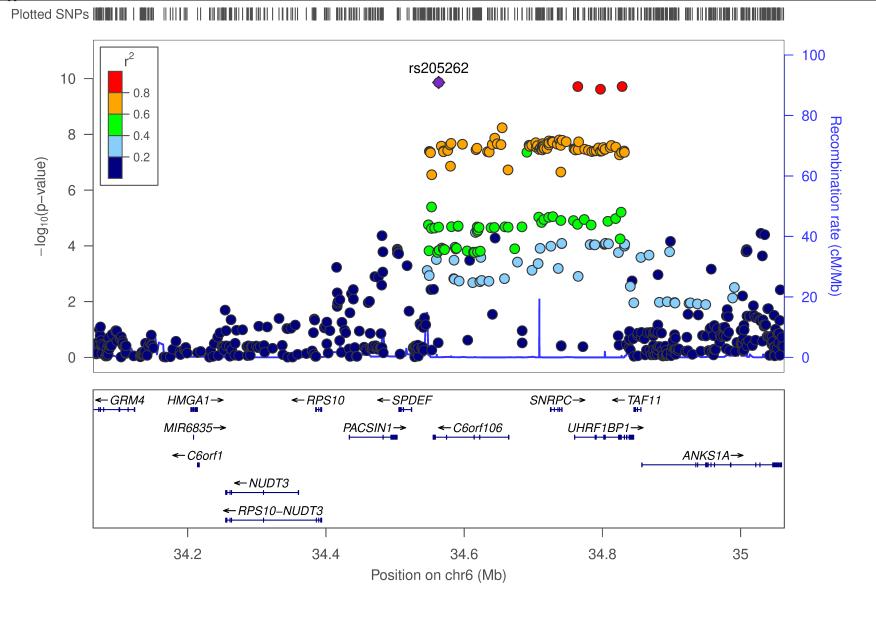


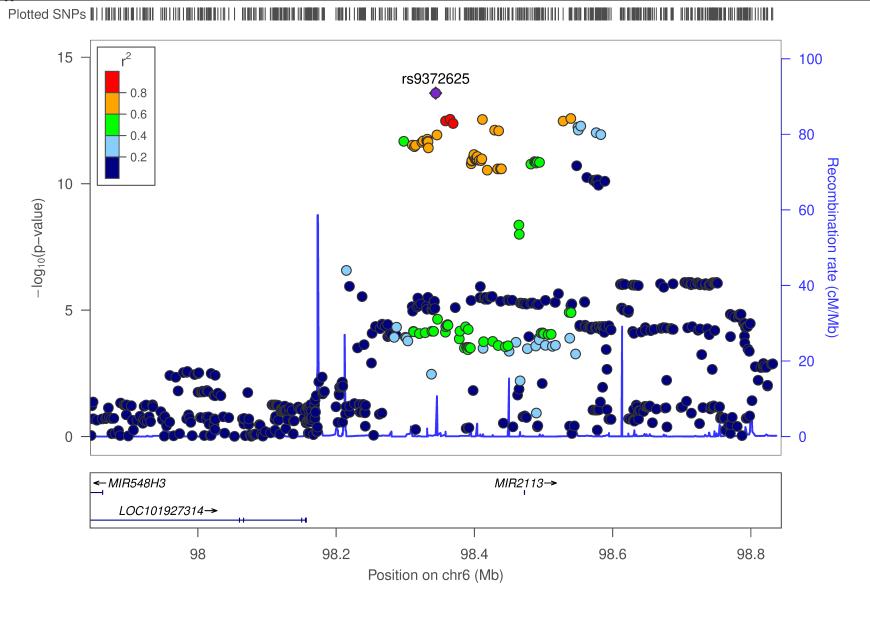


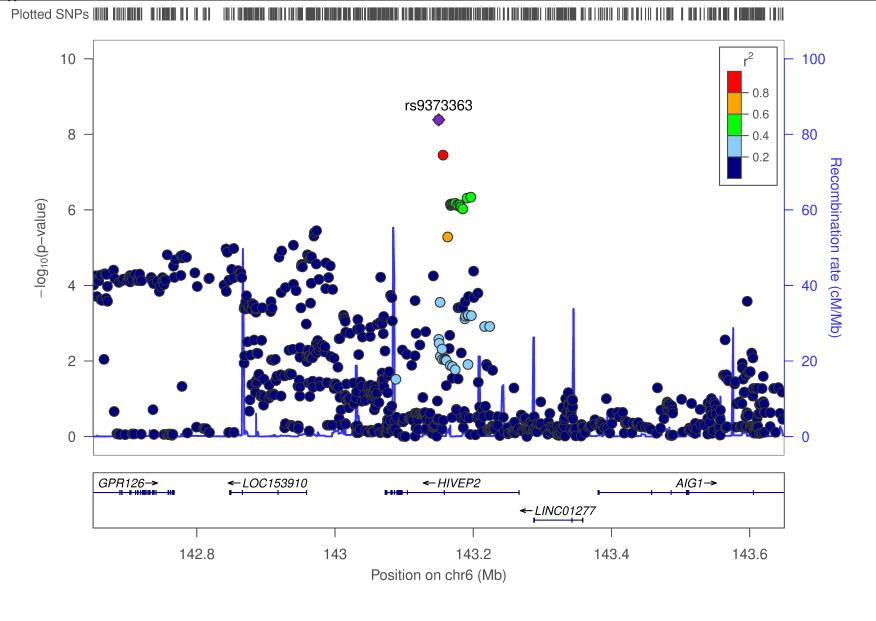


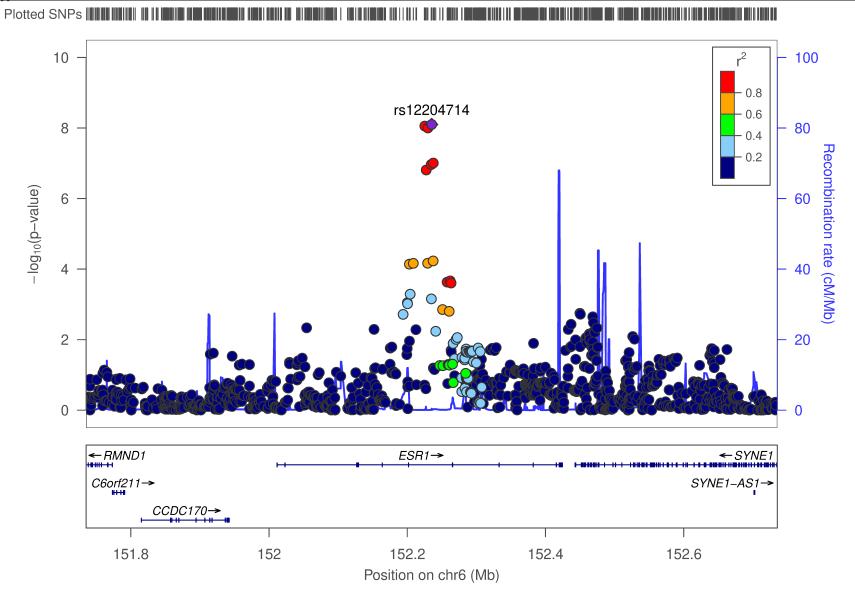




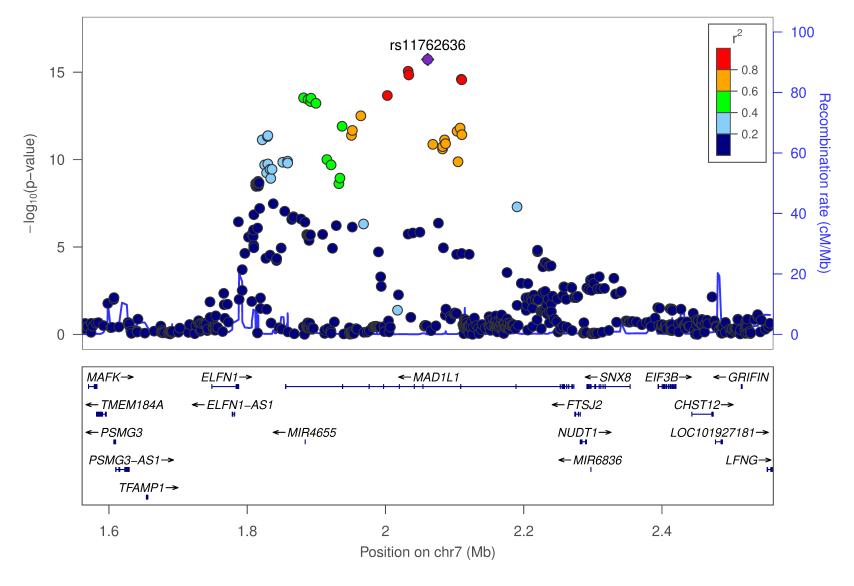


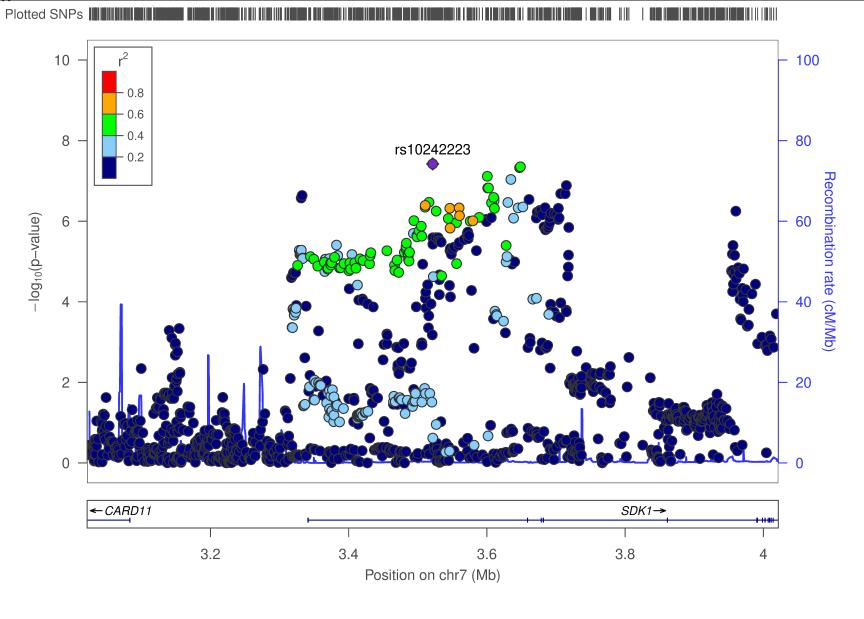


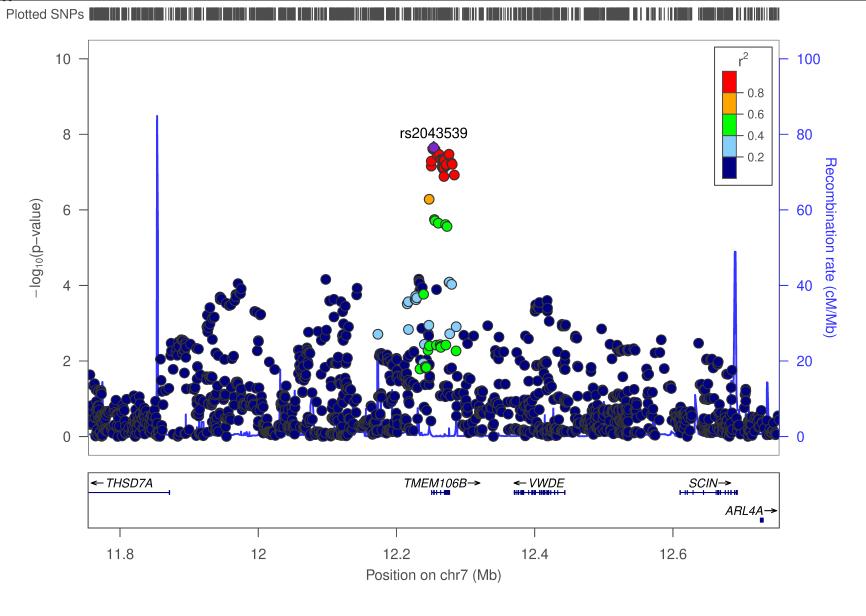


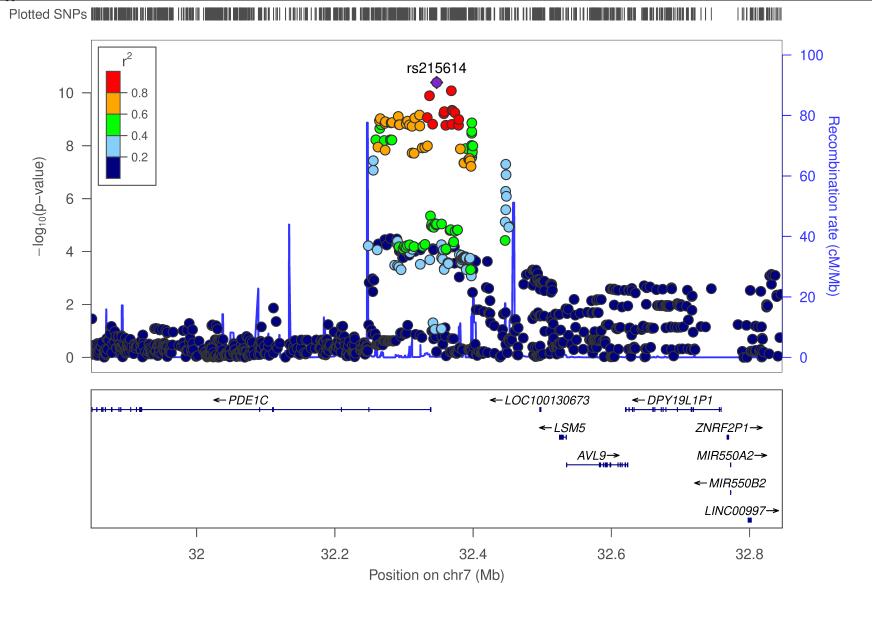


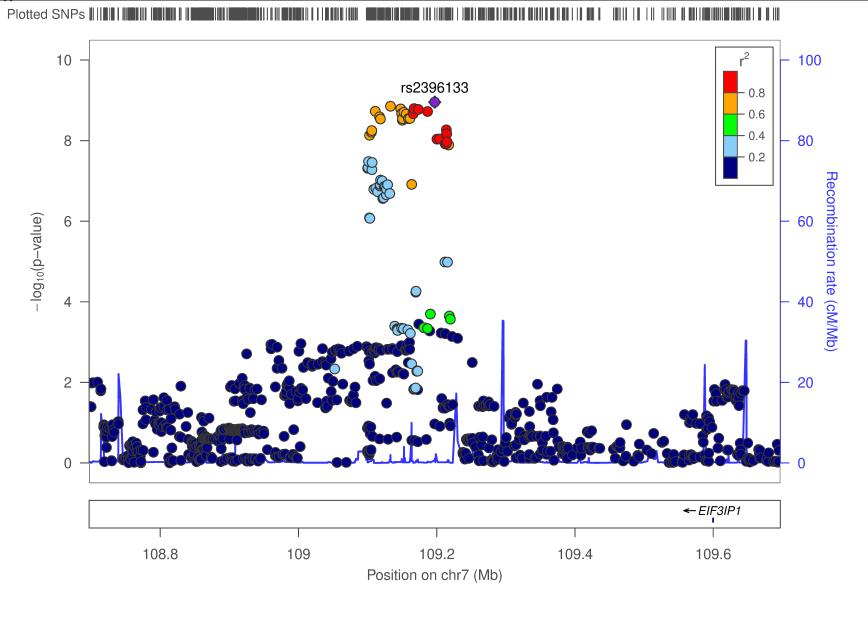


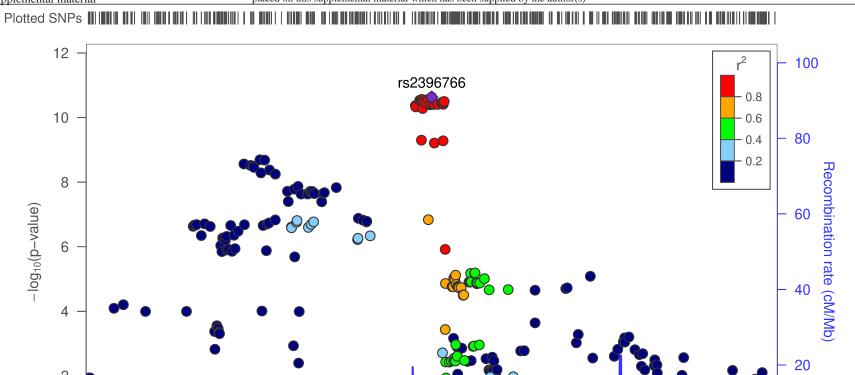












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Position on chr7 (Mb)

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114.2

FOXP2→

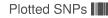
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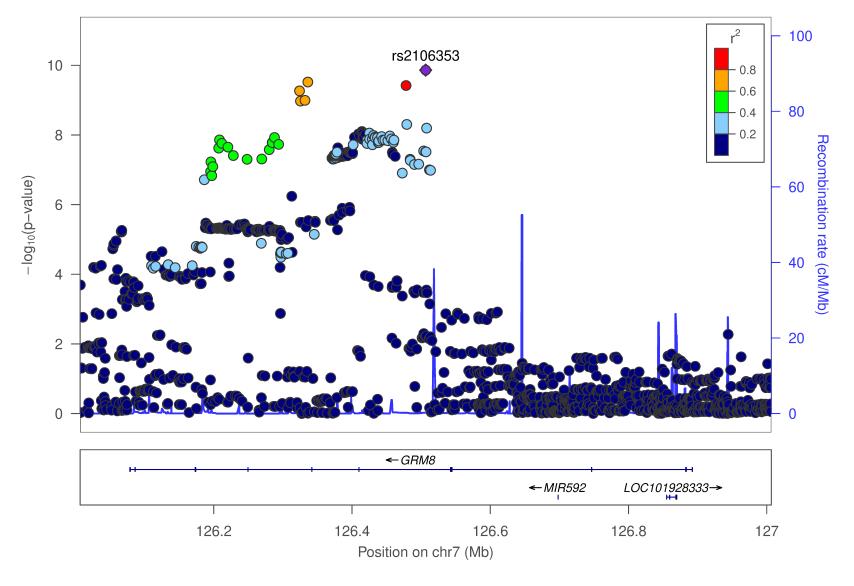
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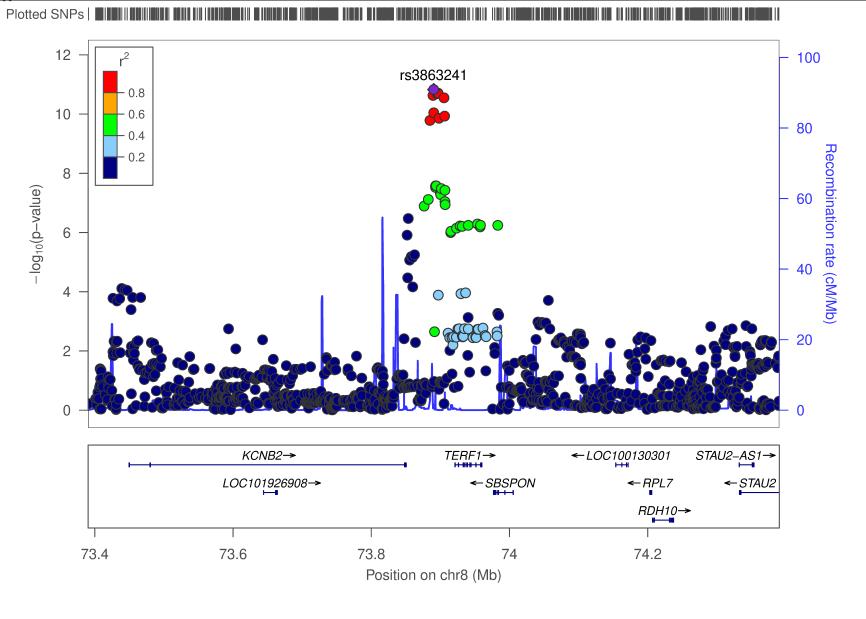
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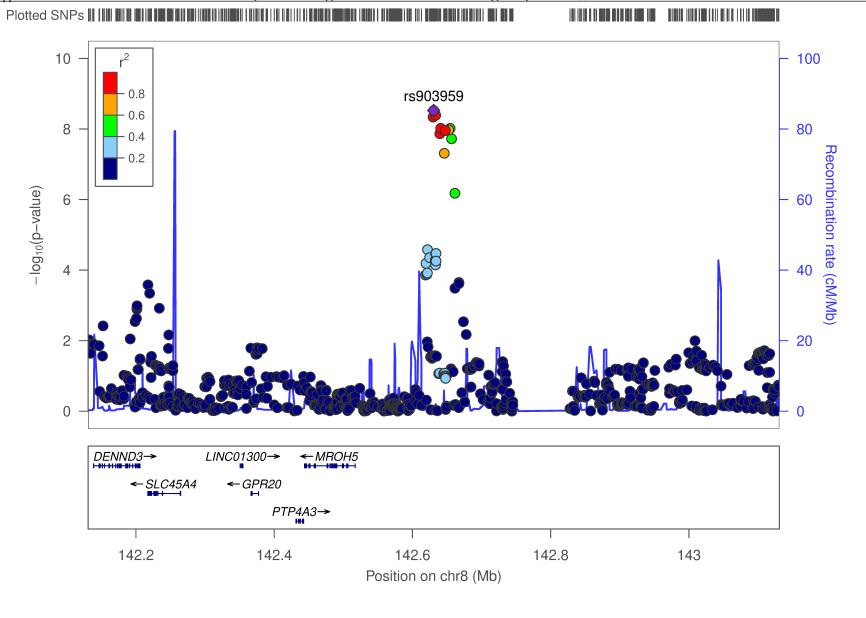
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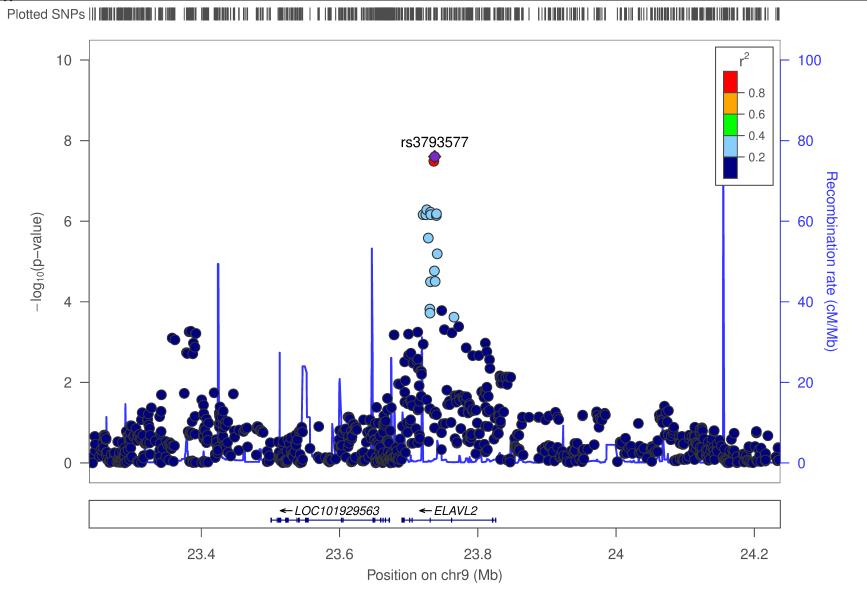
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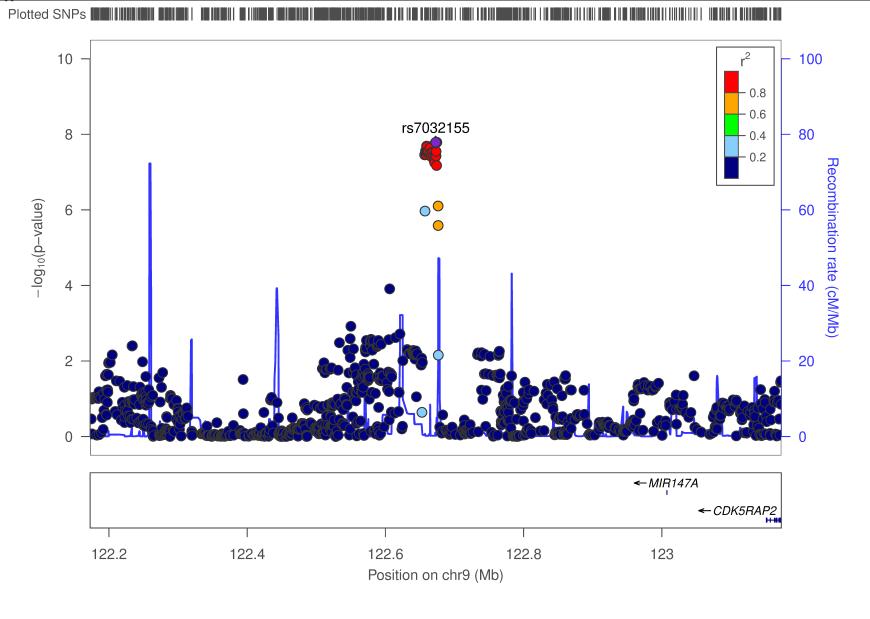


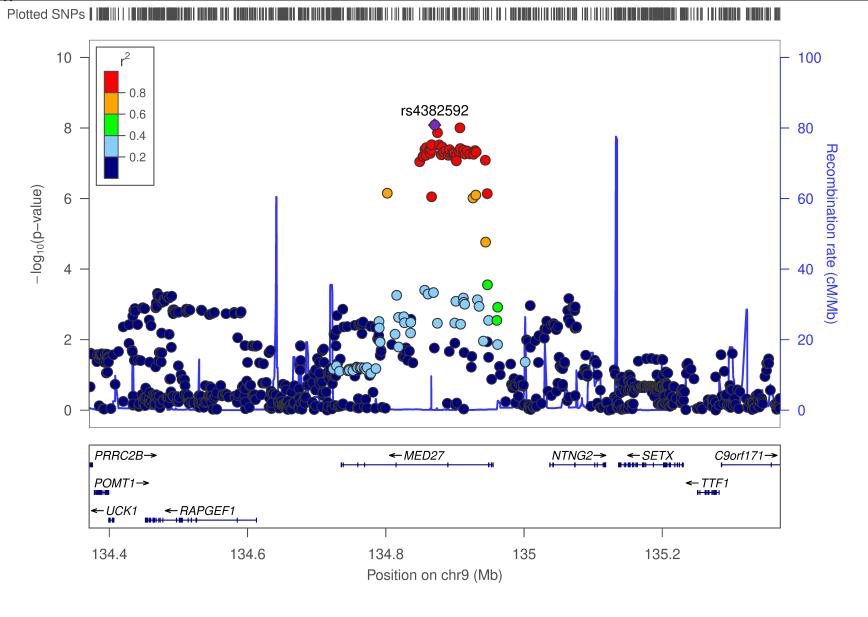


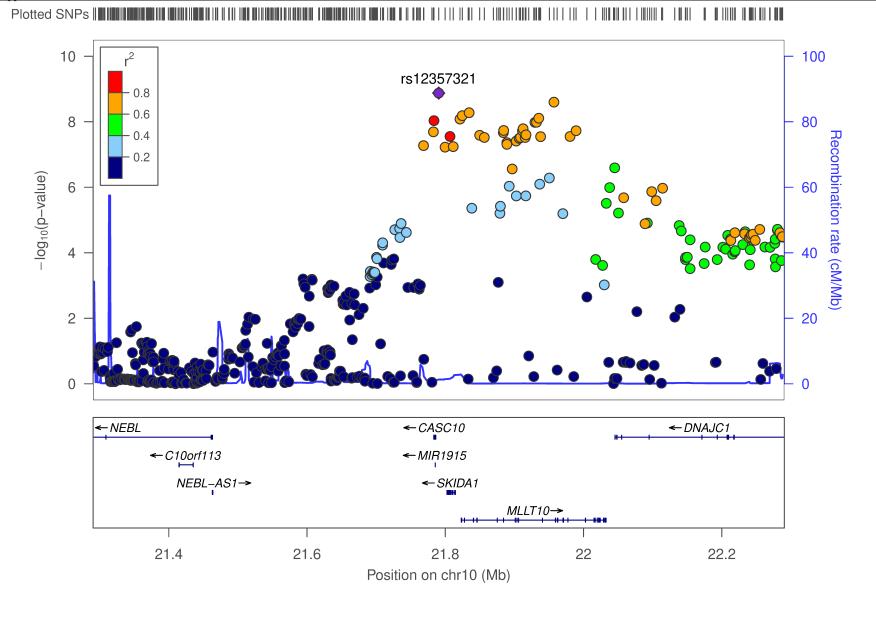


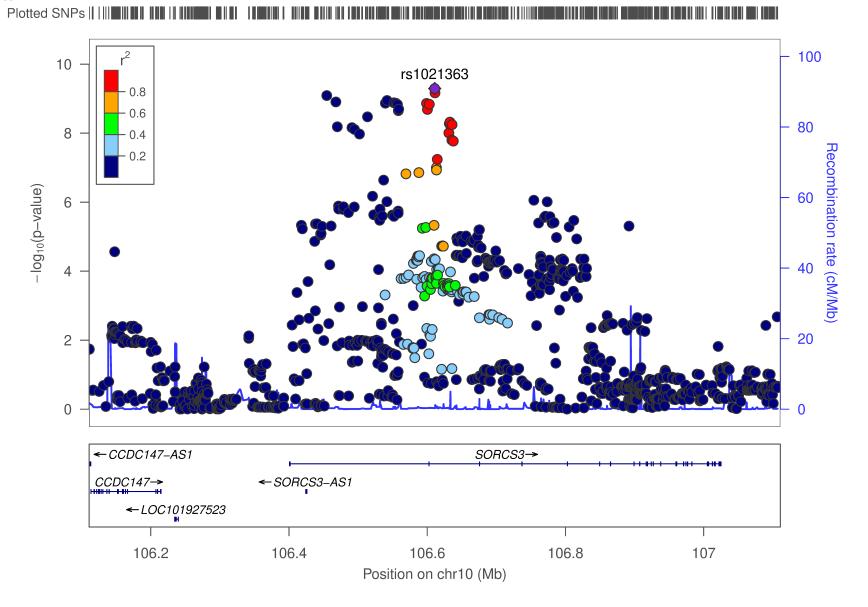


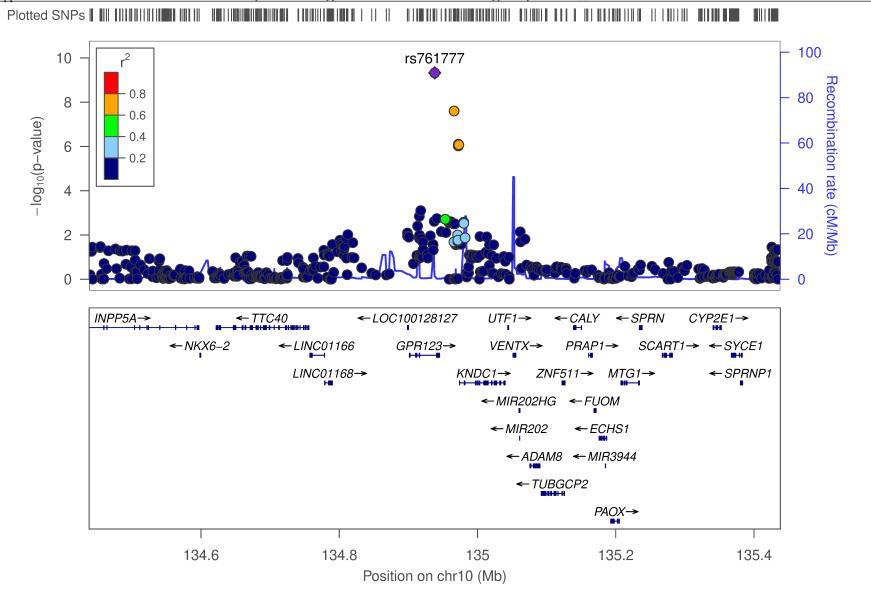


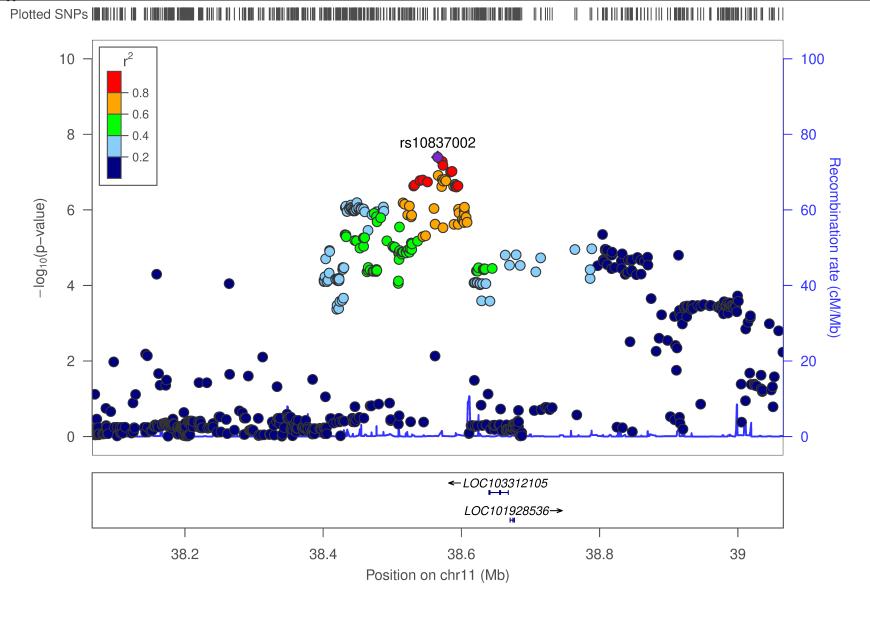


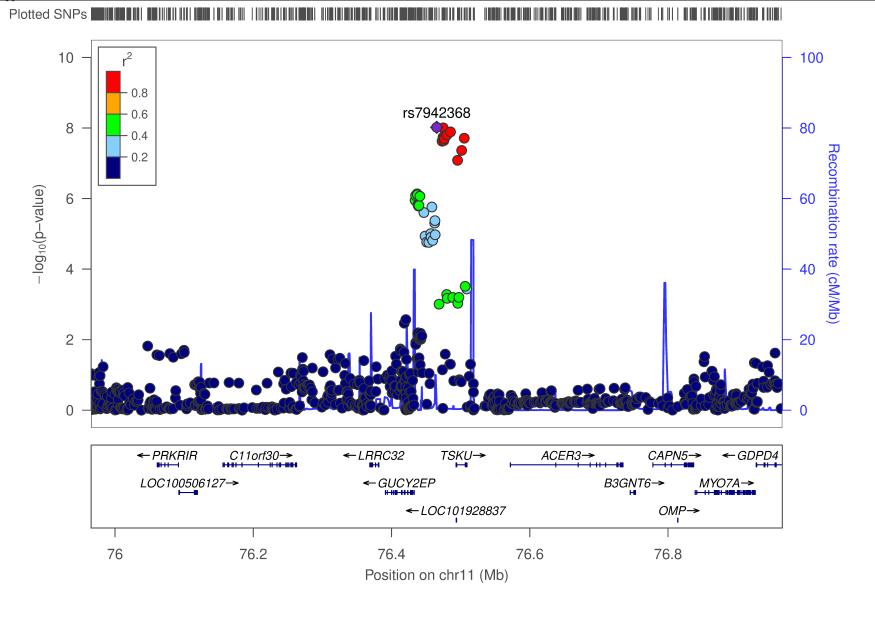


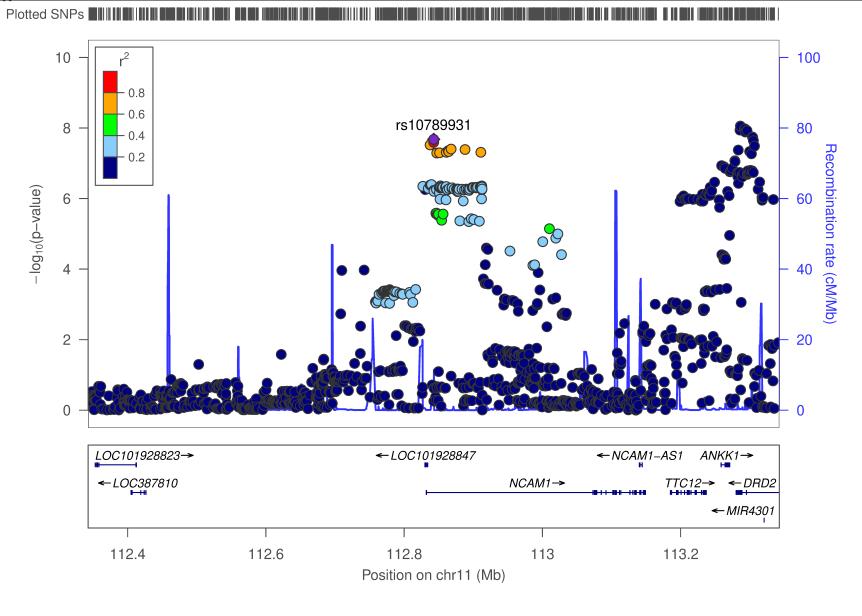


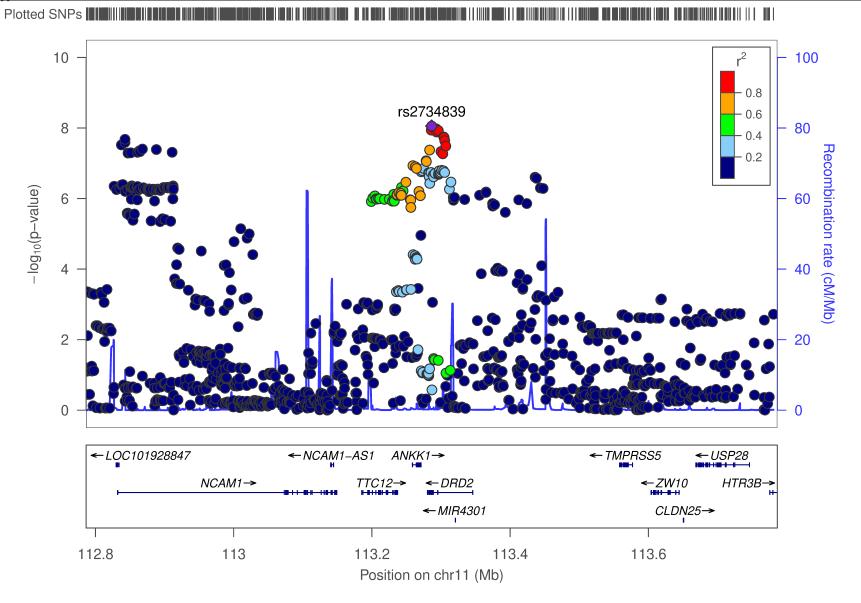


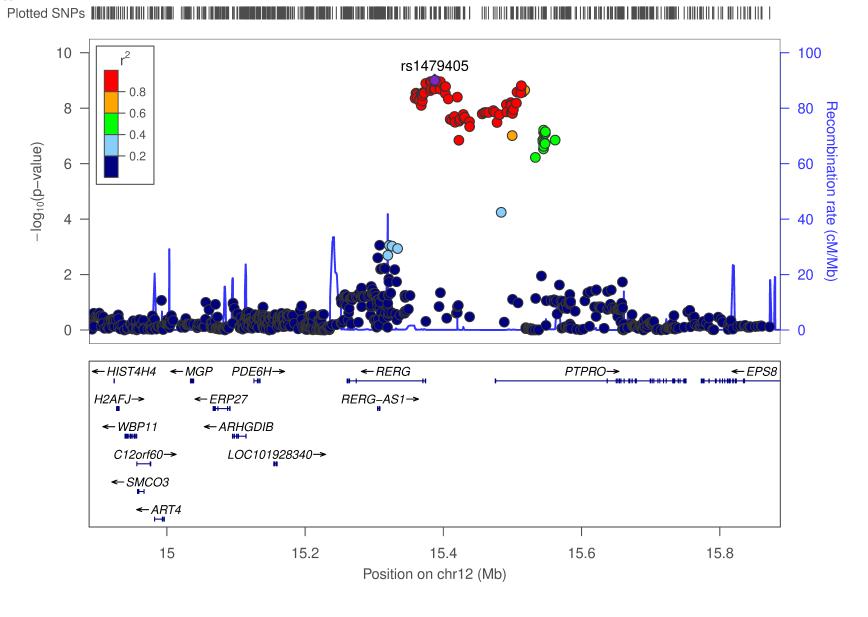


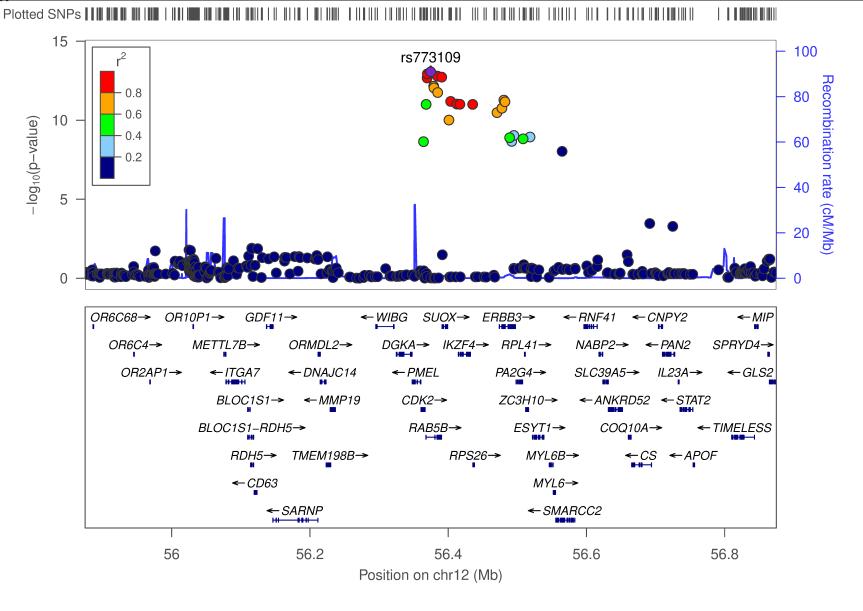




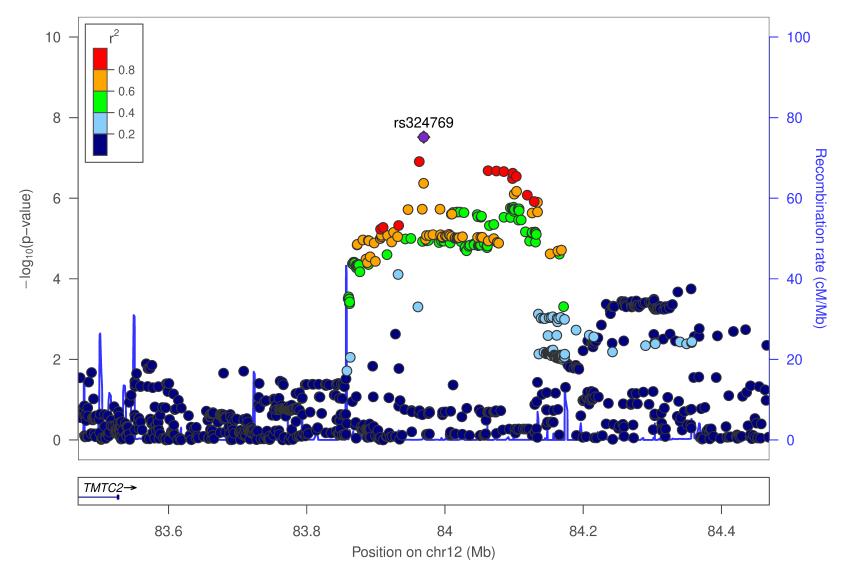


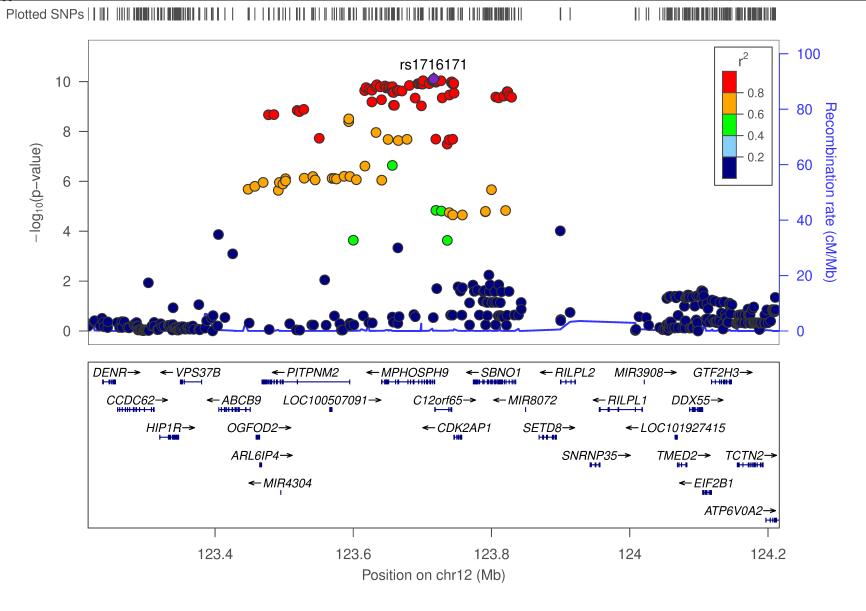


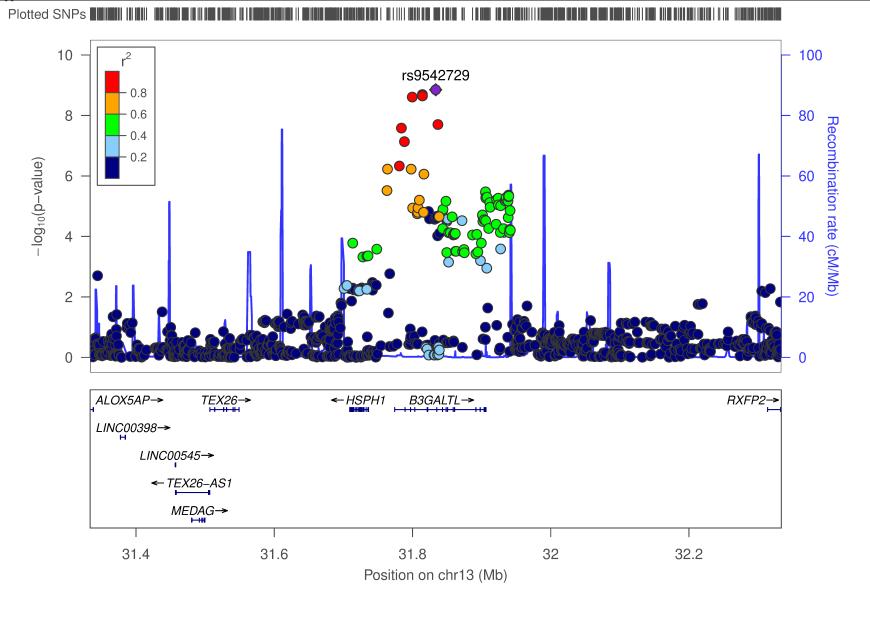




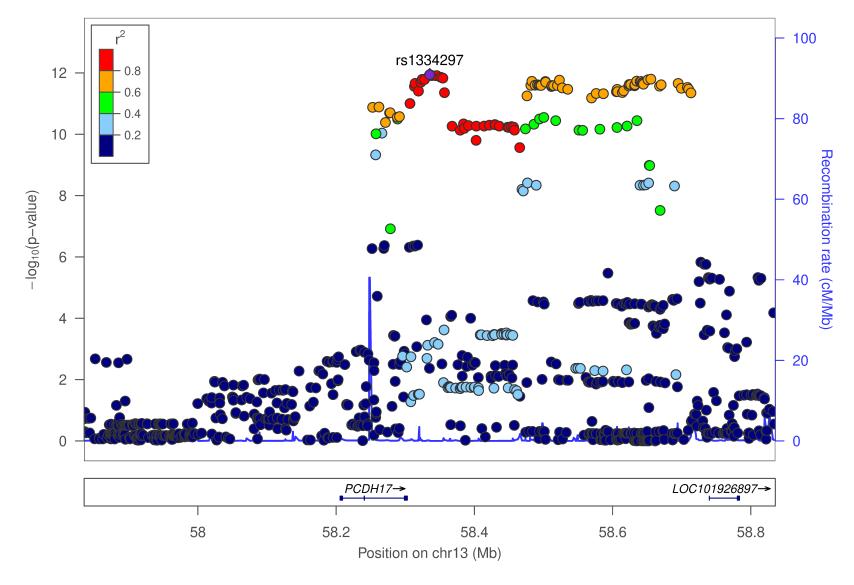


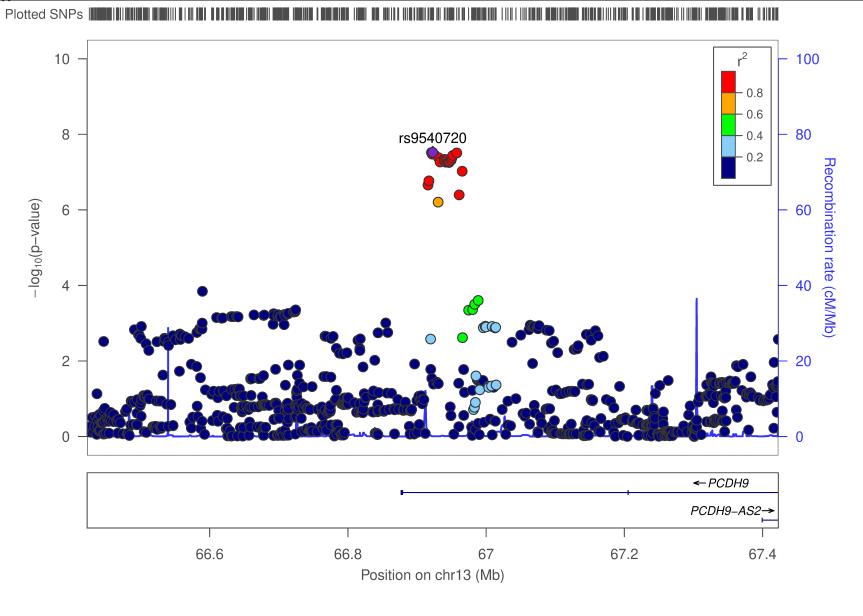


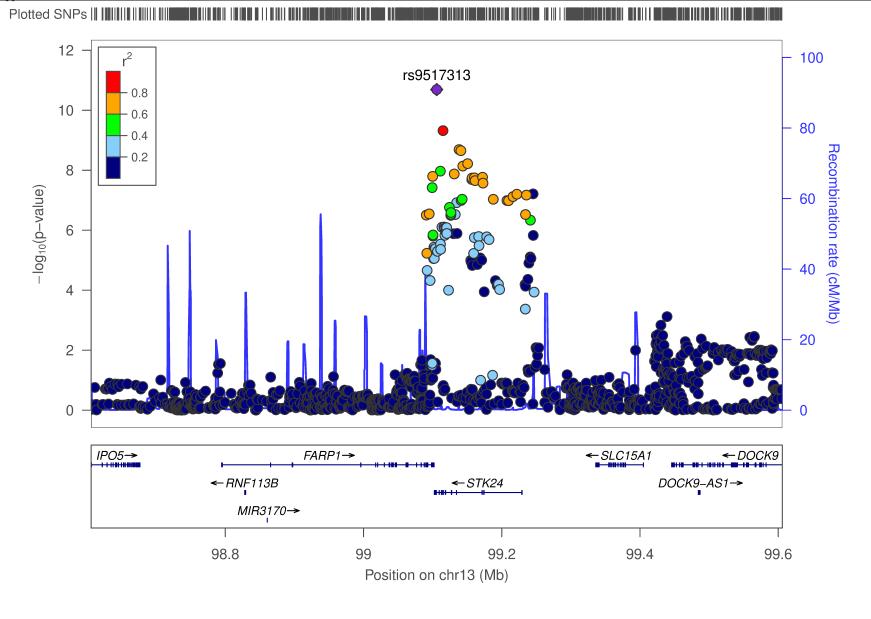


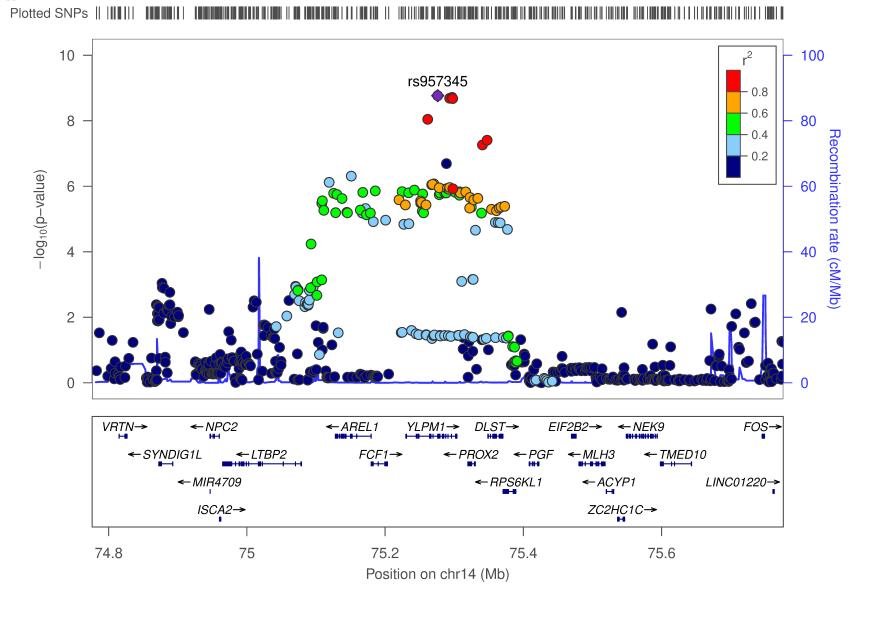


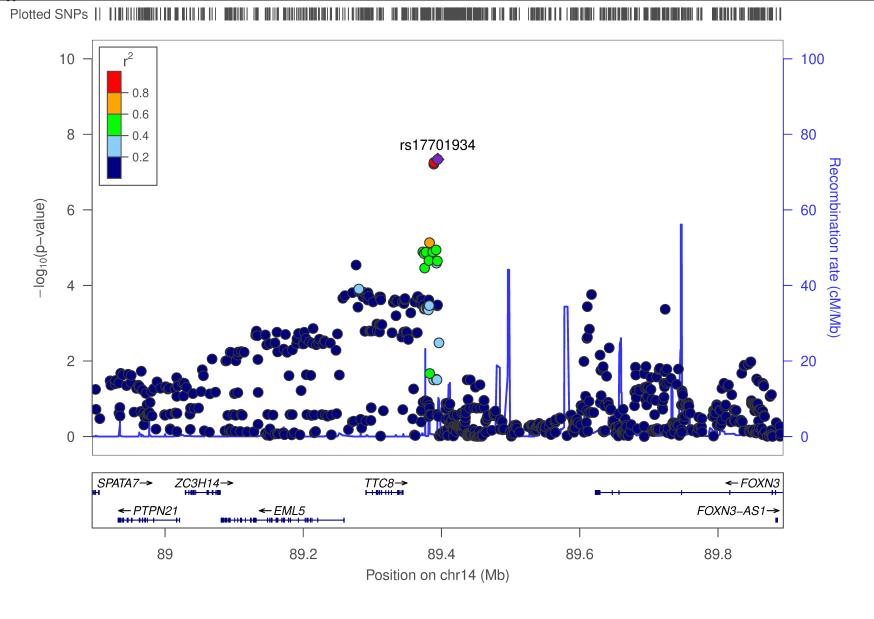


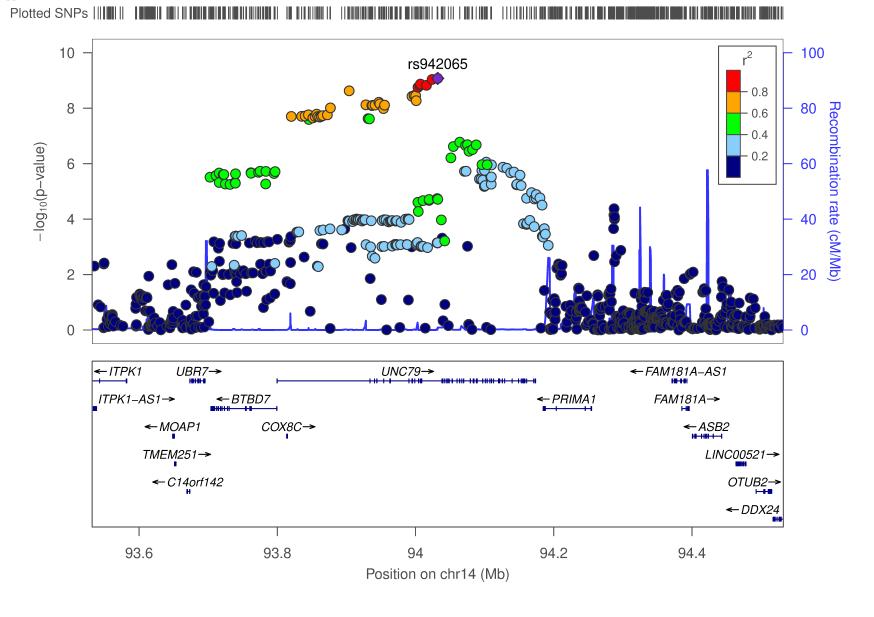


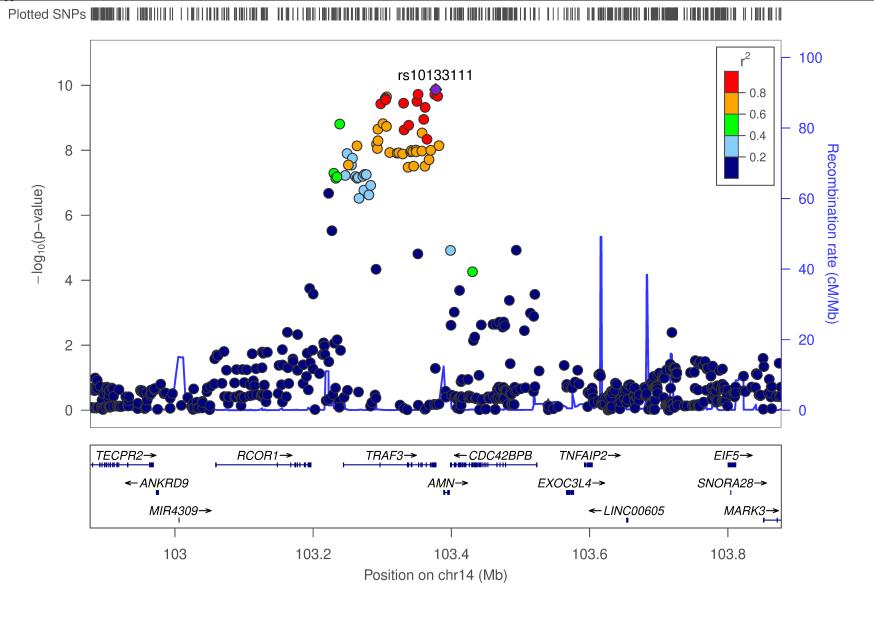


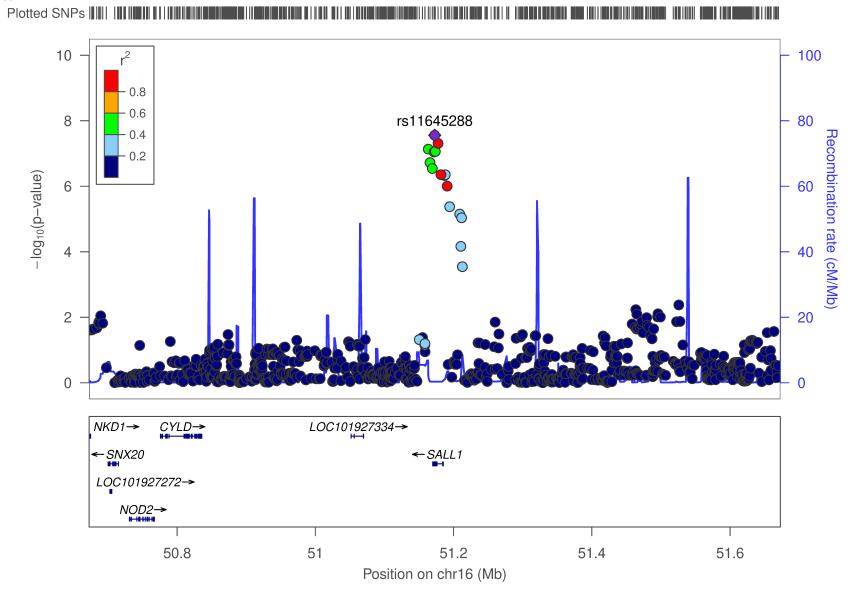


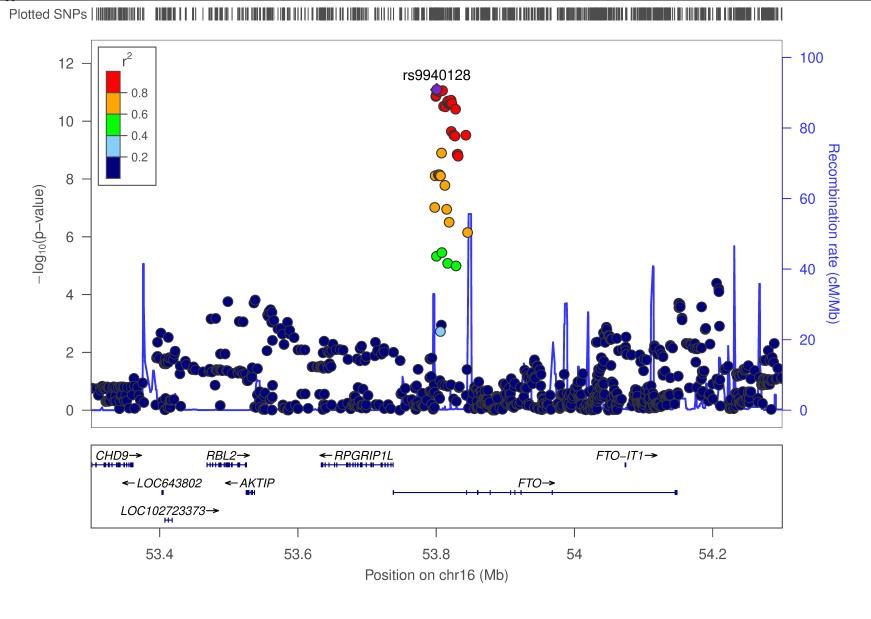




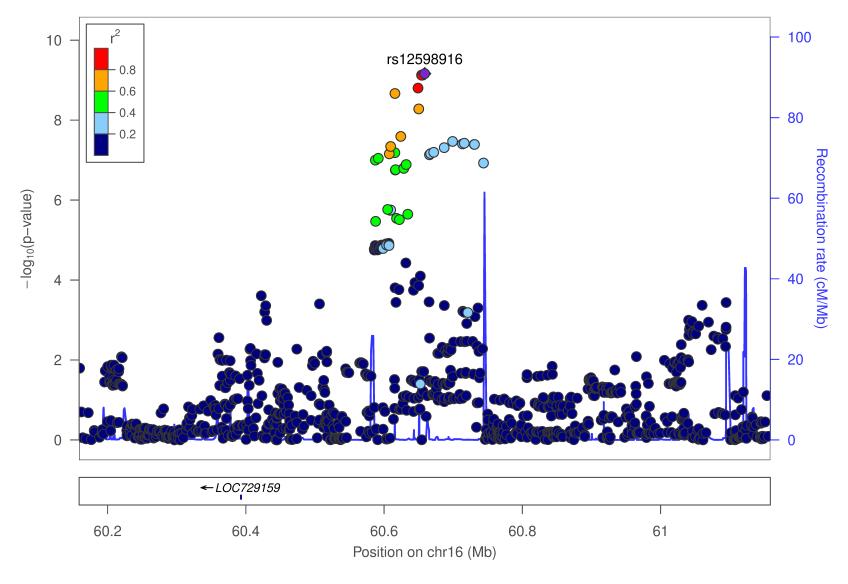


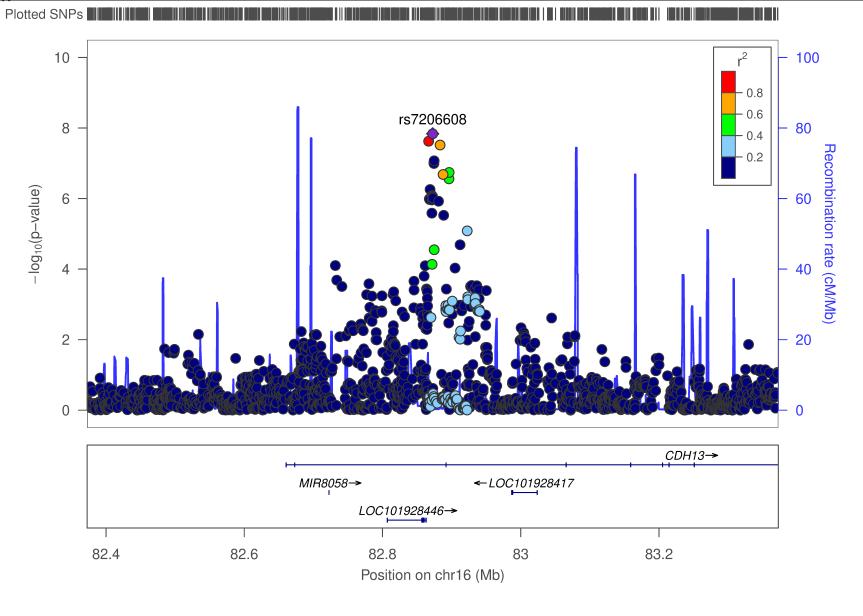


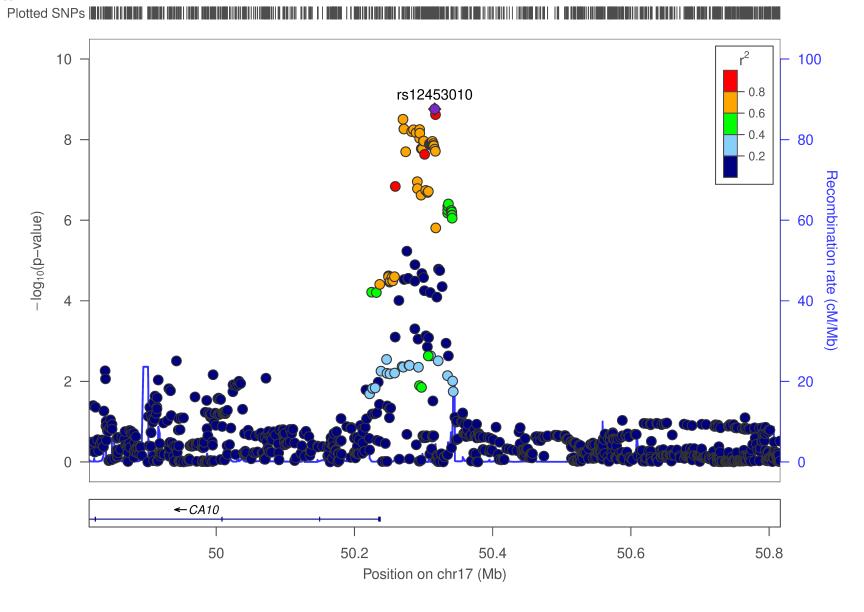




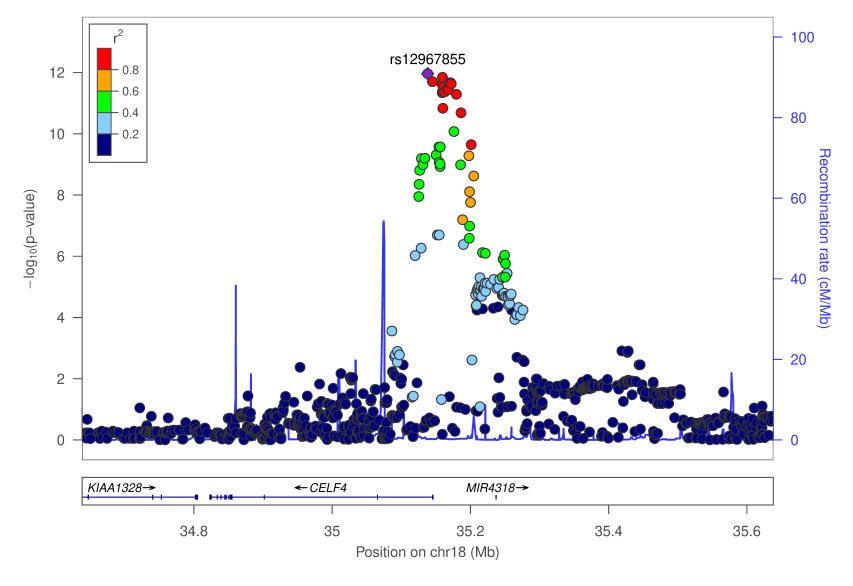


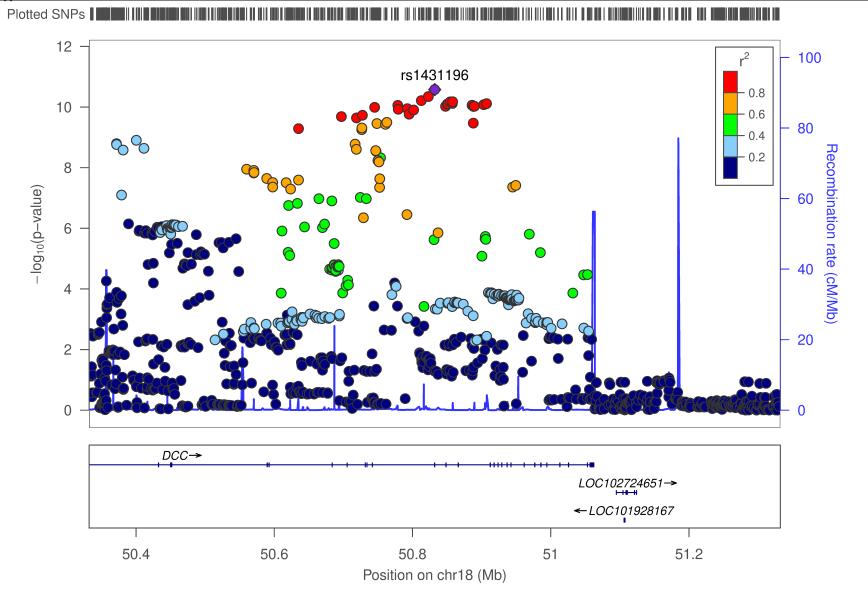


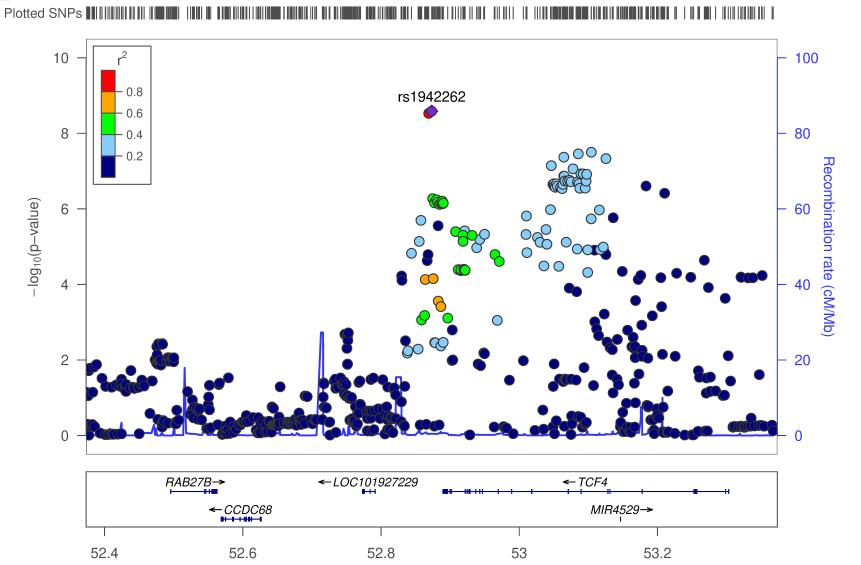






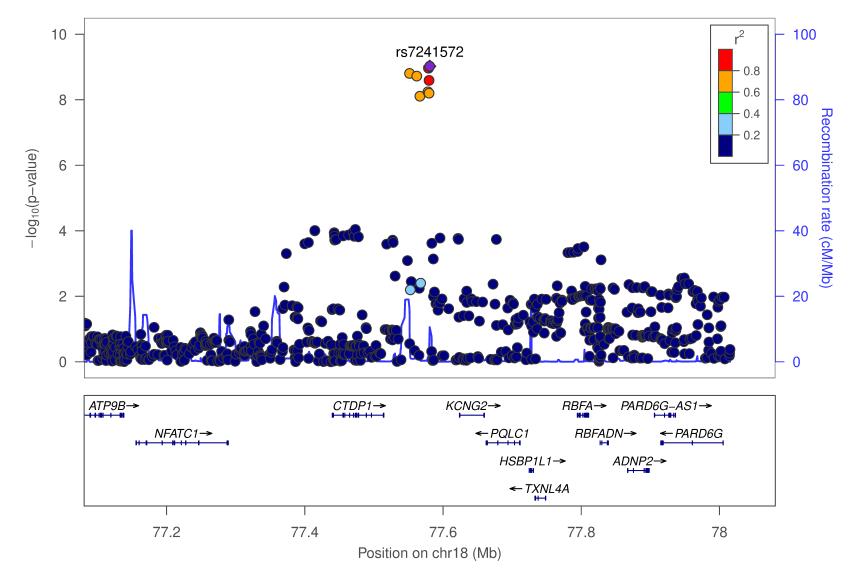


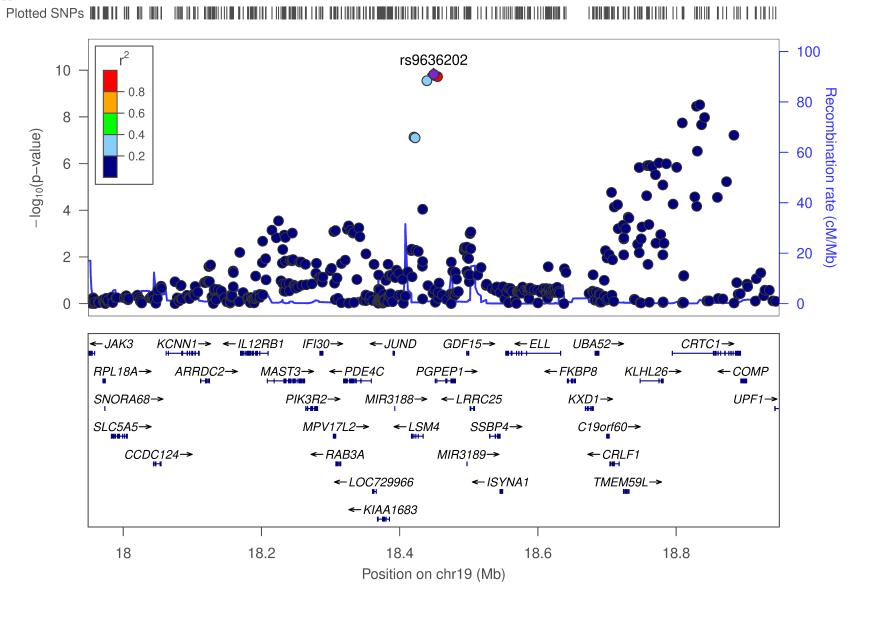


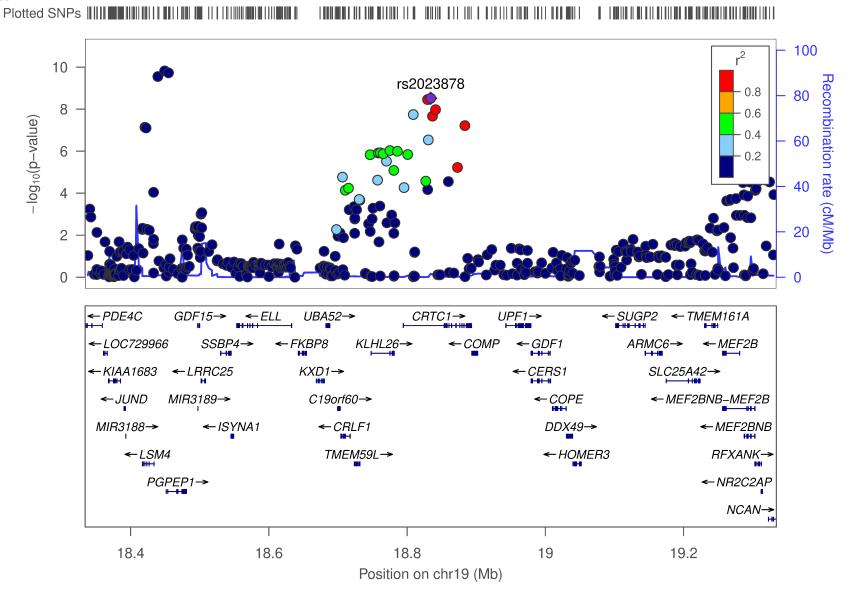


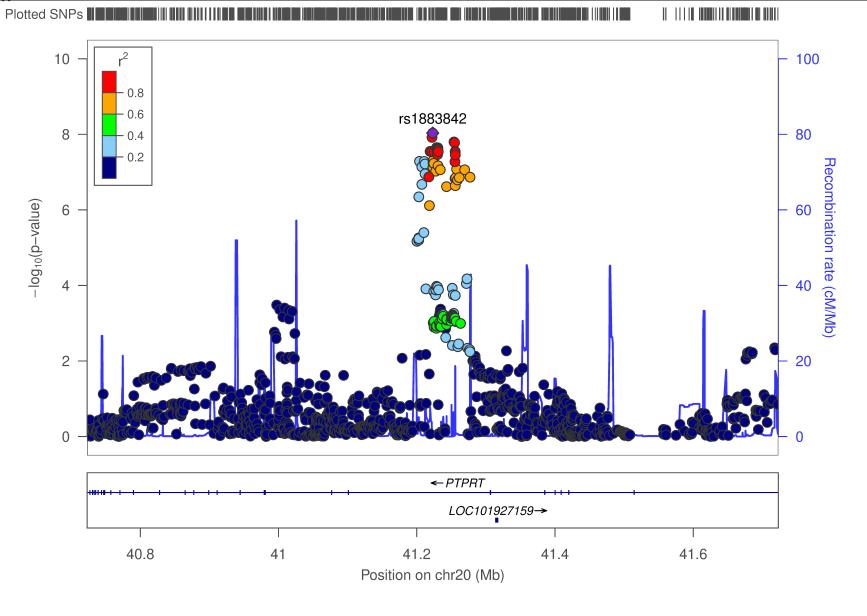
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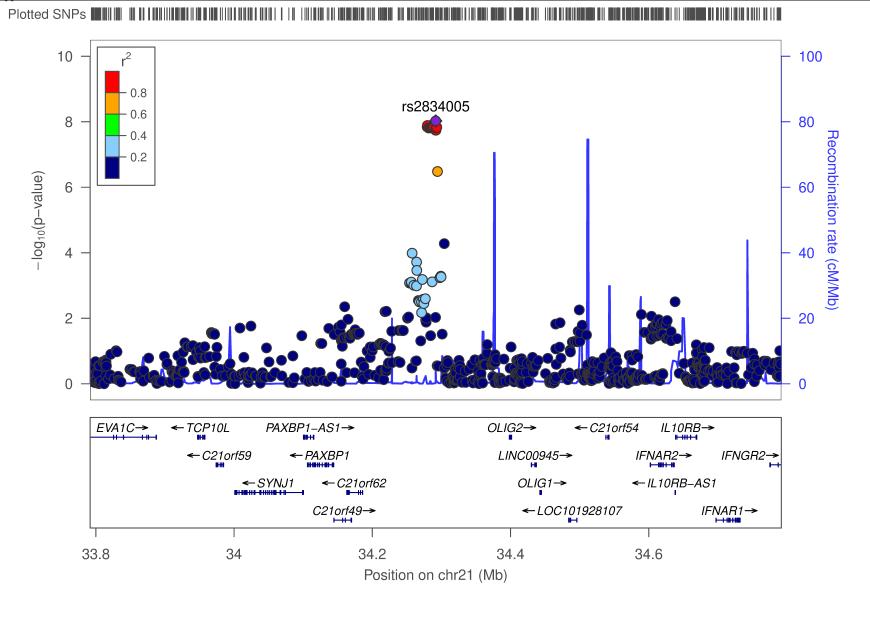


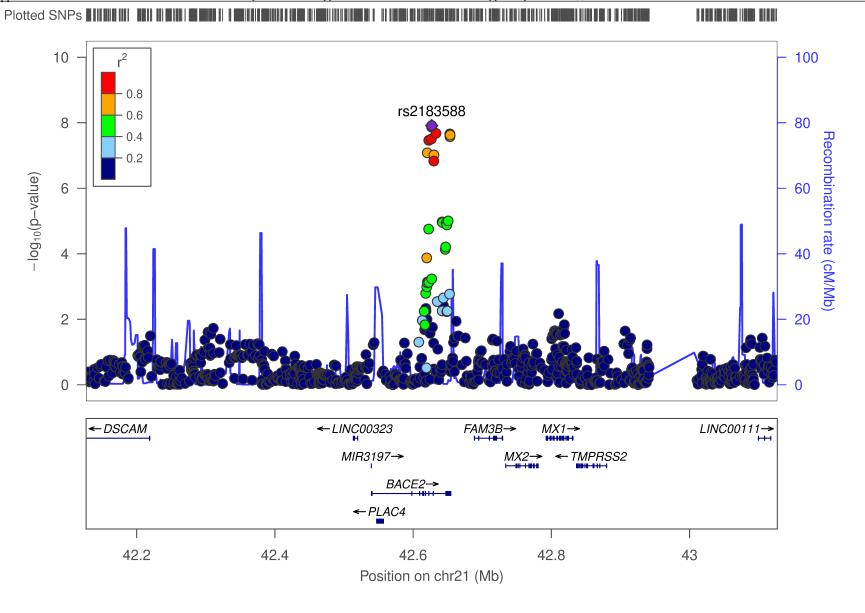


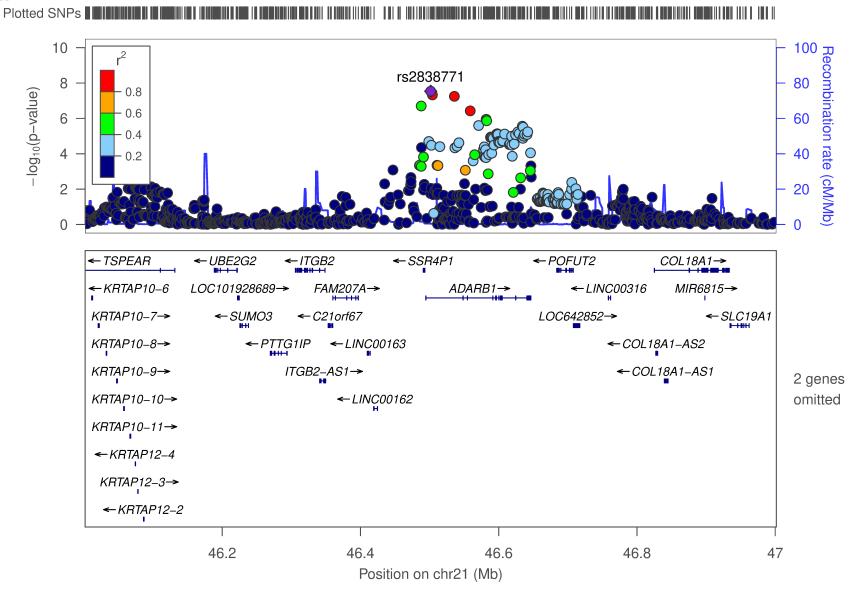


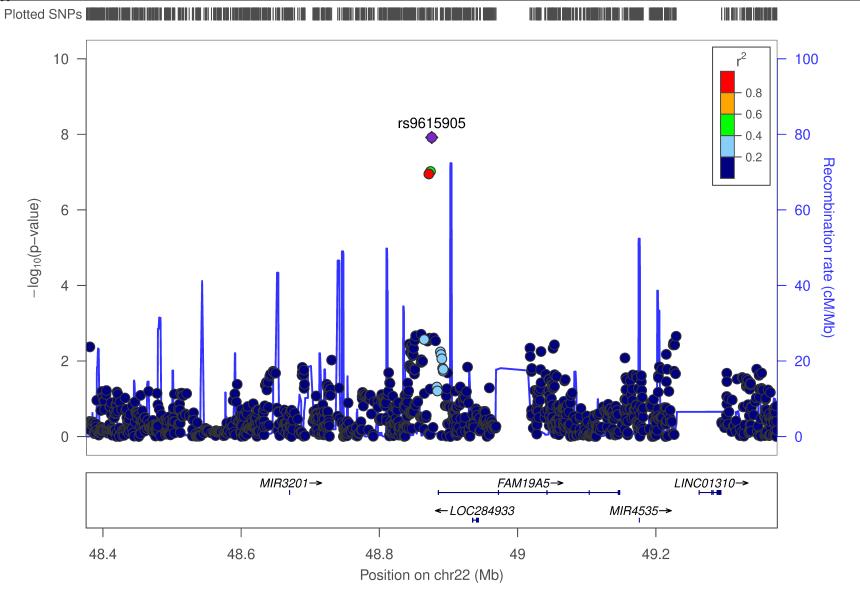


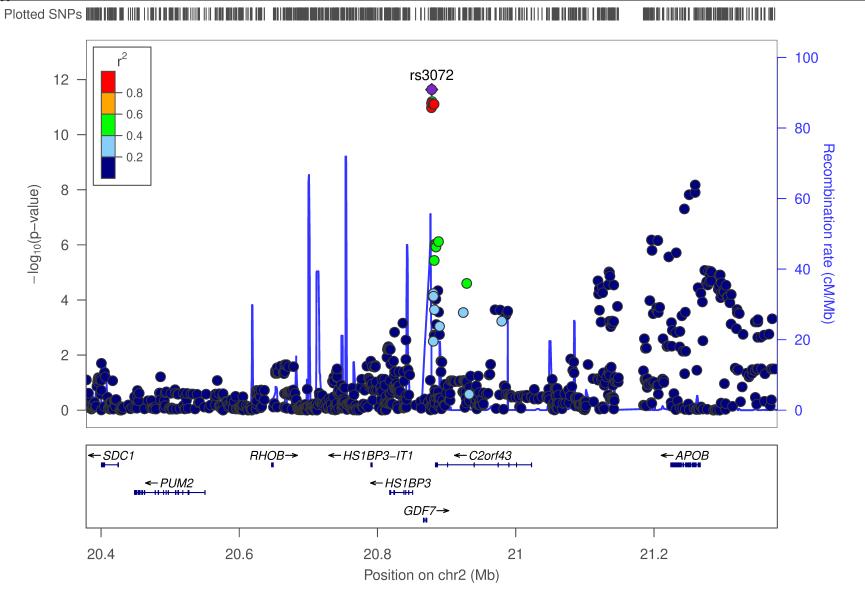


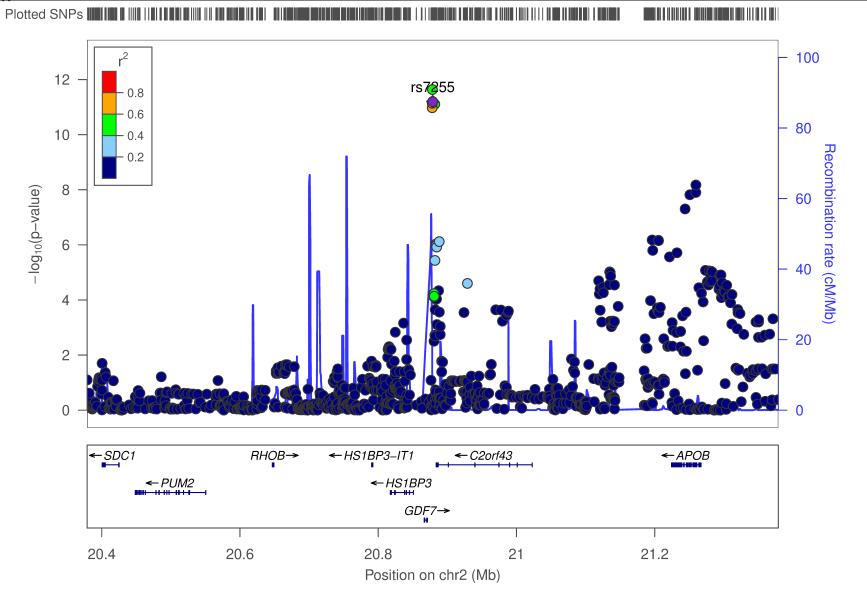


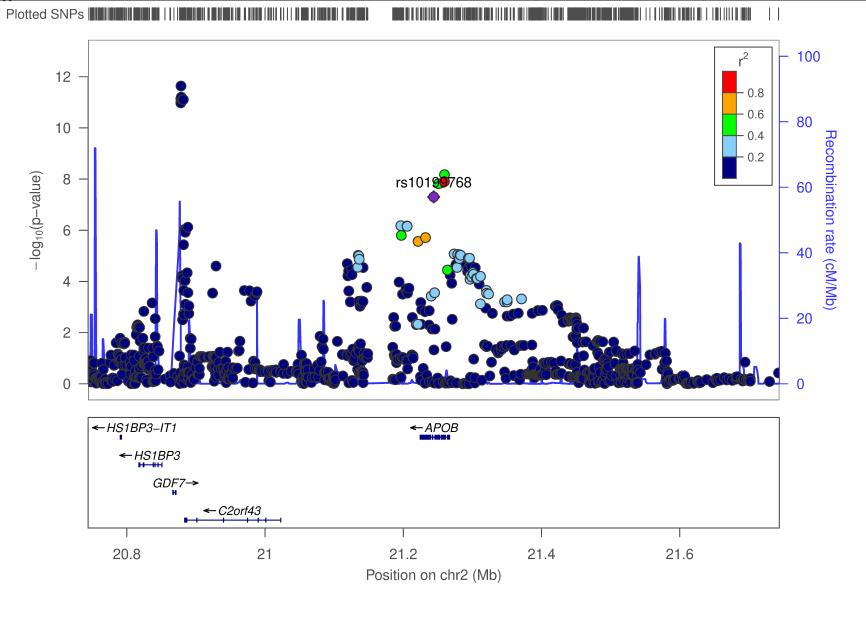


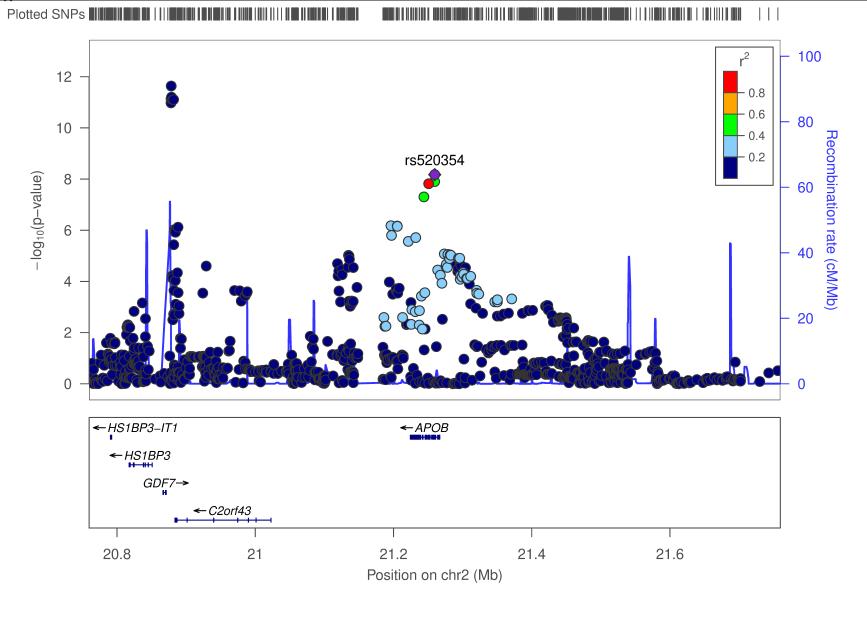


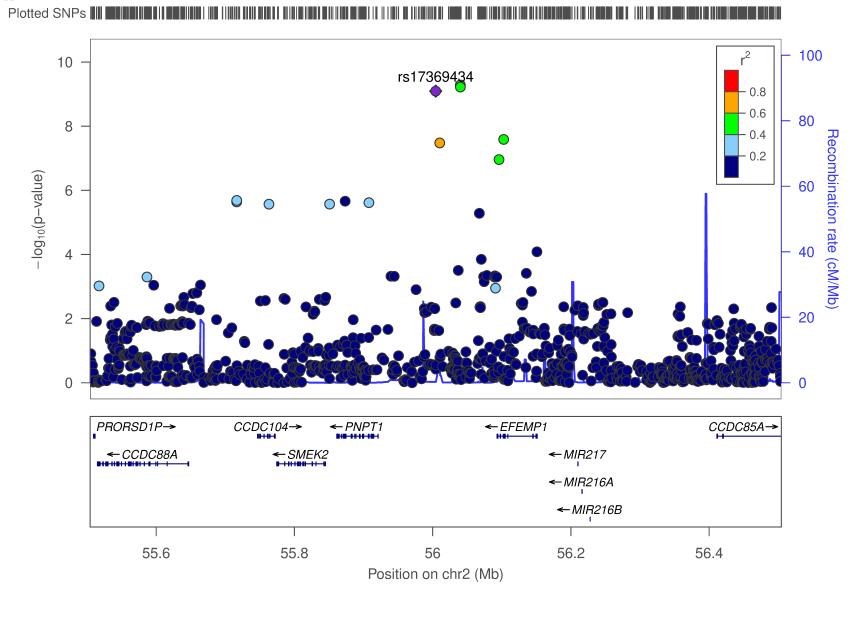


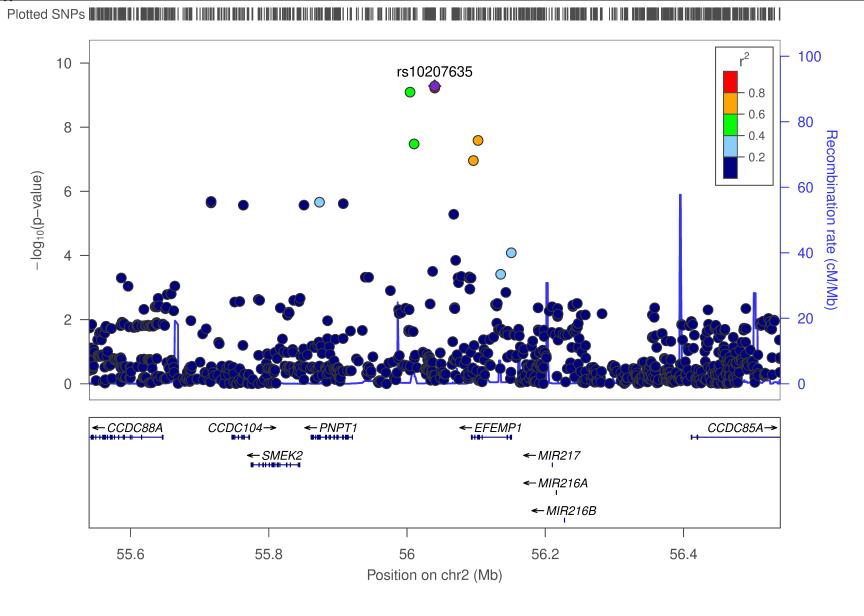


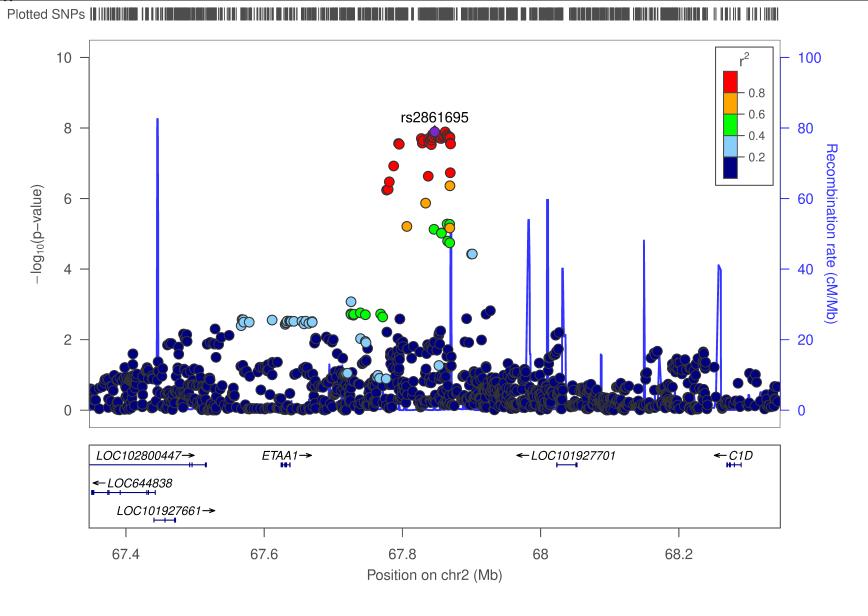


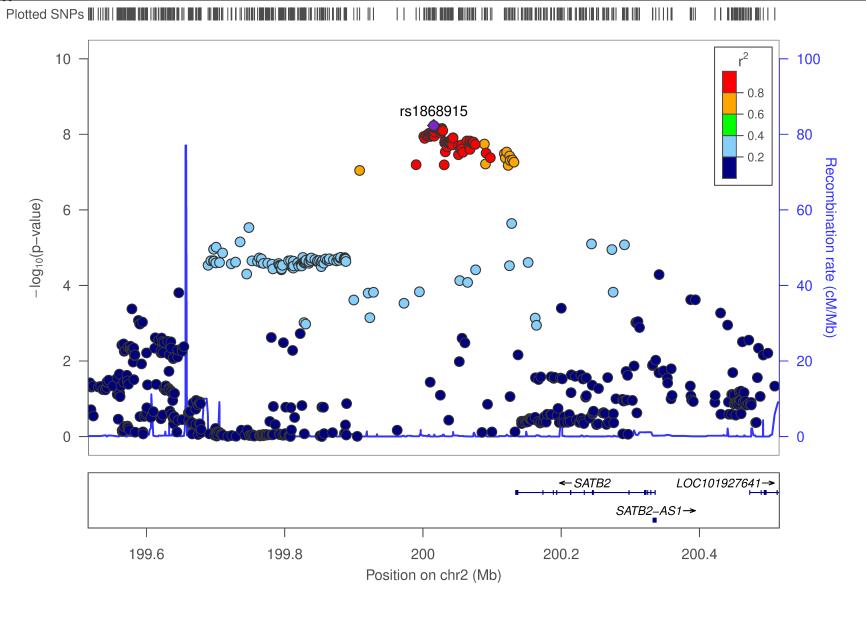


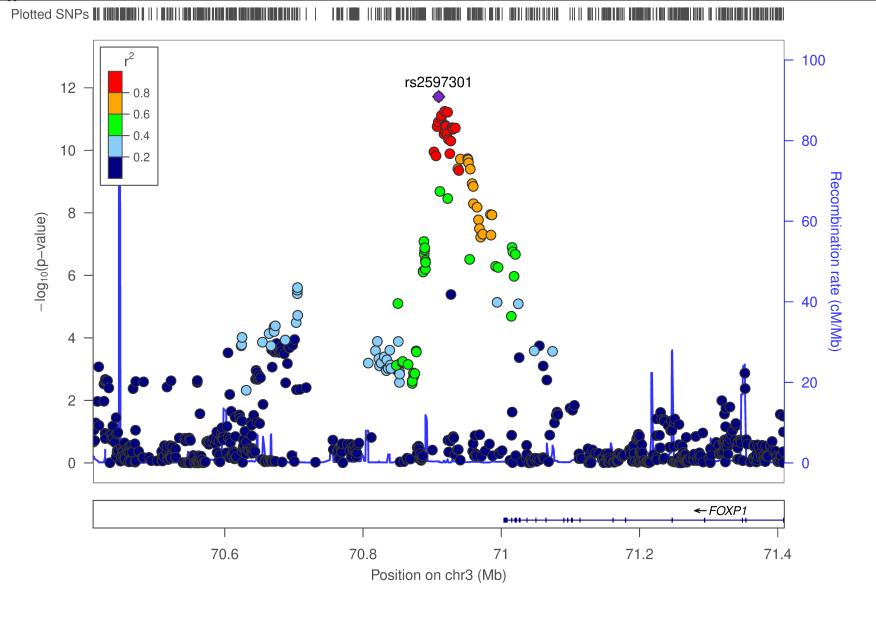


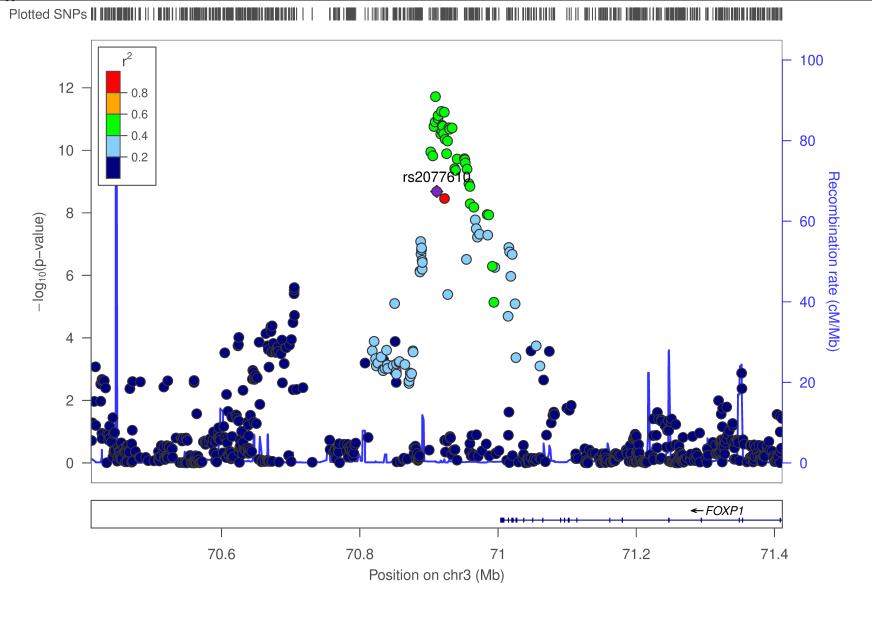


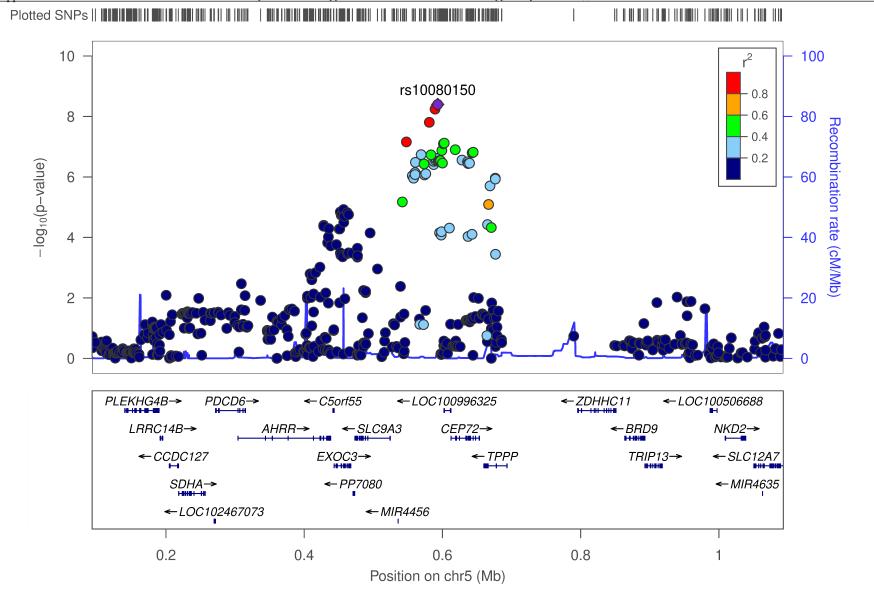


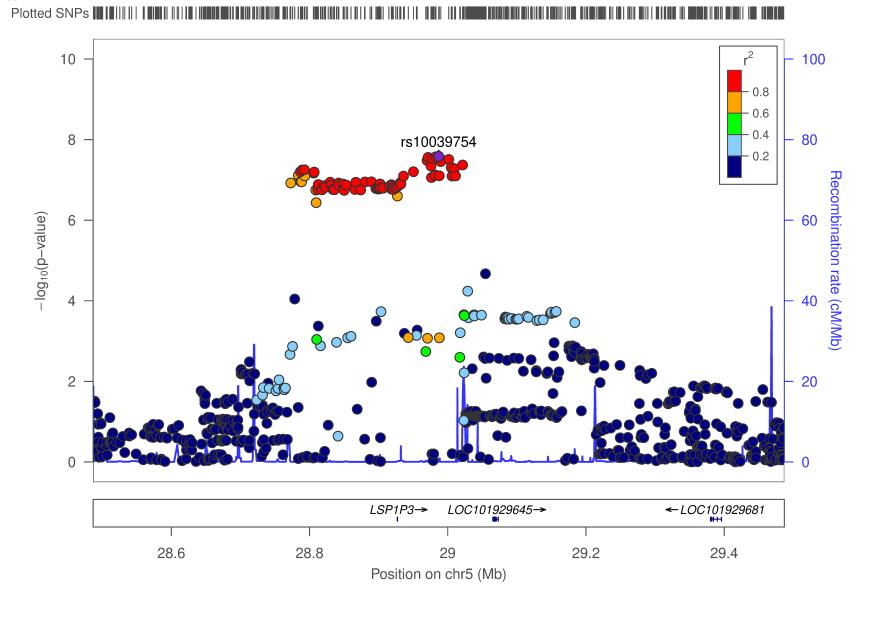


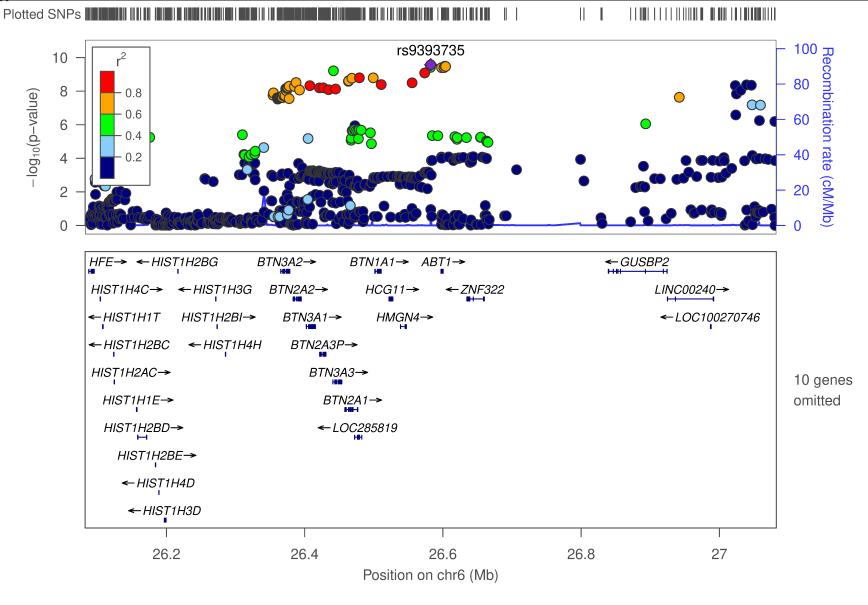


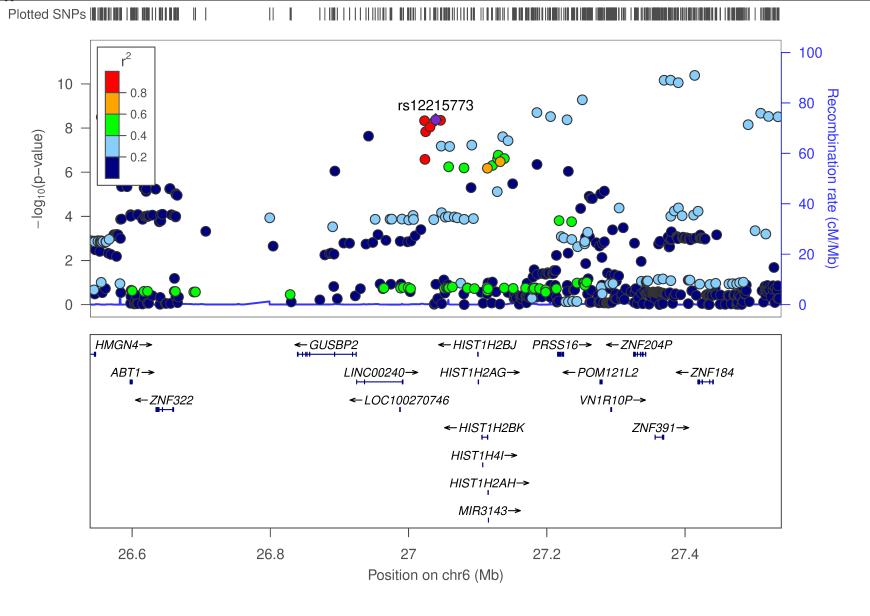


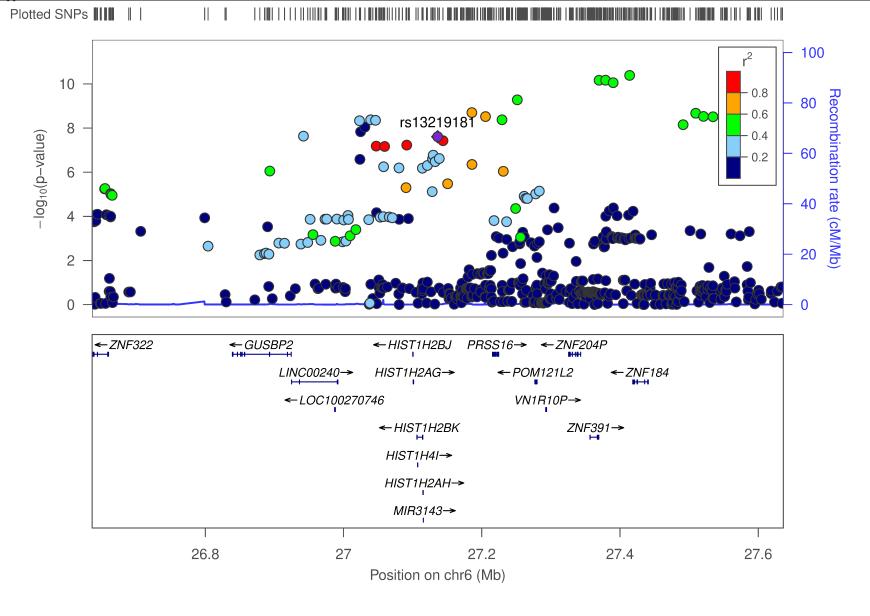


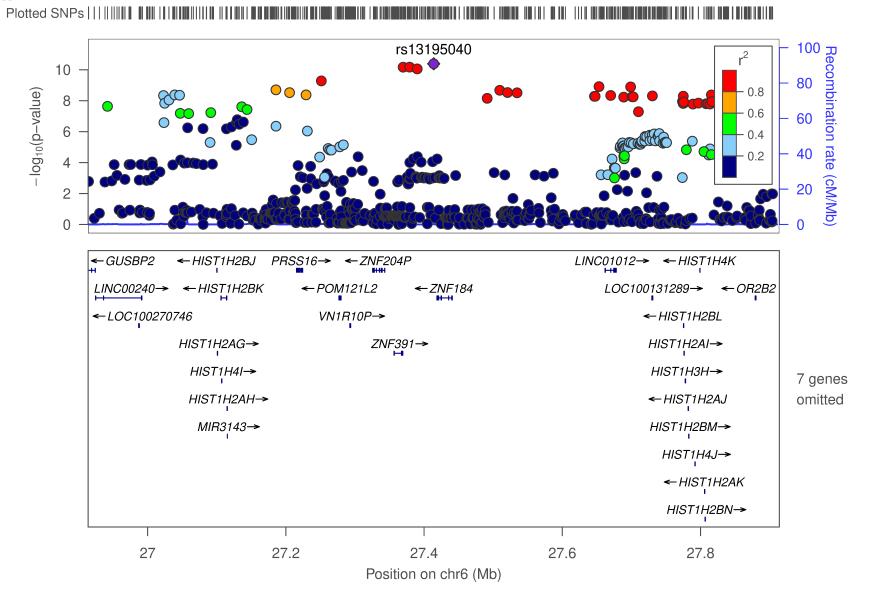


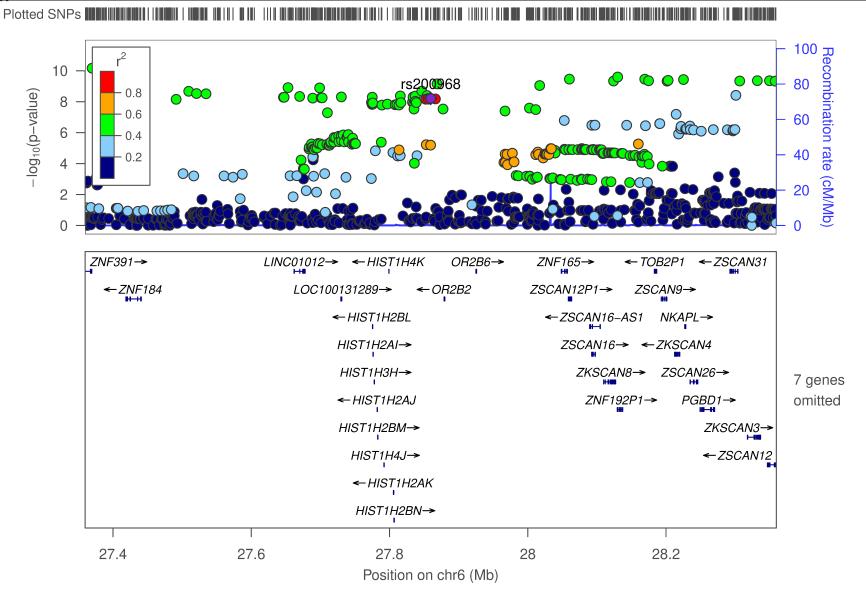


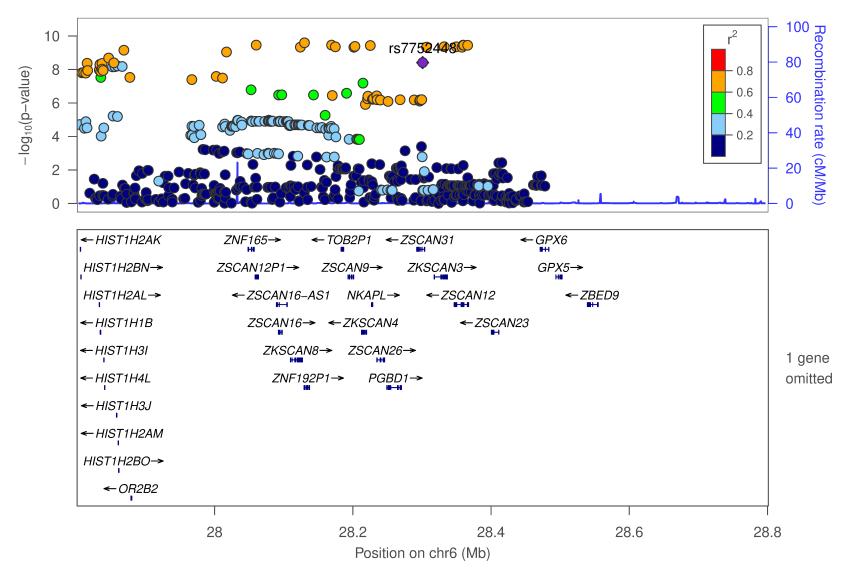


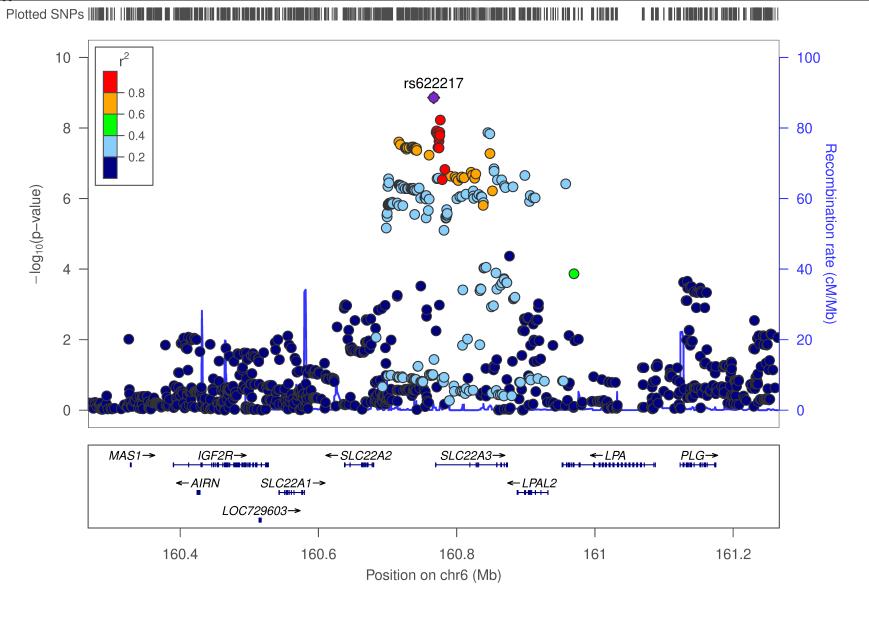


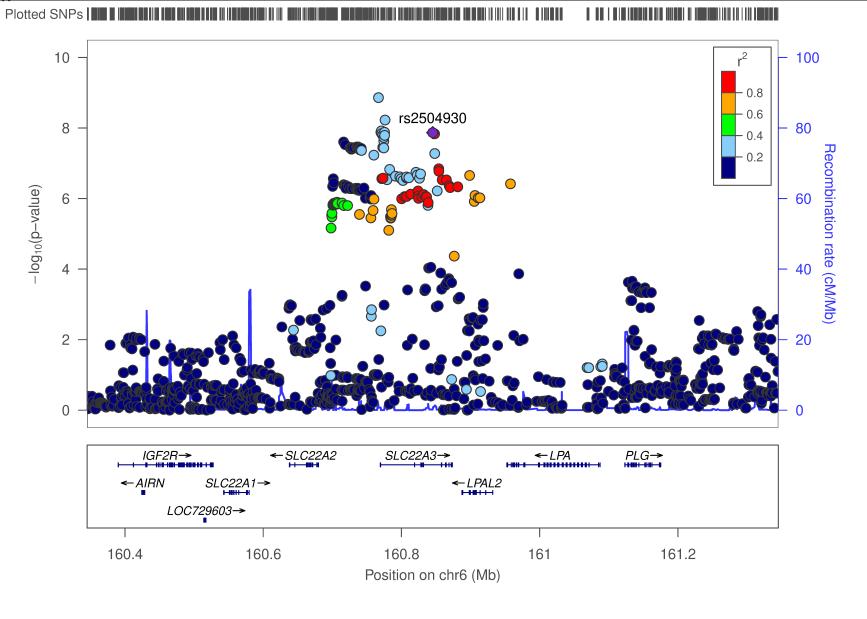


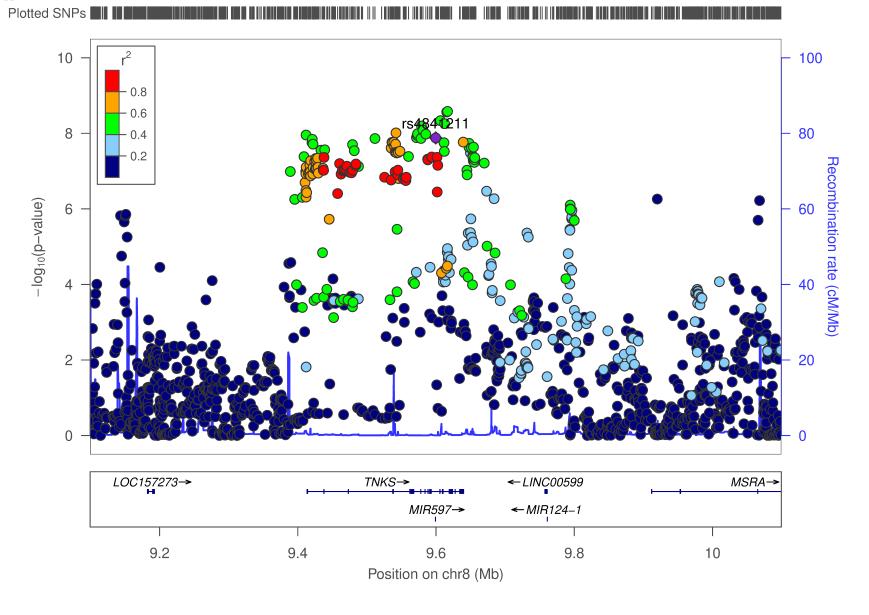


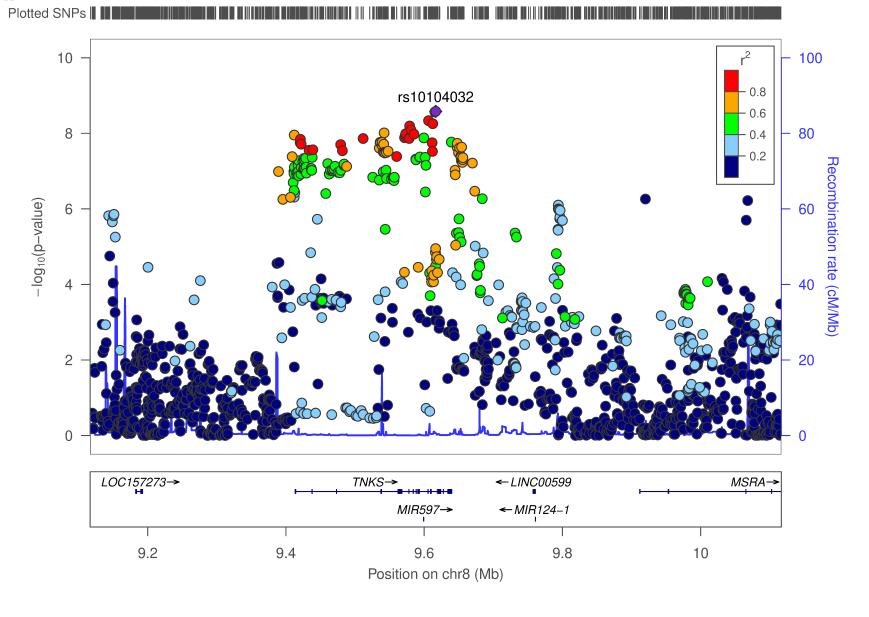


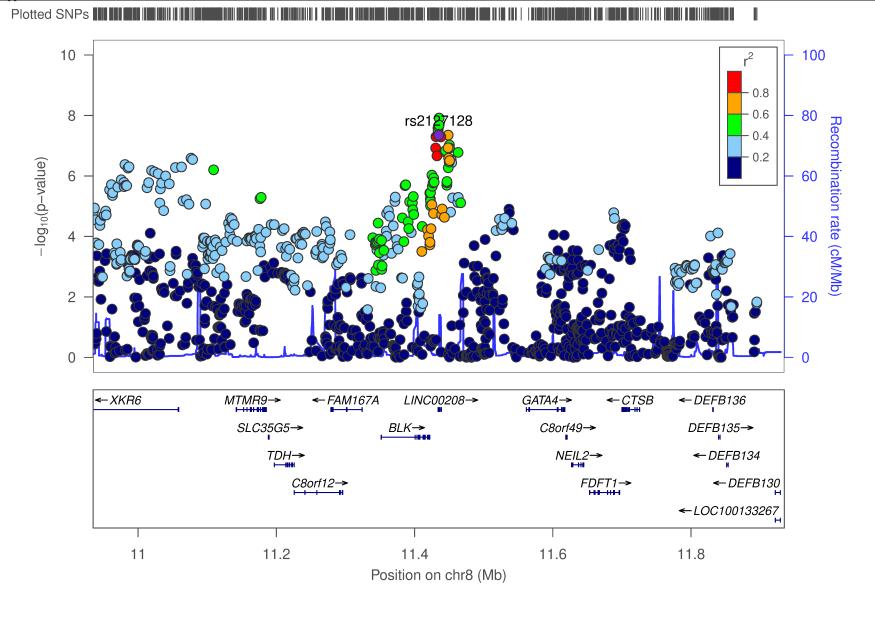


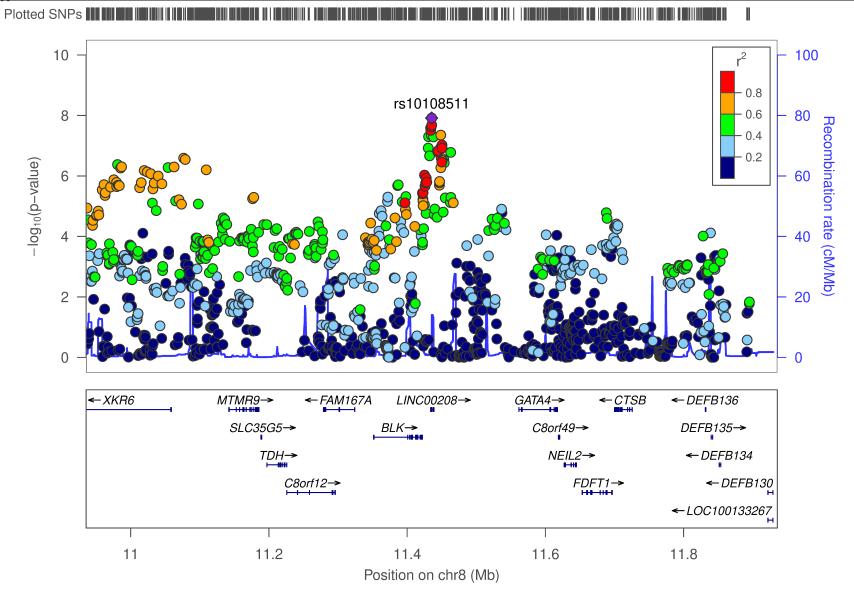


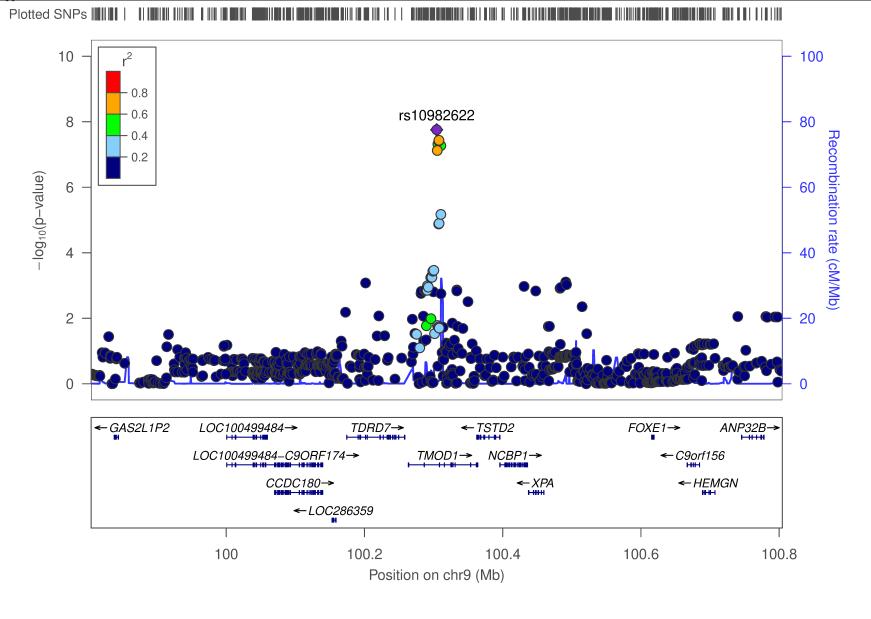


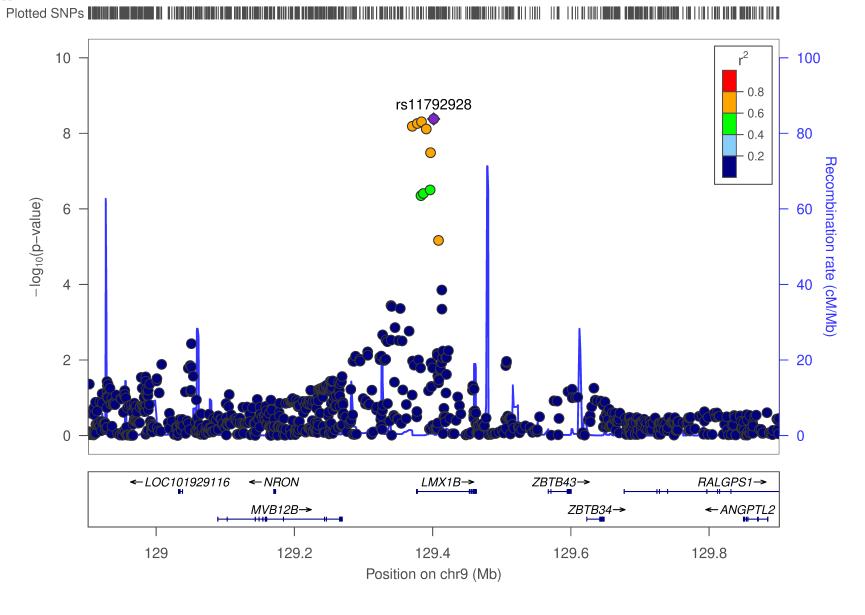


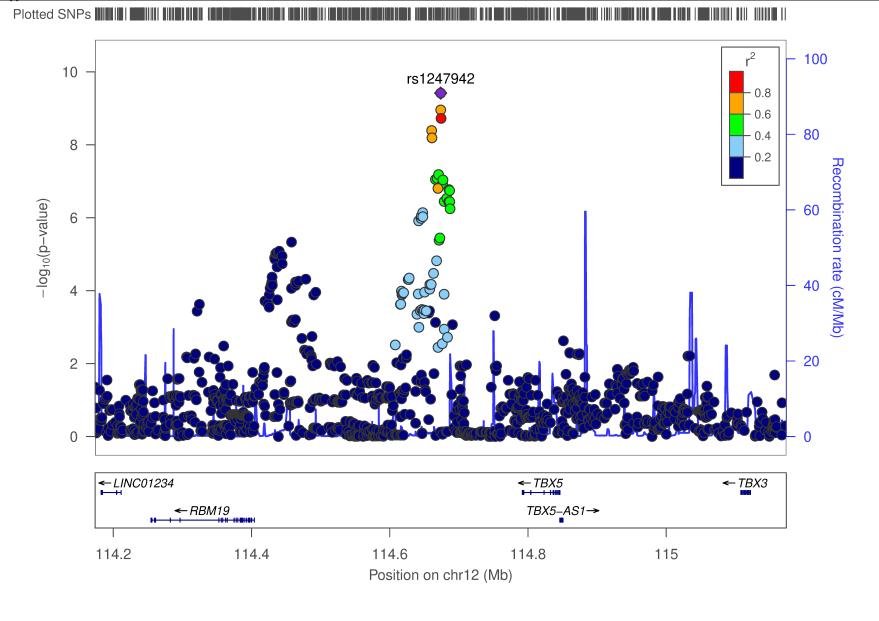


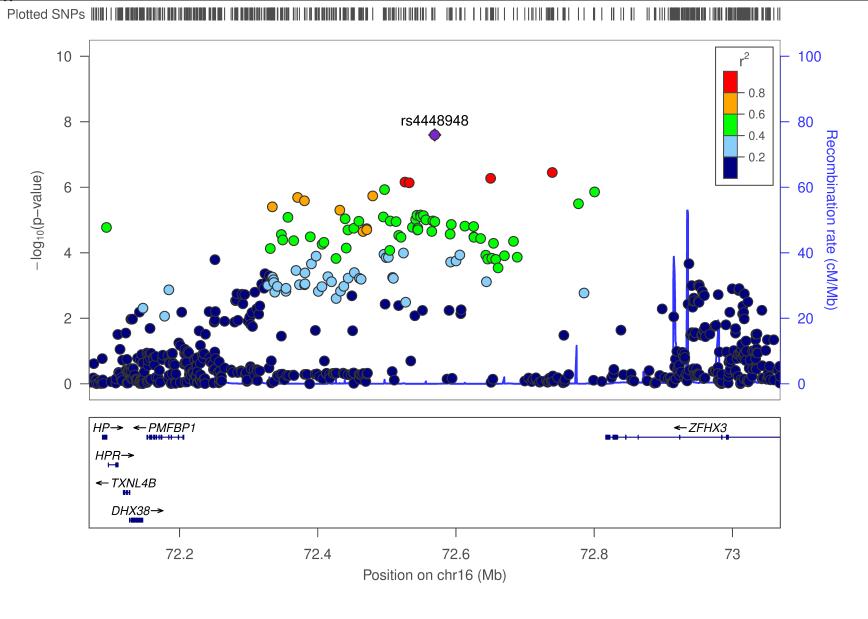


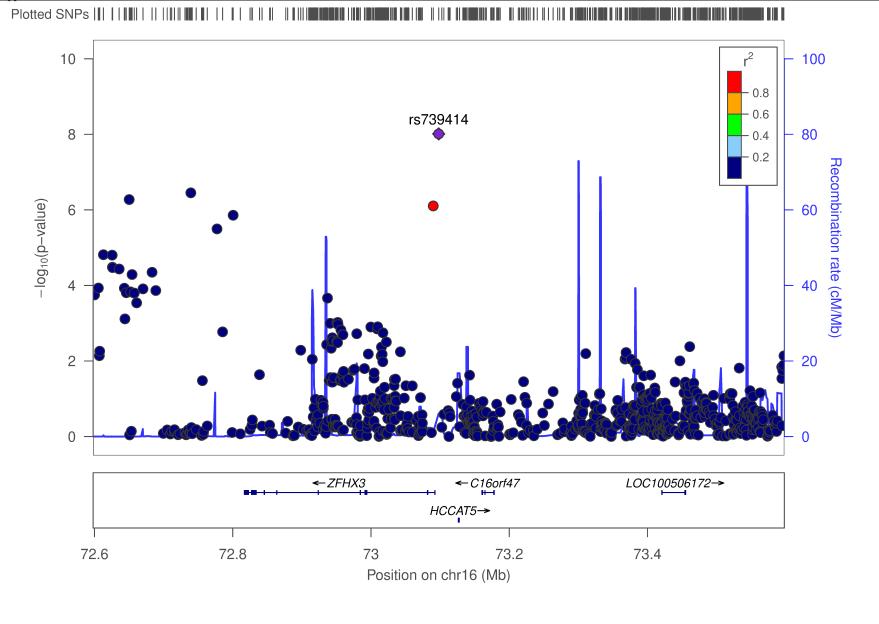


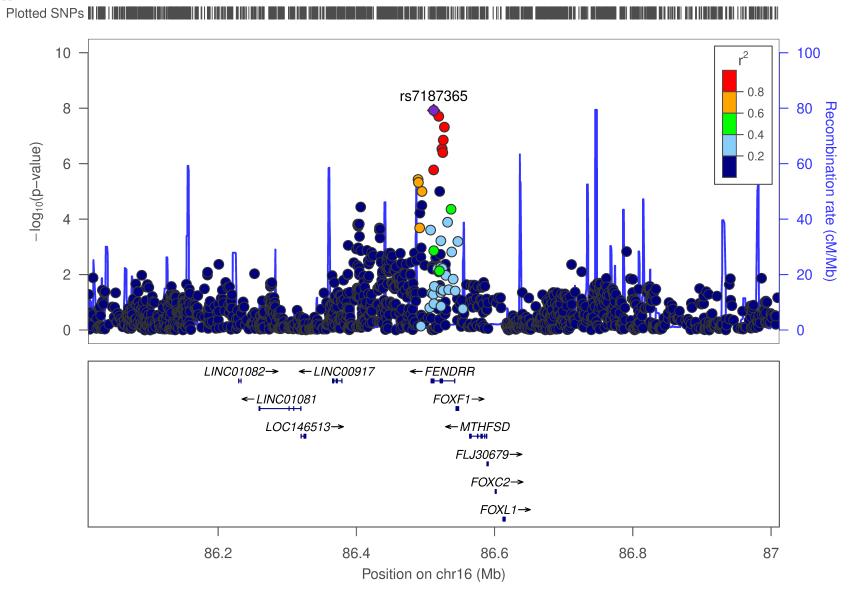


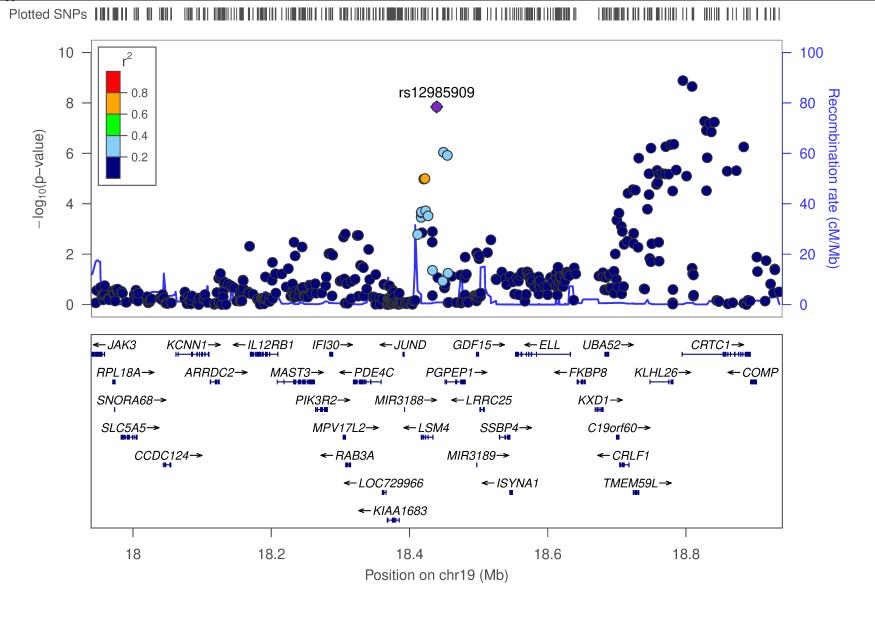


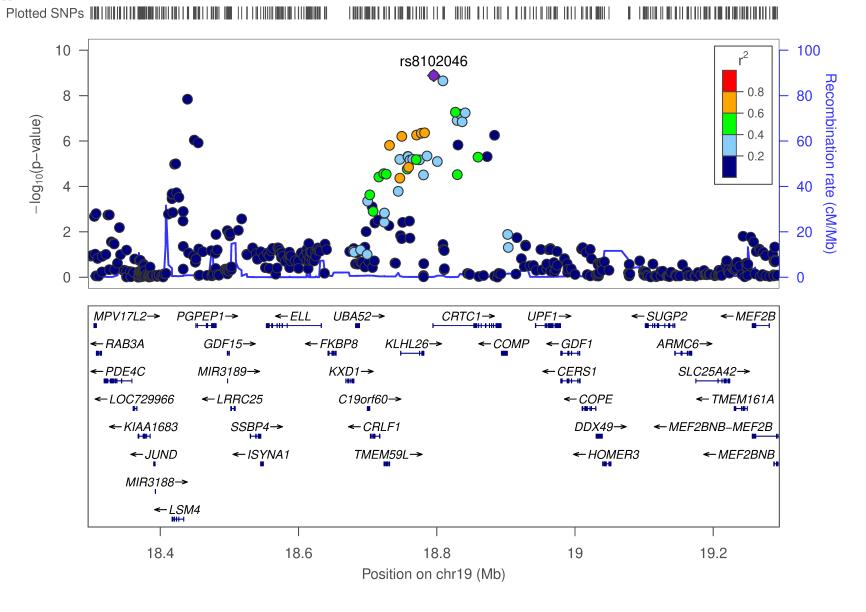


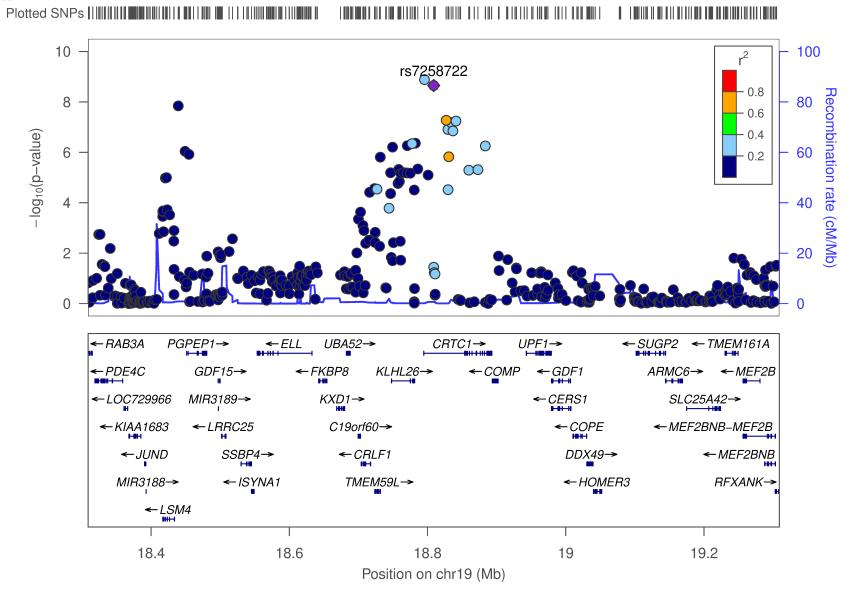


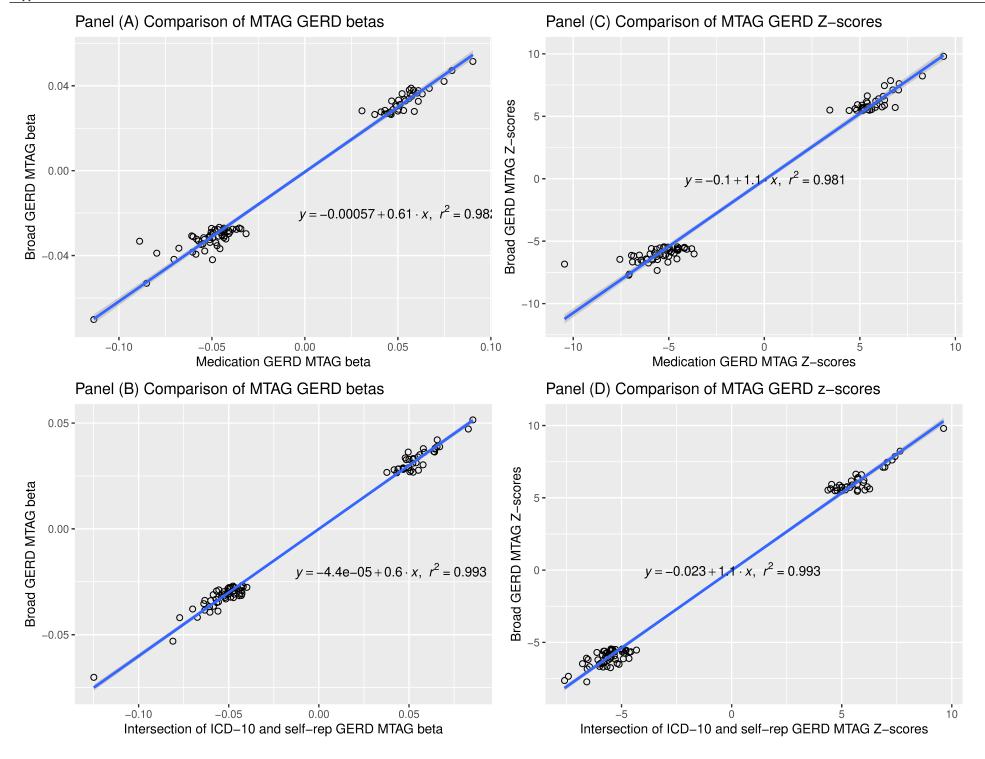


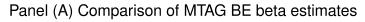


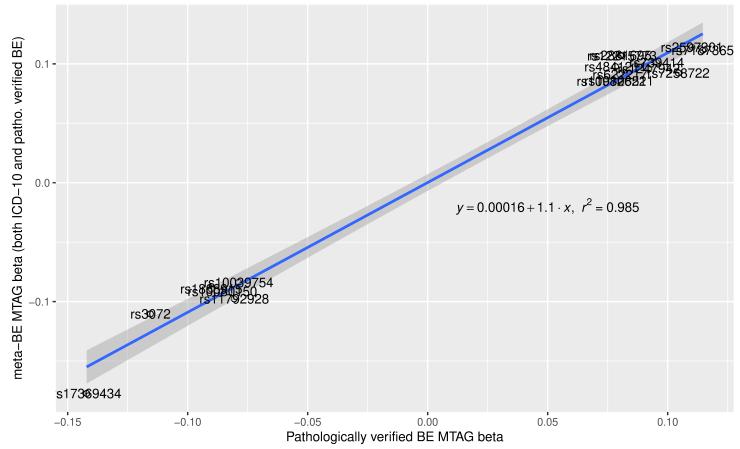




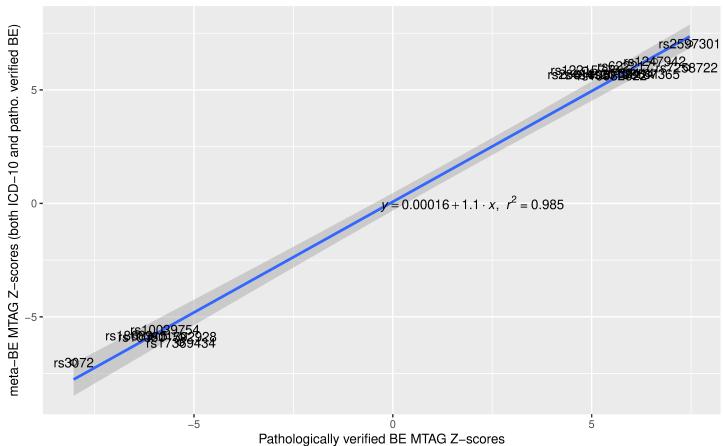




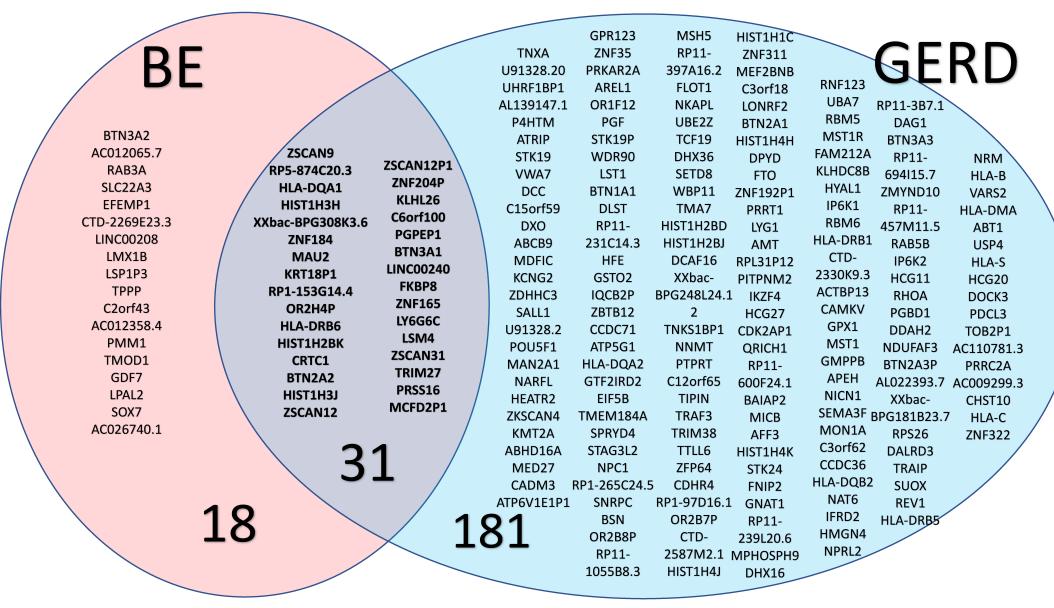


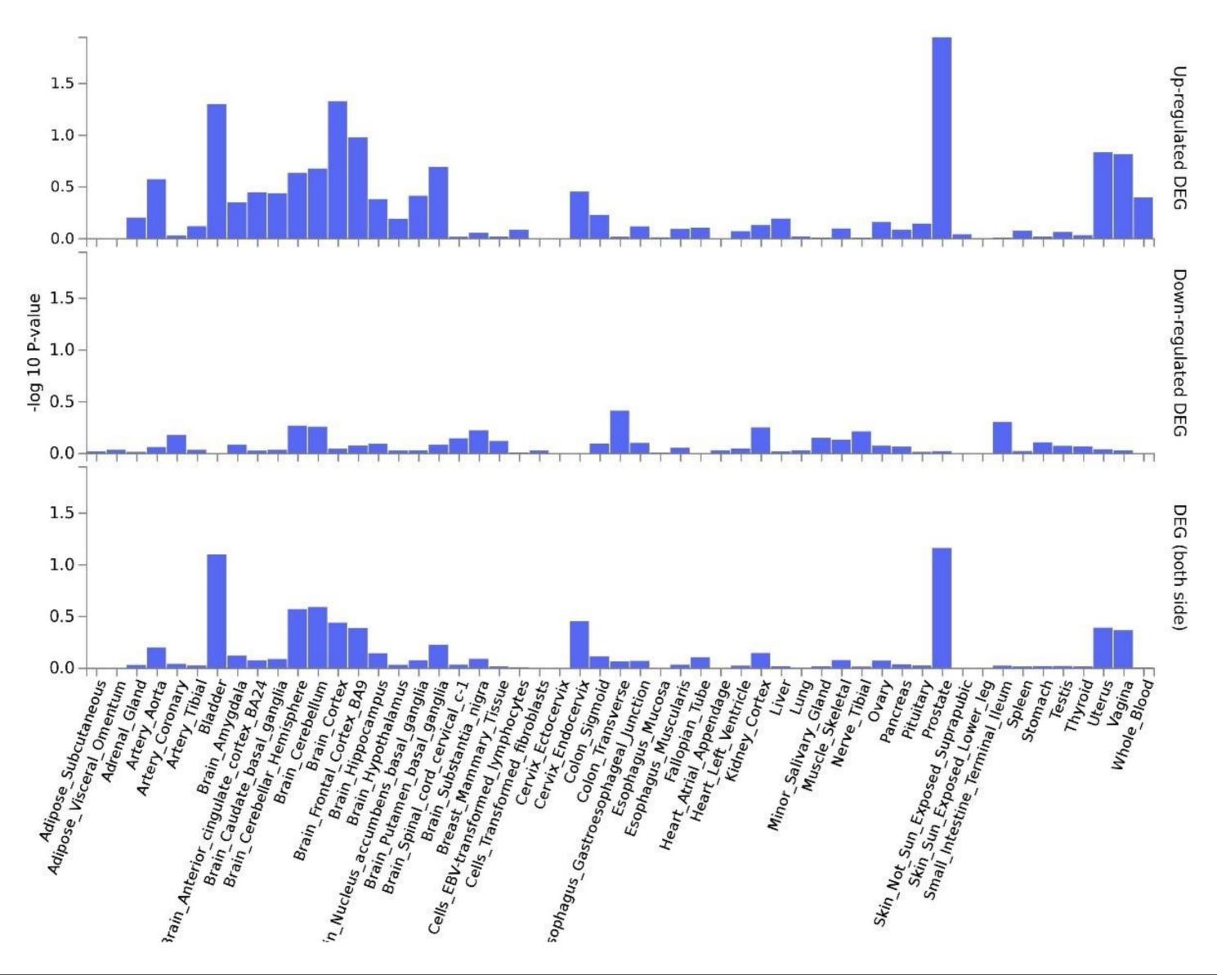


Panel (B) Comparison of MTAG BE Z-scores

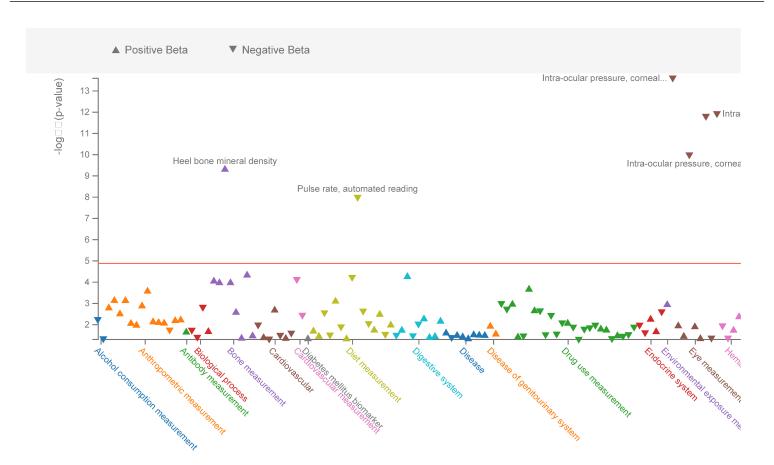


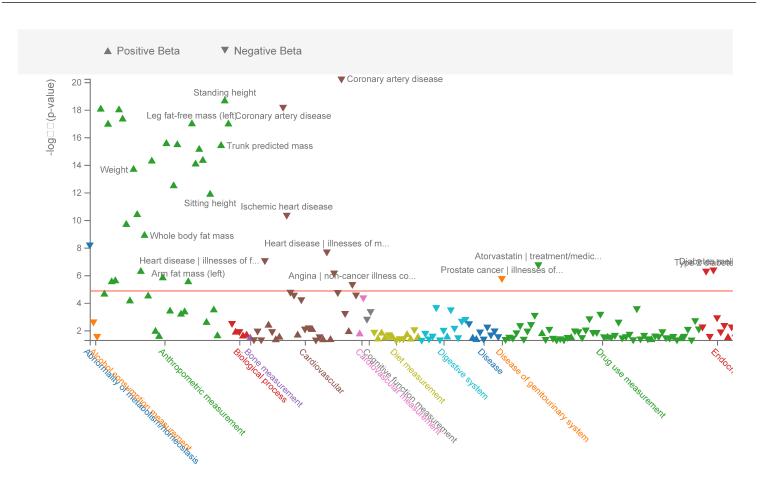
Putative genes identified with GERD and BE susceptibility from the MTAG model using multiXcan

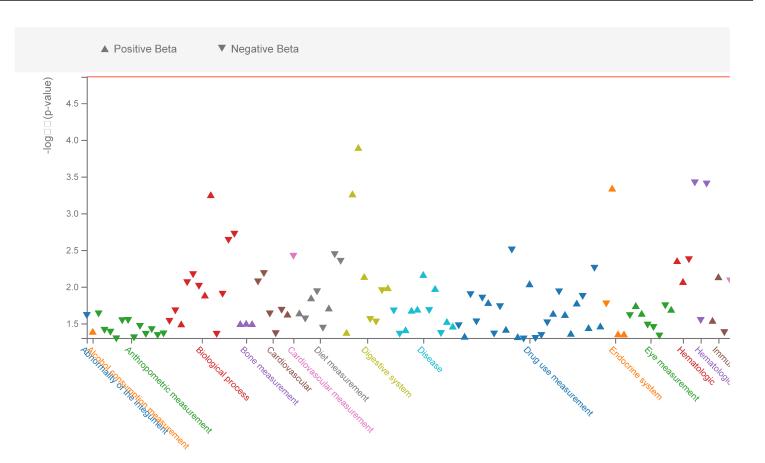


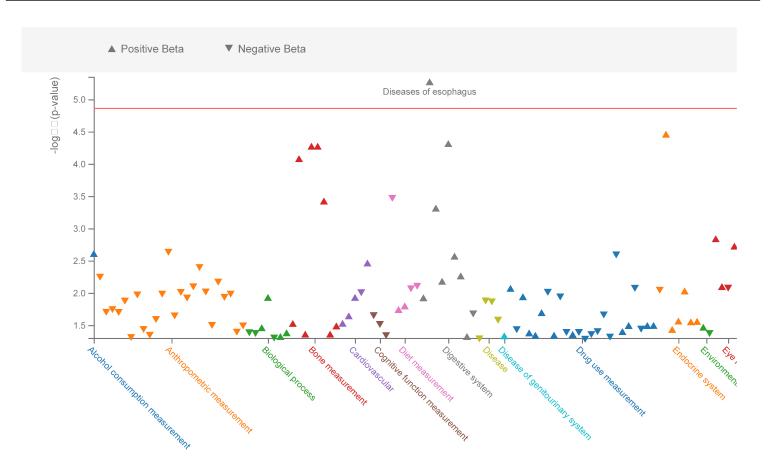


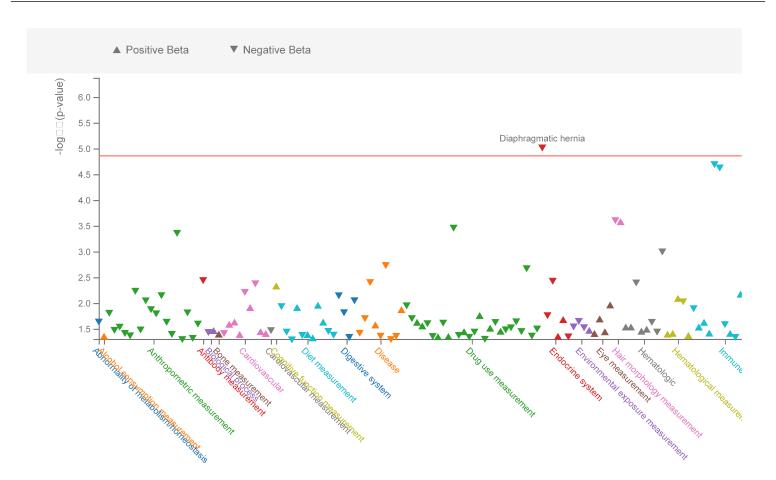
Iron status biomarkers (total iron binding capacity) – Hand grip strength – Feeling guilty – Iron status biomarkers – Number of sexual partners – Cognitive ability – Social science traits (pleiotropy) (HIPO component 1) – Smoking status (ever vs never smokers) – Depression – Household income – Worry too long after an embarrassing experience – General risk tolerance (MTAG) – Iron status biomarkers (transferrin saturation) – Age at first sexual intercourse – Cholangiocarcinoma in primary sclerosing cholangitis (time to event) – Takayasu arteritis – Risk-taking tendency (4-domain principal component model) – Iron status biomarkers (iron levels) – Coronary artery disease – Feeling fed-up Feeling tense Attention deficit hyperactivity disorder or cannabis use – Daytime sleep phenotypes – Adventurousness – Body mass index (joint analysis main effects and physical activity interaction) – Smoking initiation – Irritable mood – Insomnia symptoms (never/rarely vs. sometimes/usually) – Body mass index in physically active individuals – Allergic disease (asthma, hay fever or eczema) – Diastolic blood pressure – Alcohol consumption (drinks per week) – Parental longevity (combined parental attained age, Martingale residuals) – Menarche (age at onset) – Mental health study participation (completed survey) – Insomnia symptoms (never/rarely vs. usually) – BMI in non-smokers – Body mass index (joint analysis main effects and smoking interaction) – BMI (adjusted for smoking behaviour) – Chronotype – Height – Feeling worry – Self-reported risk-taking behaviour Vitiligo – Ovarian cancer Amyotrophic lateral sclerosis (age of onset) – Asthma or allergic disease (pleiotropy) – Sleep duration – Waist-to-hip ratio adjusted for BMI (additive genetic model) – Hodgkin's lymphoma – Gait speed in old age – Alcohol use disorder – Subcutaneous adipose tissue – Type 1 diabetes – Urate levels in overweight individuals – Prostate cancer (advanced) – Resting heart rate – Mental health study participation (provided email address) –

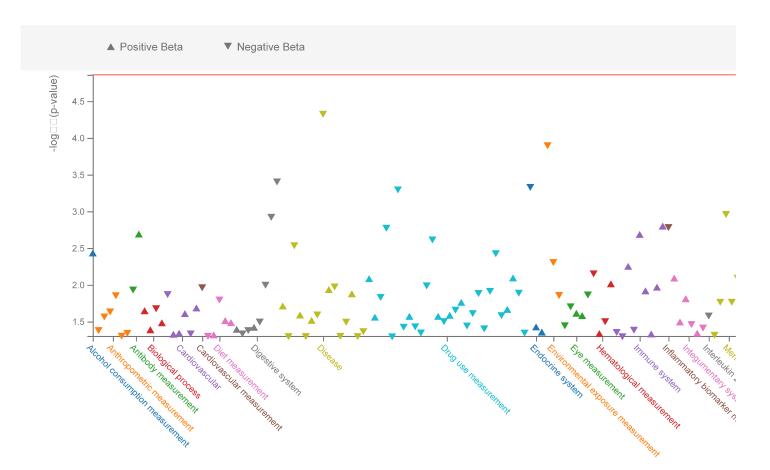


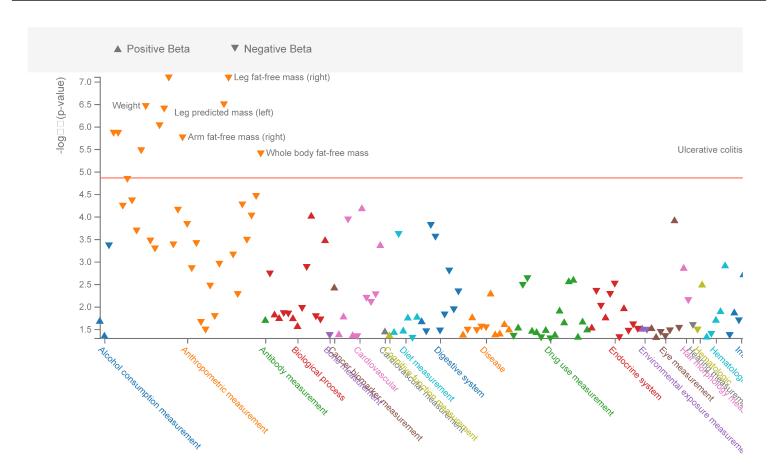


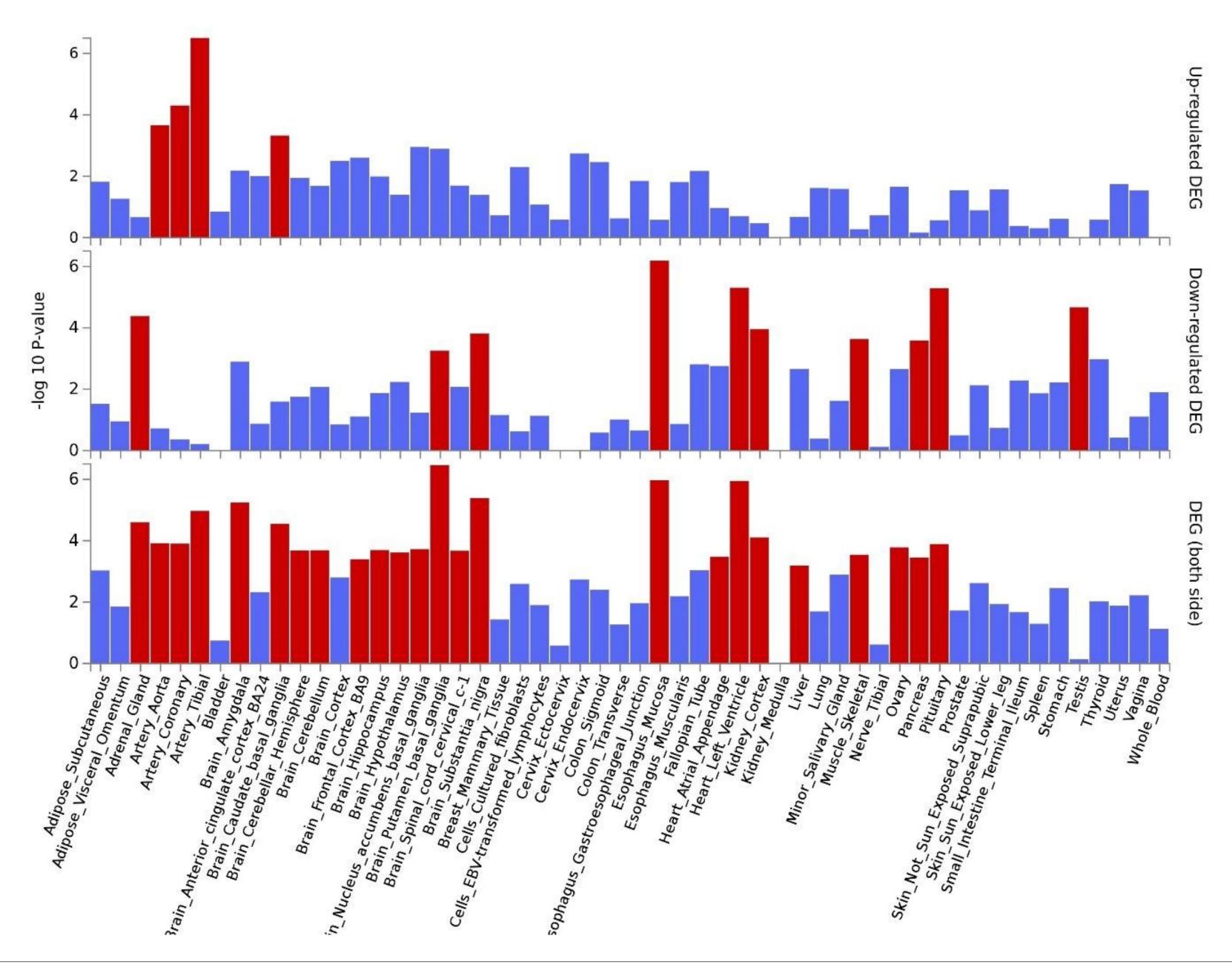


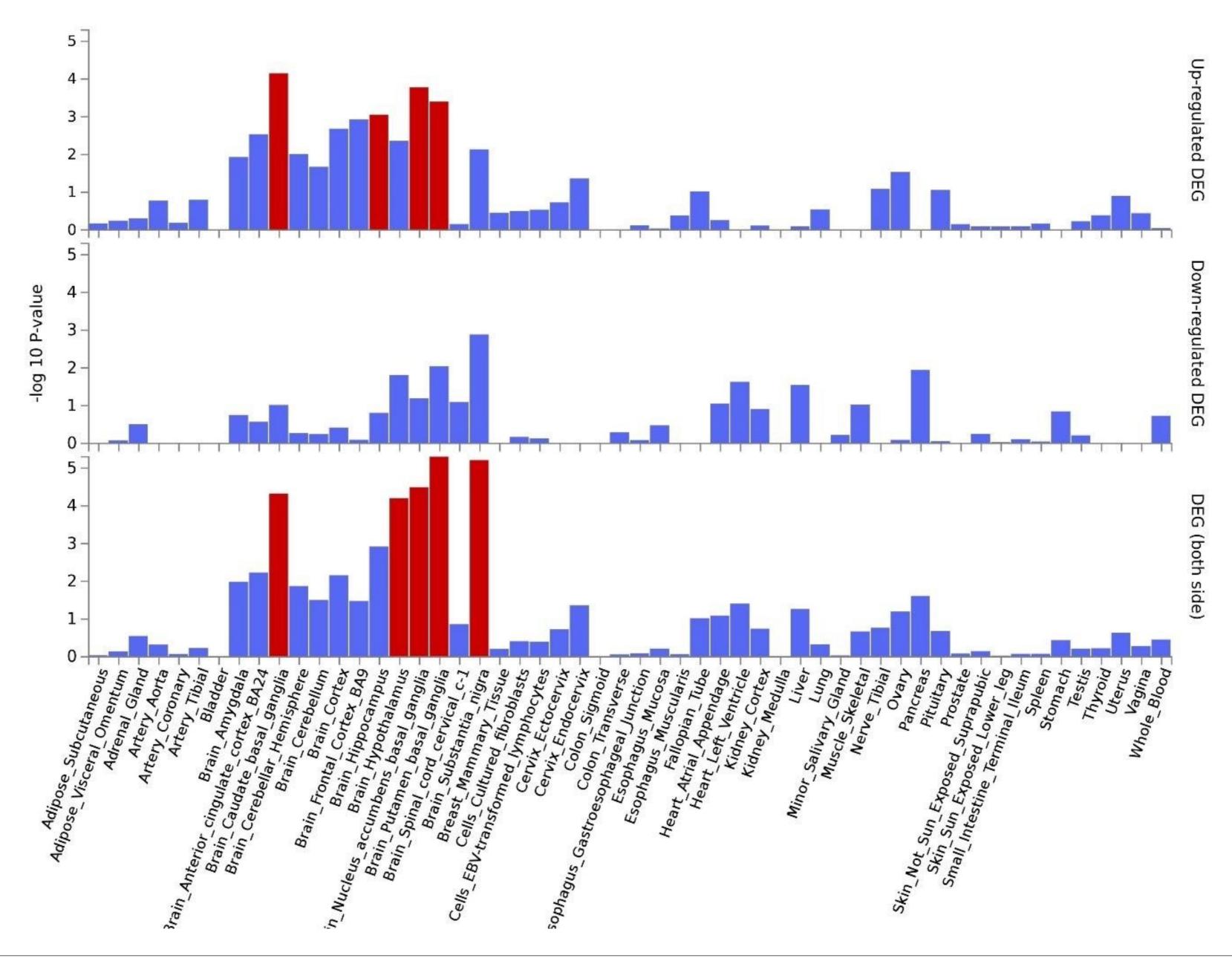


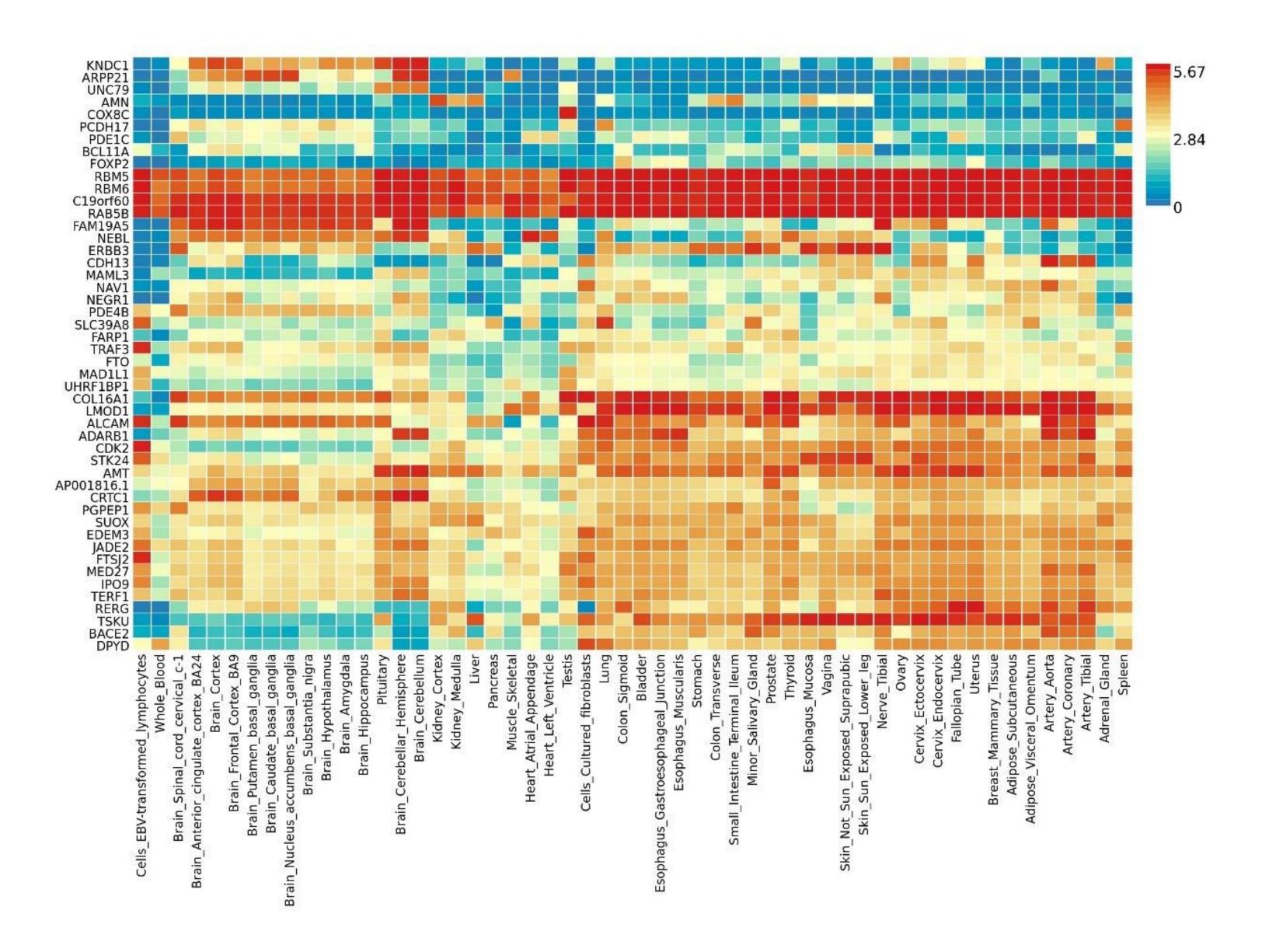


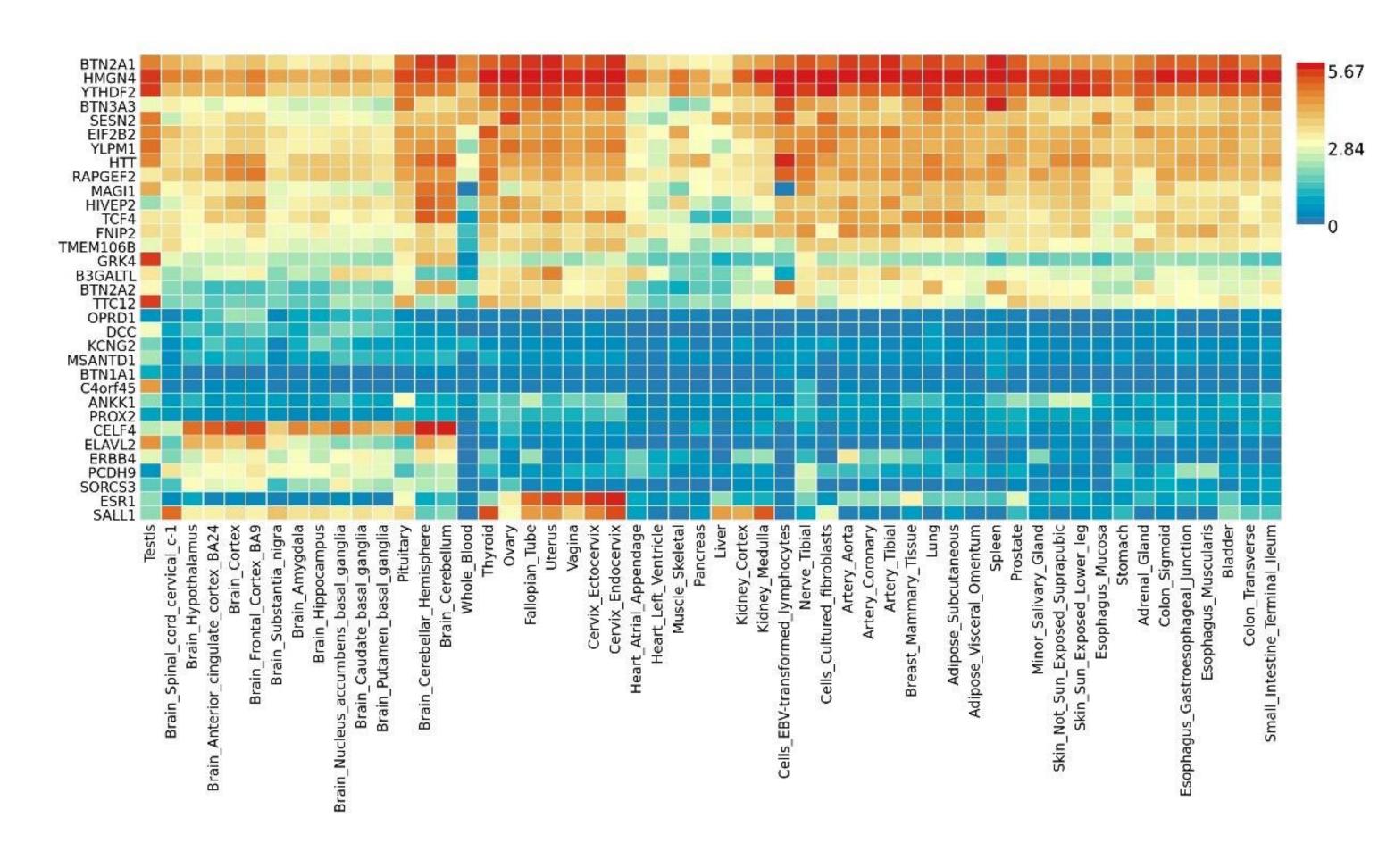




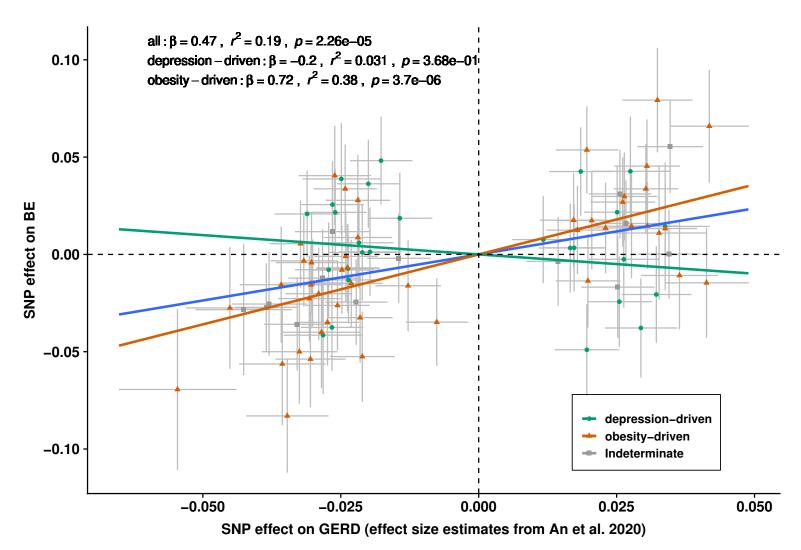








Genetic association between genome-wide significant MTAG GERD loci and risk of Barrett's Esophagus



Genetic association between genome-wide significant MTAG GERD loci and risk of Esophageal adenocarcinoma

