

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*

Table of Contents

Supplementary Figure captions.....	2
Supplementary Figure 1. The Quantile-to-Quantile plot for the MTAG GERD GWAS.	4
Supplementary Figure 2. Regional LocusZoom plot for all genome-wide GERD loci (n=88) identified in the GERD MTAG analysis.....	5-92
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.....	93-125
Supplementary Figure 4. Comparison of MTAG GERD genome-wide significant loci effect sizes using alternative case definitions for GERD.....	126
Supplementary Figure 5. Comparison of MTAG BE genome-wide significant loci effect sizes between ICD-10 defined BE and pathologically verified BE cases.....	127
Supplementary Figure 6. Venn diagram illustrating the number of genes identified to be associated with GERD and BE susceptibility using multiXcan.....	128
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.	129
Supplementary Figure 8. GWAS catalog lookup on GERD-associated genes in FUMA.	130
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.....	131-137
Supplementary Figure 10. Regulation of differential gene expression for obesity-driven GERD genes on 53 human tissues evaluated via MAGMA.	138
Supplementary Figure 11. Regulation of differential gene expression for depression-driven GERD genes on 53 human tissues evaluated via MAGMA.	139
Supplementary Figure 12. Gene expression heatmap showing the average expression per label (log ₂ transformed) across 53 human tissues for obesity-driven GERD genes.....	140
Supplementary Figure 13. Gene expression heatmap showing the average expression per label (log ₂ transformed) across 53 human tissues for depression-driven GERD genes.	141
Supplementary Figure 14. Estimation of the genetic association between GERD and risk of Barrett's Esophagus only, stratified by genetic GERD subtypes.....	142
Supplementary Figure 15. Estimation of the genetic association between GERD and risk of Esophageal Adenocarcinoma only, stratified by genetic GERD subtypes.	143

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 \log_{10} 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 $-\log_{10}(p\text{-value})$ 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 $-\log_{10}$ 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.

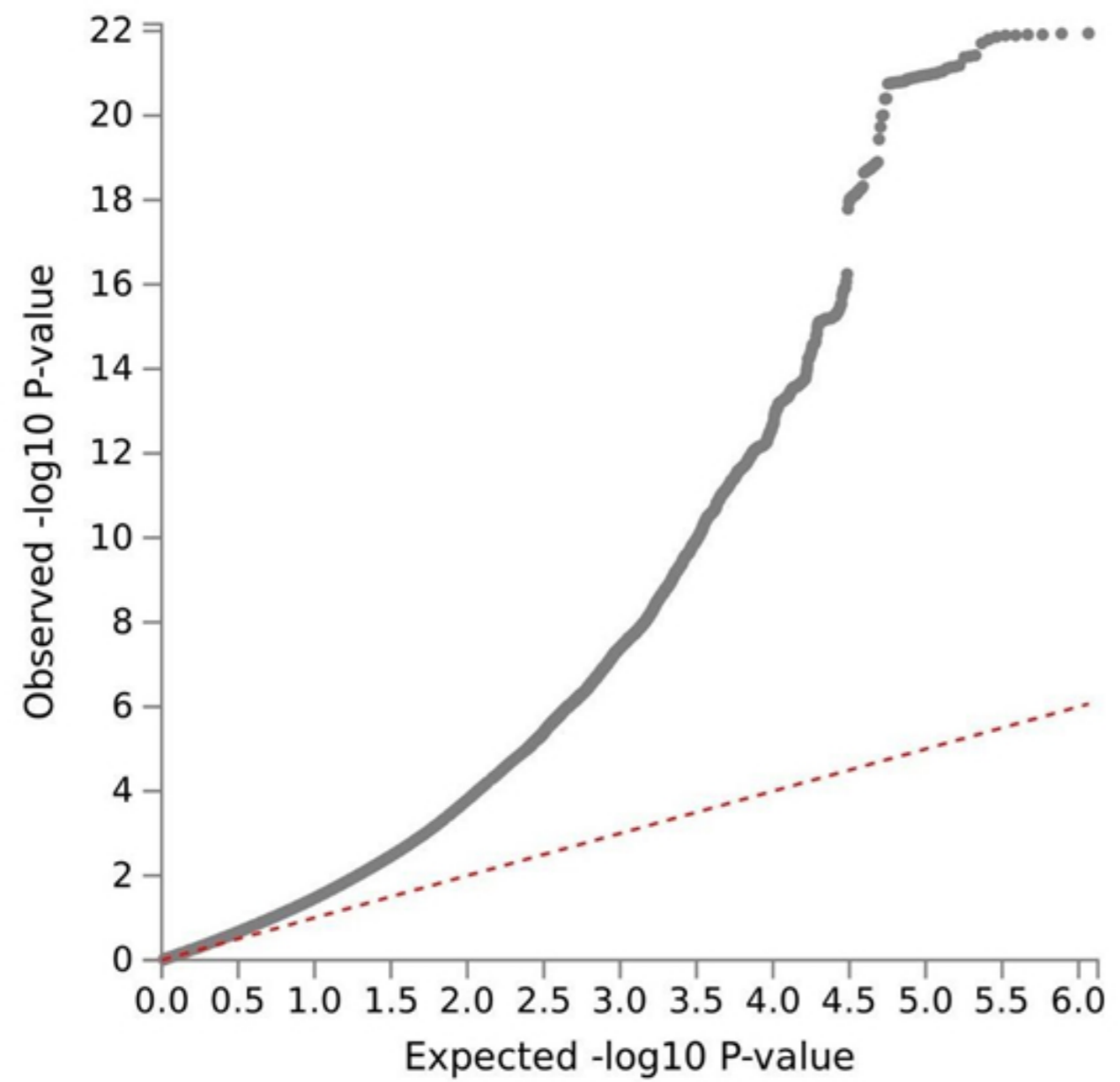
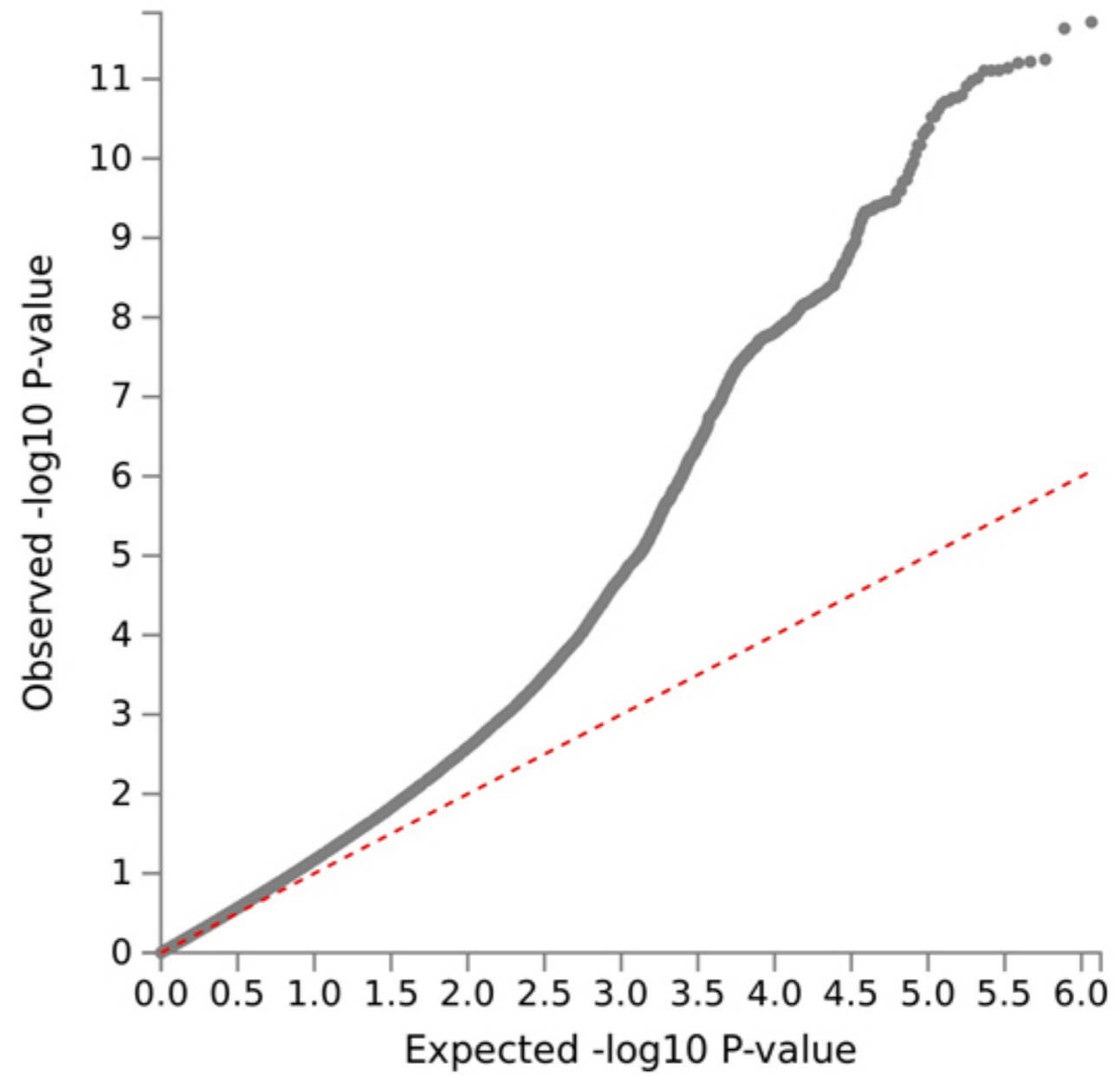
Supplementary Figure 11. Regulation of differential gene expression for depression-driven GERD genes on 53 human tissues evaluated via MAGMA. Tissue expression data extracted from the GTEx v8 database.

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.

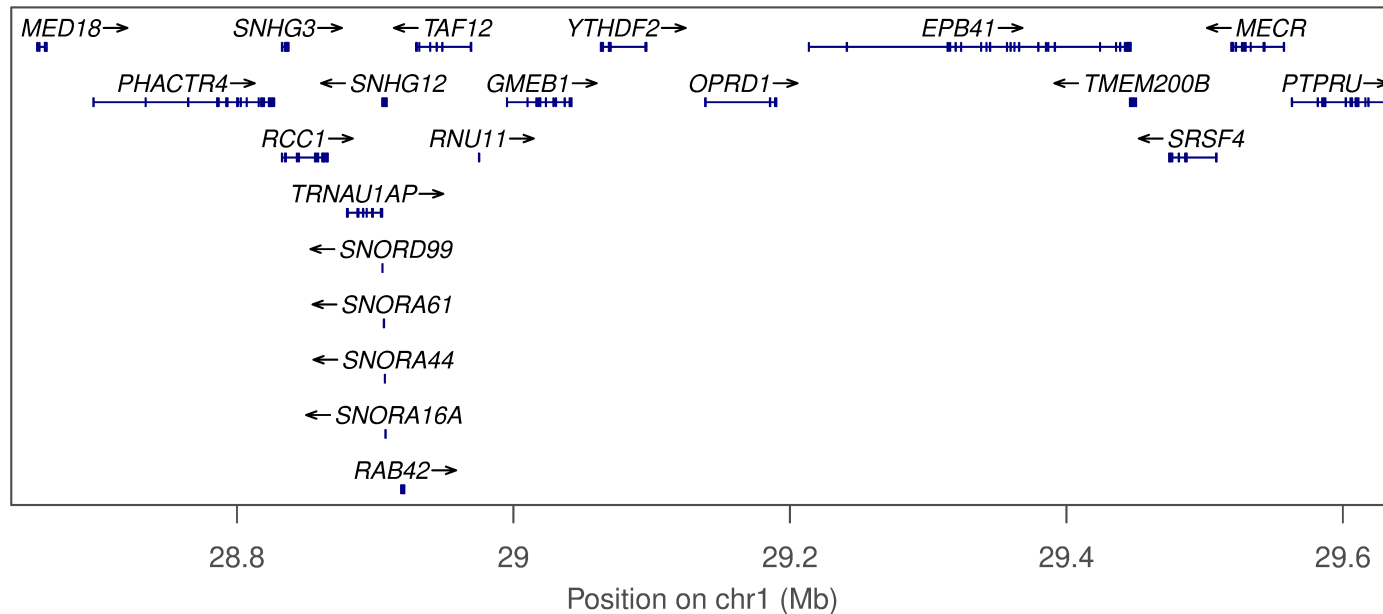
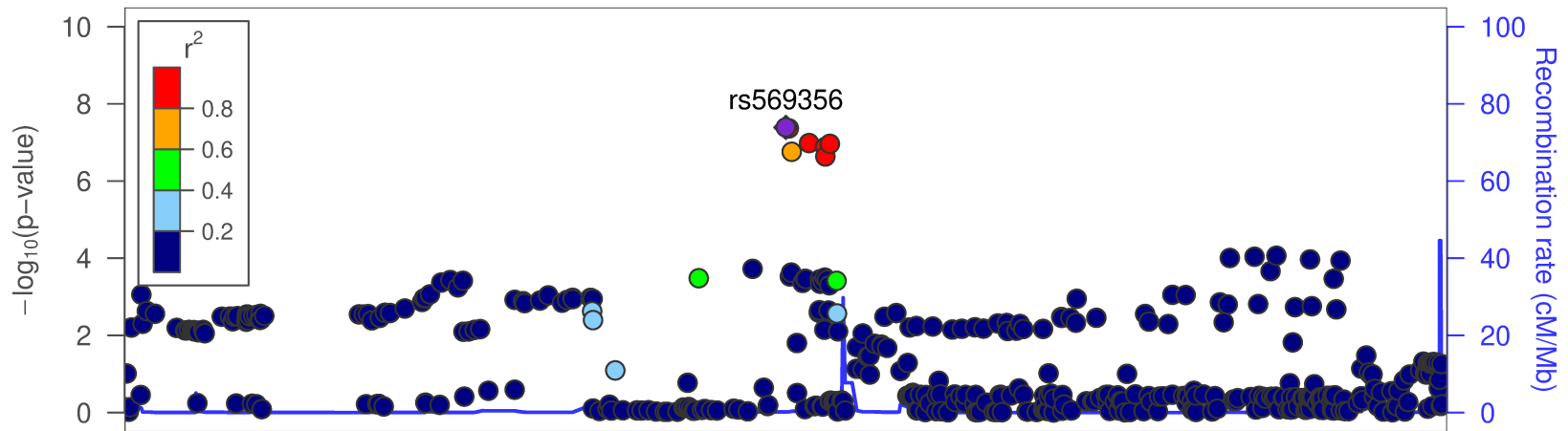
Supplementary Figure 13. Gene expression heatmap showing the average expression per label (log₂ transformed) across 53 human tissues for depression-driven GERD genes. Tissue expression data extracted from the GTEx v8 database.

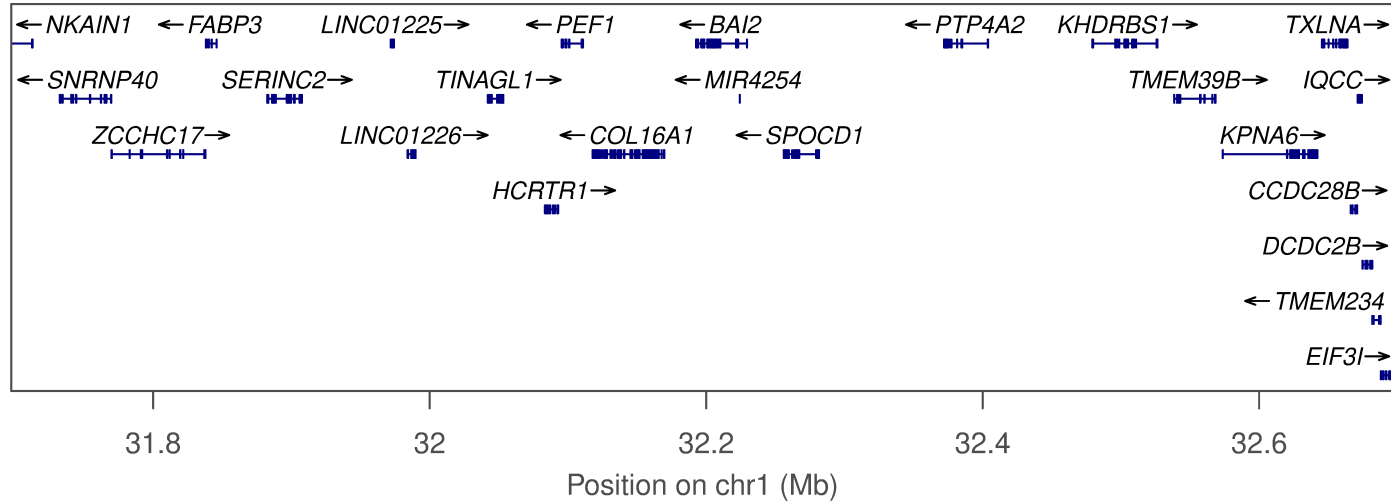
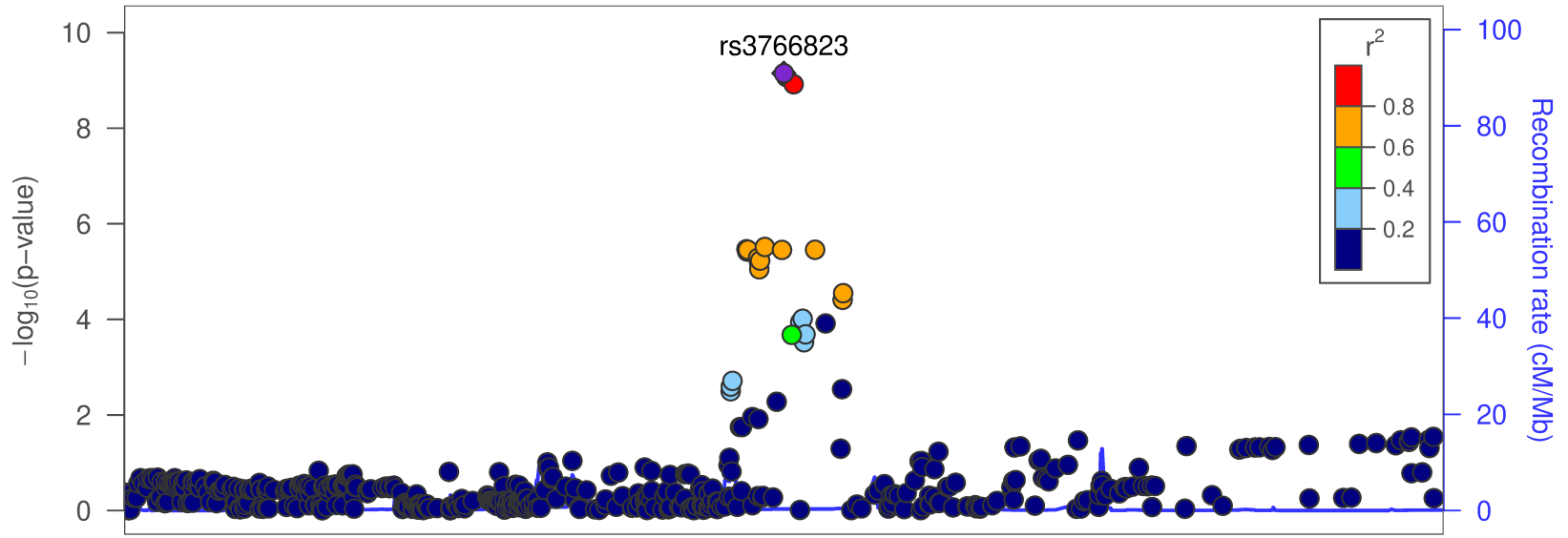
Supplementary Figure 14. Estimation of the genetic association between GERD and risk of Barrett's Esophagus only, stratified by genetic GERD subtypes. Each of the slopes represent the estimated magnitude of association between per unit increase in log(OR) of GERD on log(OR) of BE, for all GERD loci (in 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.

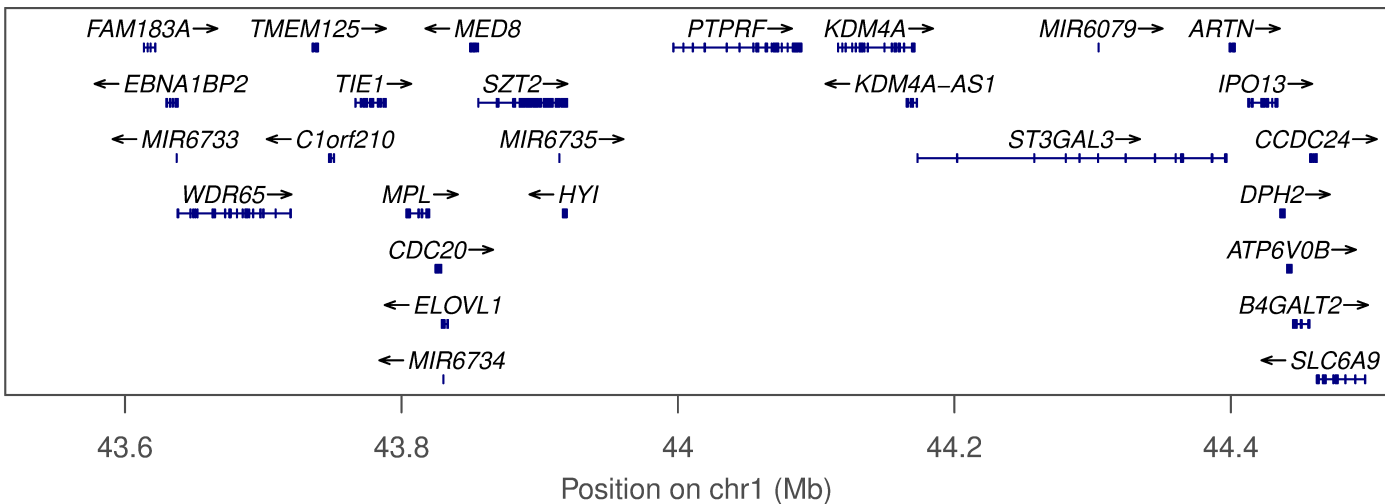
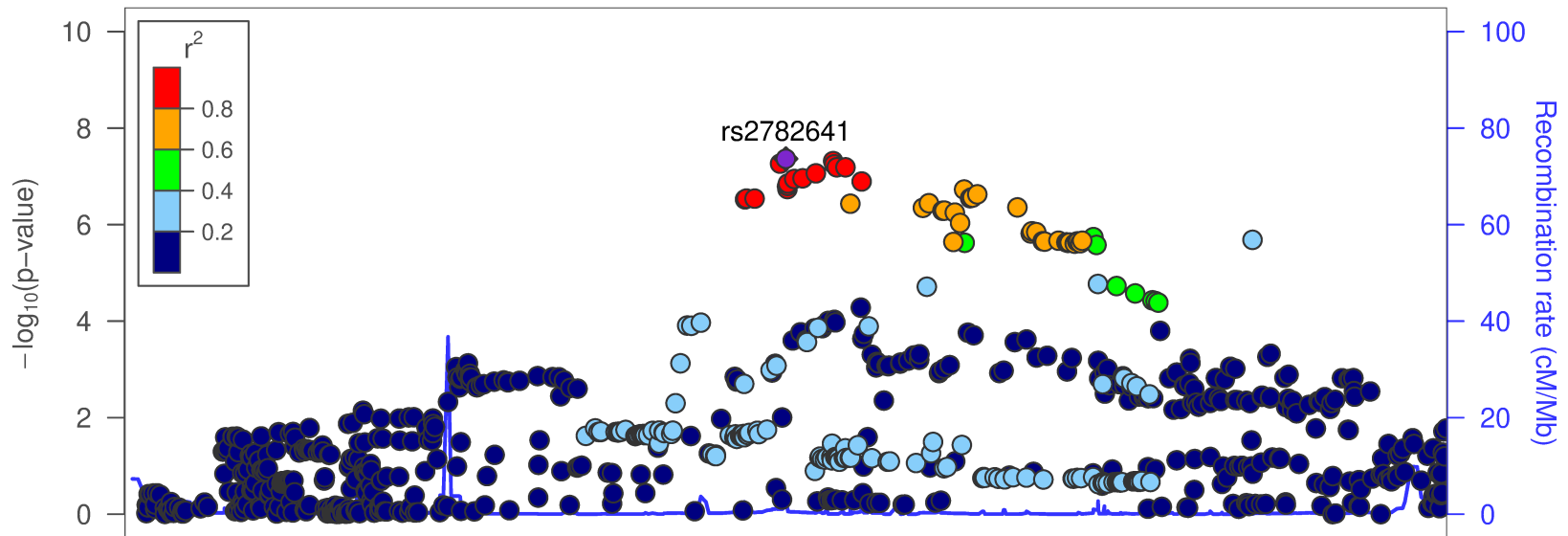
(A) QQ plot for MTAG GERD output**(B) QQ plot for BE GERD output**

Plotted SNPs

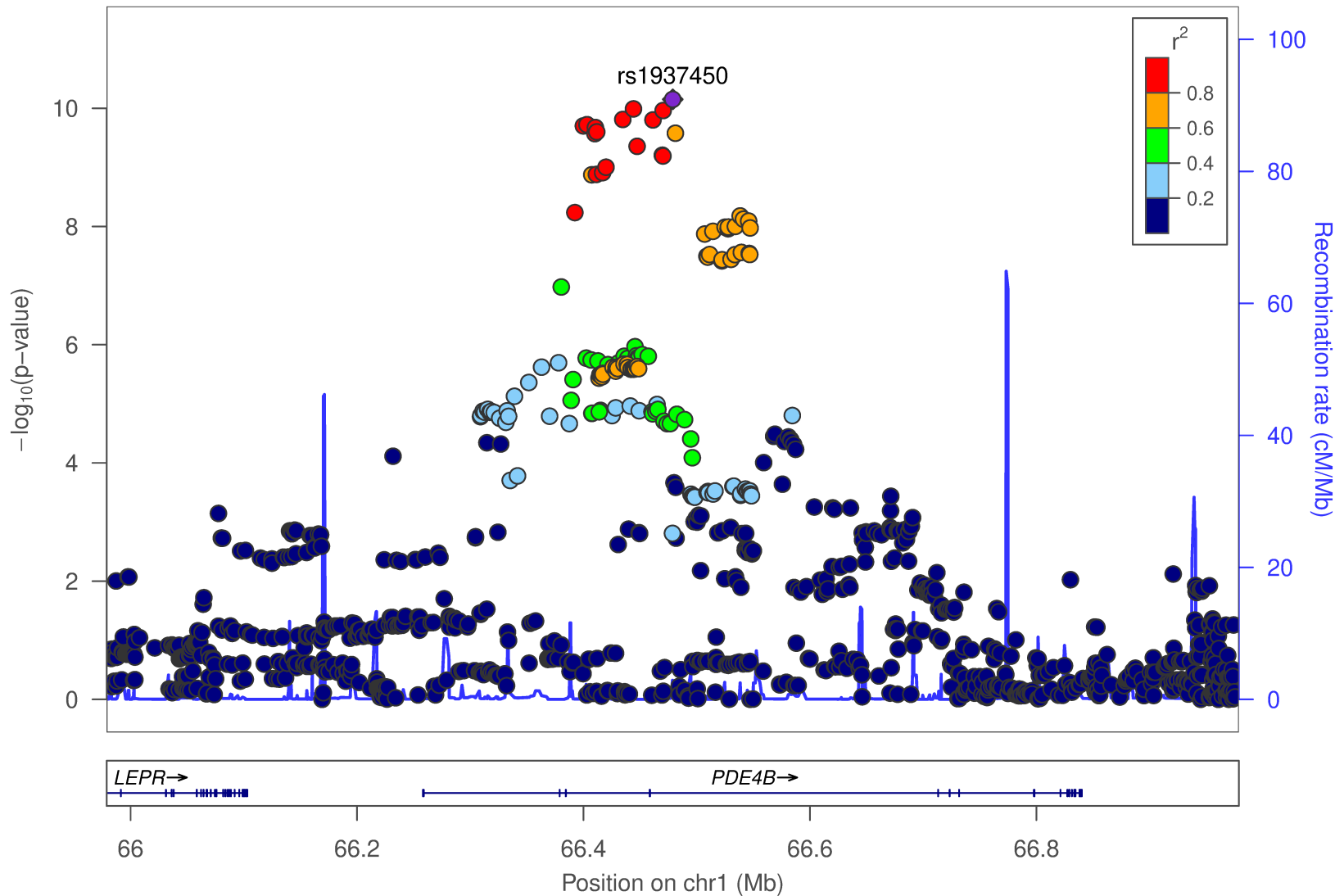




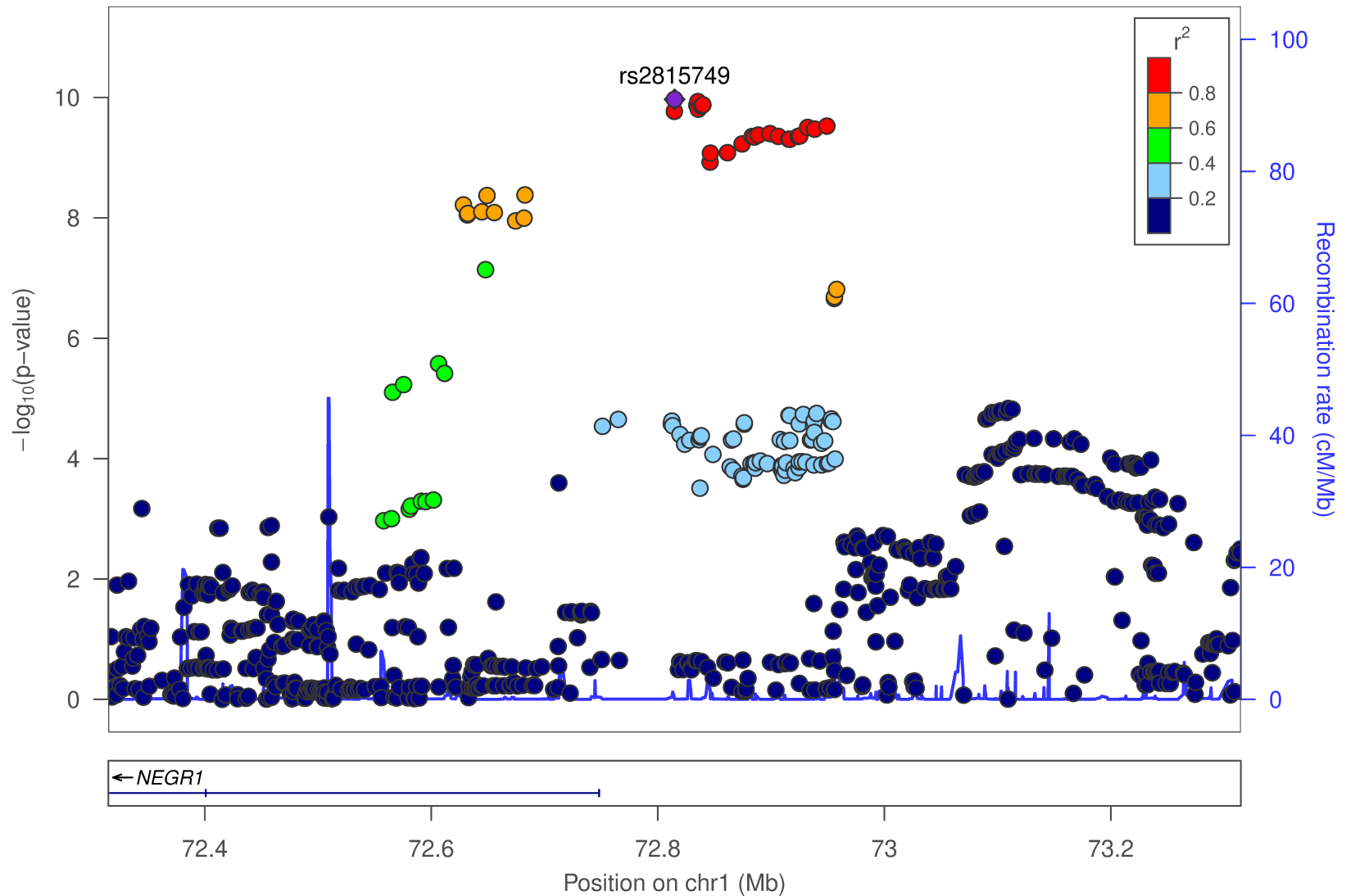
Plotted SNPs



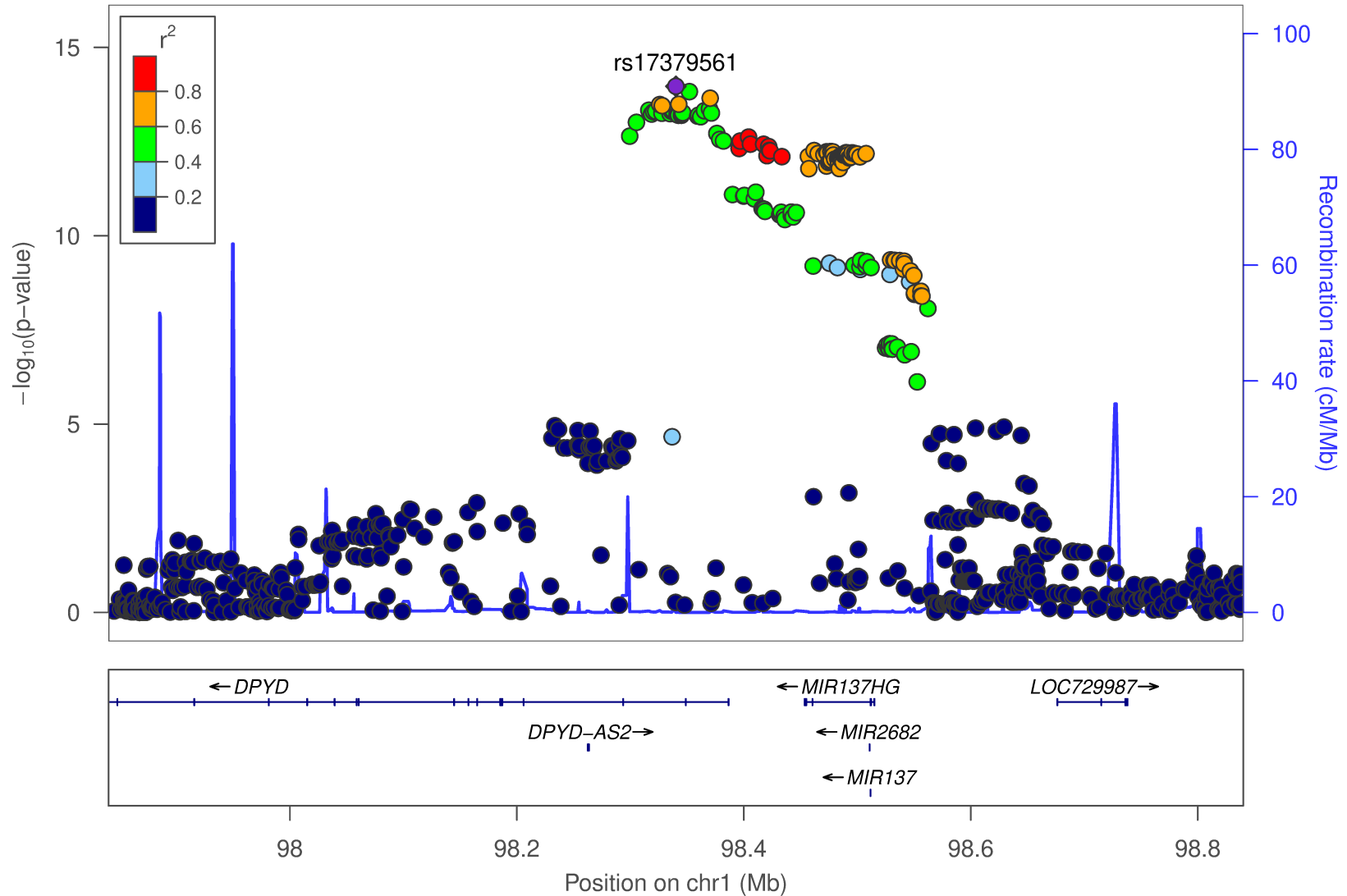
Plotted SNPs



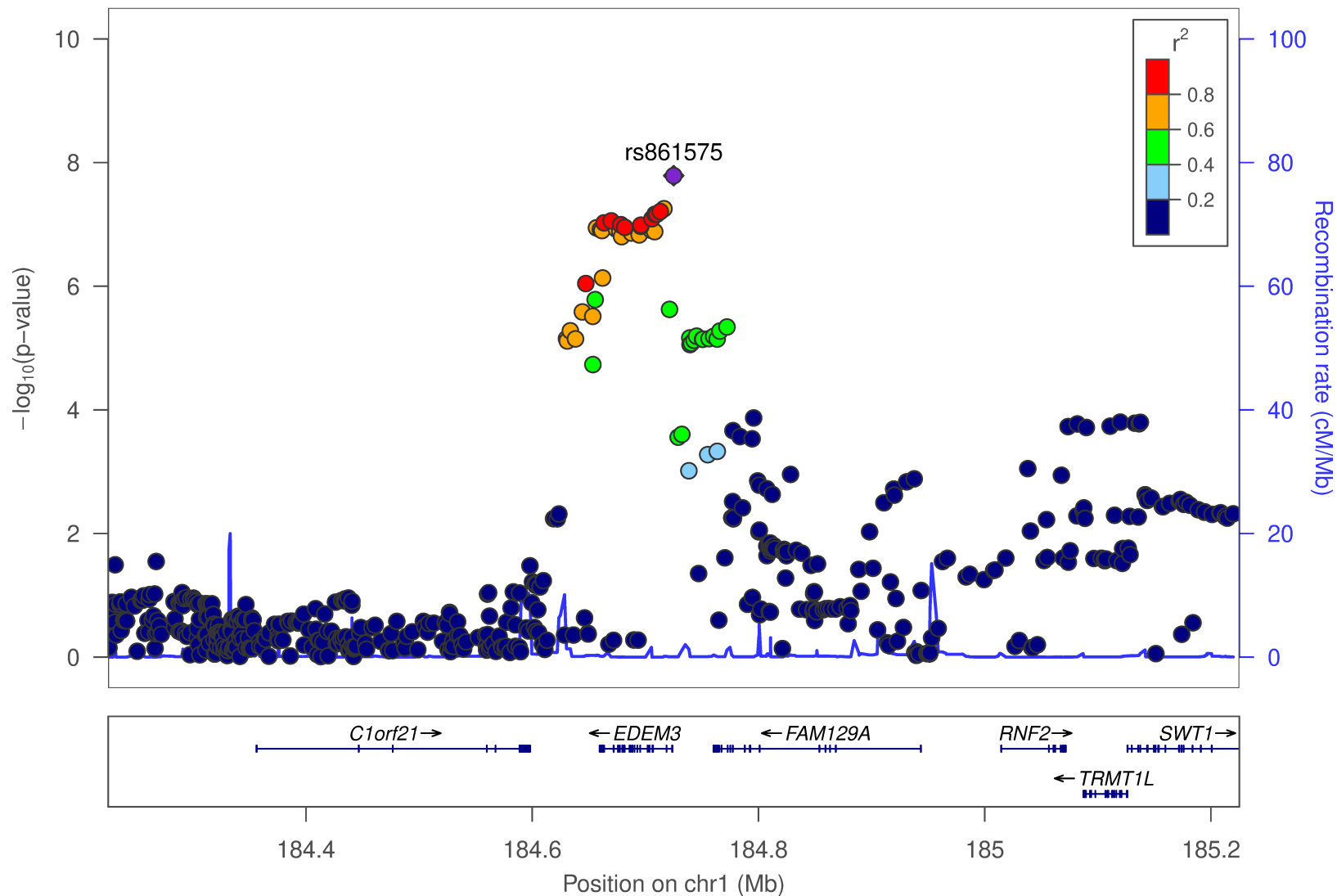
Plotted SNPs



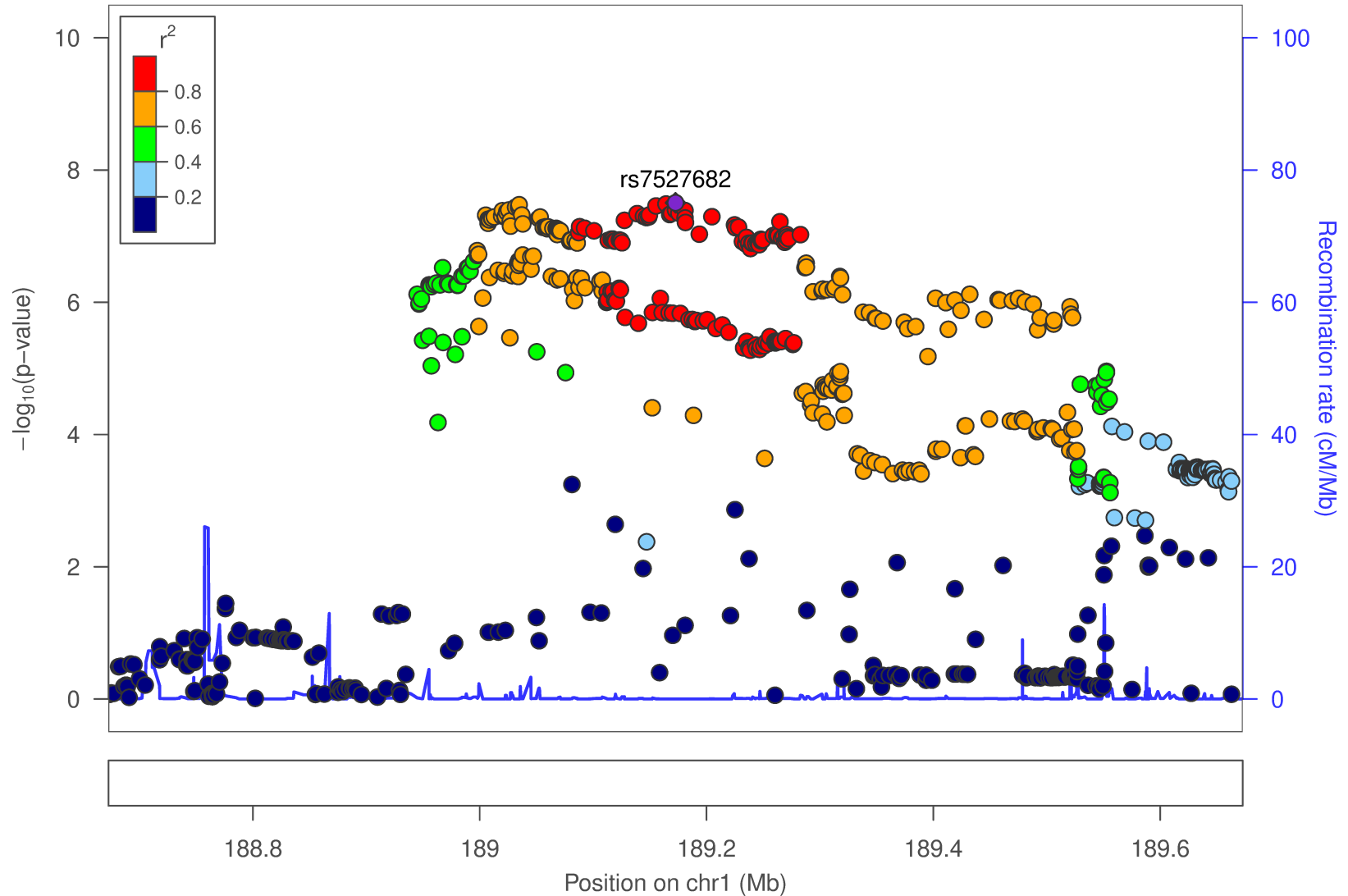
Plotted SNPs



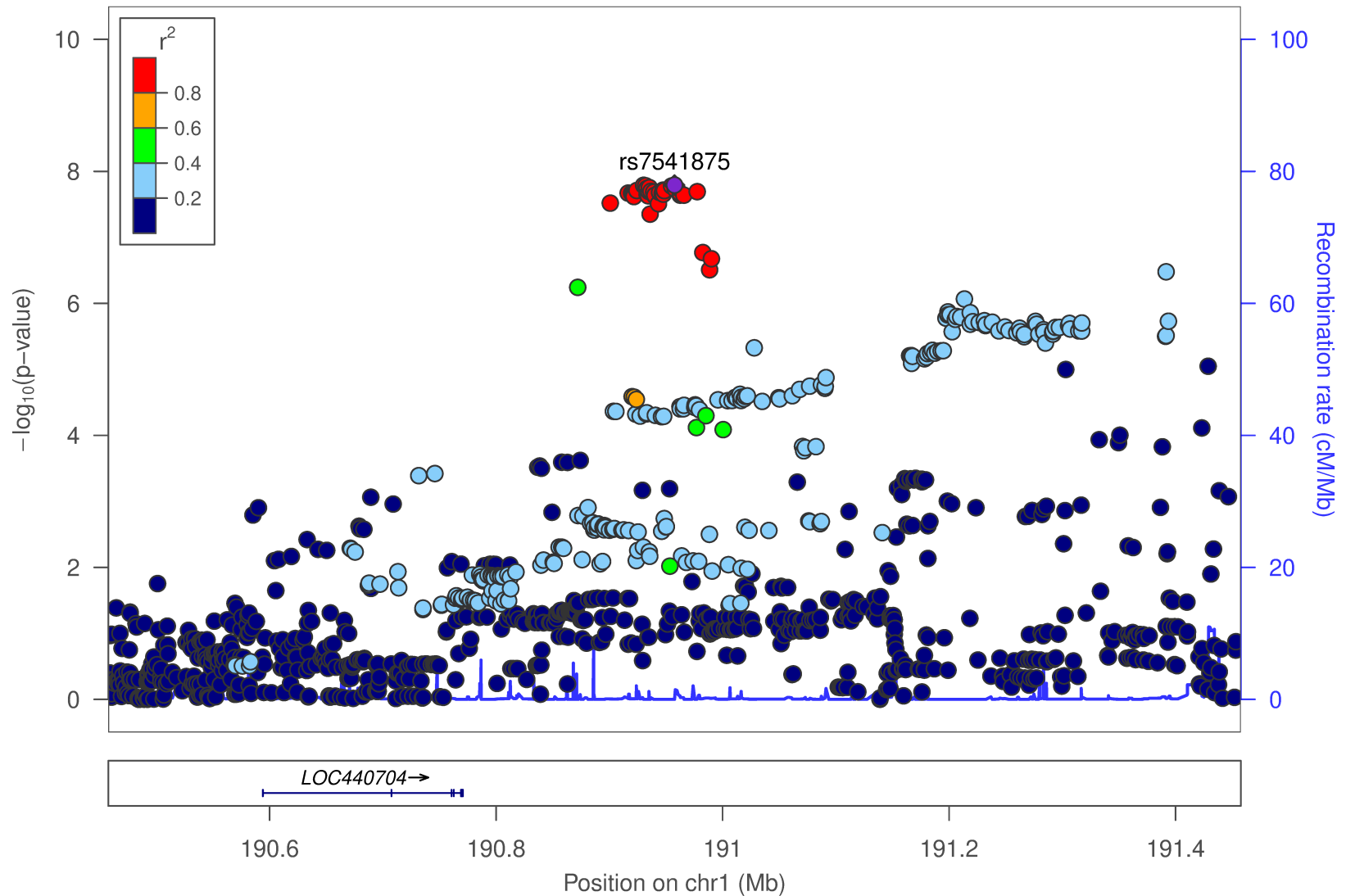
Plotted SNPs

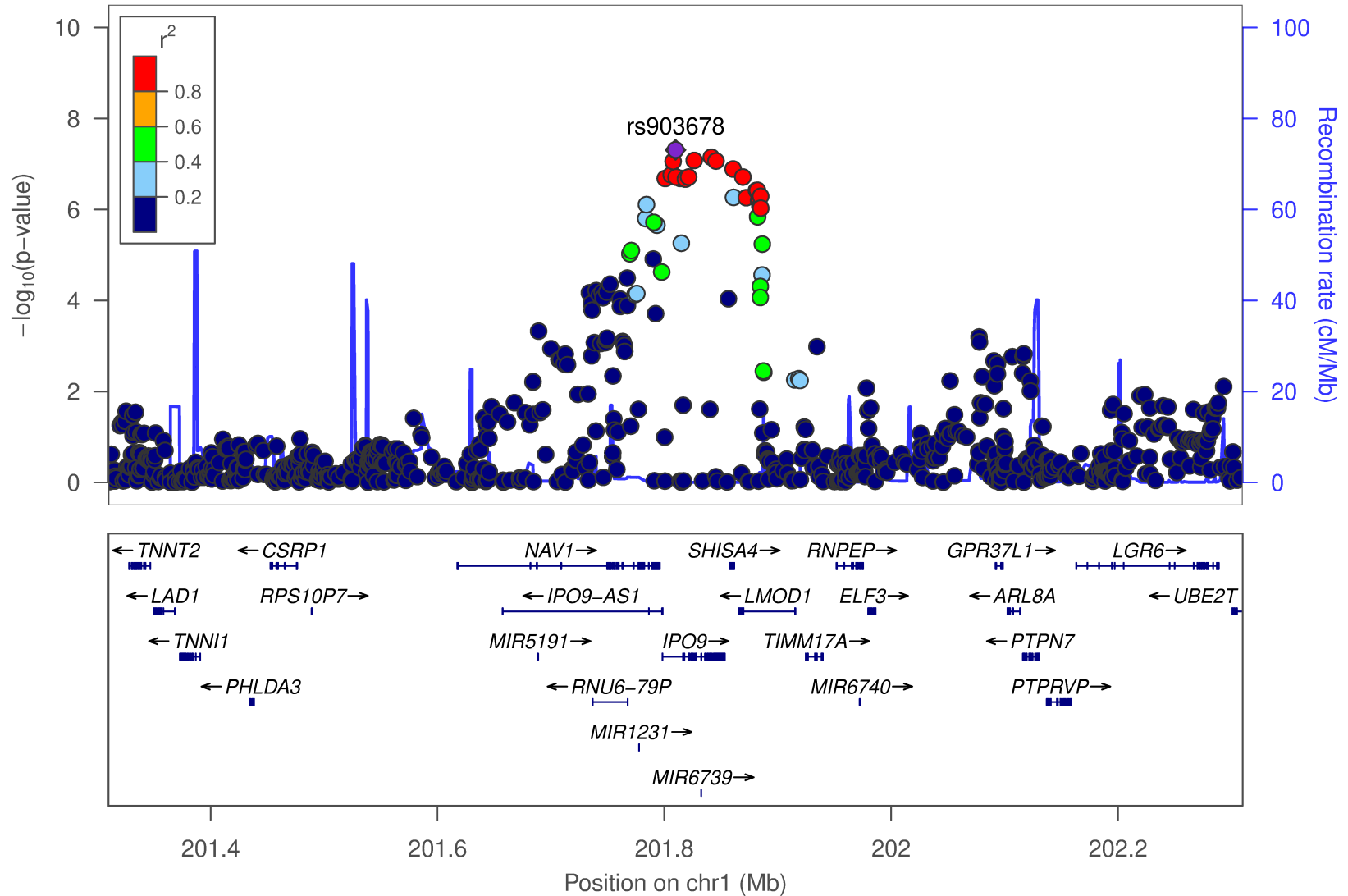


Plotted SNPs

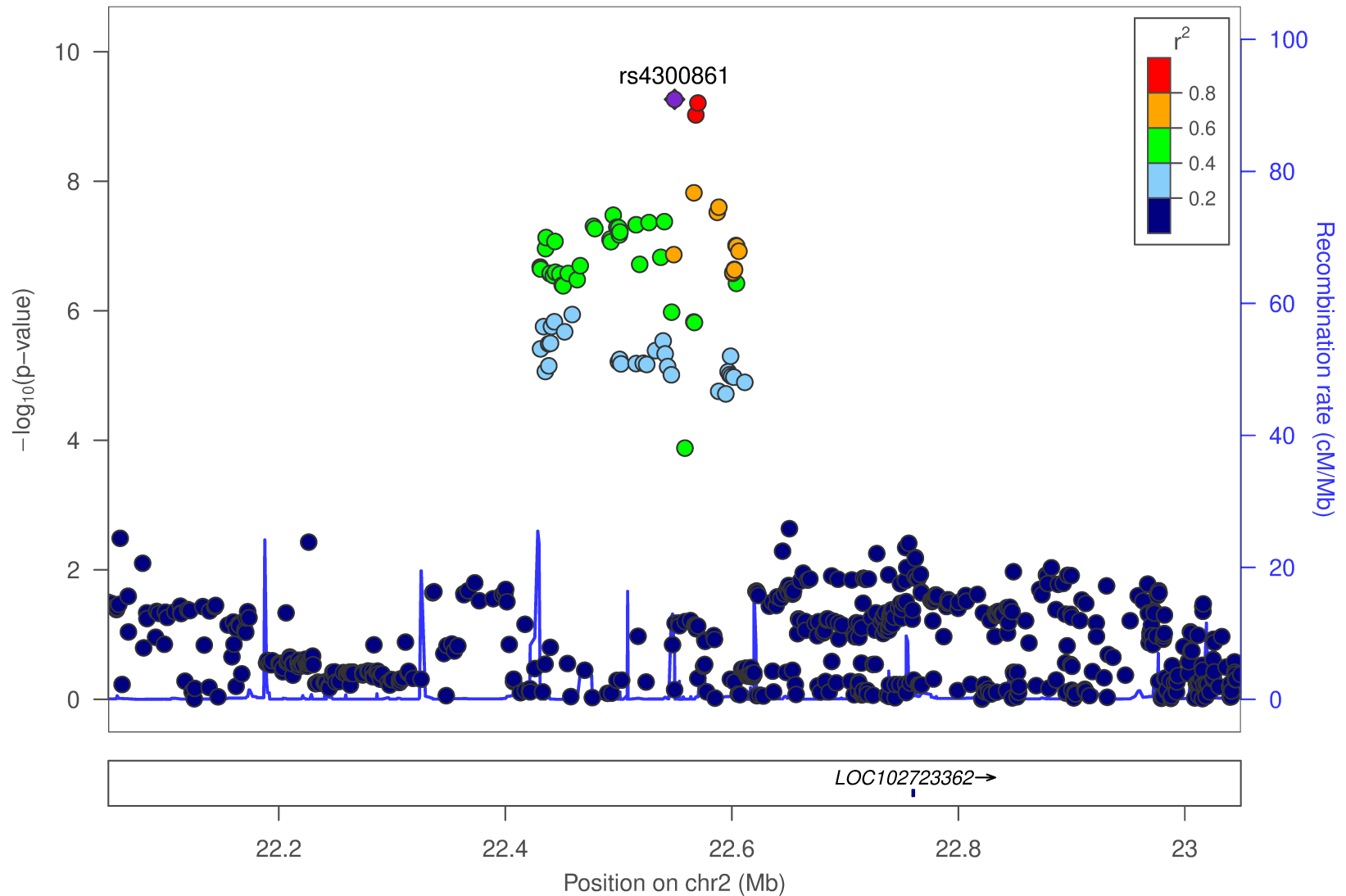


Plotted SNPs

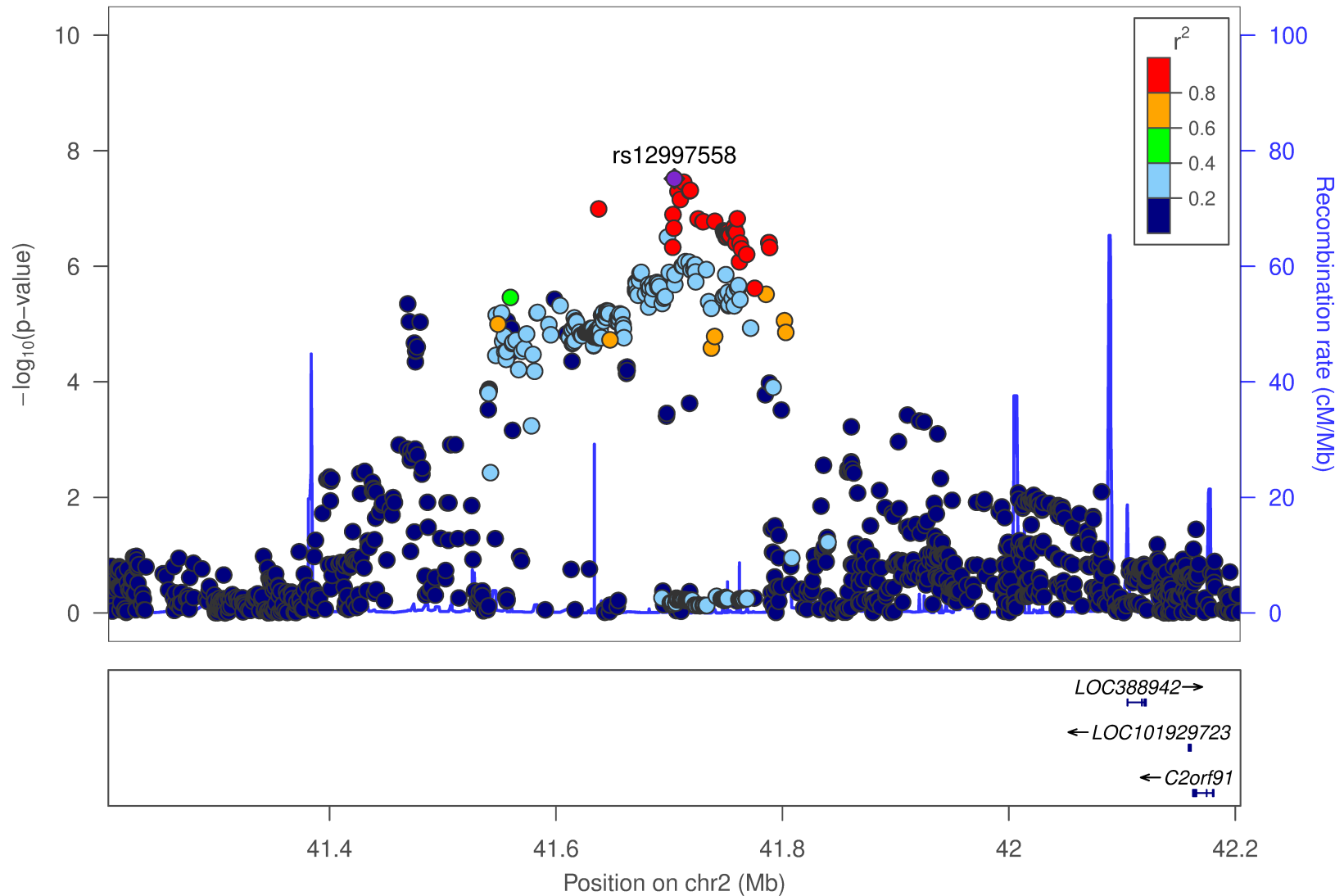


Plotted SNPs 

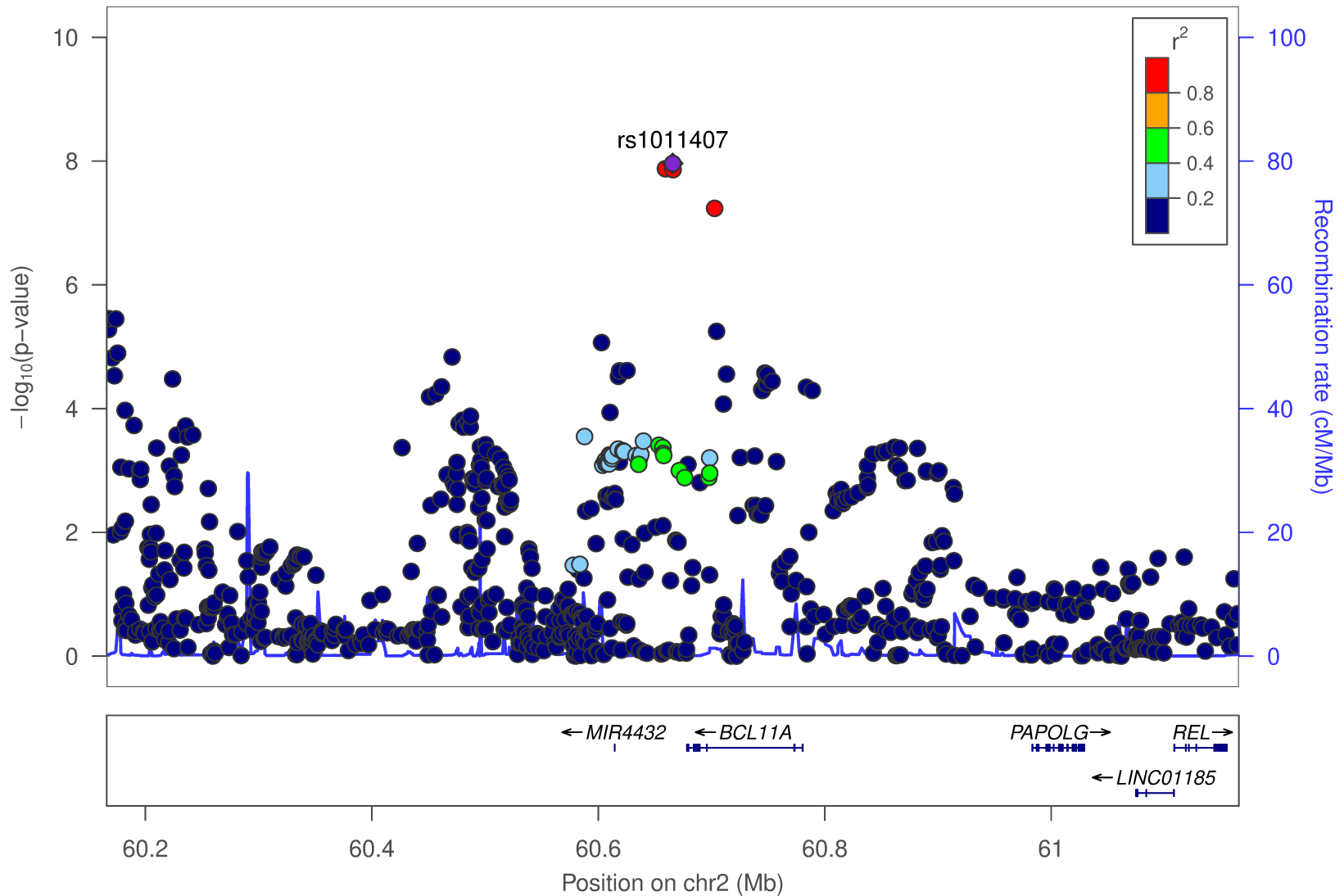
Plotted SNPs



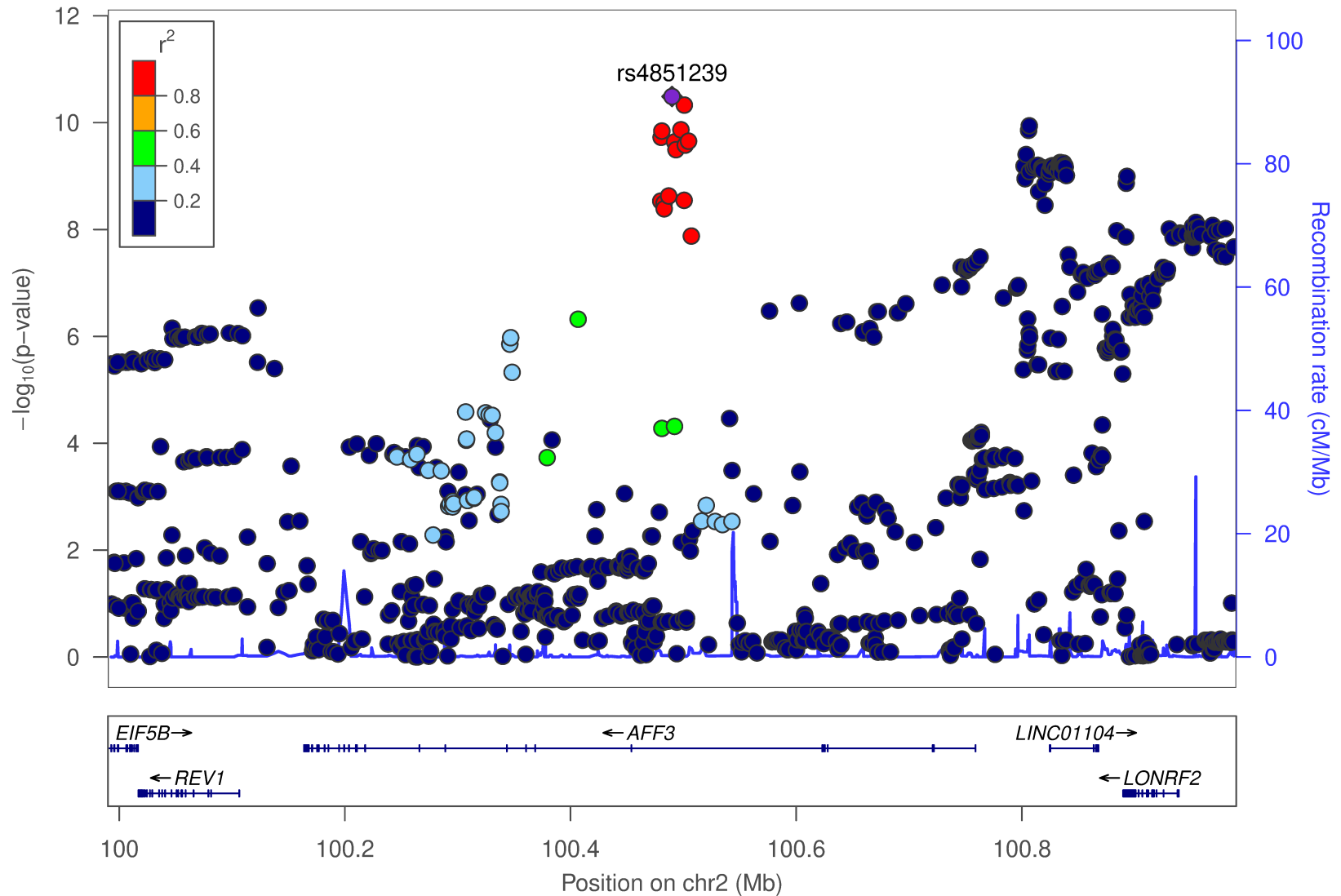
Plotted SNPs



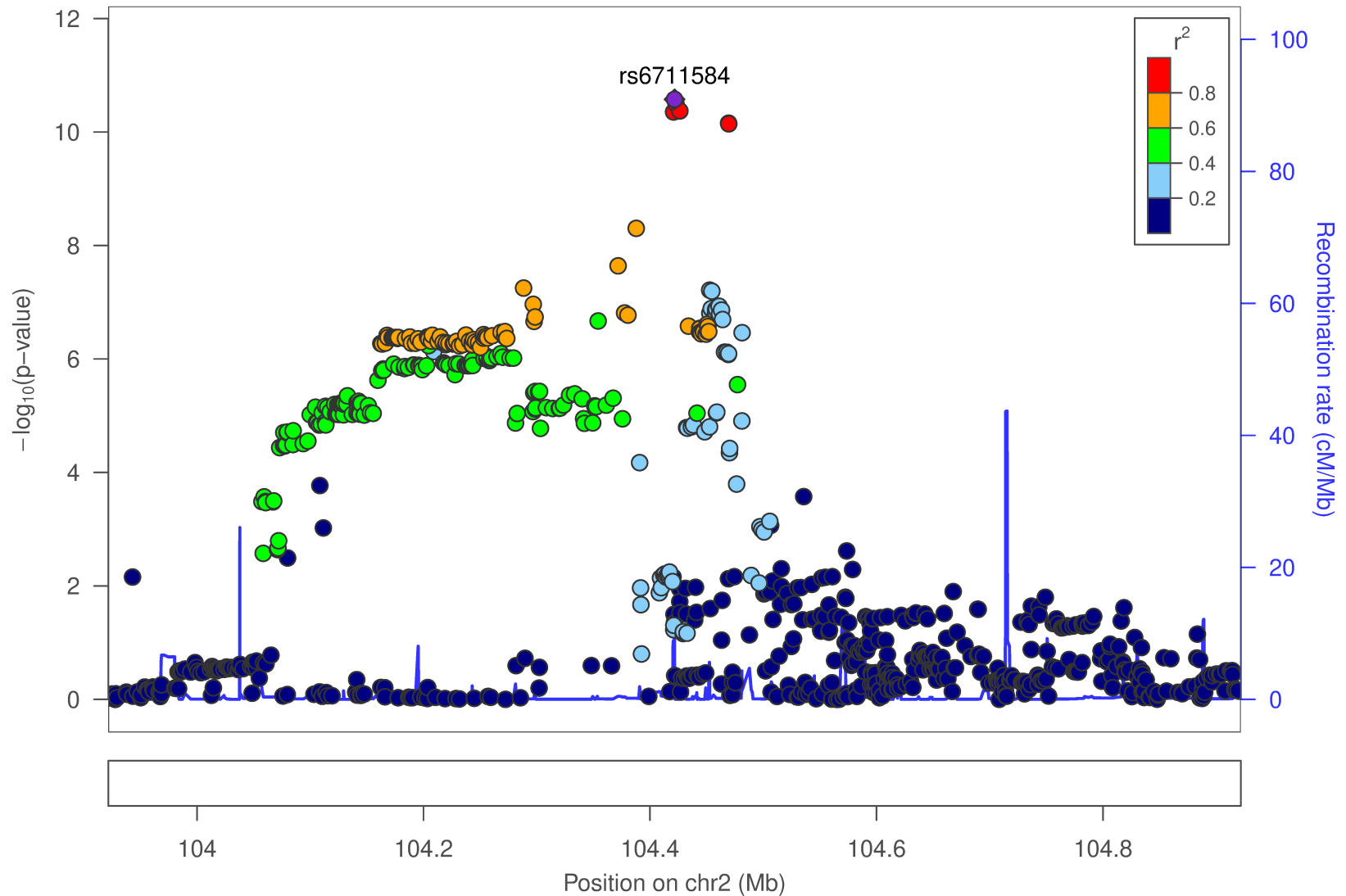
Plotted SNPs



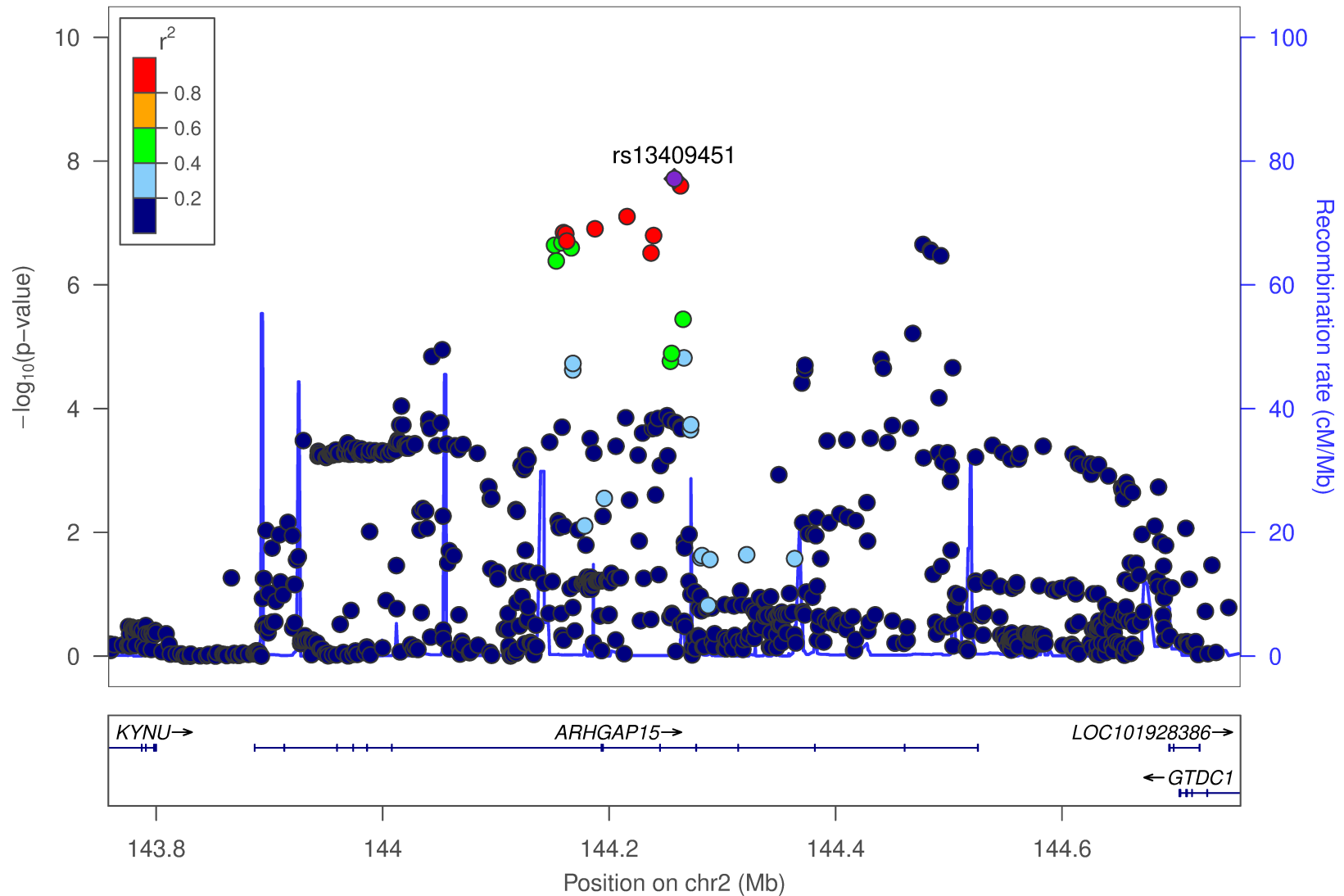
Plotted SNPs



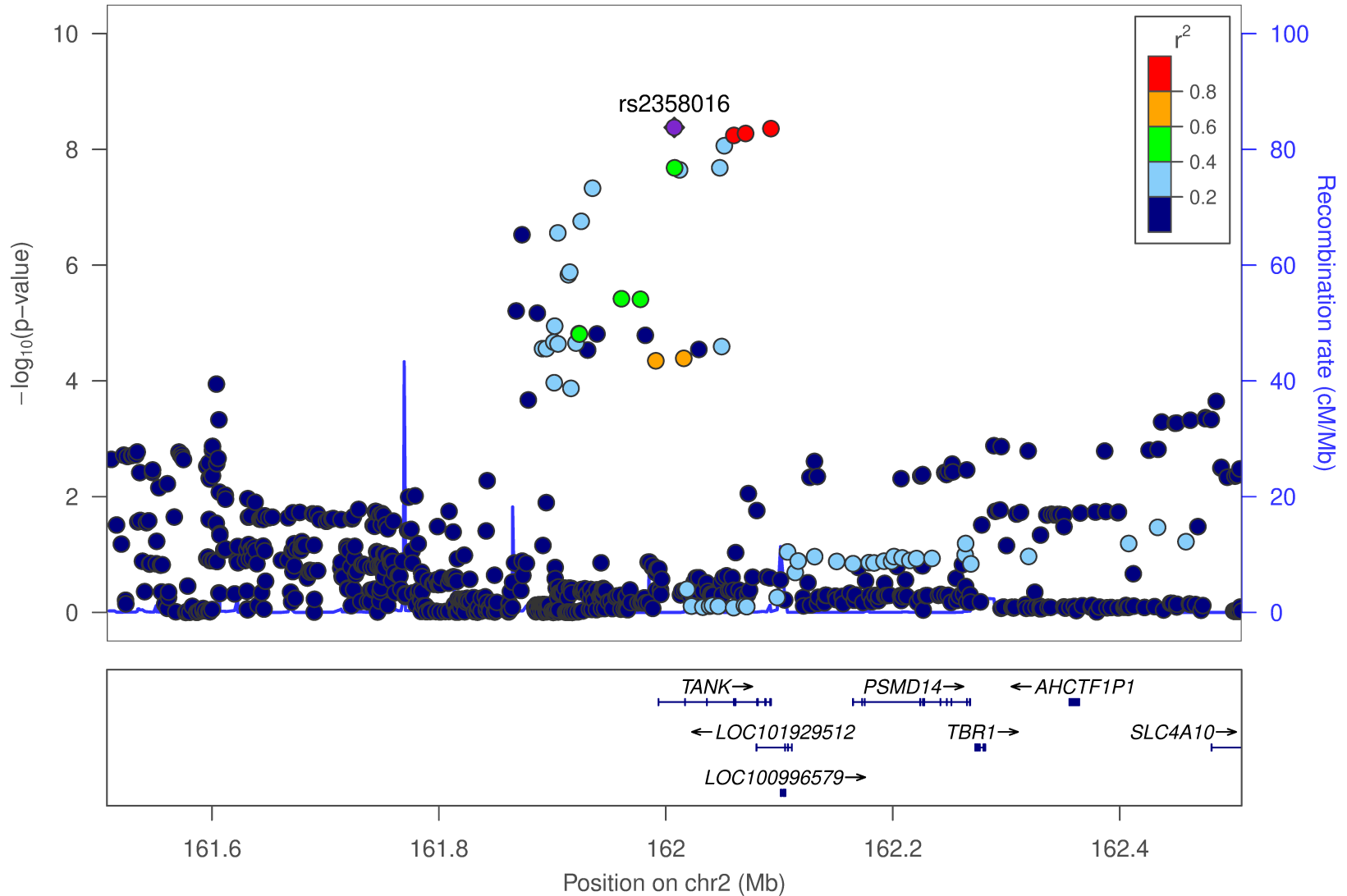
Plotted SNPs



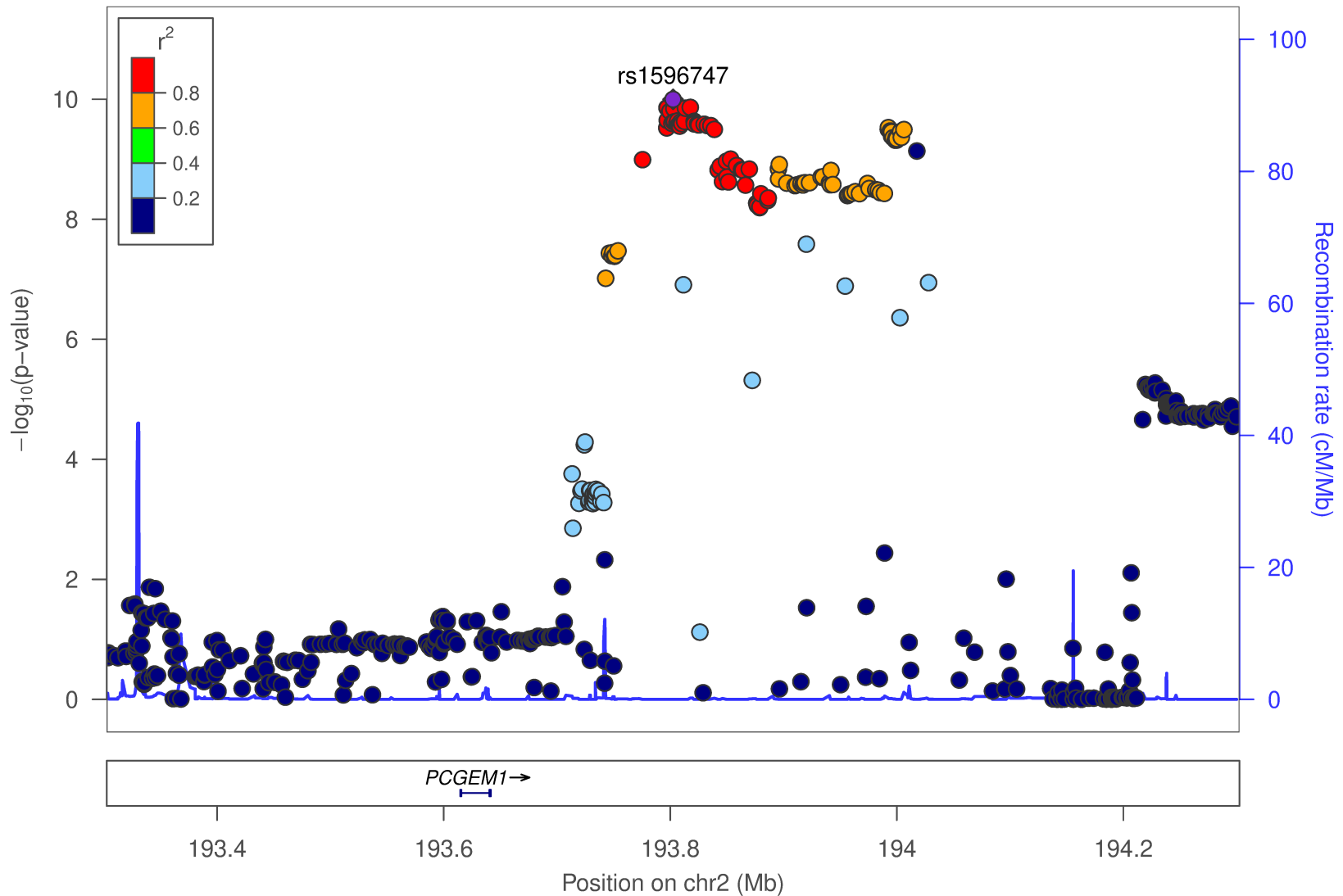
Plotted SNPs



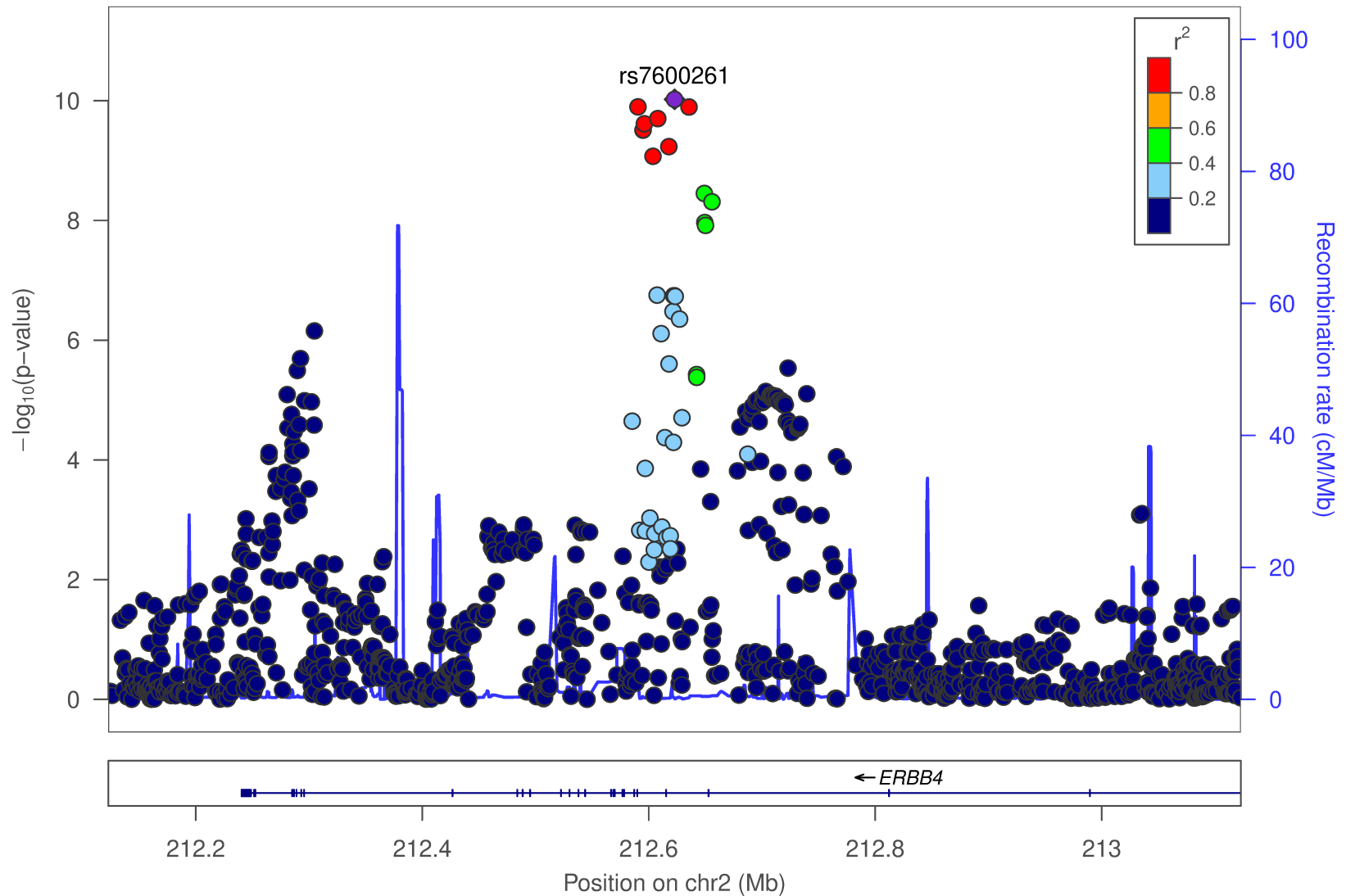
Plotted SNPs



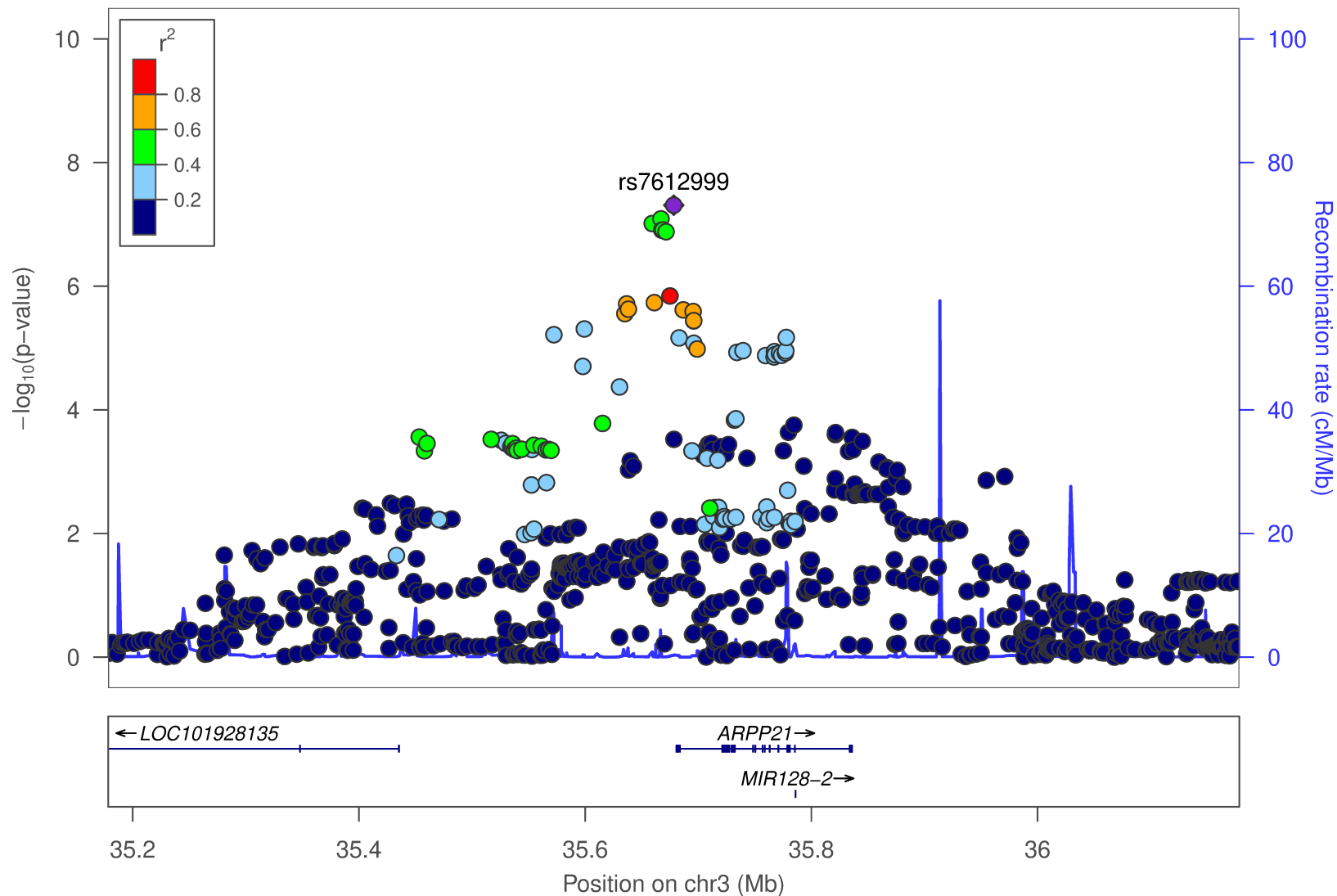
Plotted SNPs



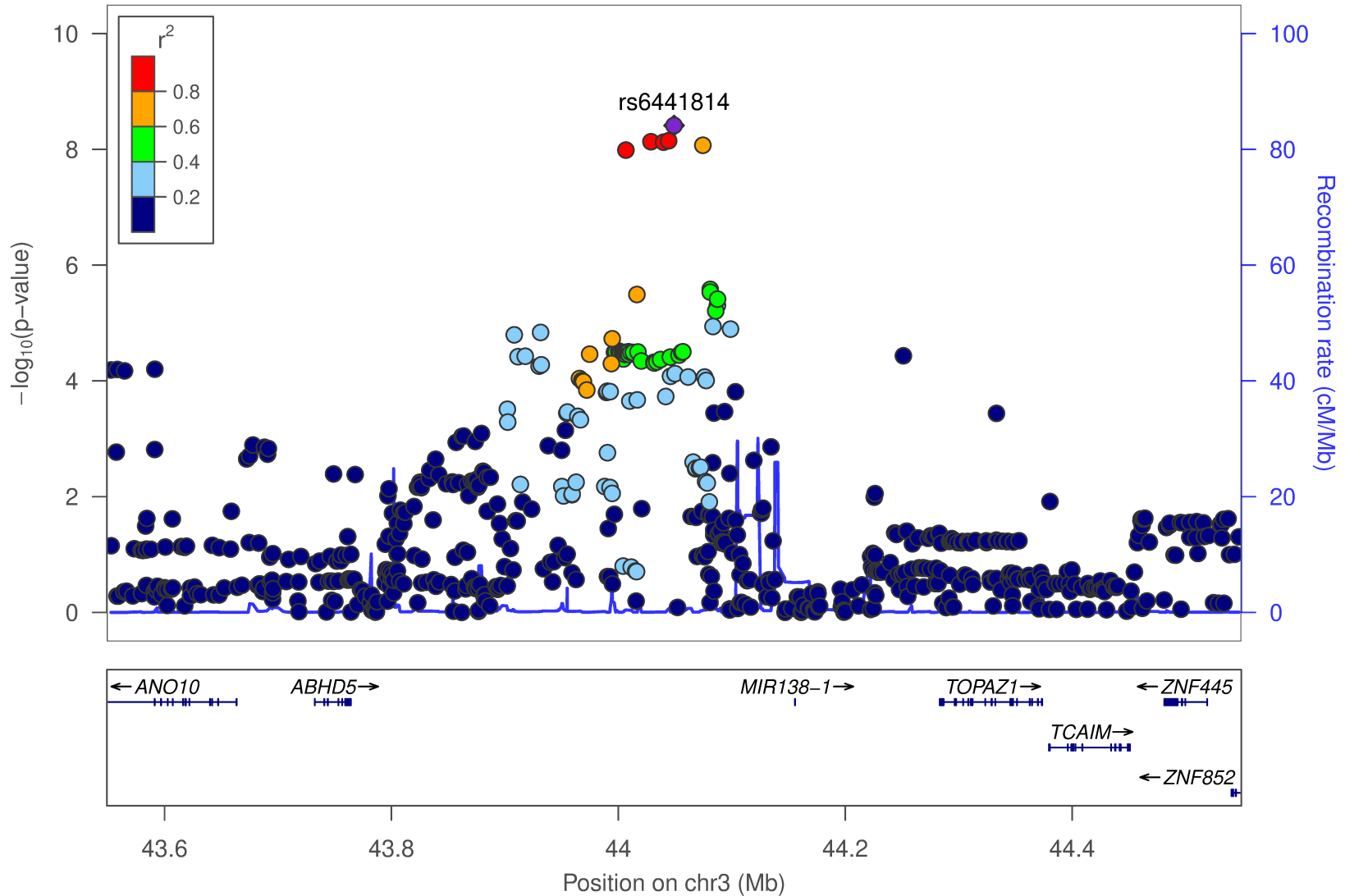
Plotted SNPs

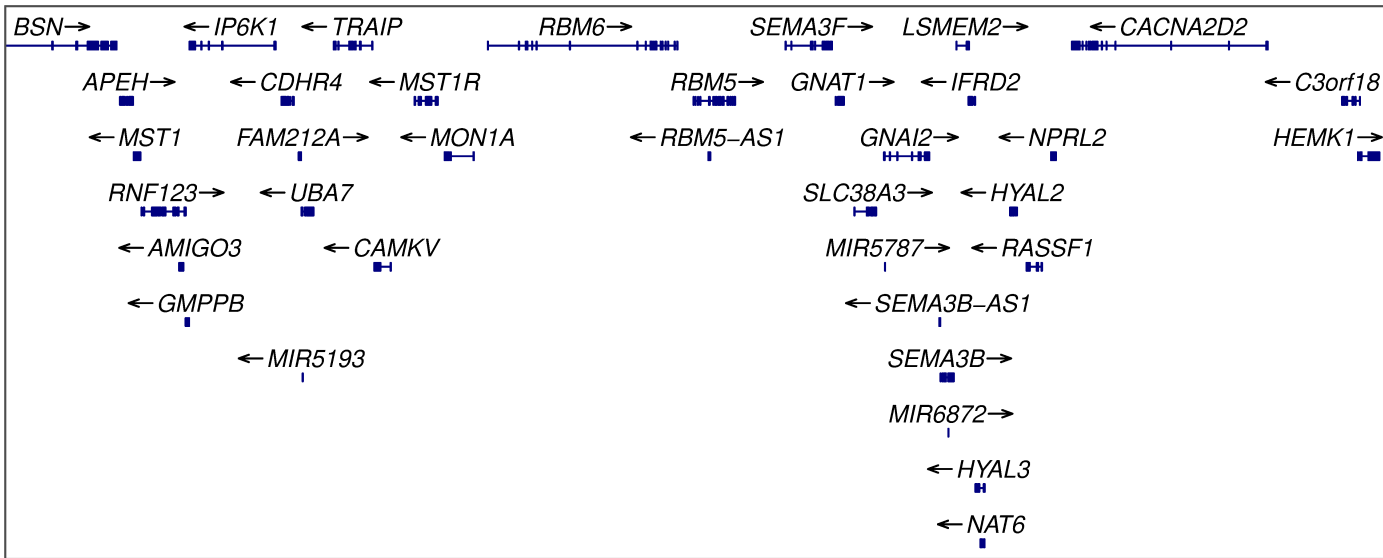
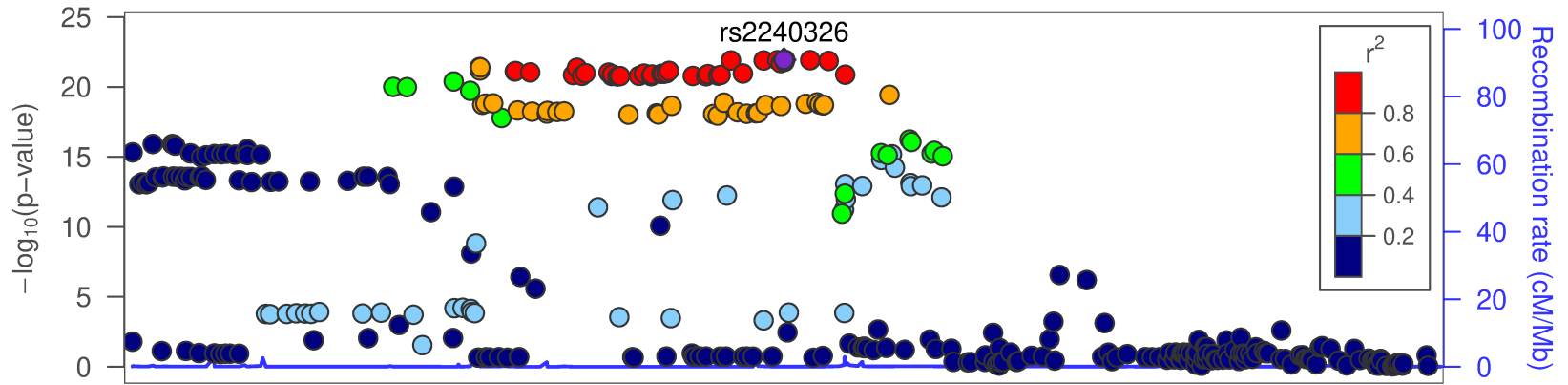


Plotted SNPs



Plotted SNPs



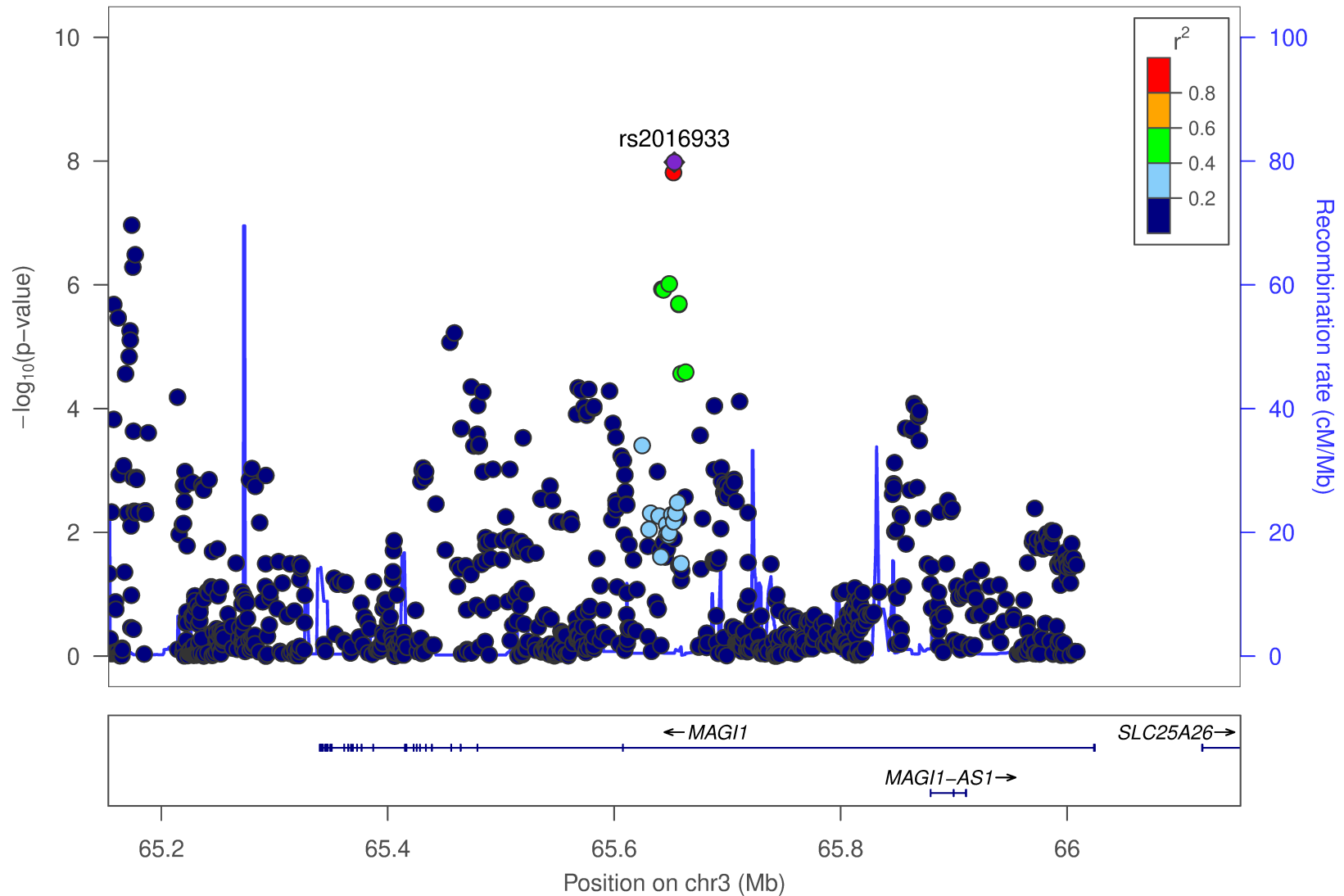


49.8 50 50.2 50.4 50.6

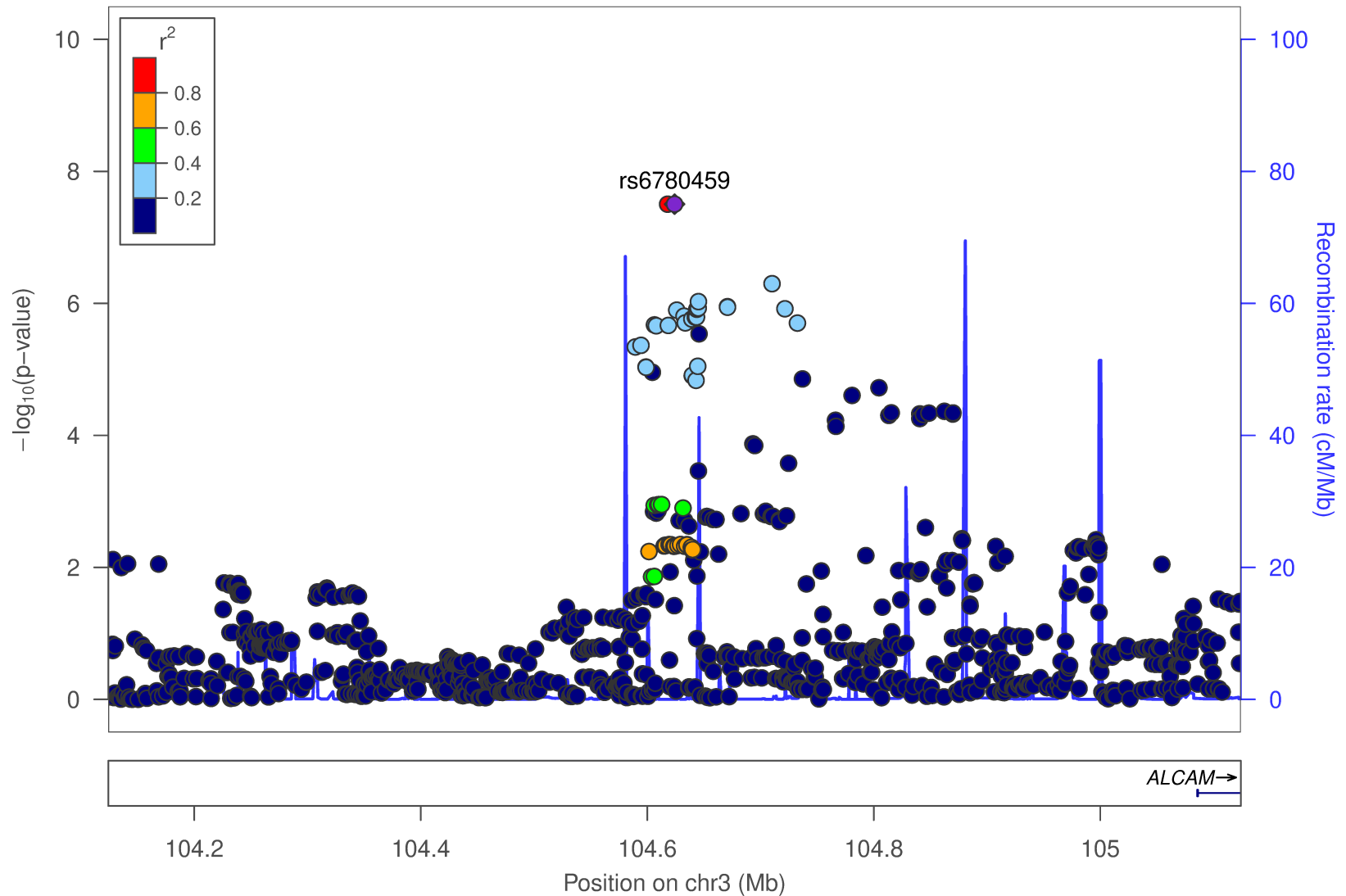
Position on chr3 (Mb)

6 genes omitted

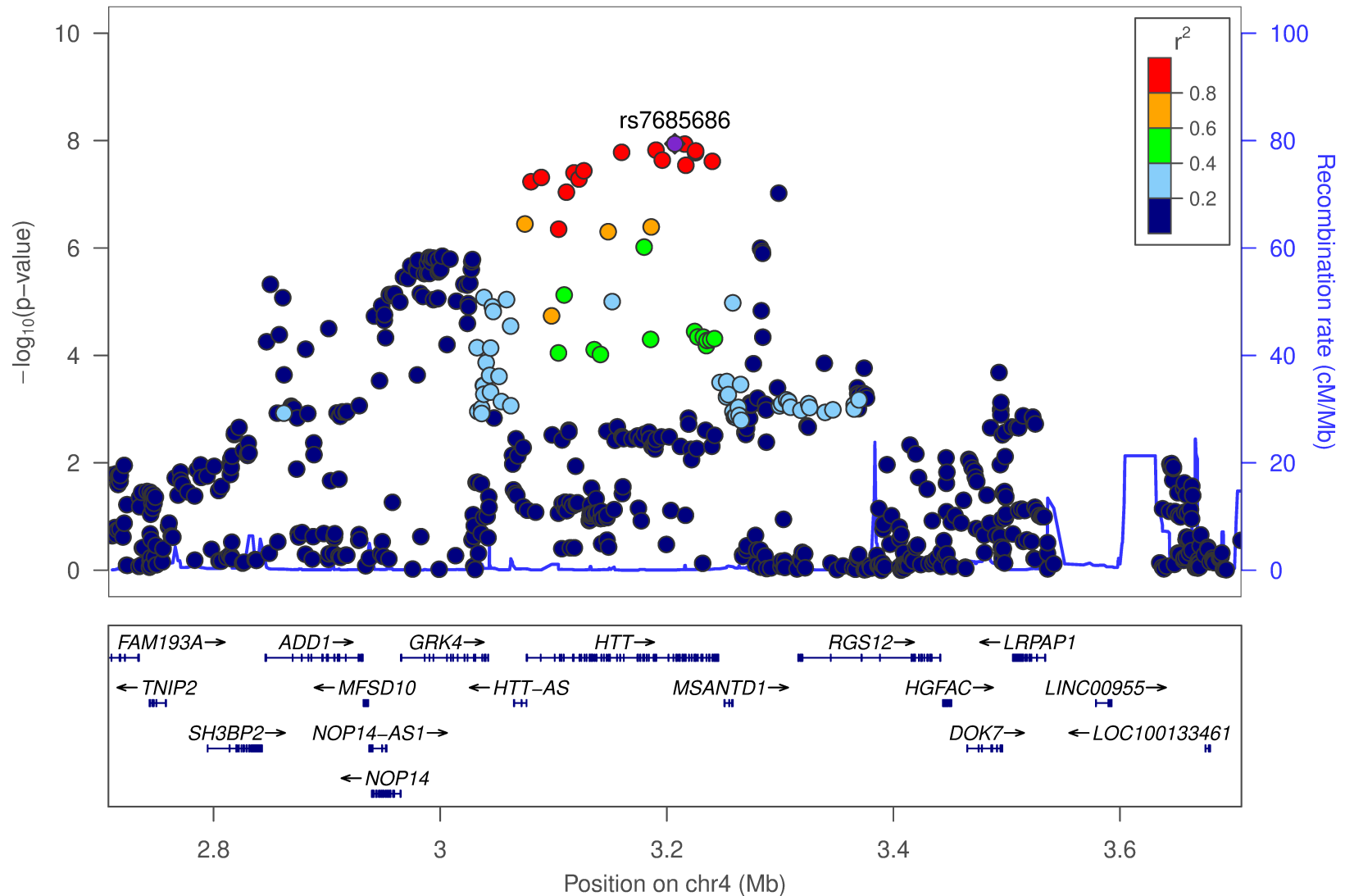
Plotted SNPs



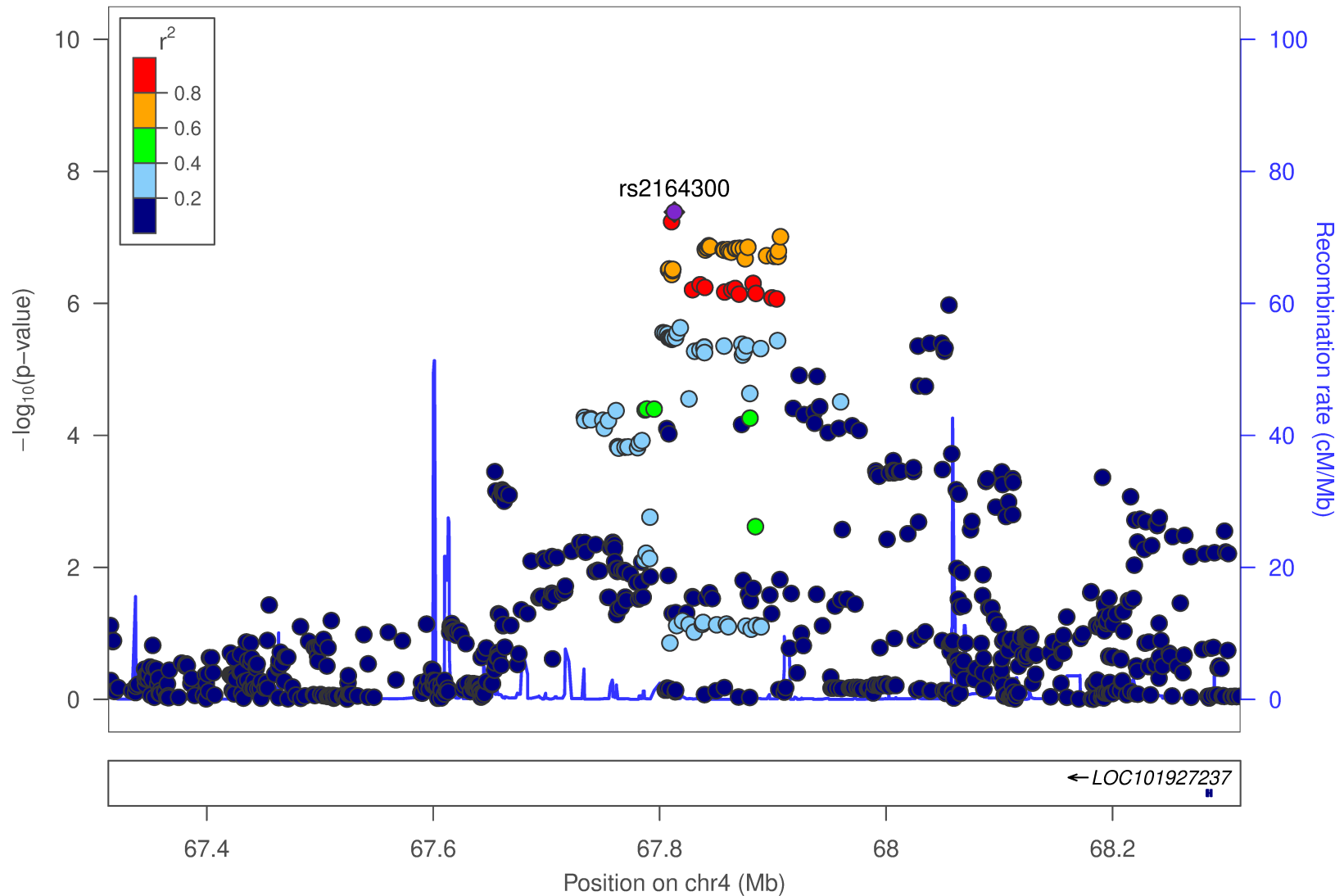
Plotted SNPs



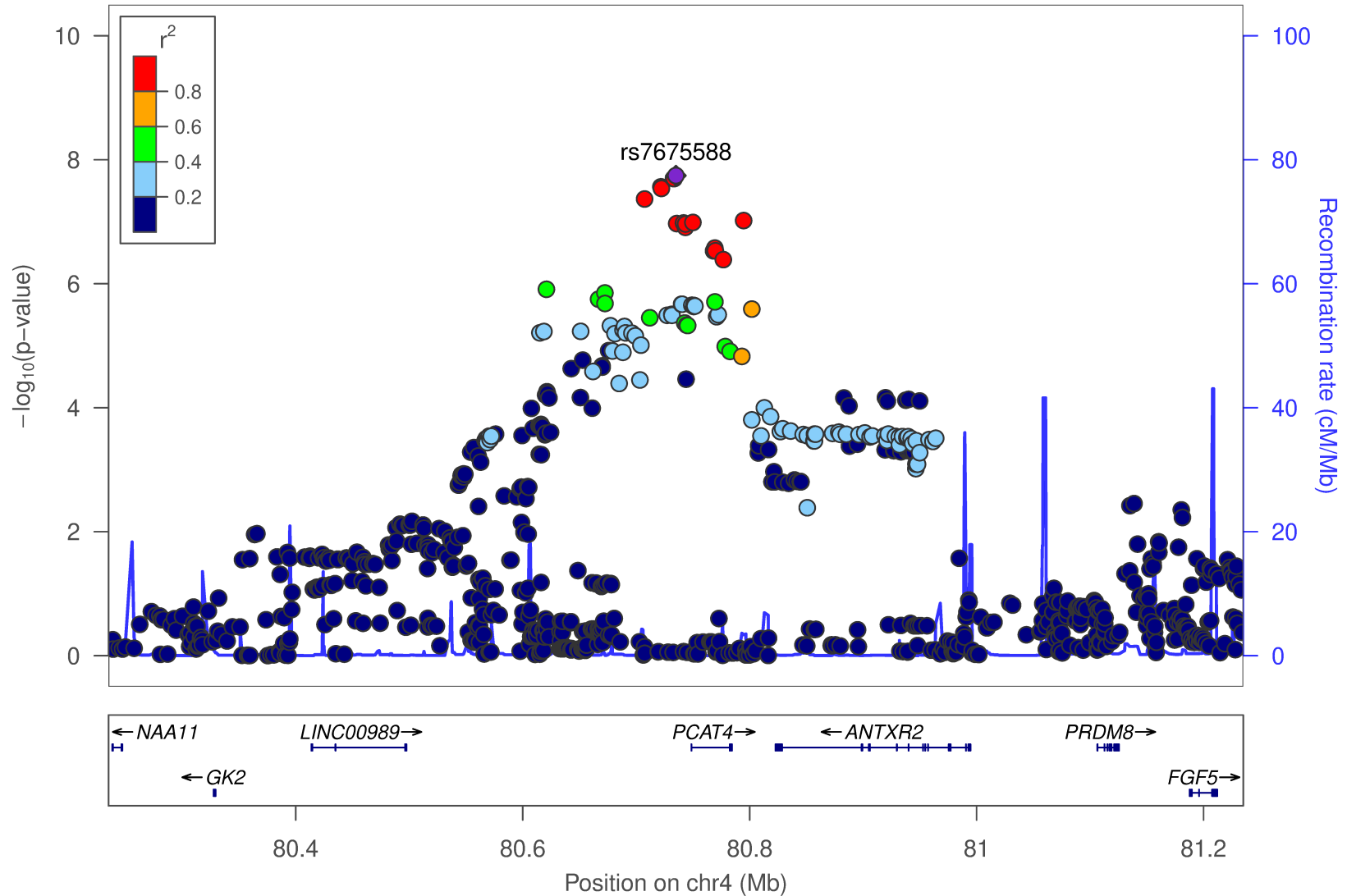
Plotted SNPs



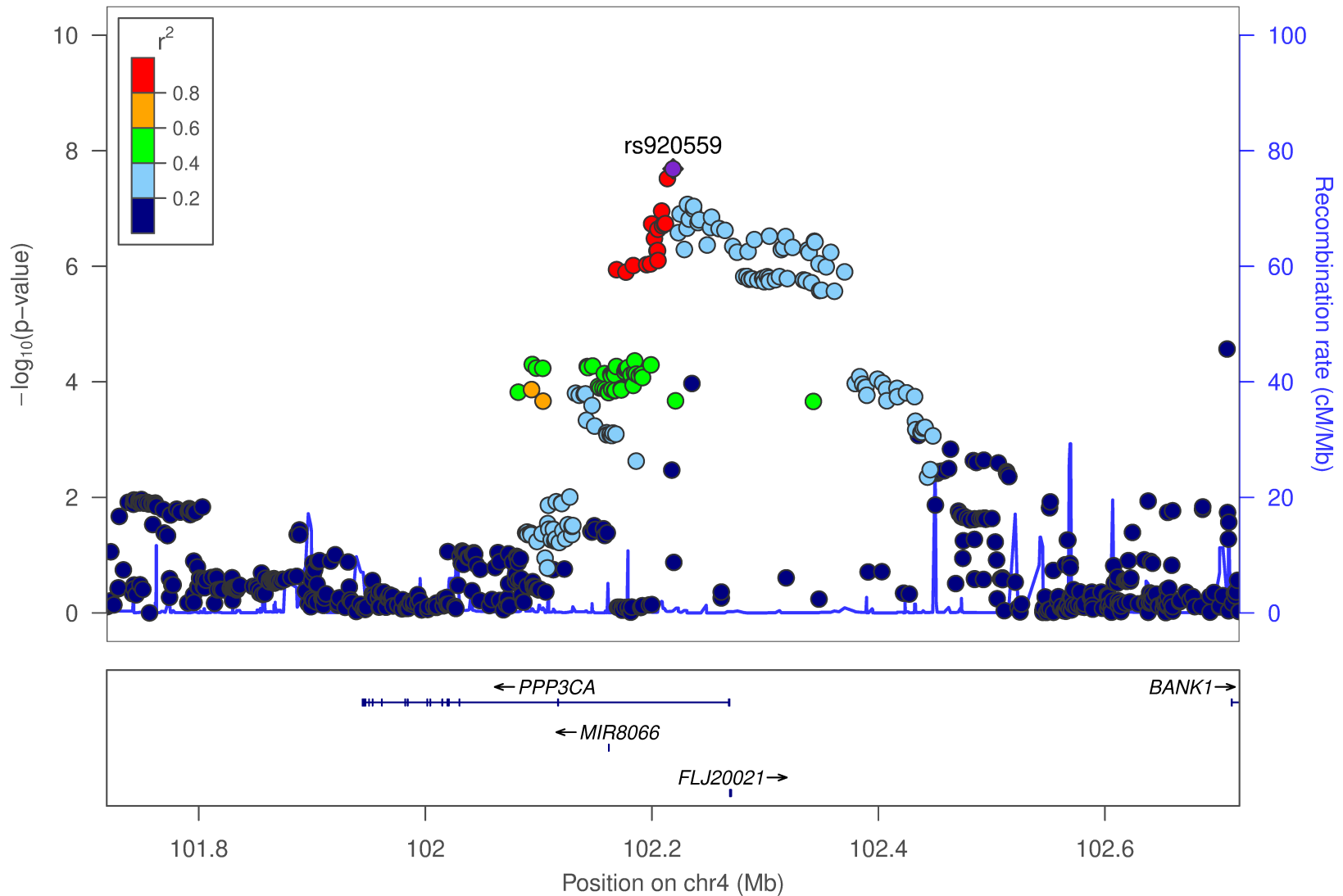
Plotted SNPs



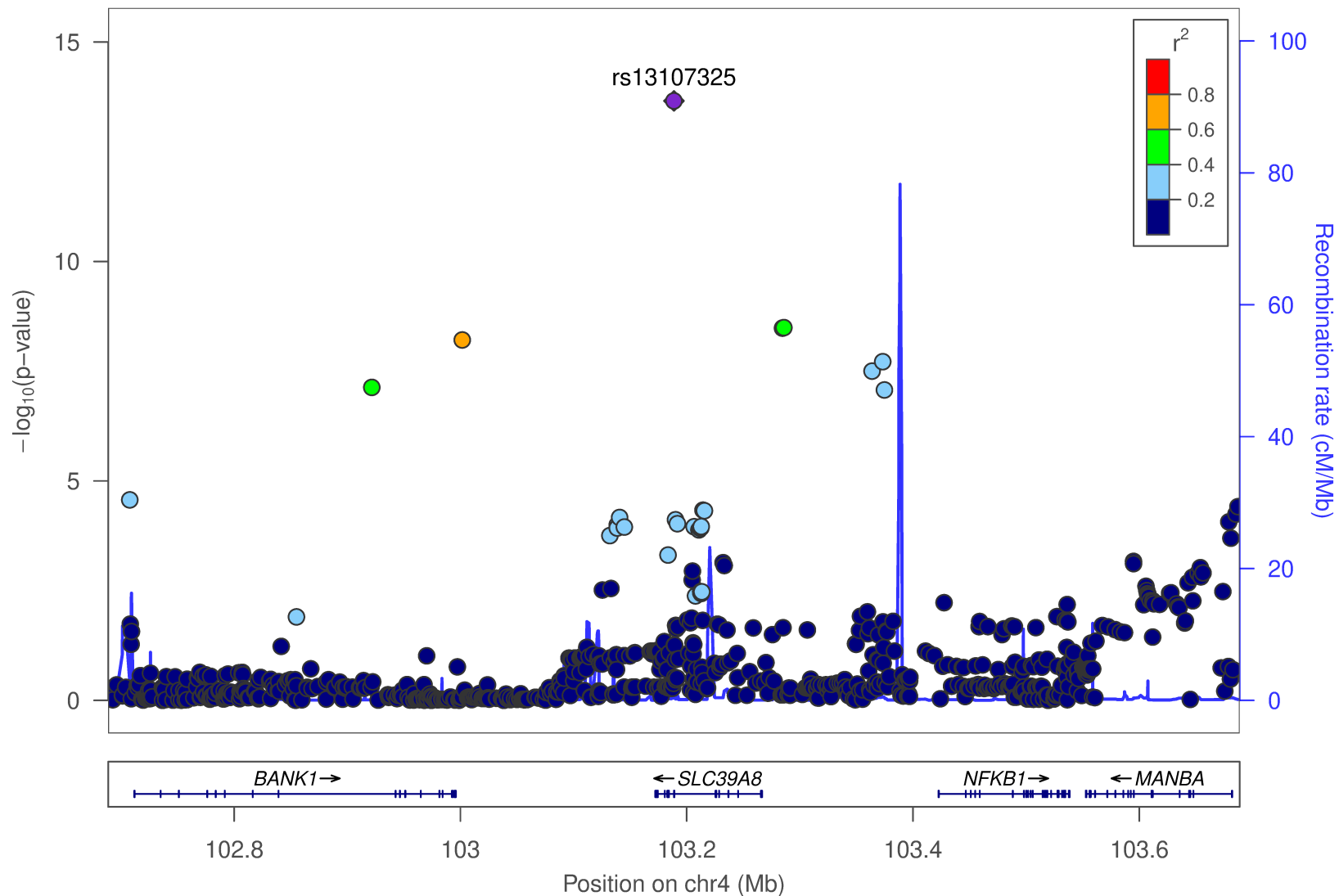
Plotted SNPs



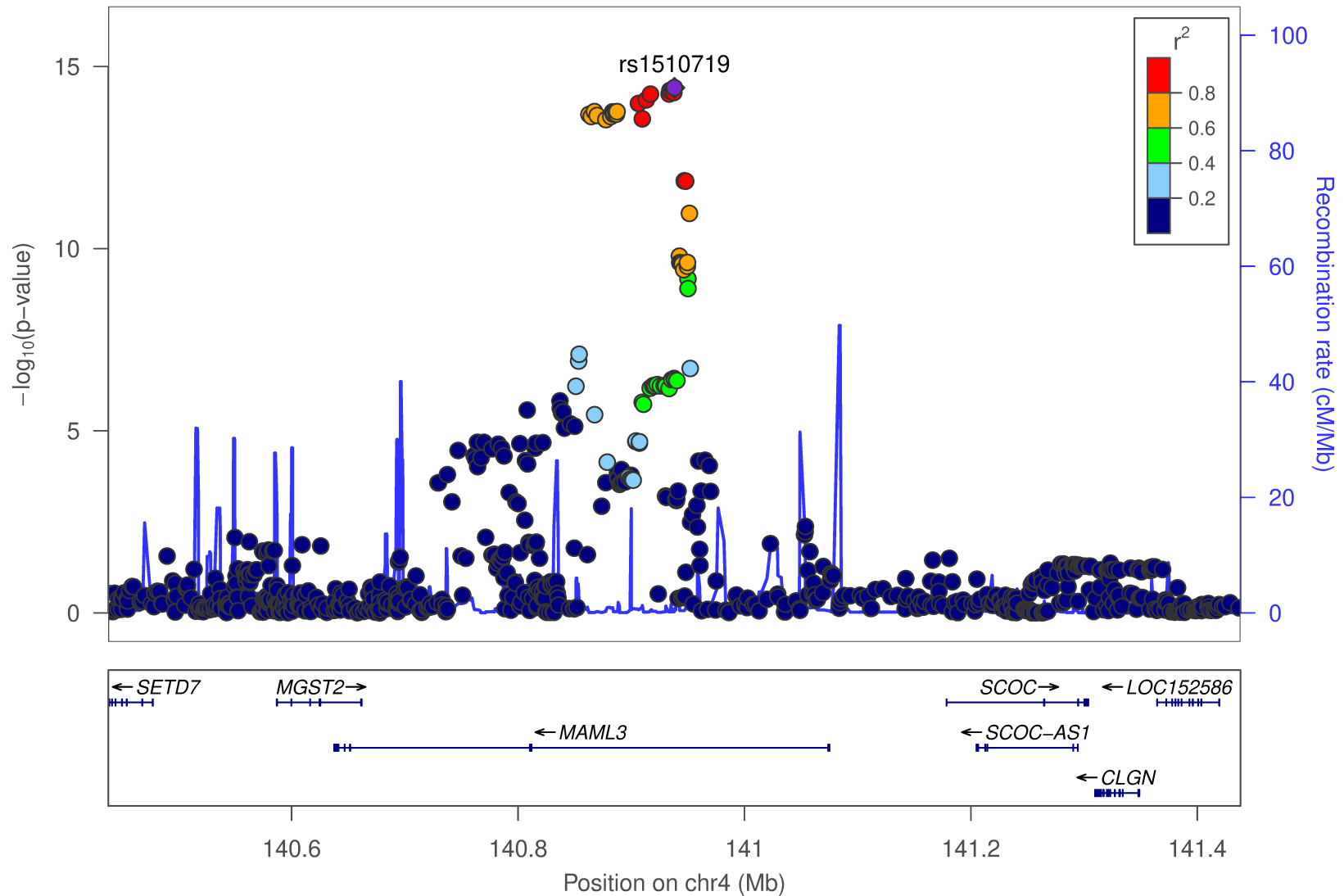
Plotted SNPs



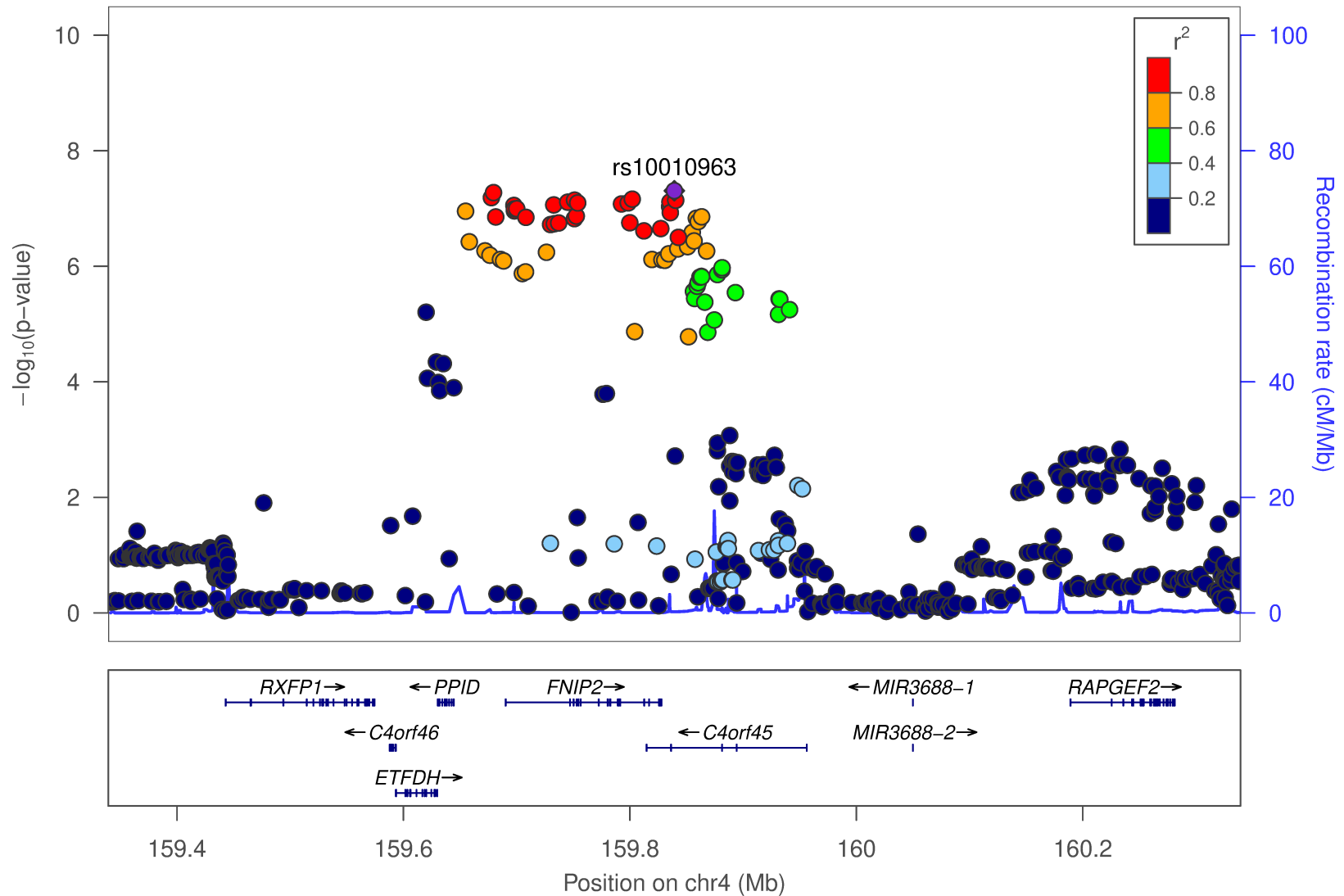
Plotted SNPs



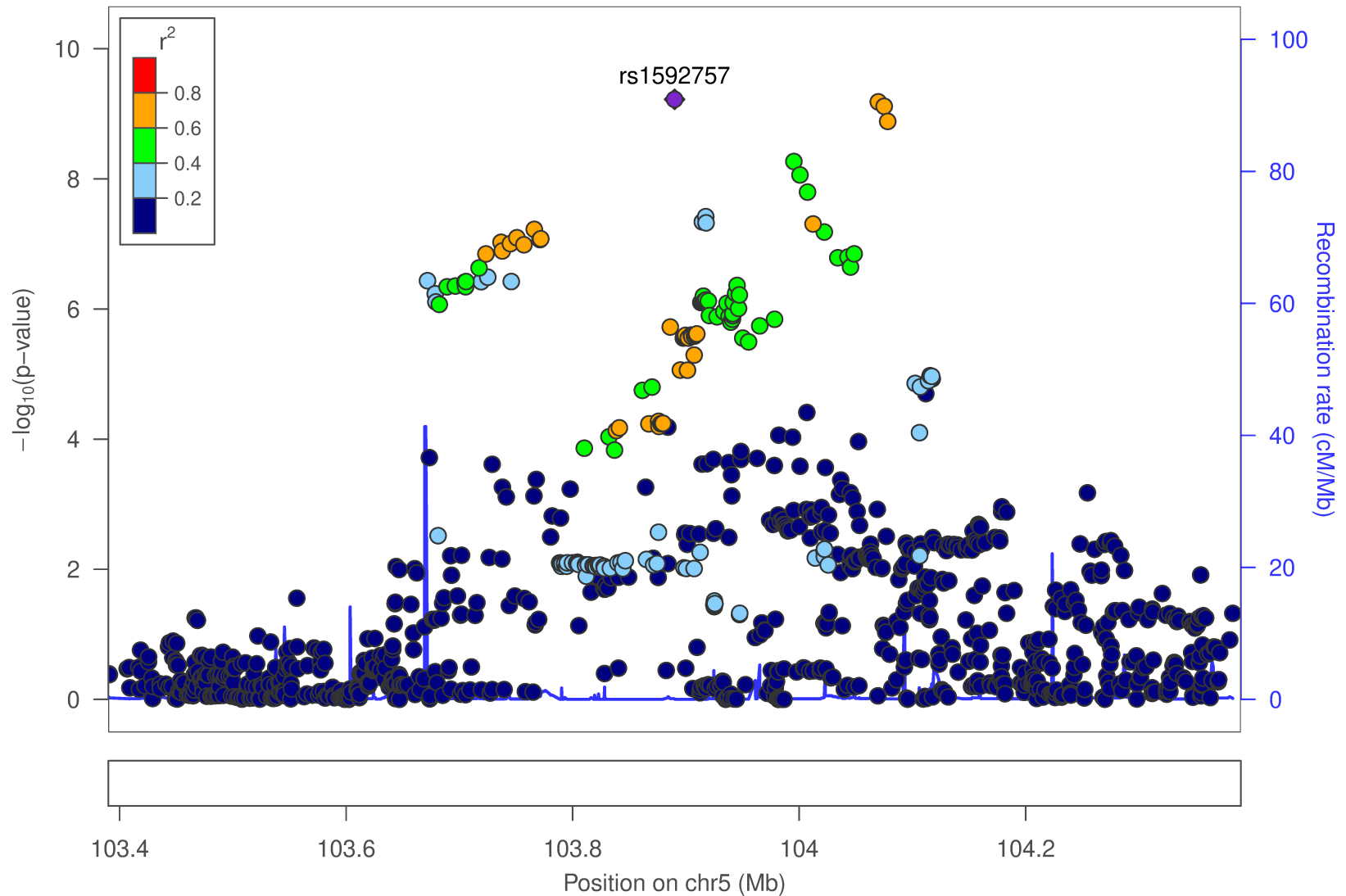
Plotted SNPs



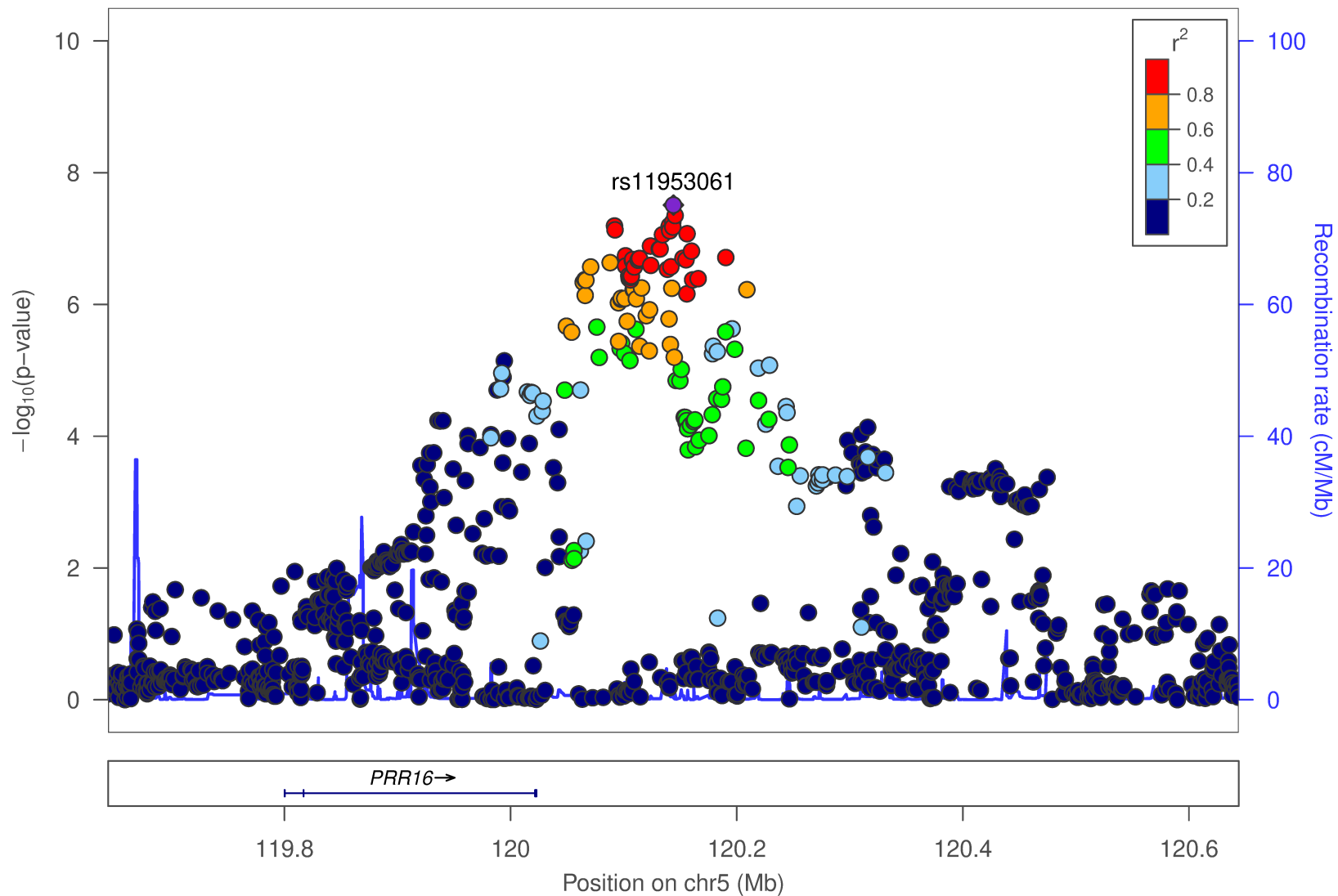
Plotted SNPs



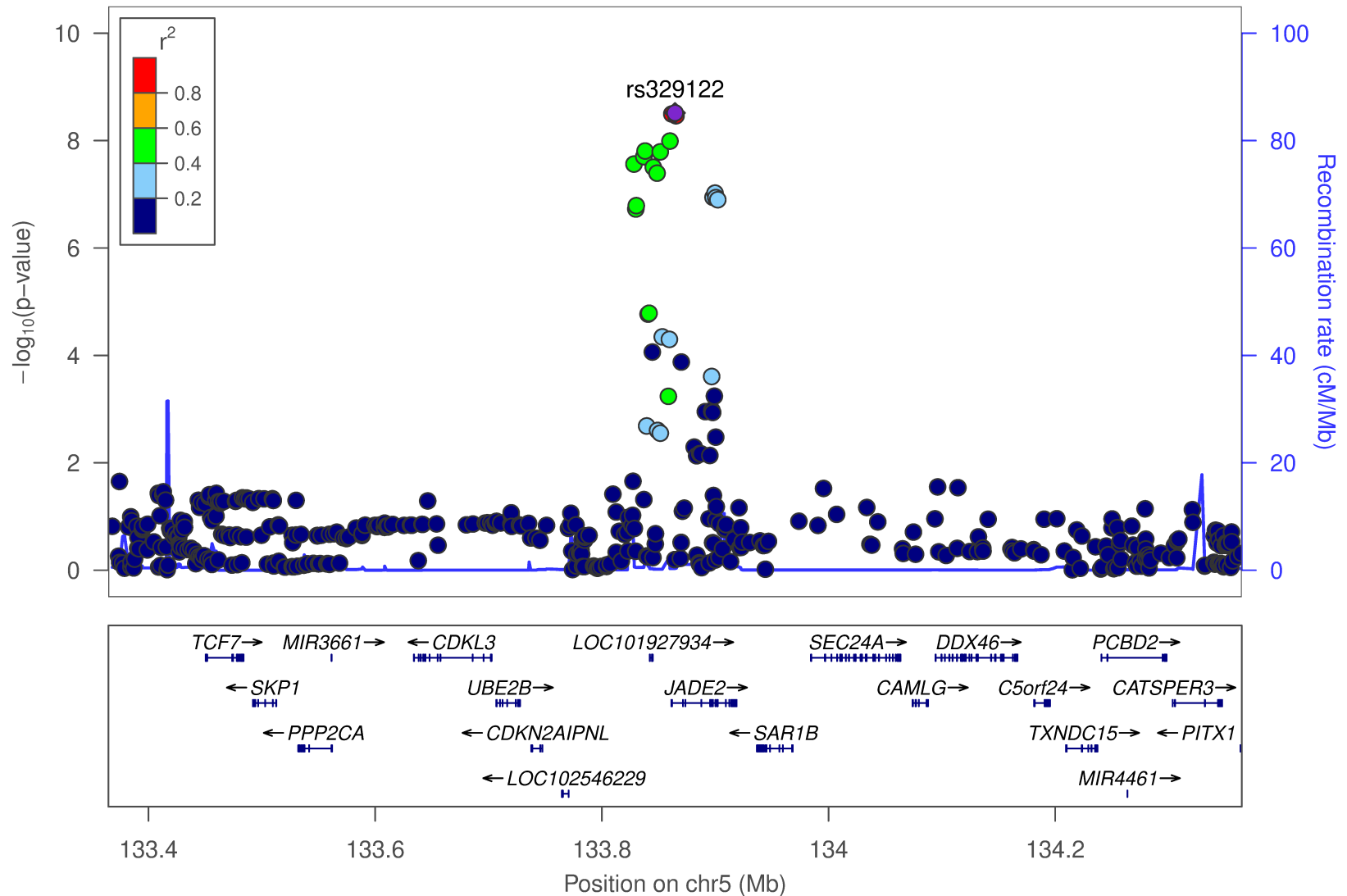
Plotted SNPs |



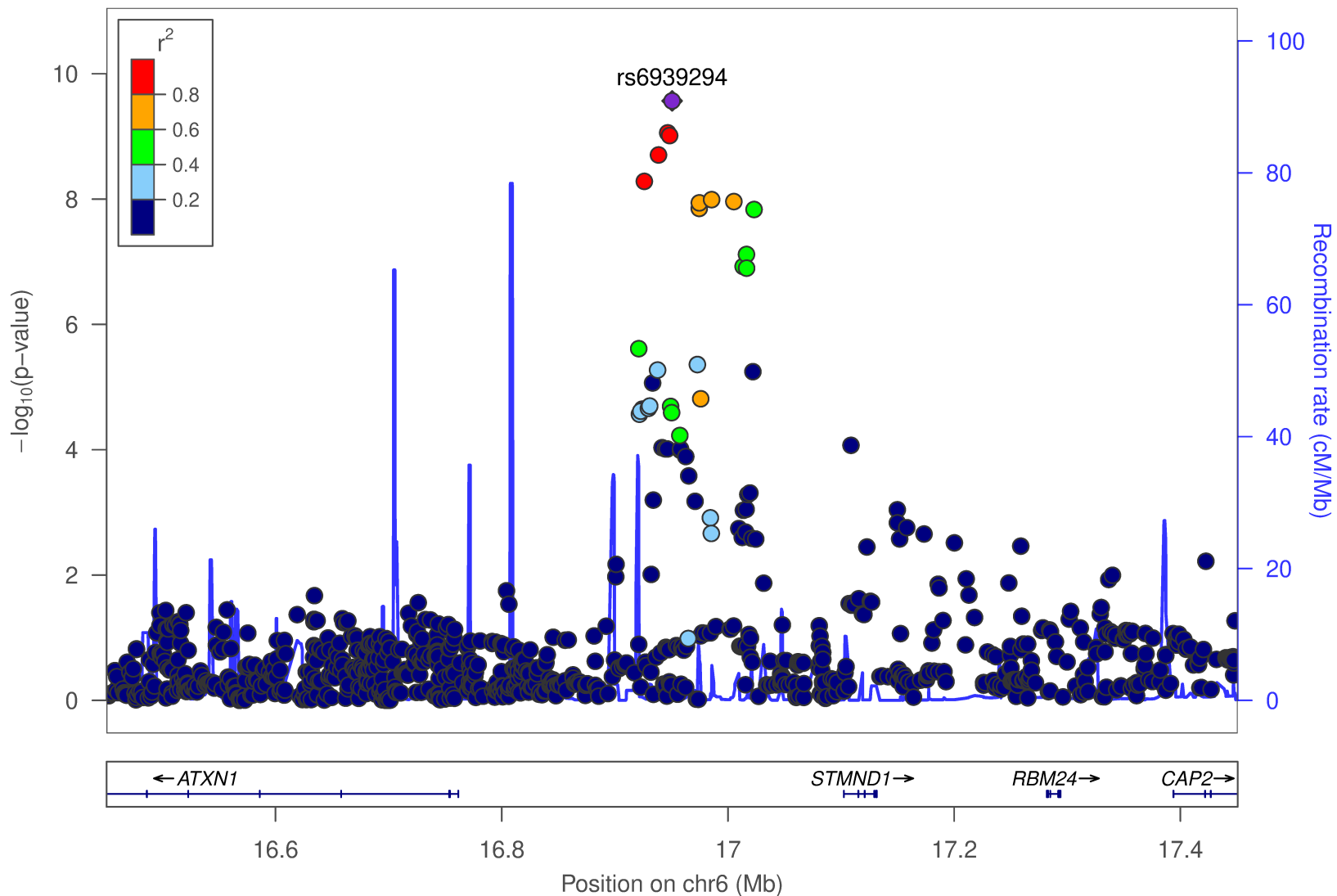
Plotted SNPs



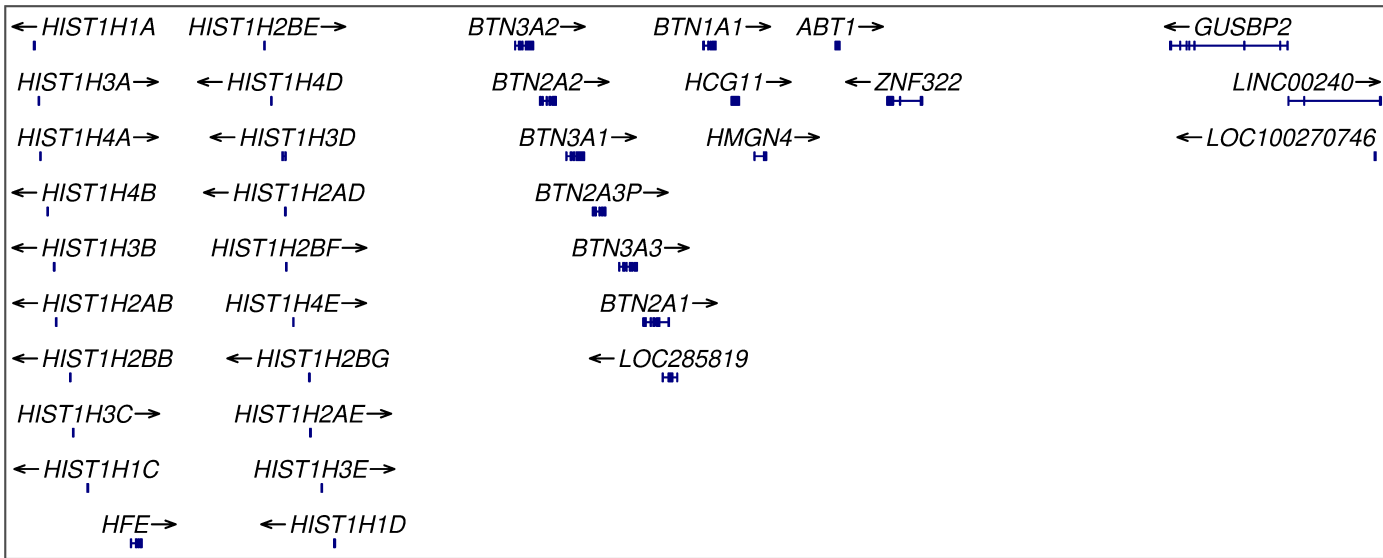
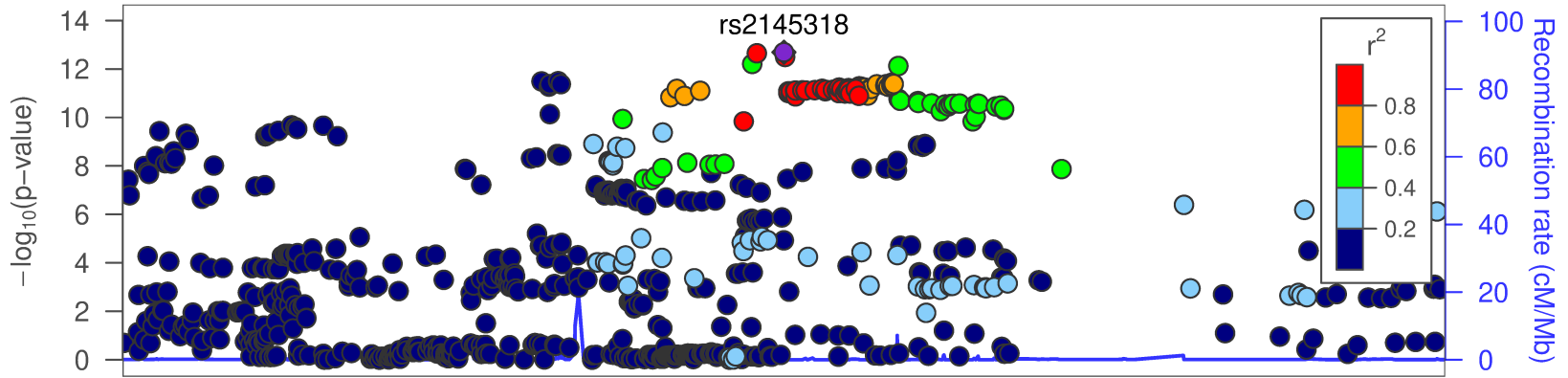
Plotted SNPs



Plotted SNPs



Plotted SNPs

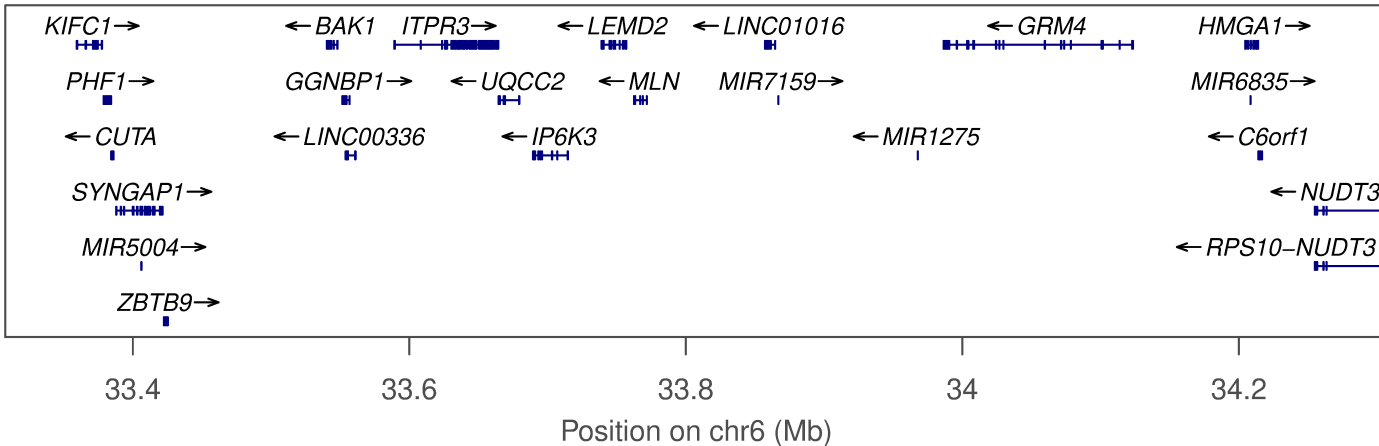
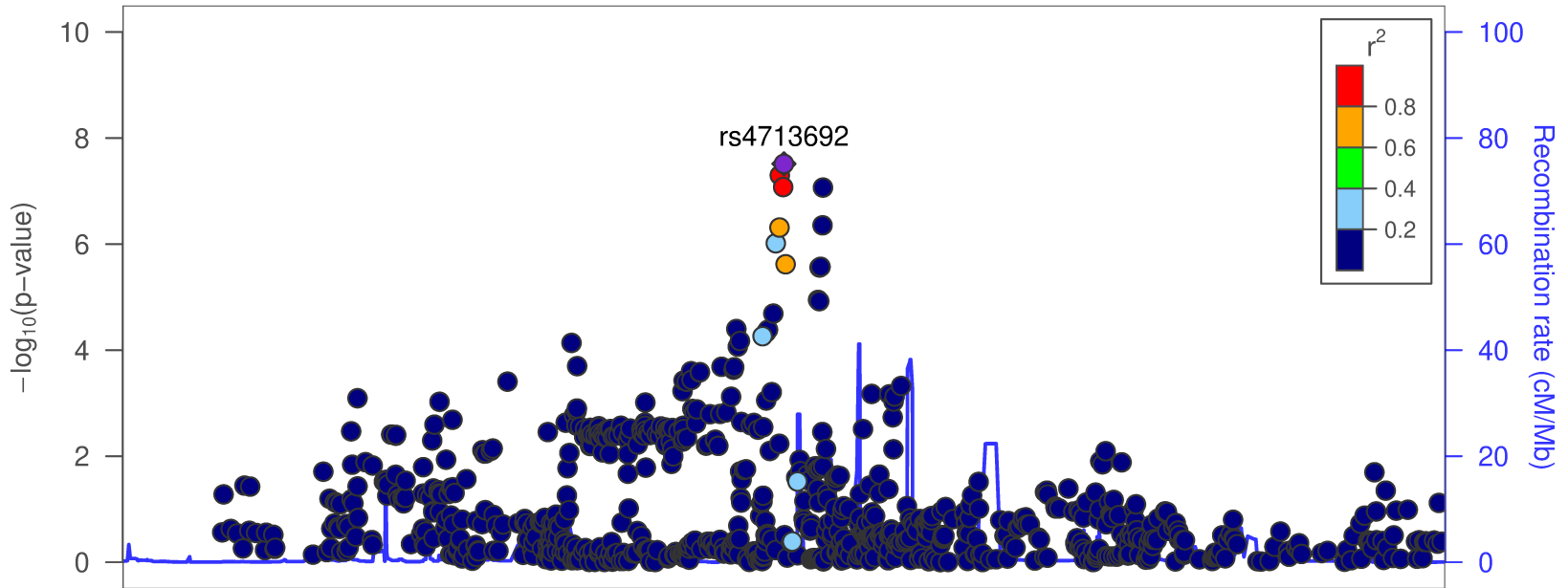


13 genes omitted

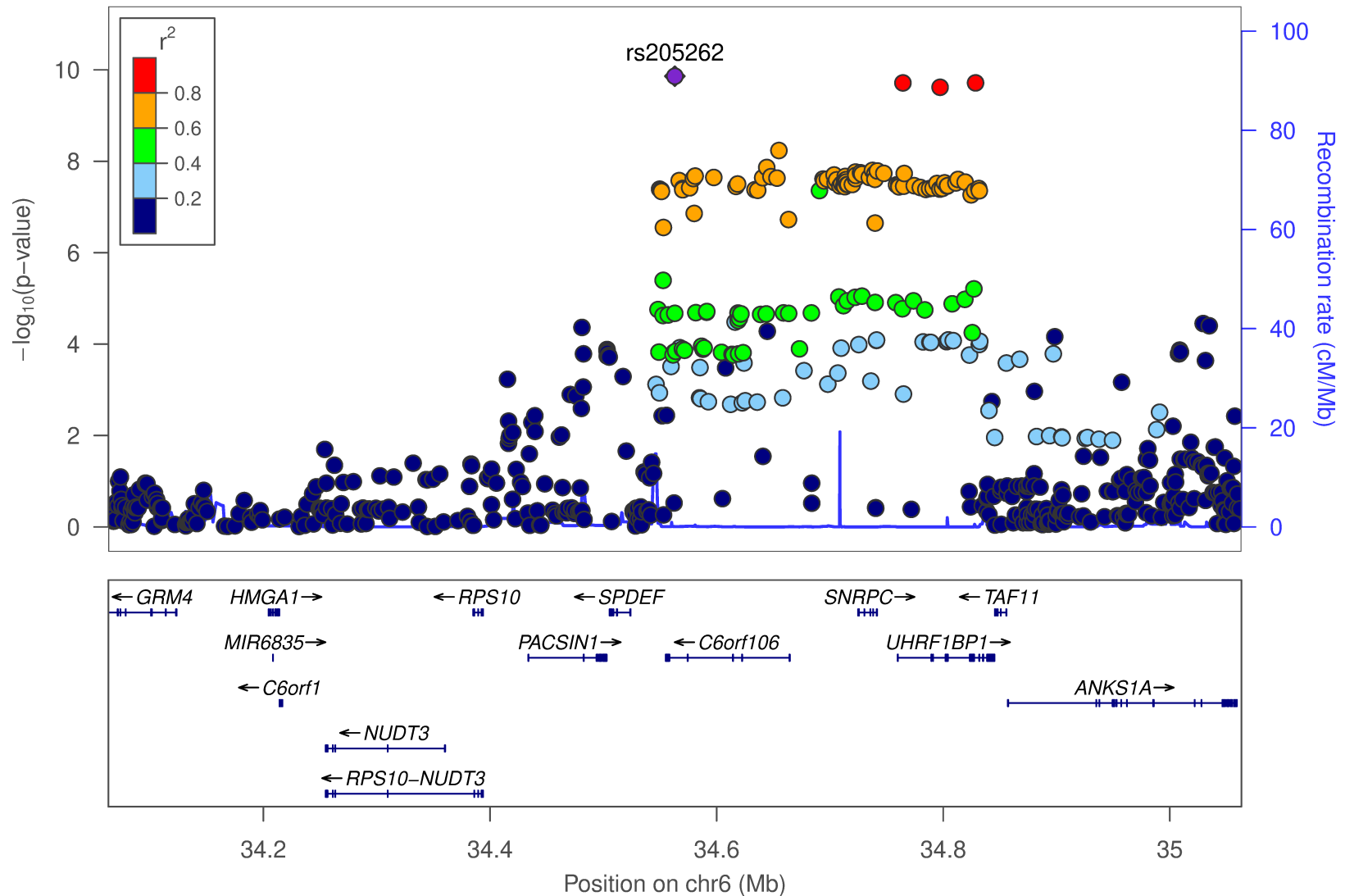
26 26.2 26.4 26.6 26.8

Position on chr6 (Mb)

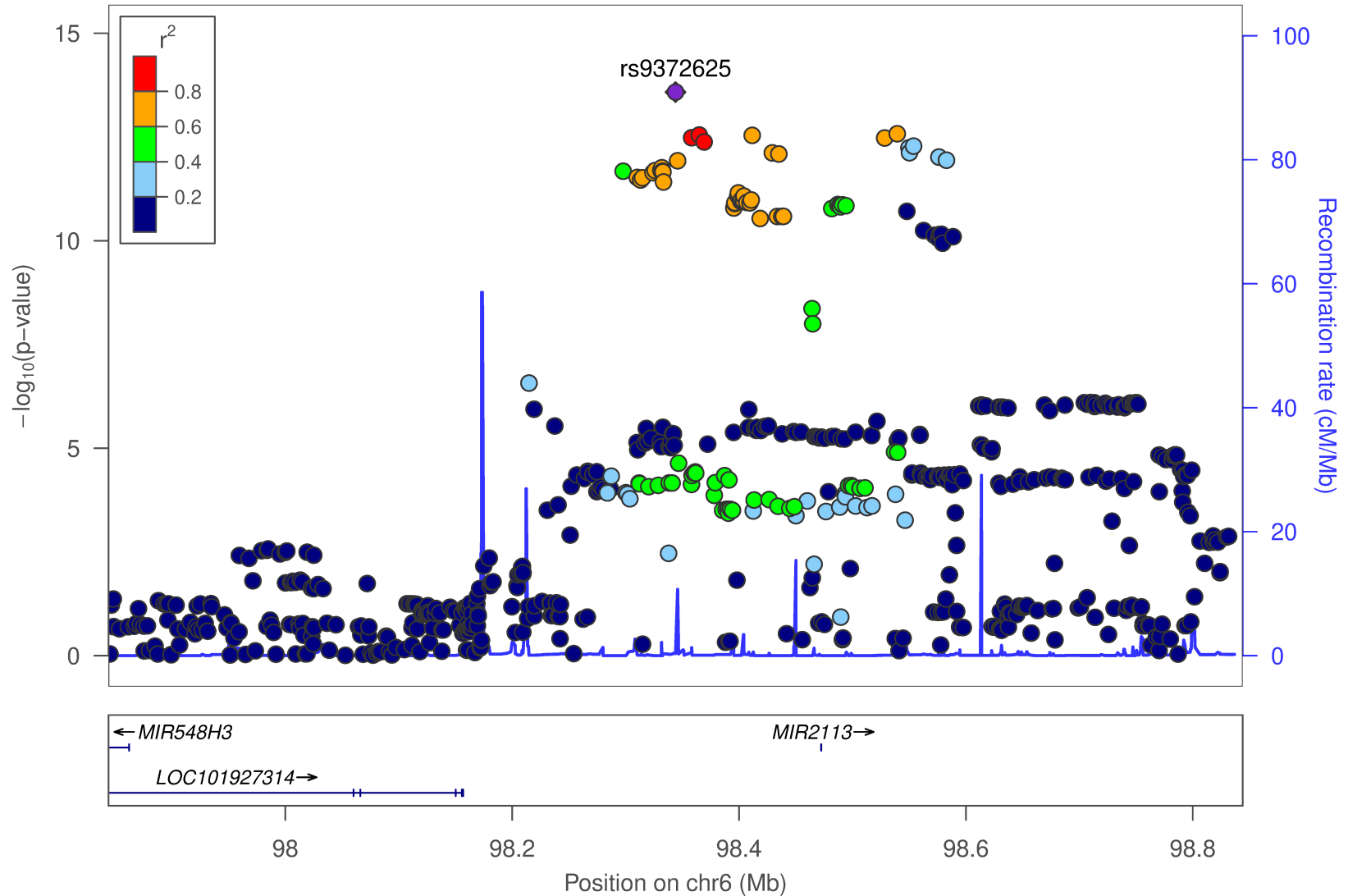
Plotted SNPs



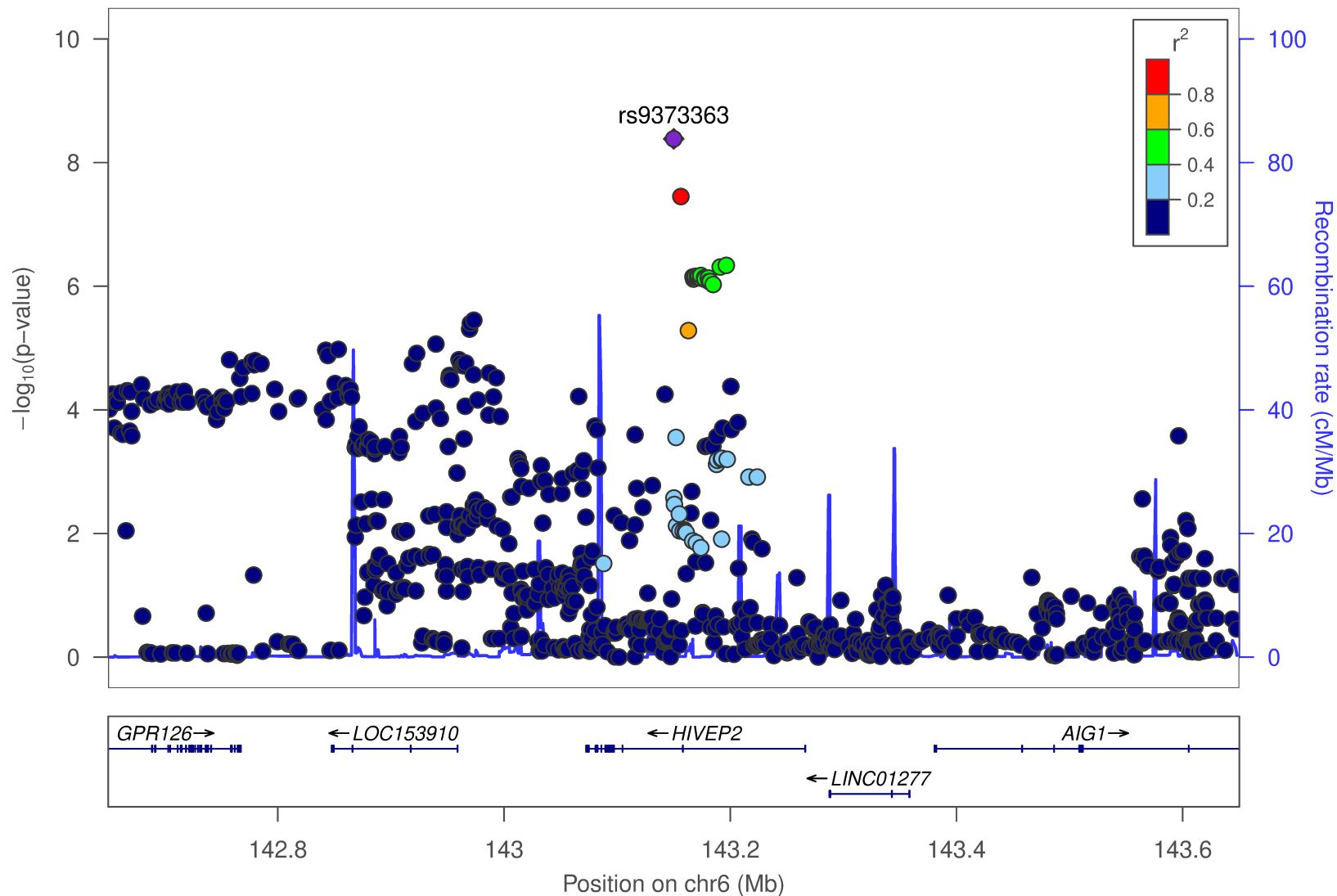
Plotted SNPs



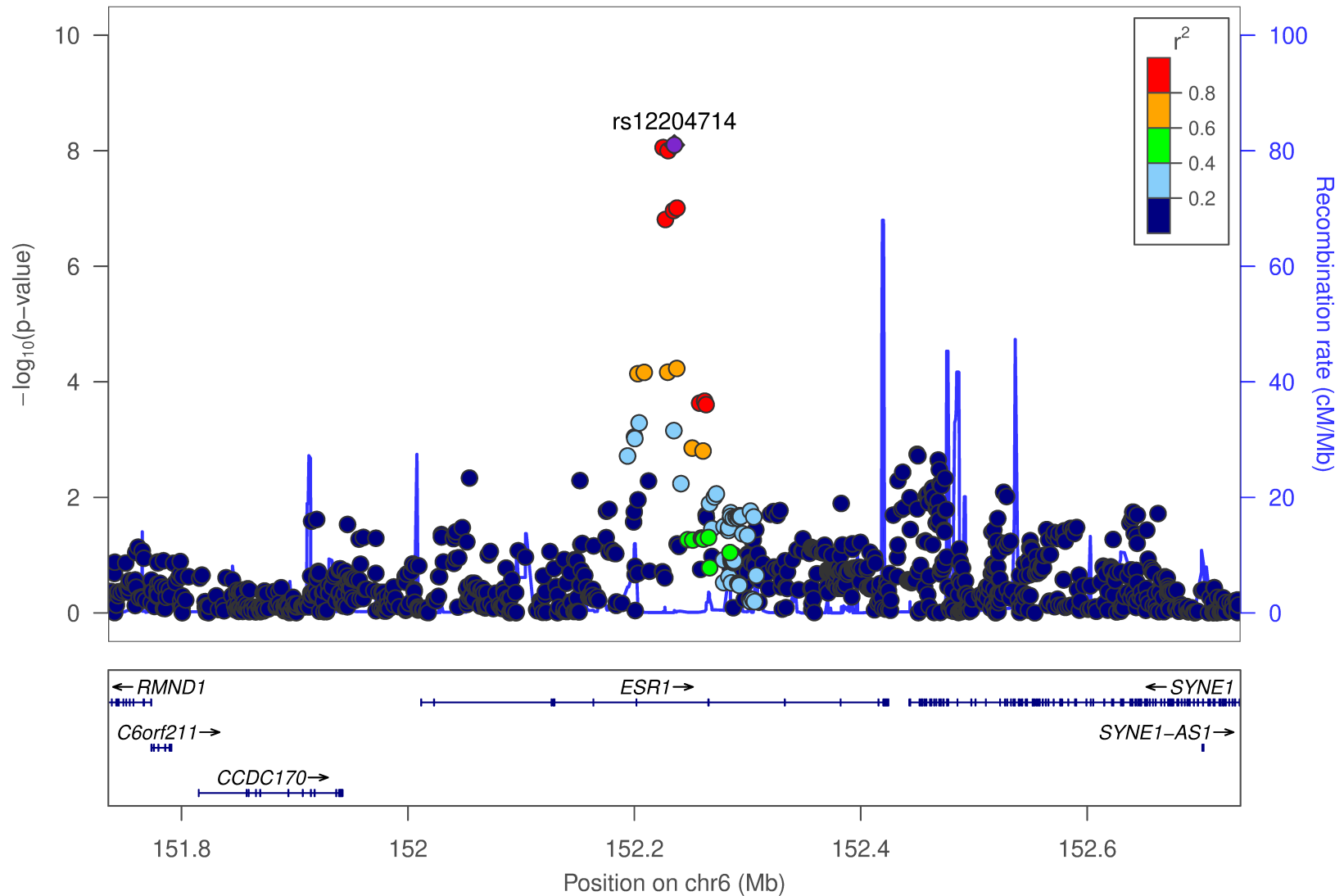
Plotted SNPs



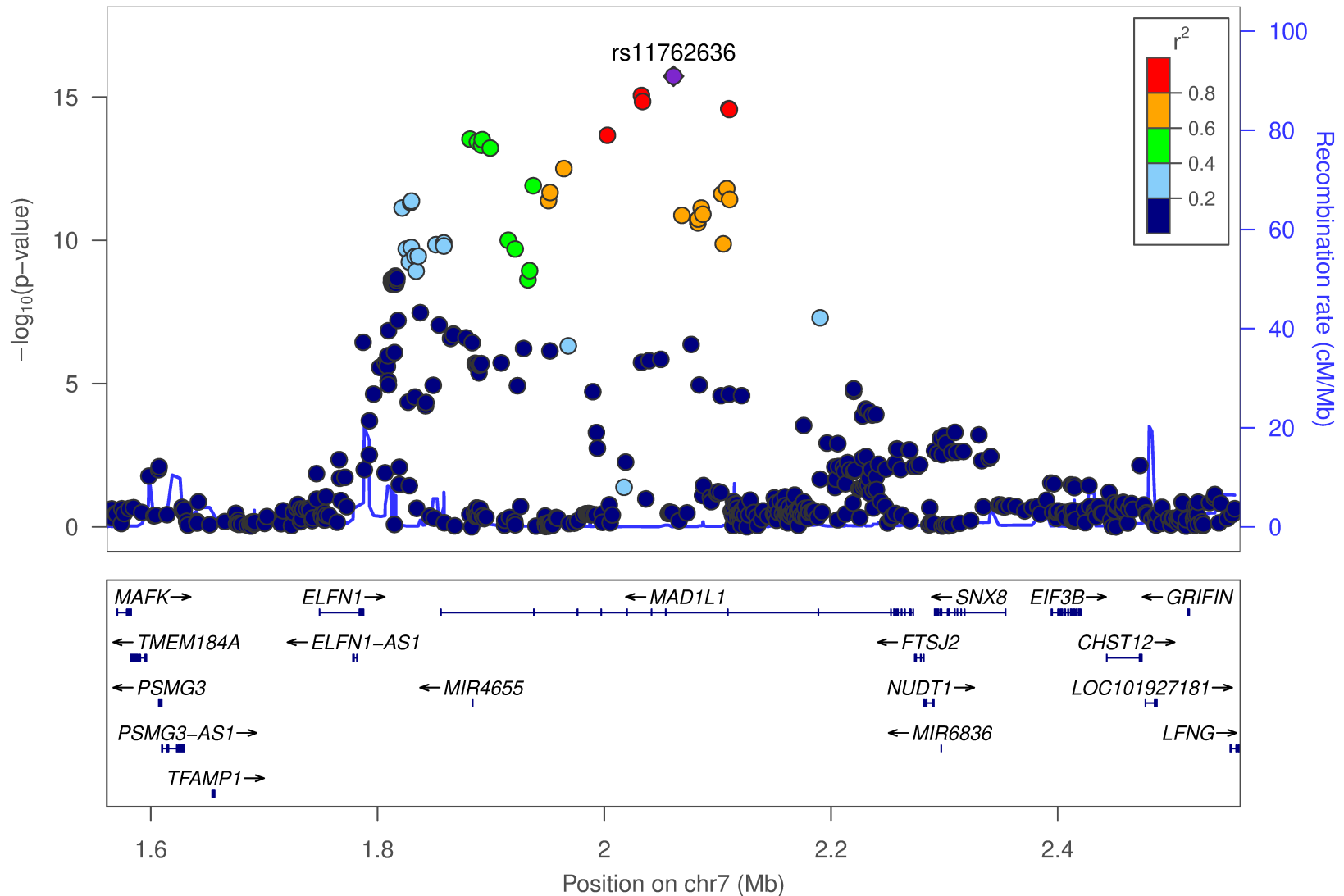
Plotted SNPs



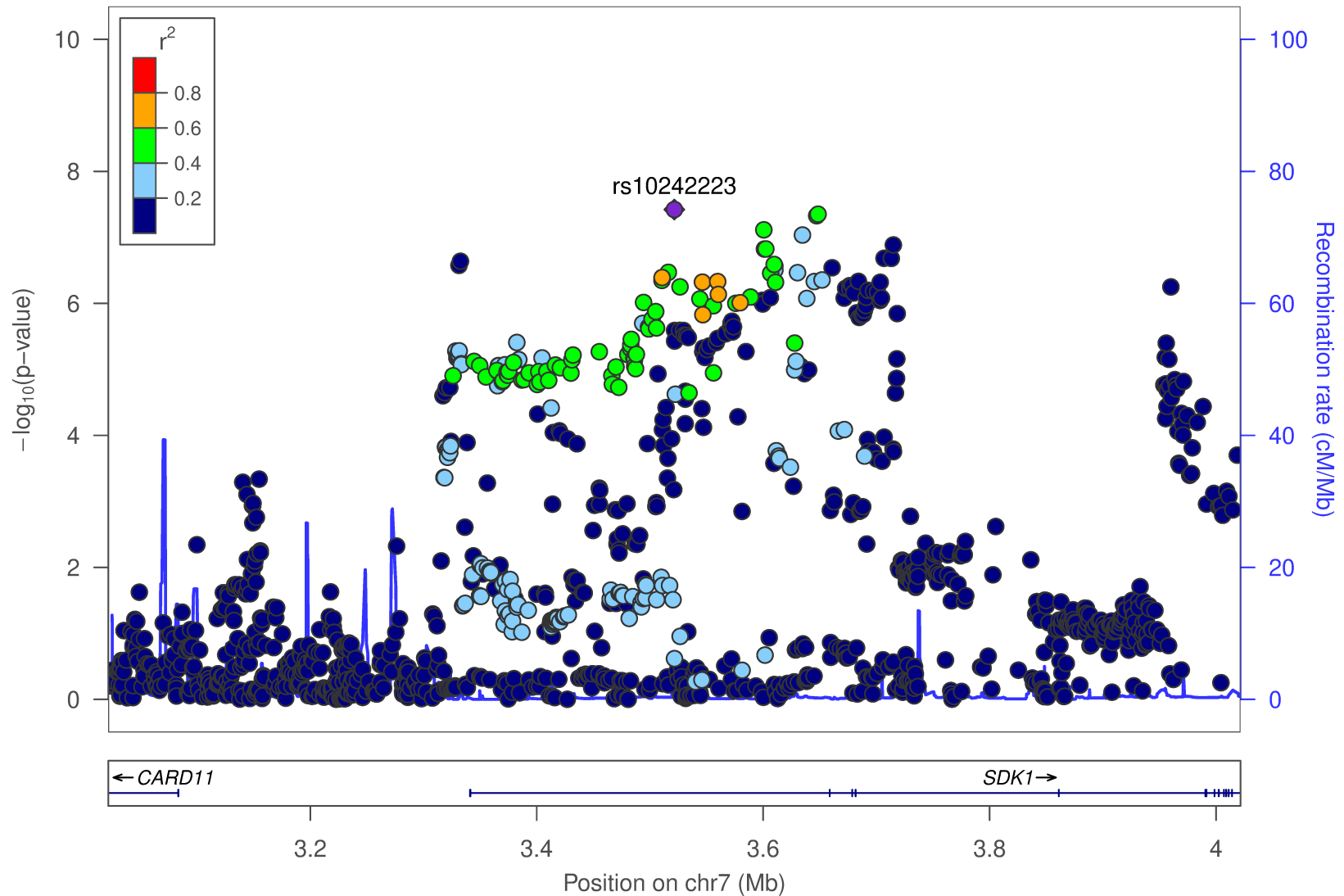
Plotted SNPs



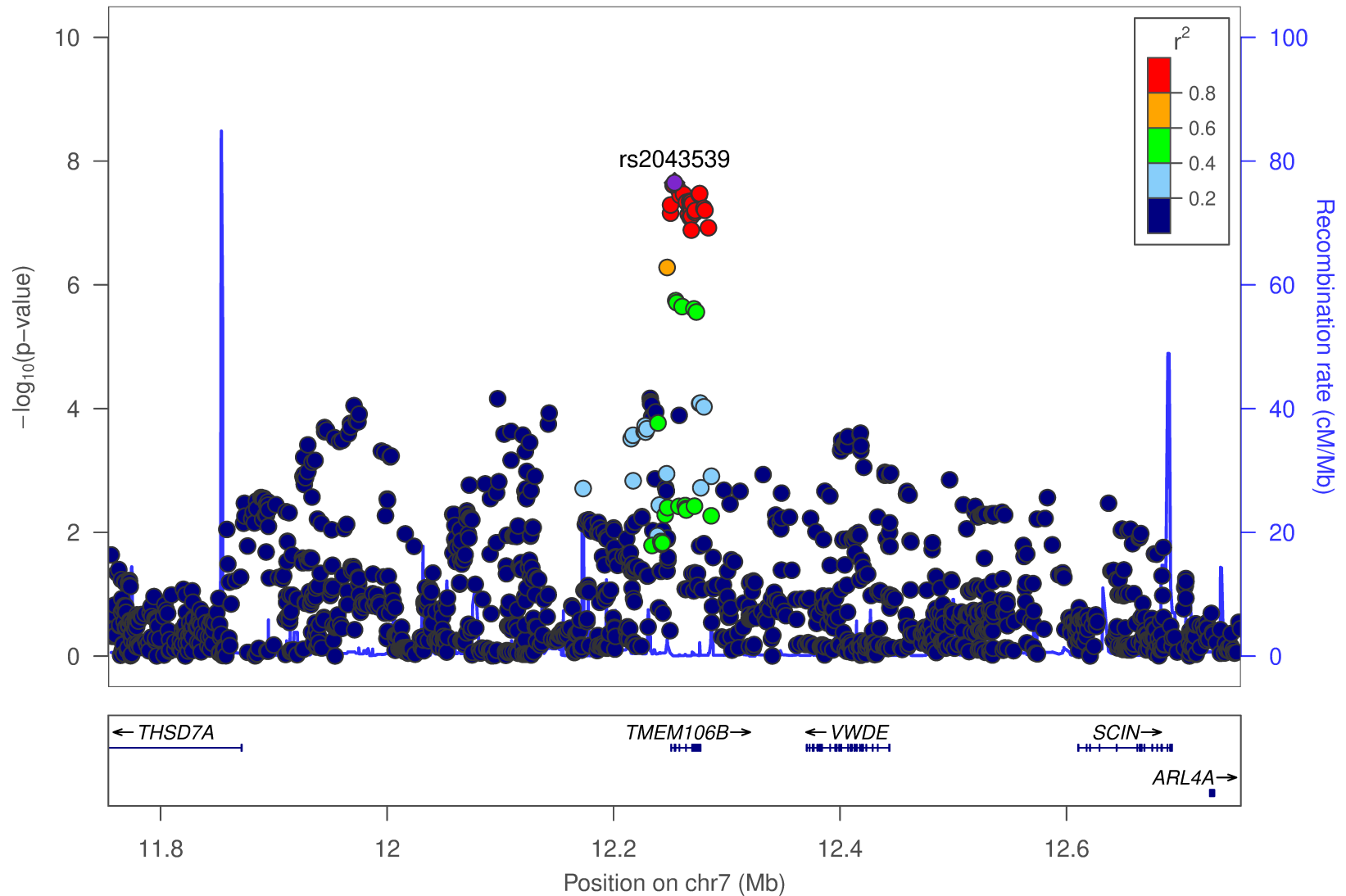
Plotted SNPs



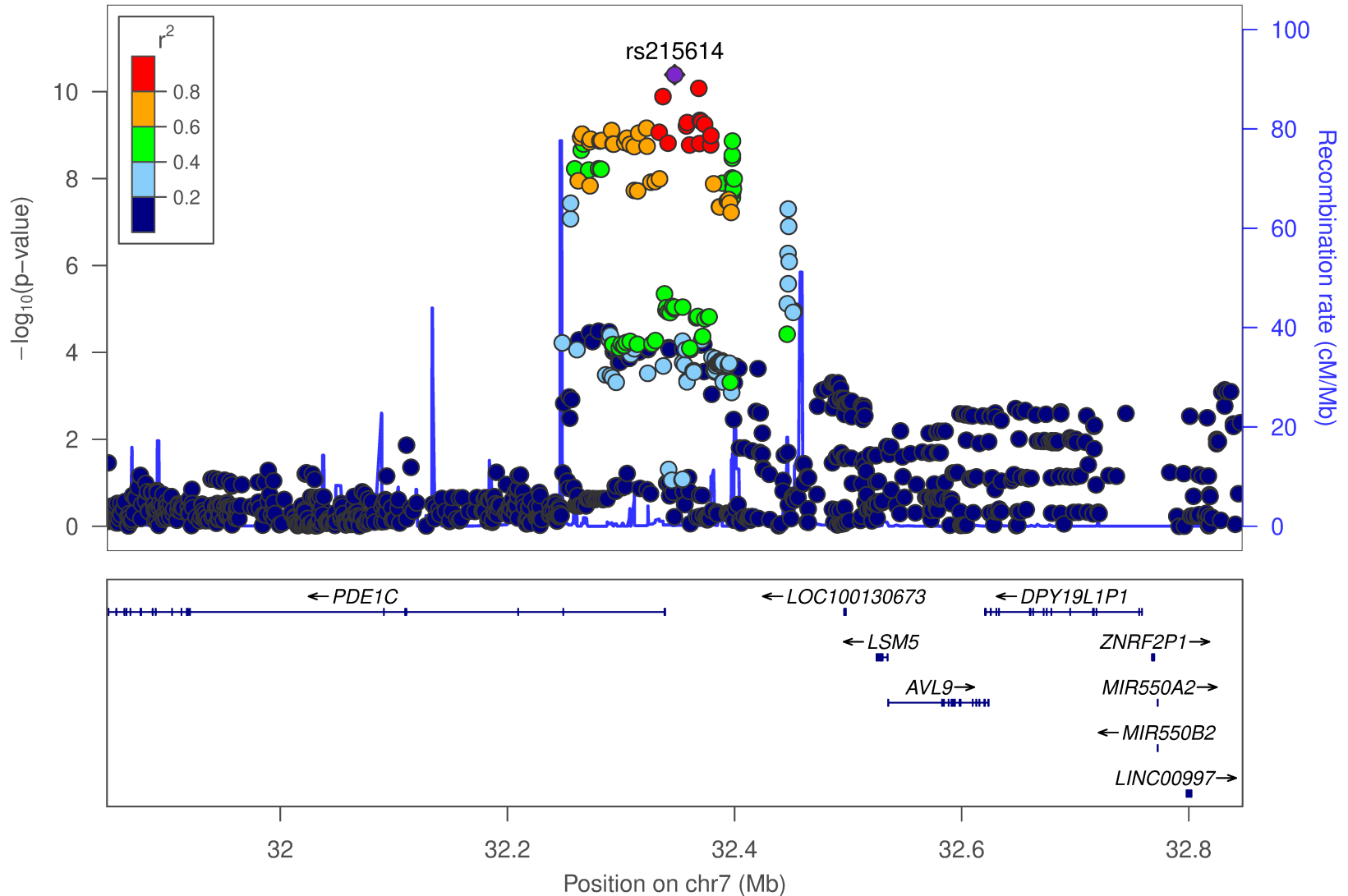
Plotted SNPs



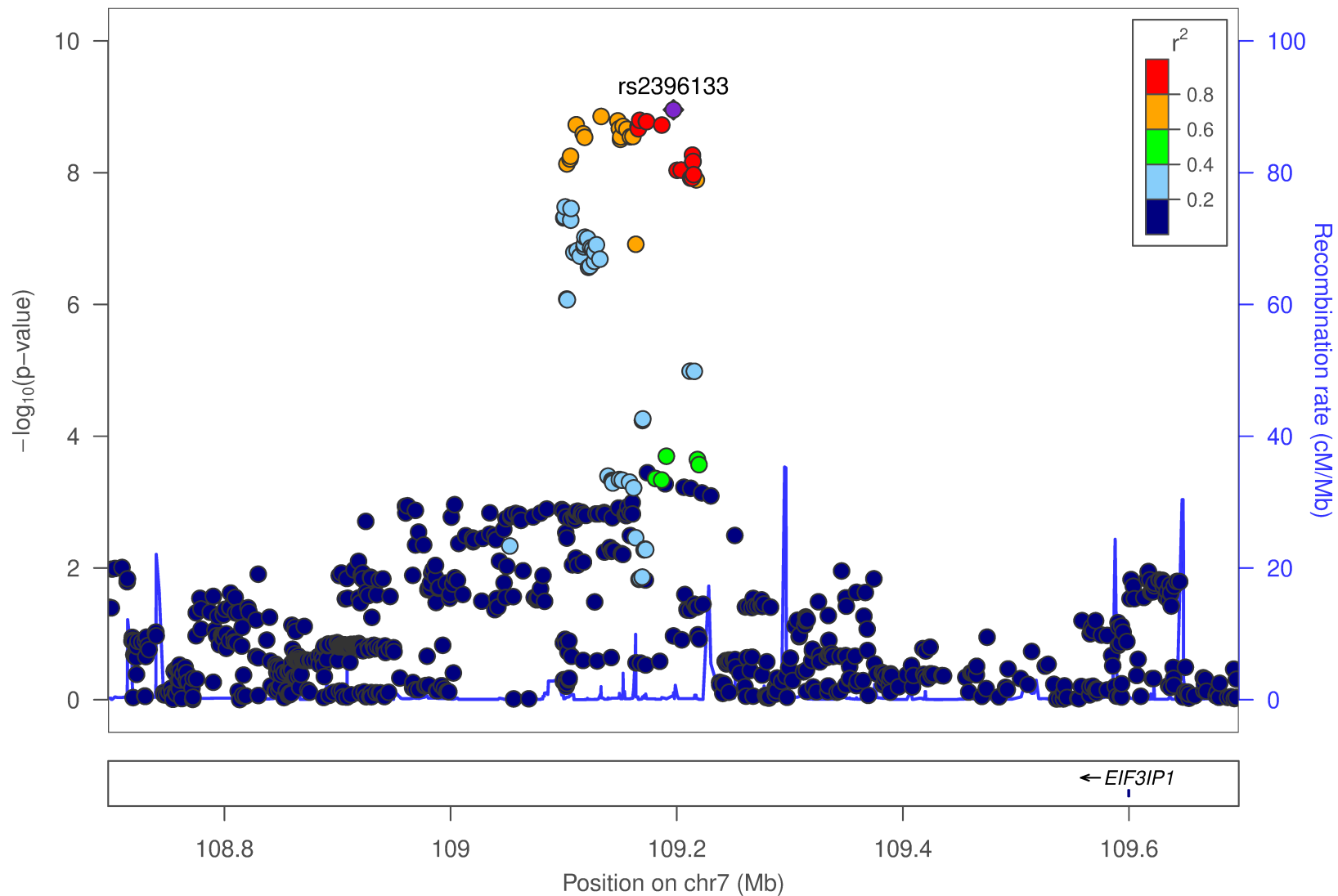
Plotted SNPs



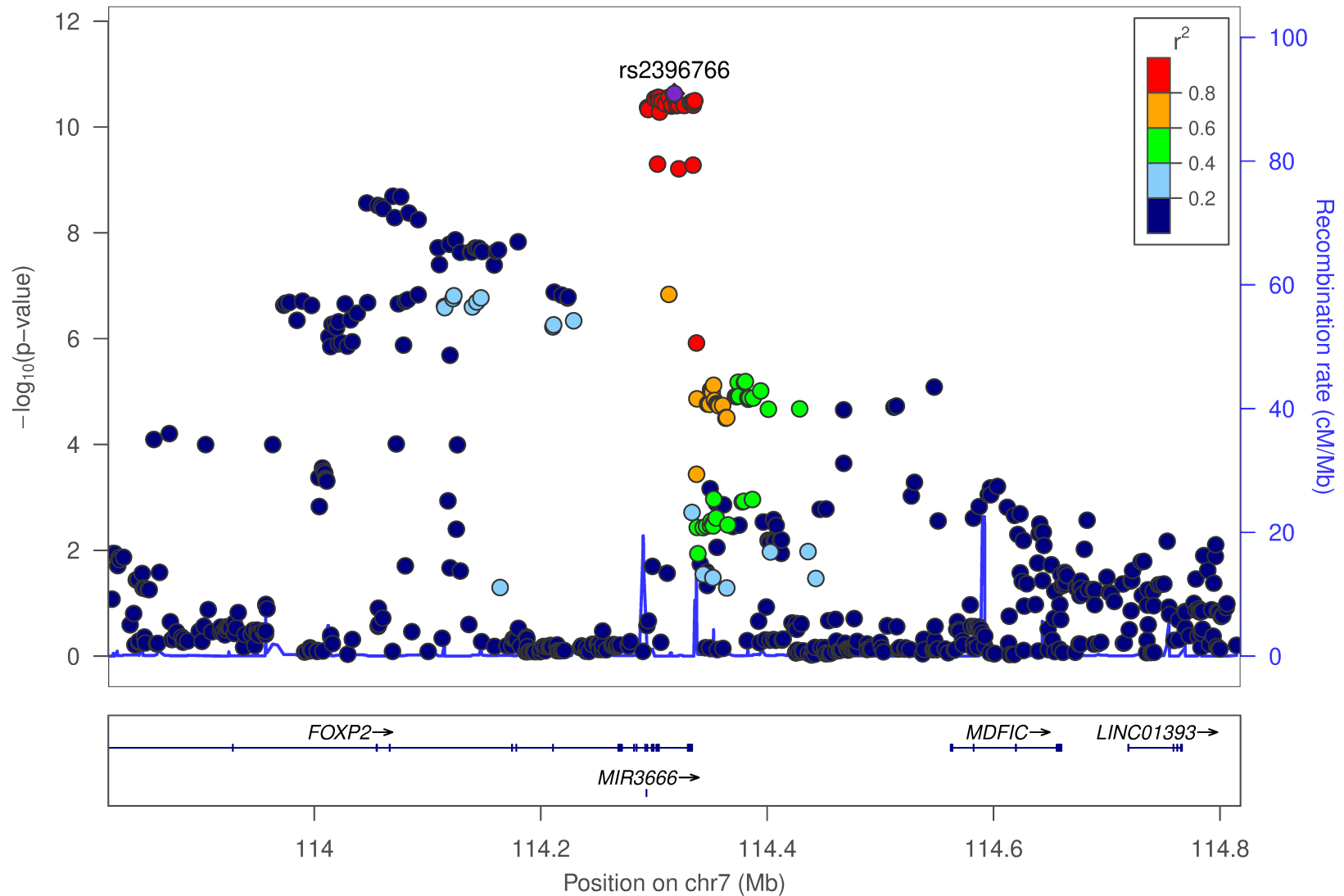
Plotted SNPs



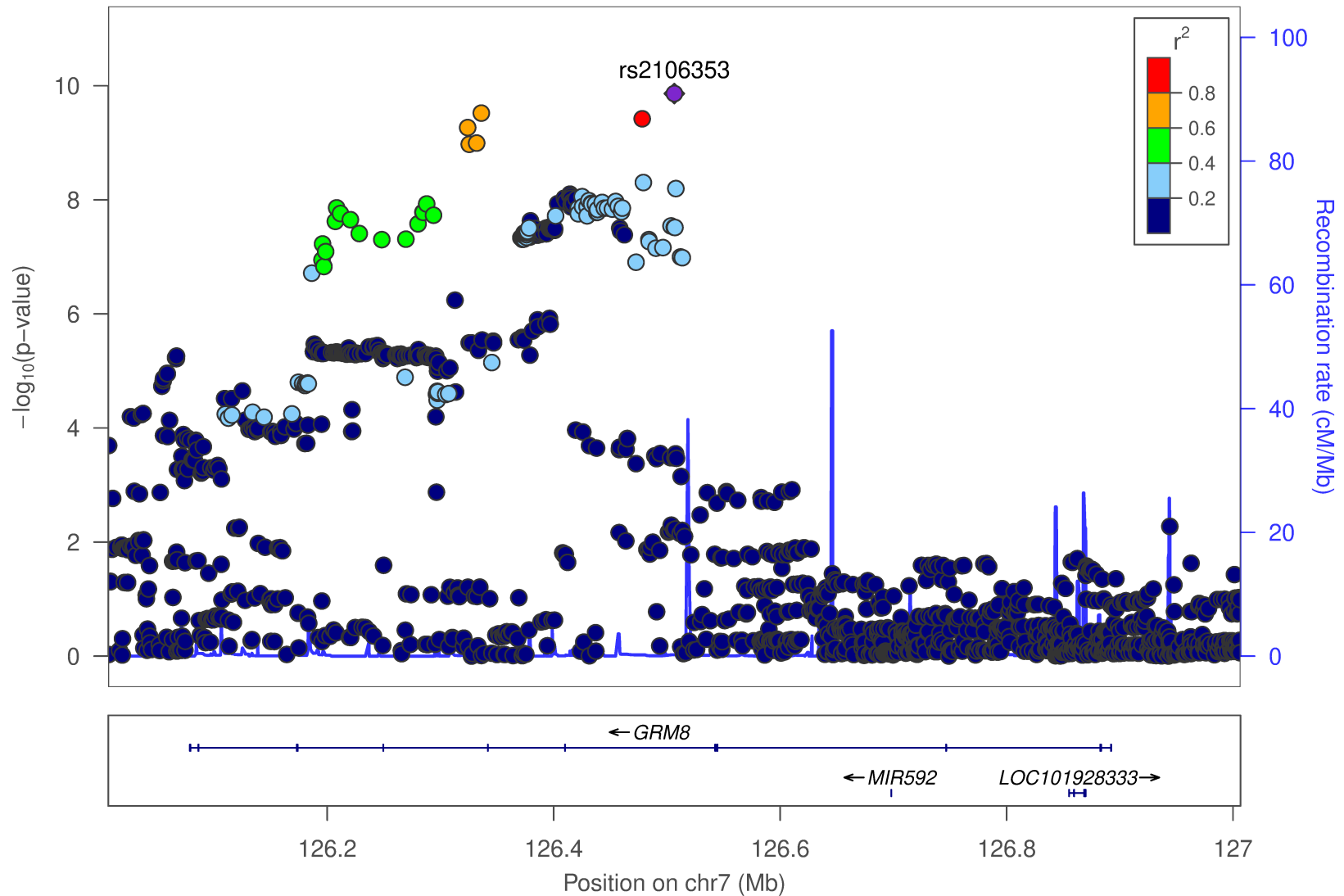
Plotted SNPs

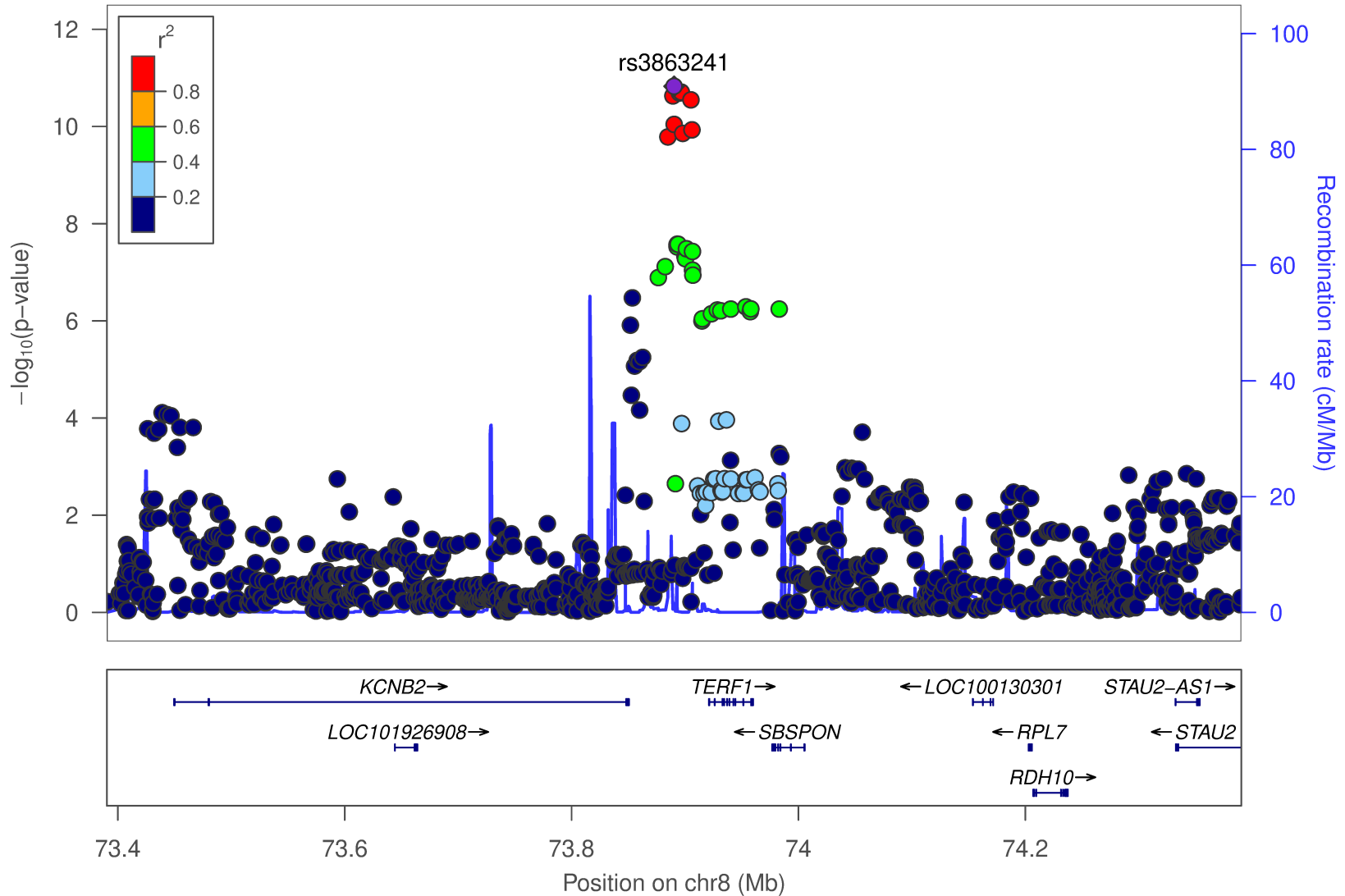


Plotted SNPs

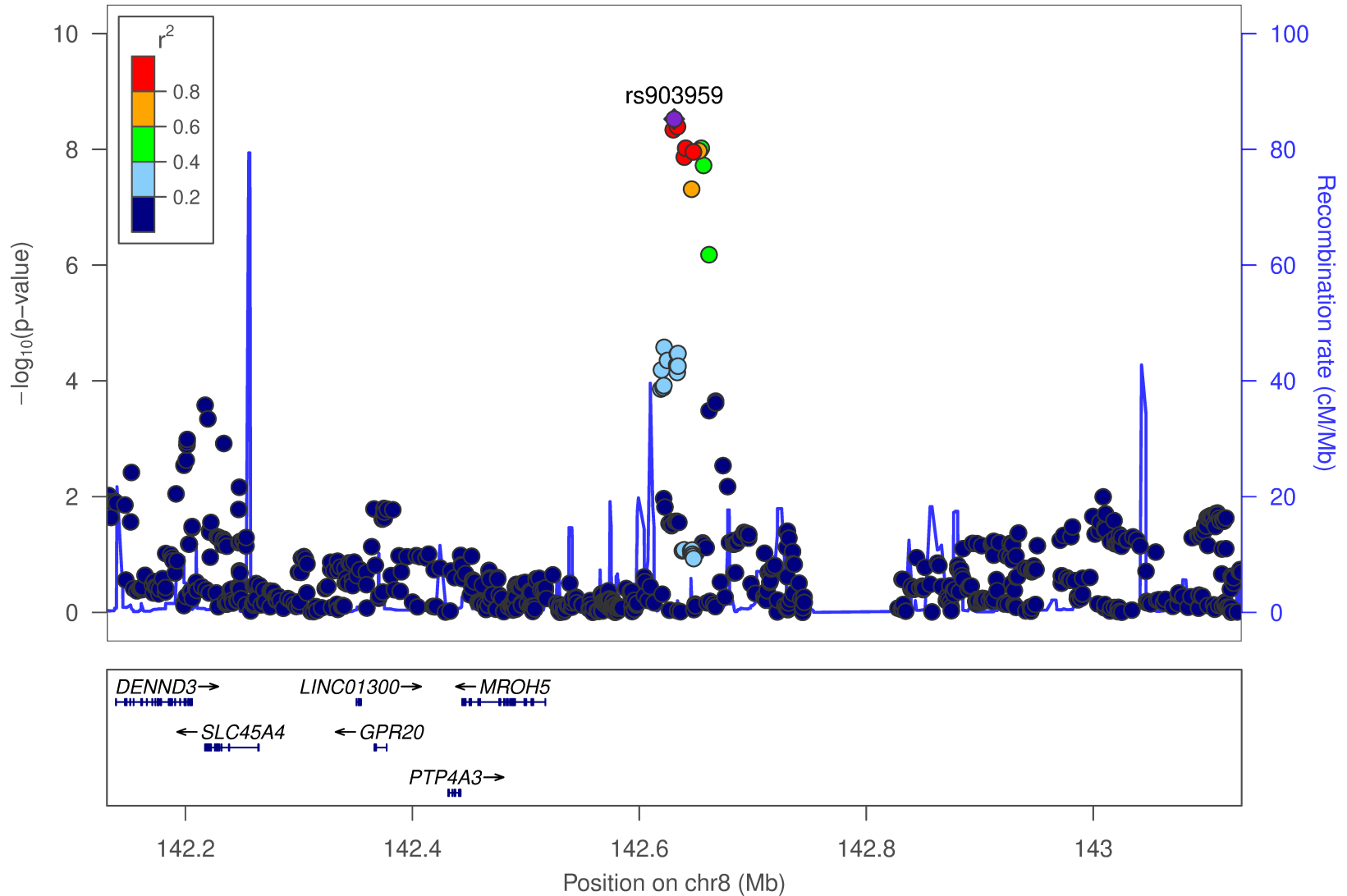


Plotted SNPs

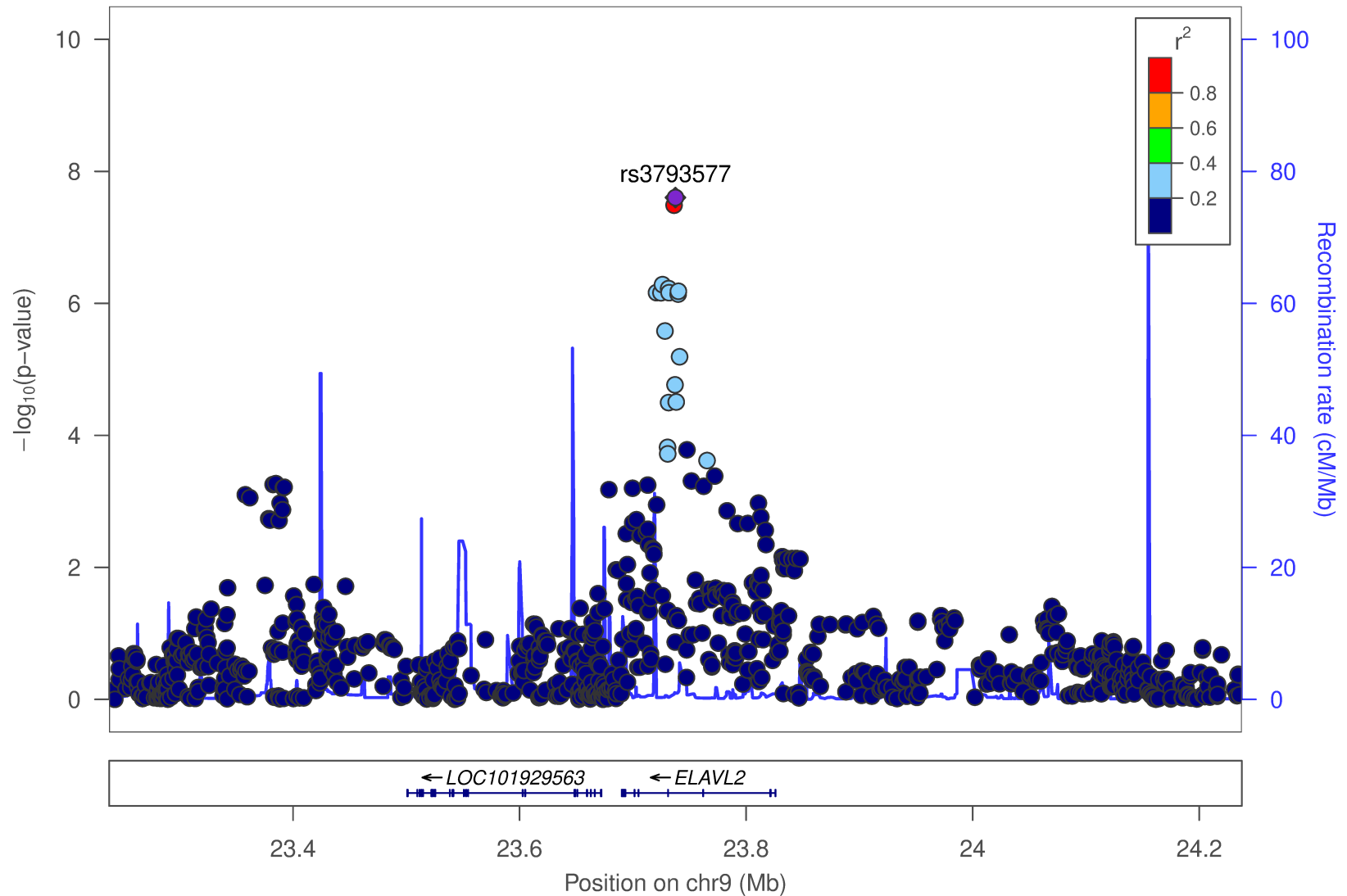


Plotted SNPs | 

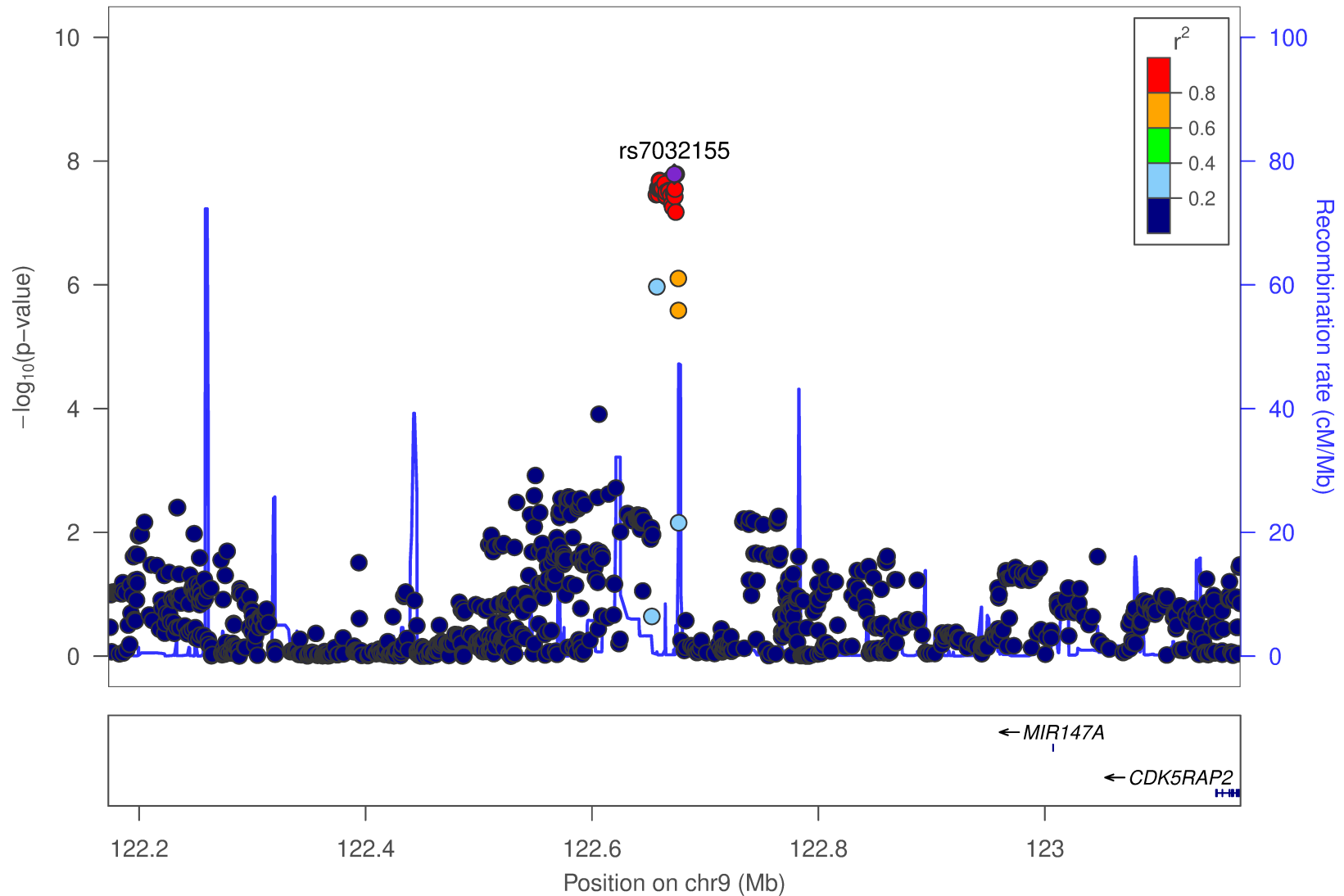
Plotted SNPs



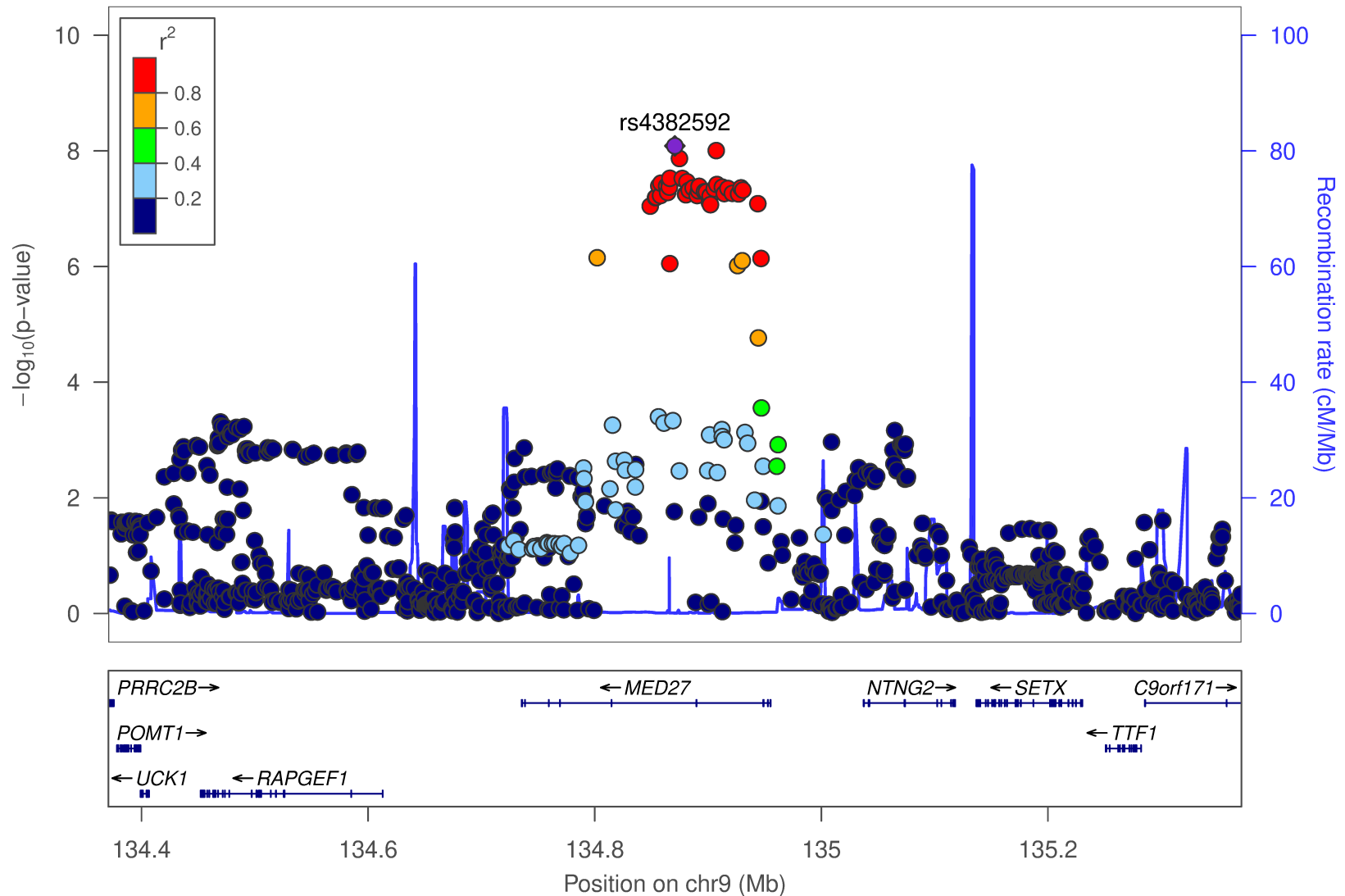
Plotted SNPs



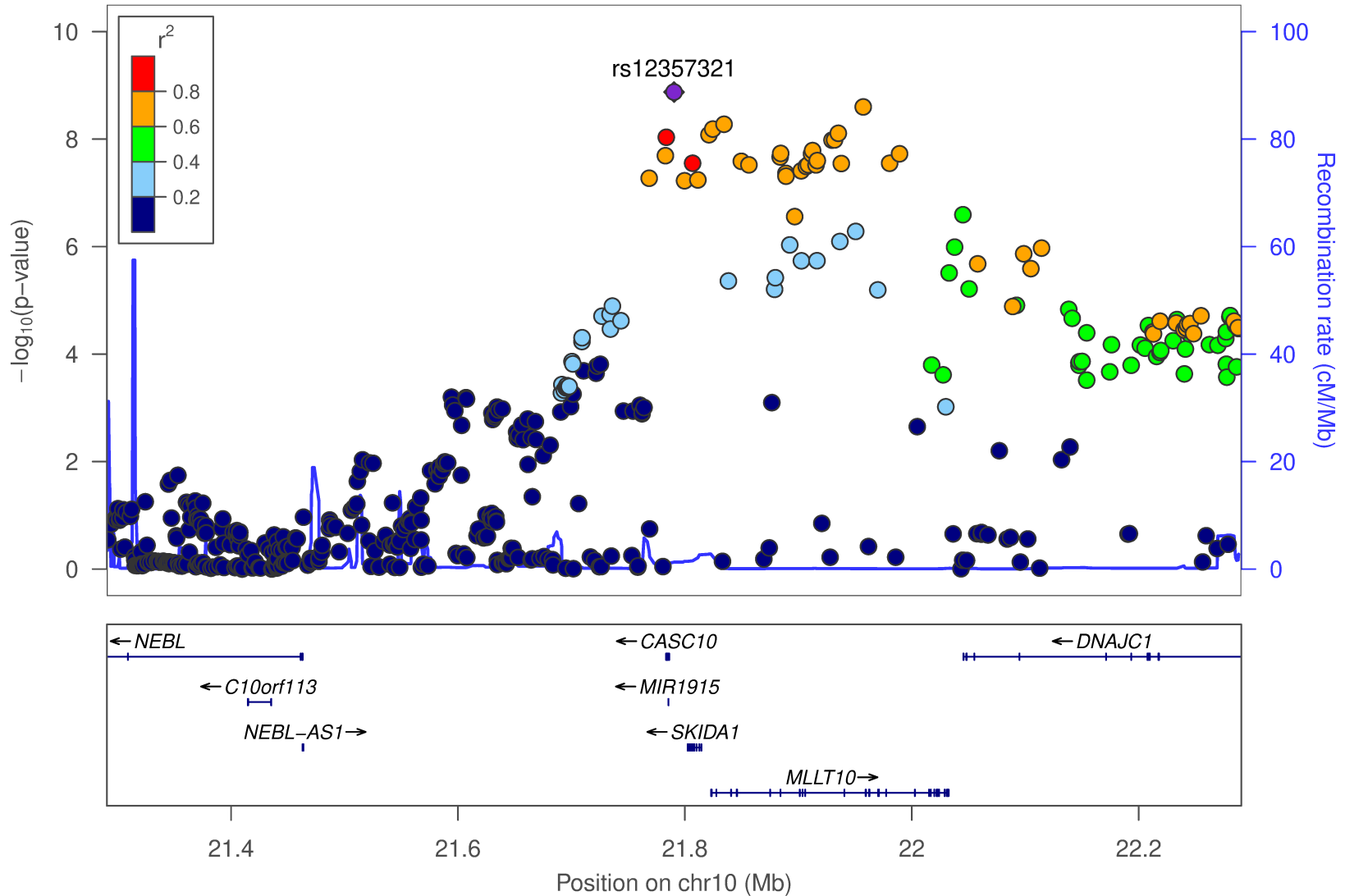
Plotted SNPs



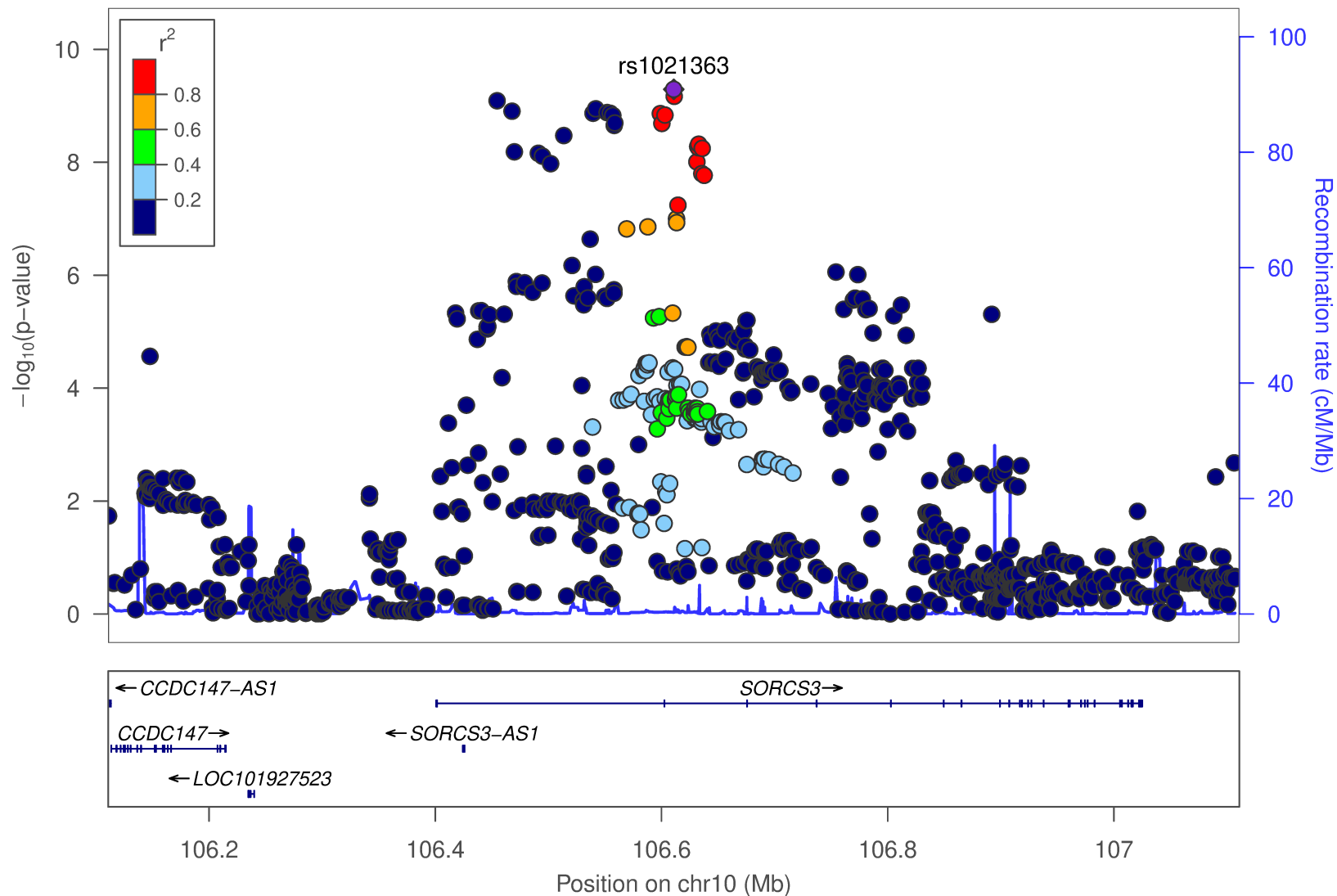
Plotted SNPs



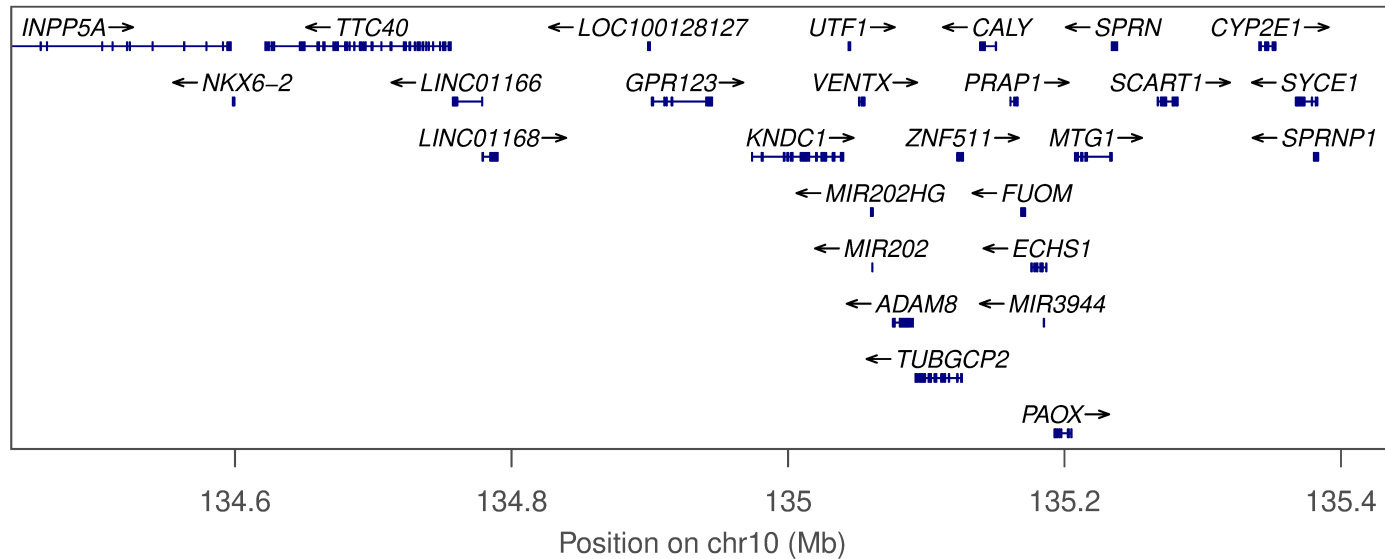
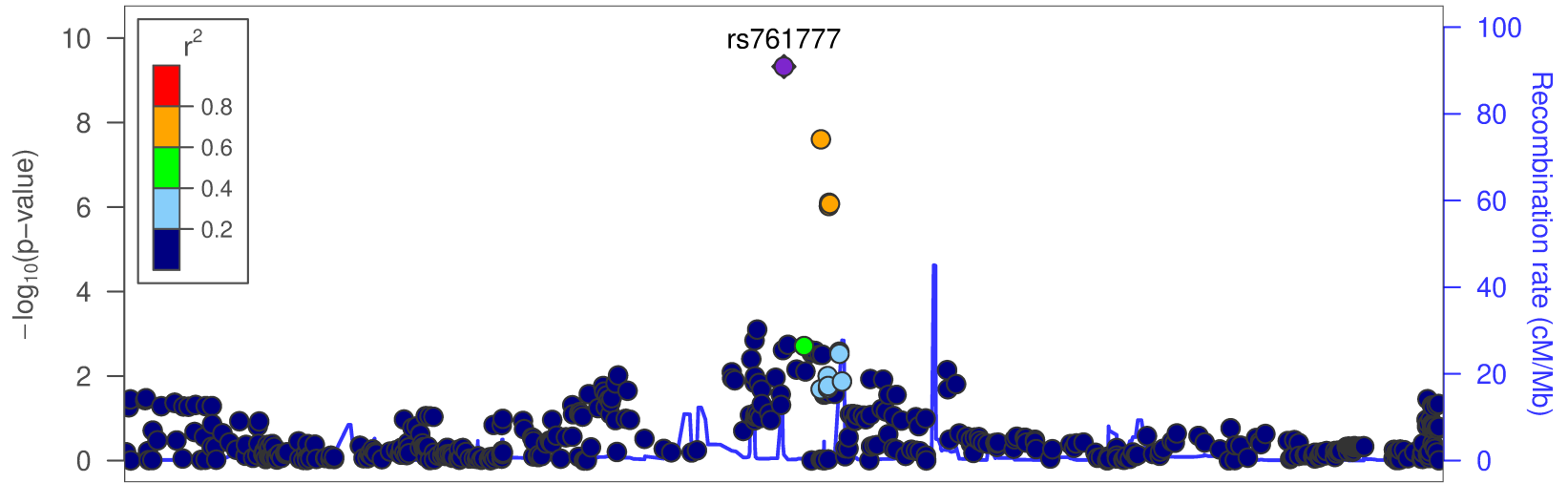
Plotted SNPs



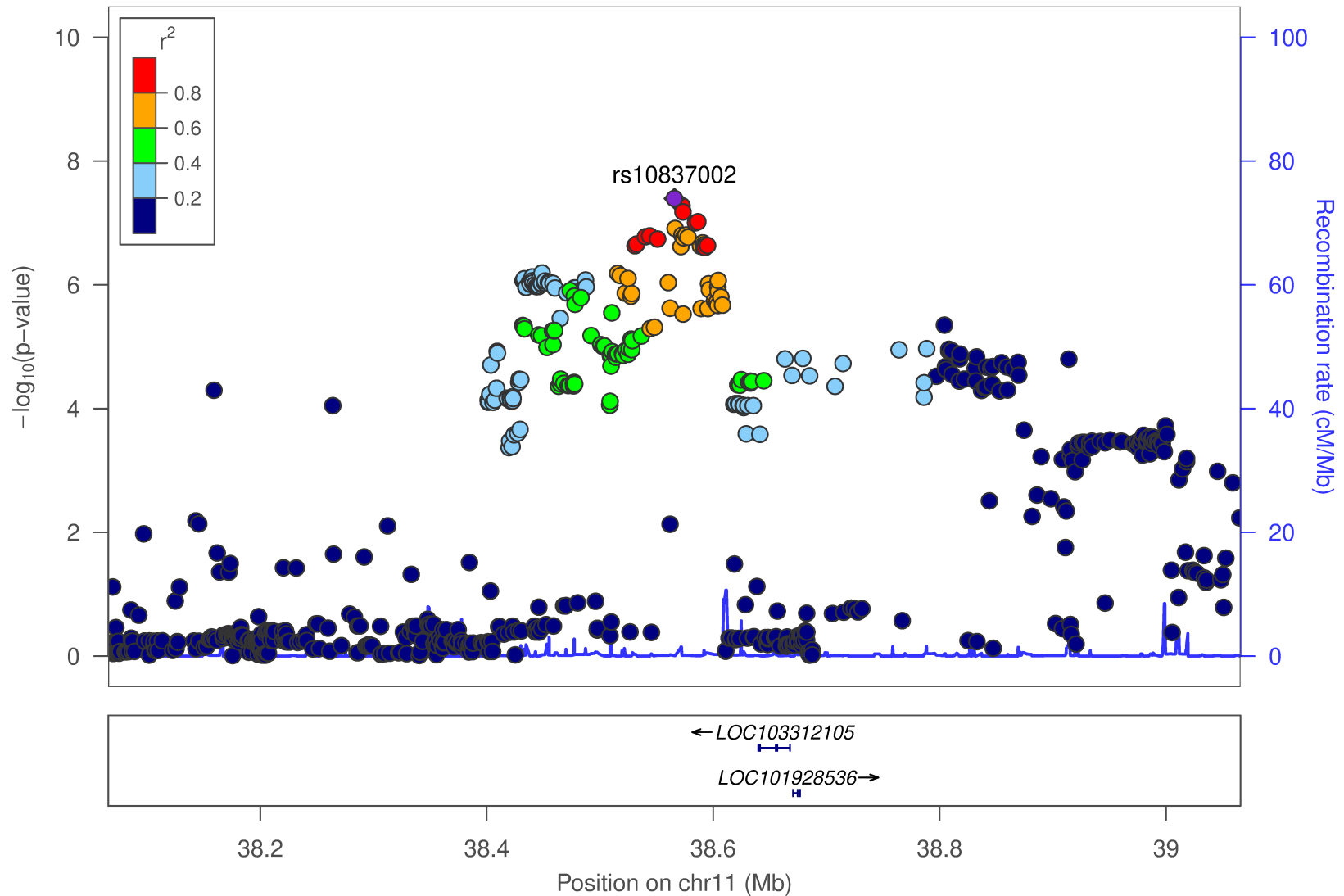
Plotted SNPs



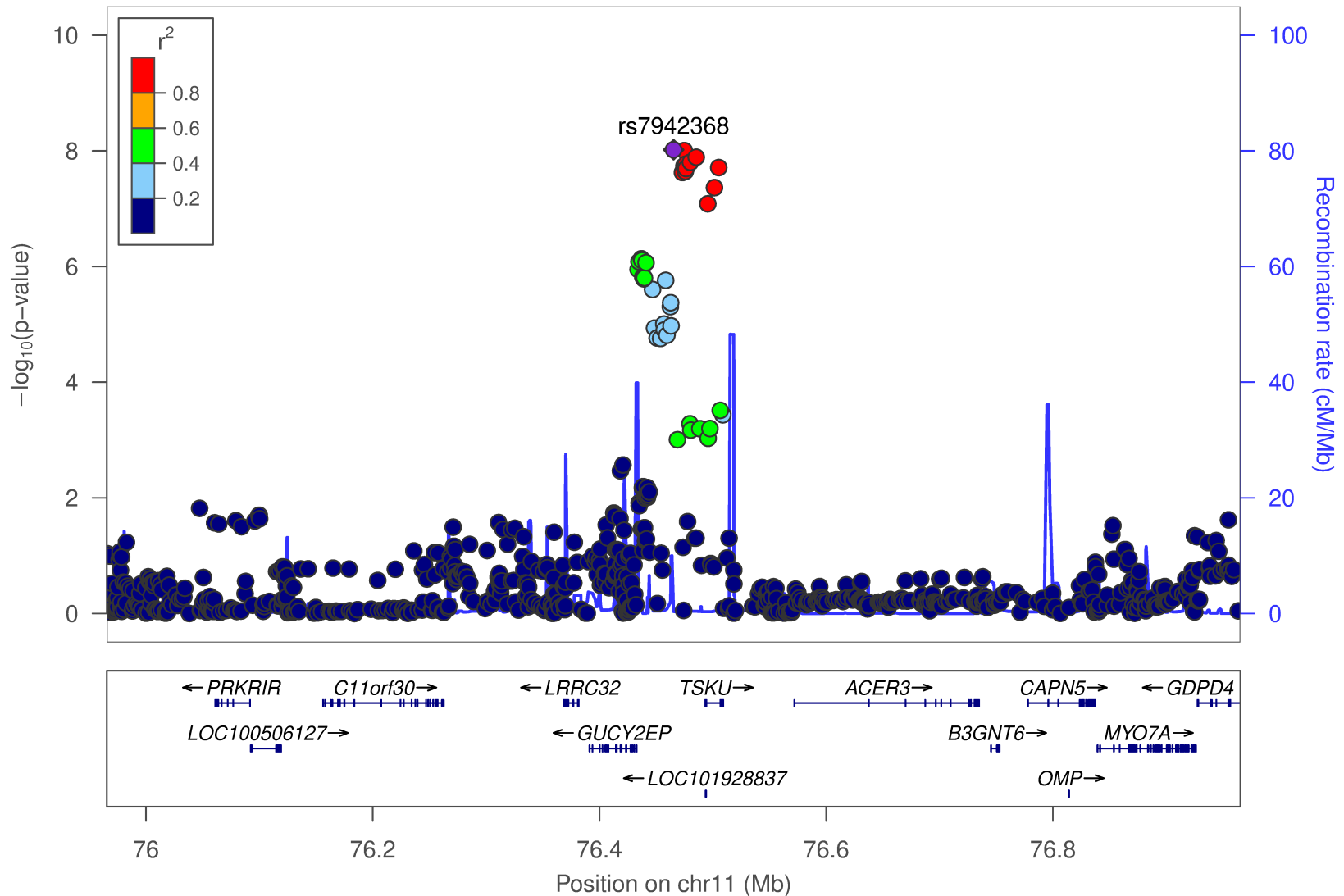
Plotted SNPs



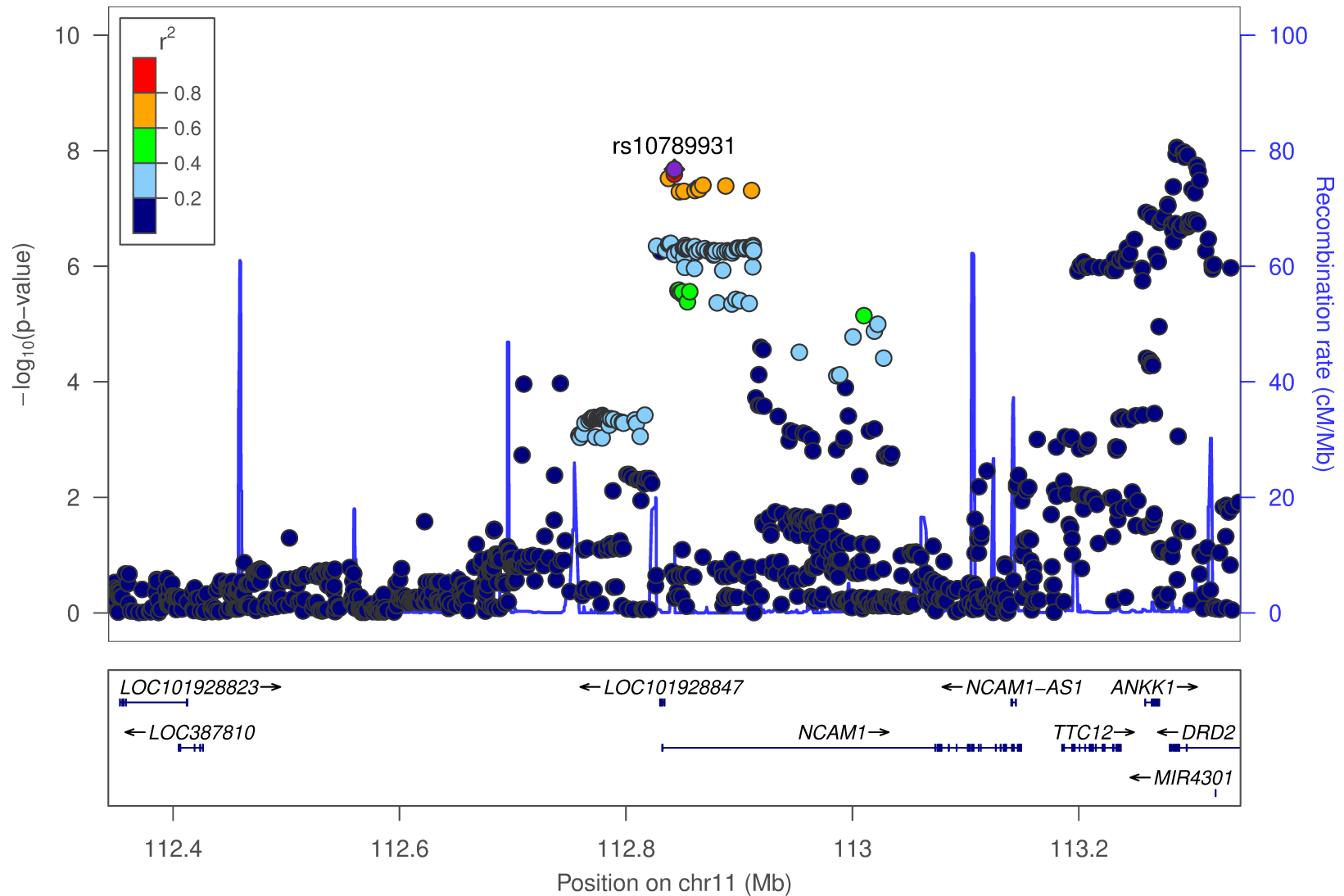
Plotted SNPs



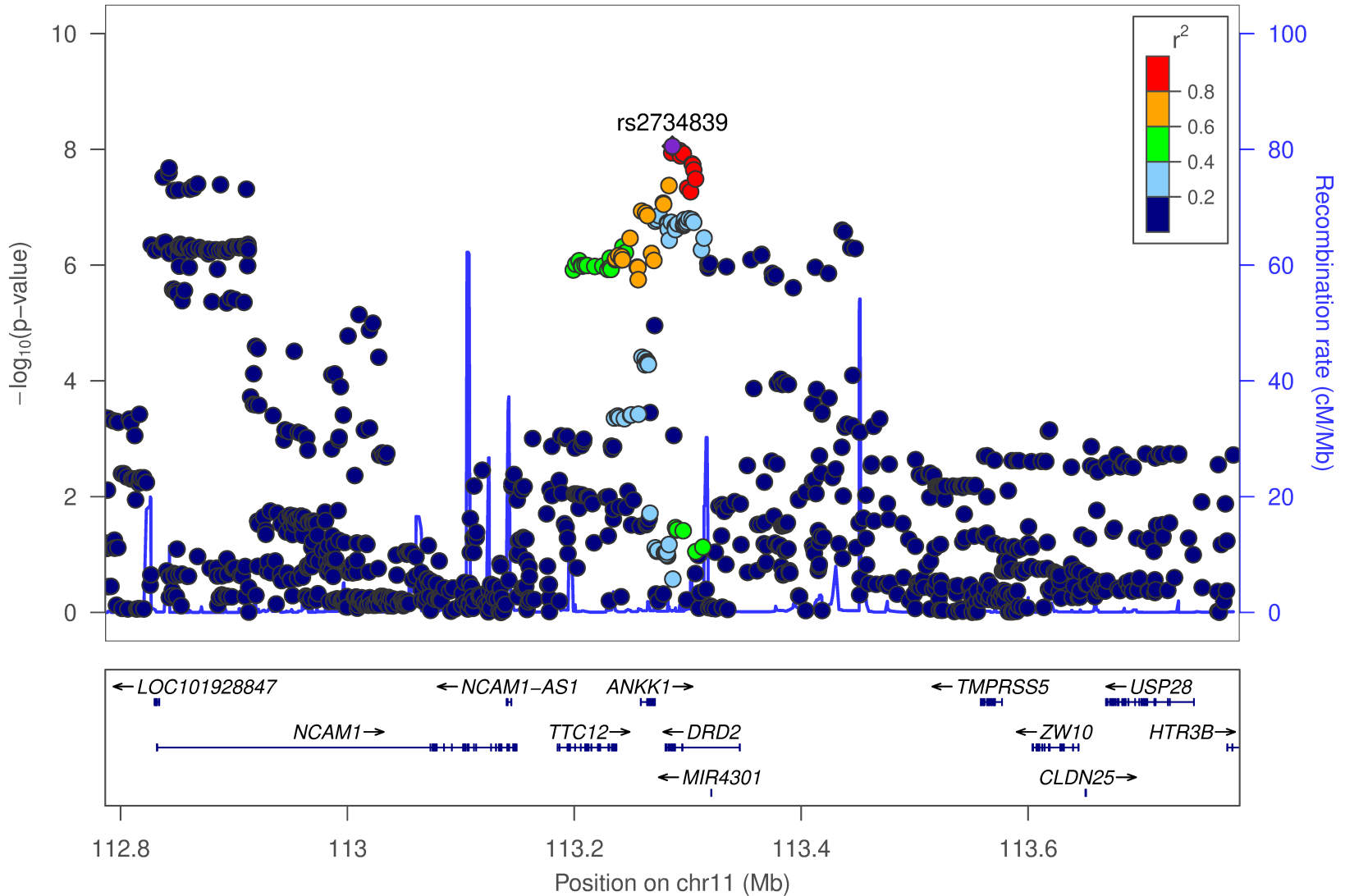
Plotted SNPs



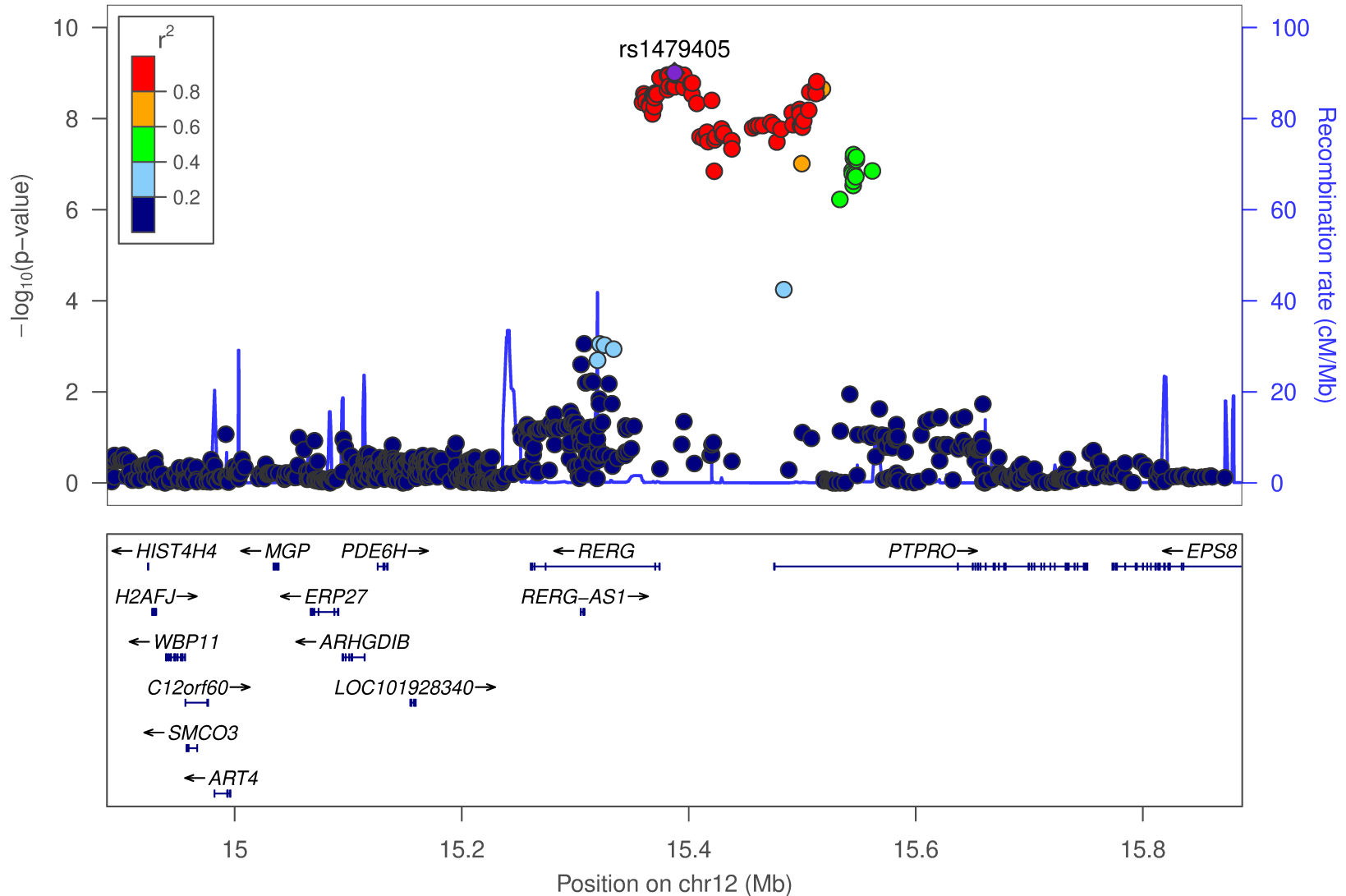
Plotted SNPs



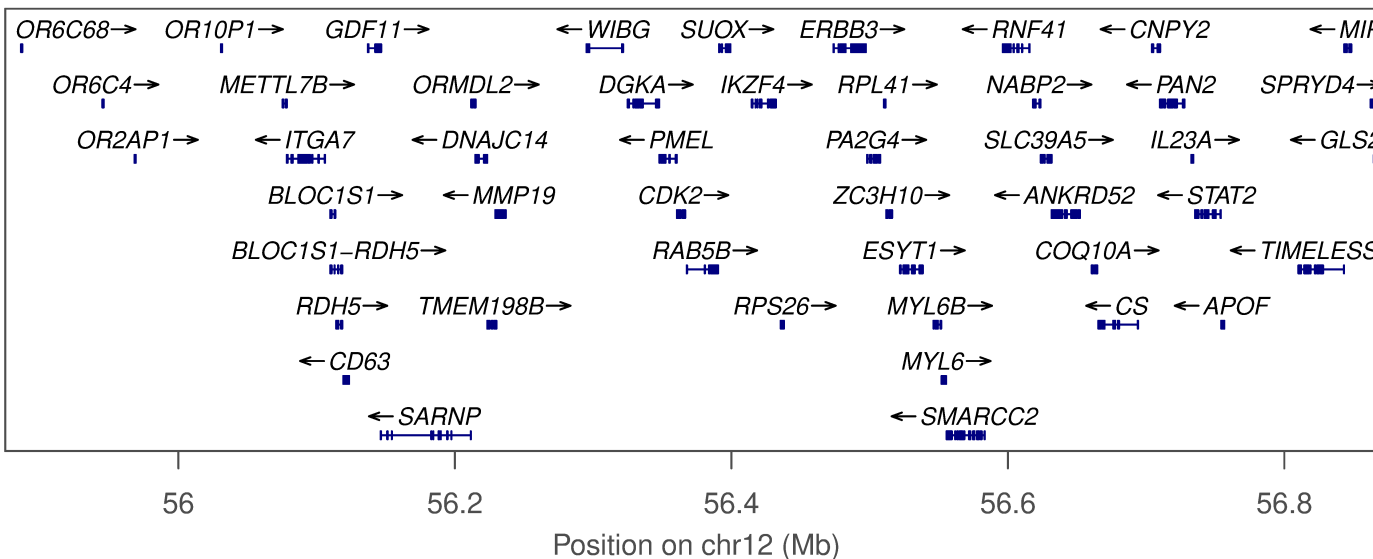
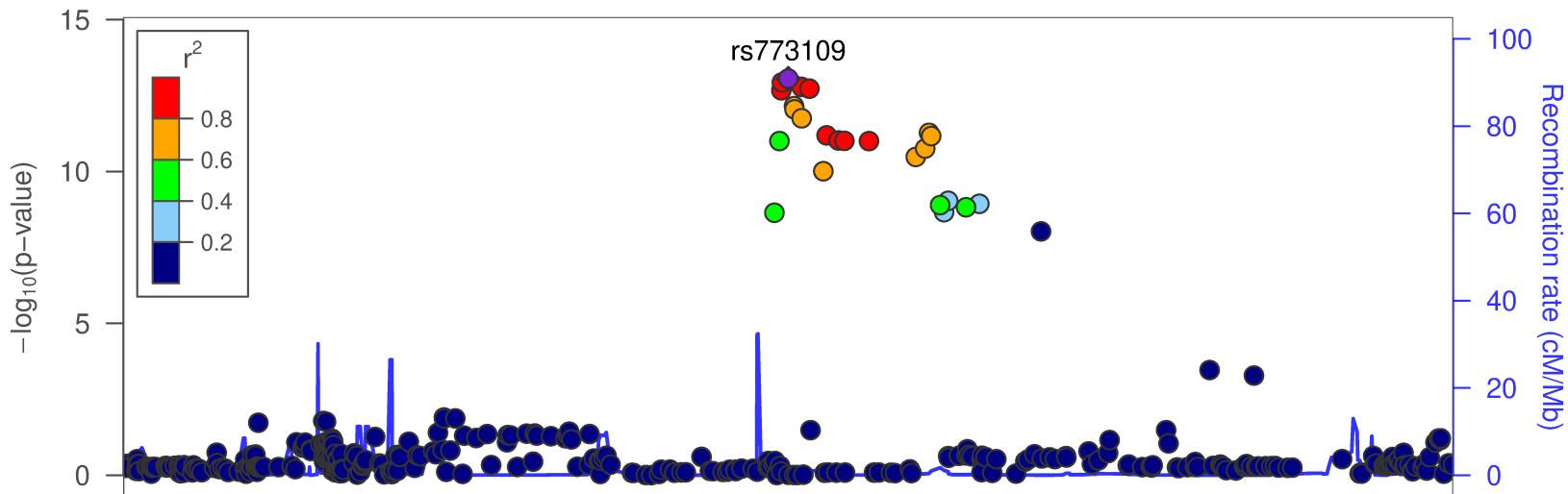
Plotted SNPs



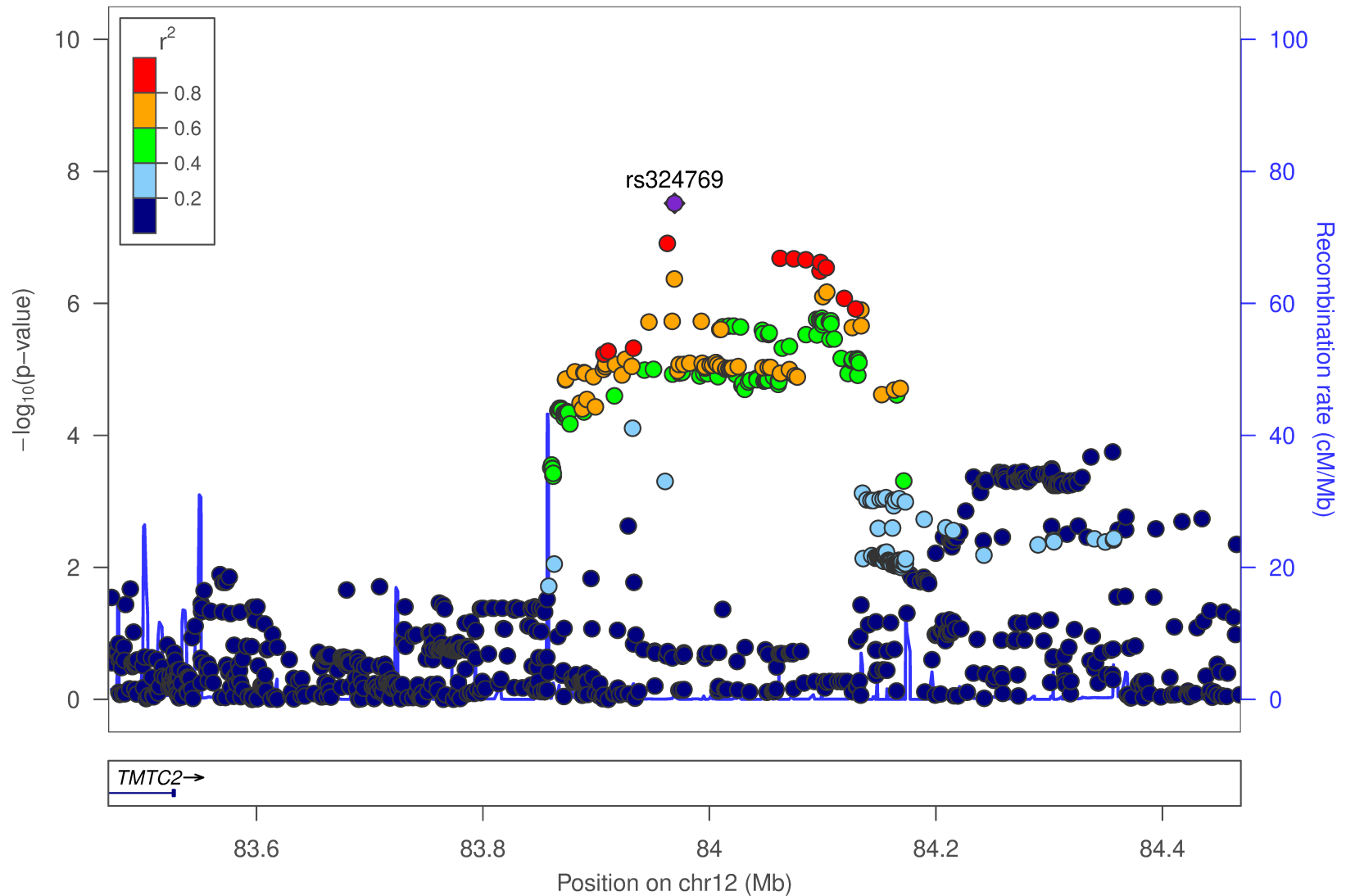
Plotted SNPs

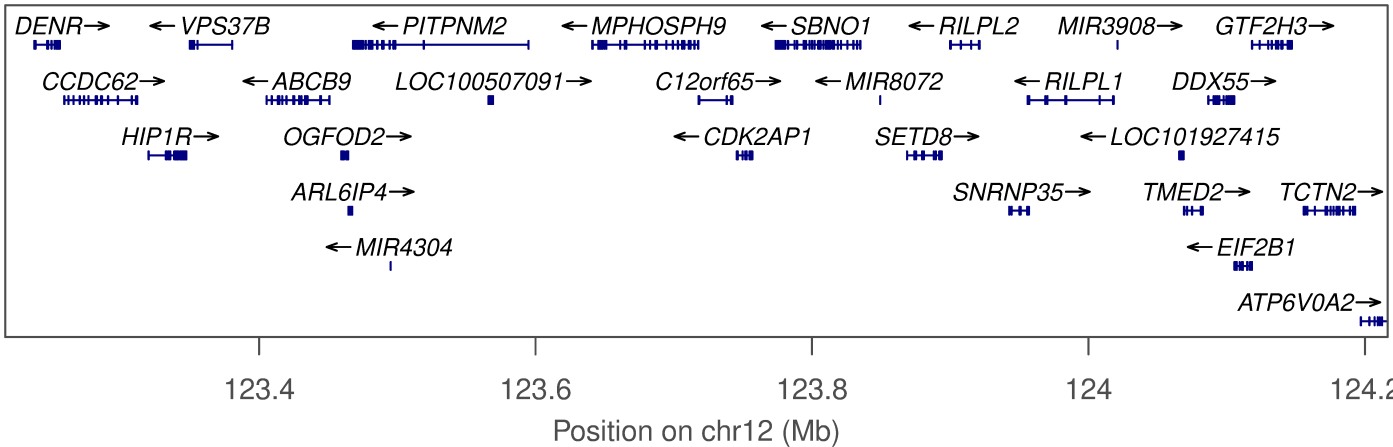
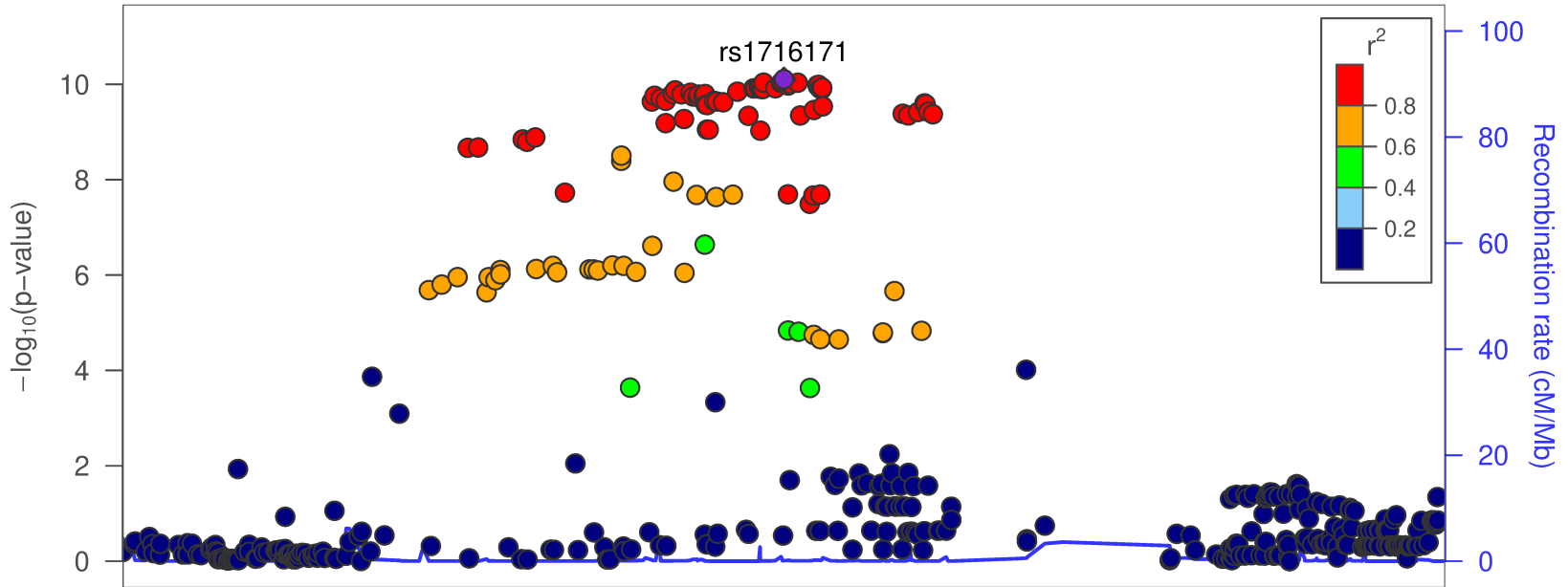


Plotted SNPs 

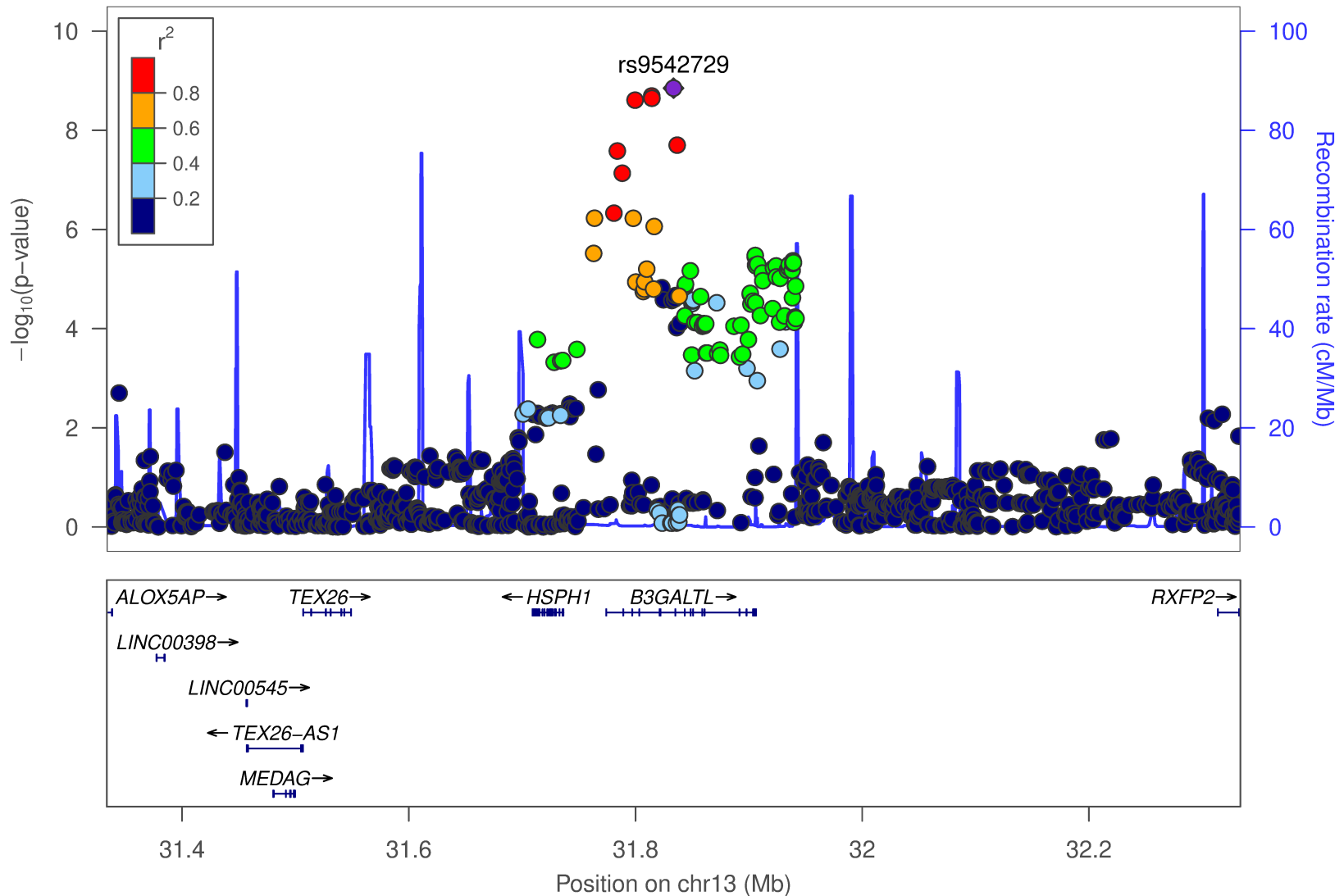


Plotted SNPs

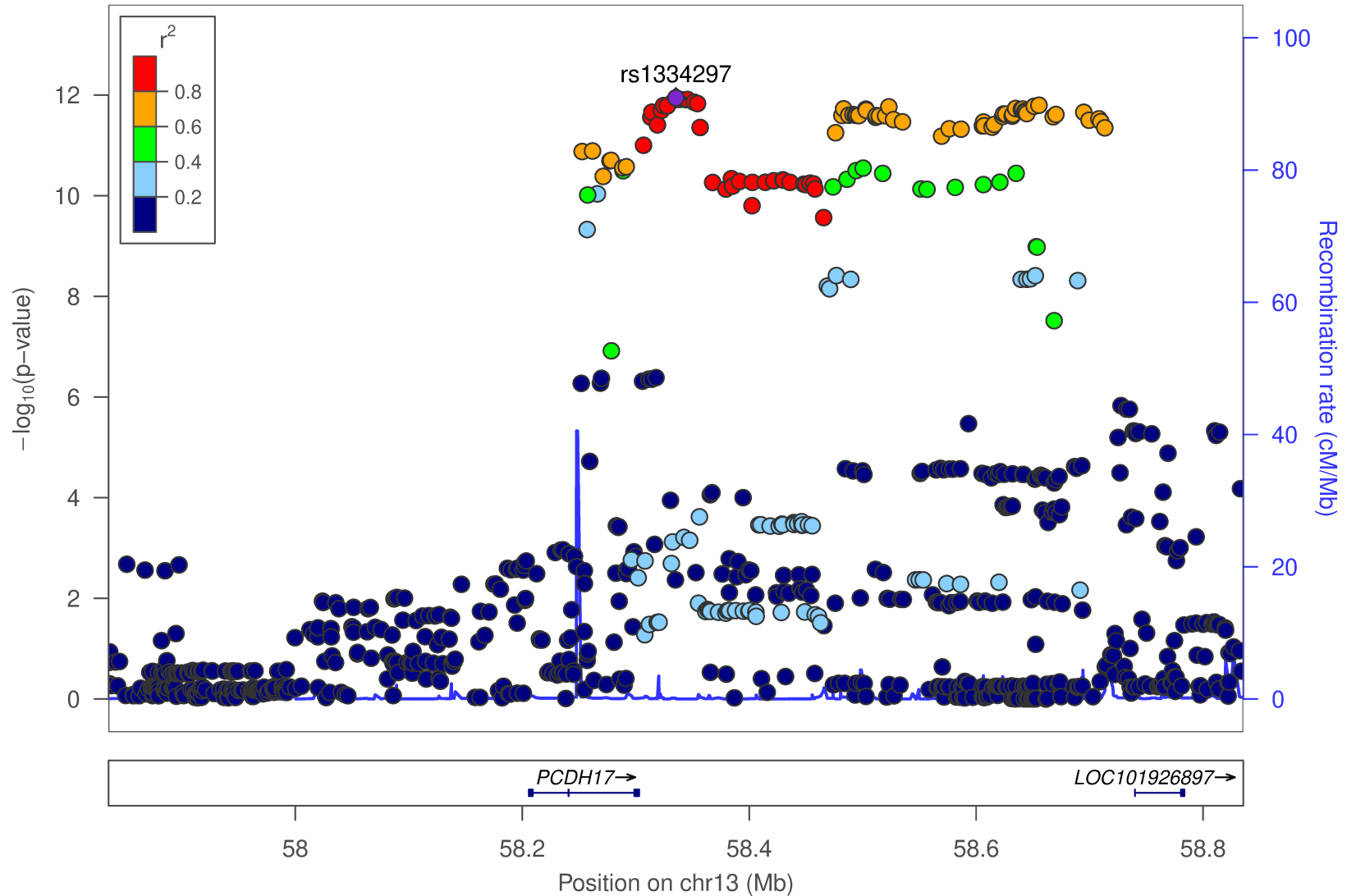




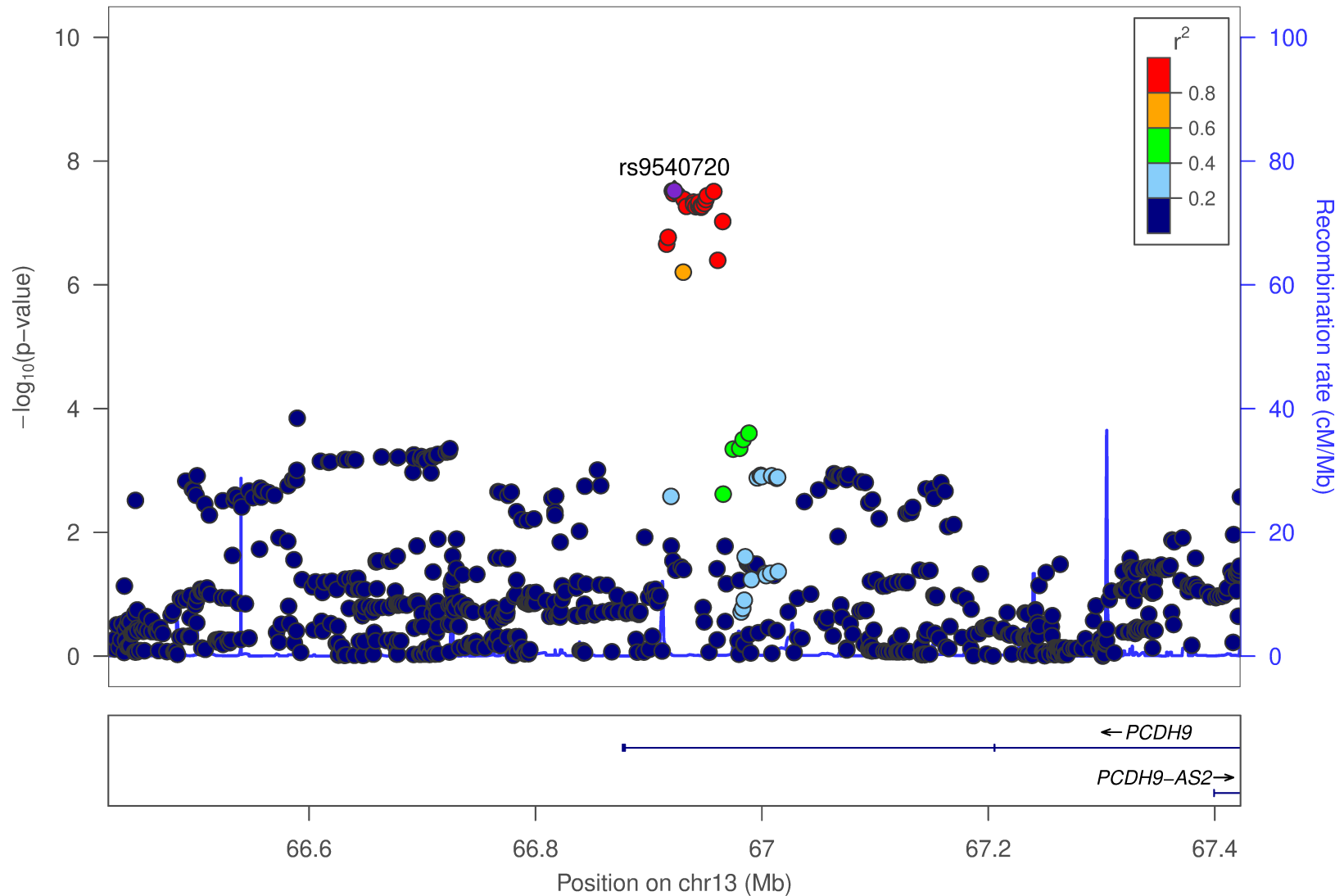
Plotted SNPs



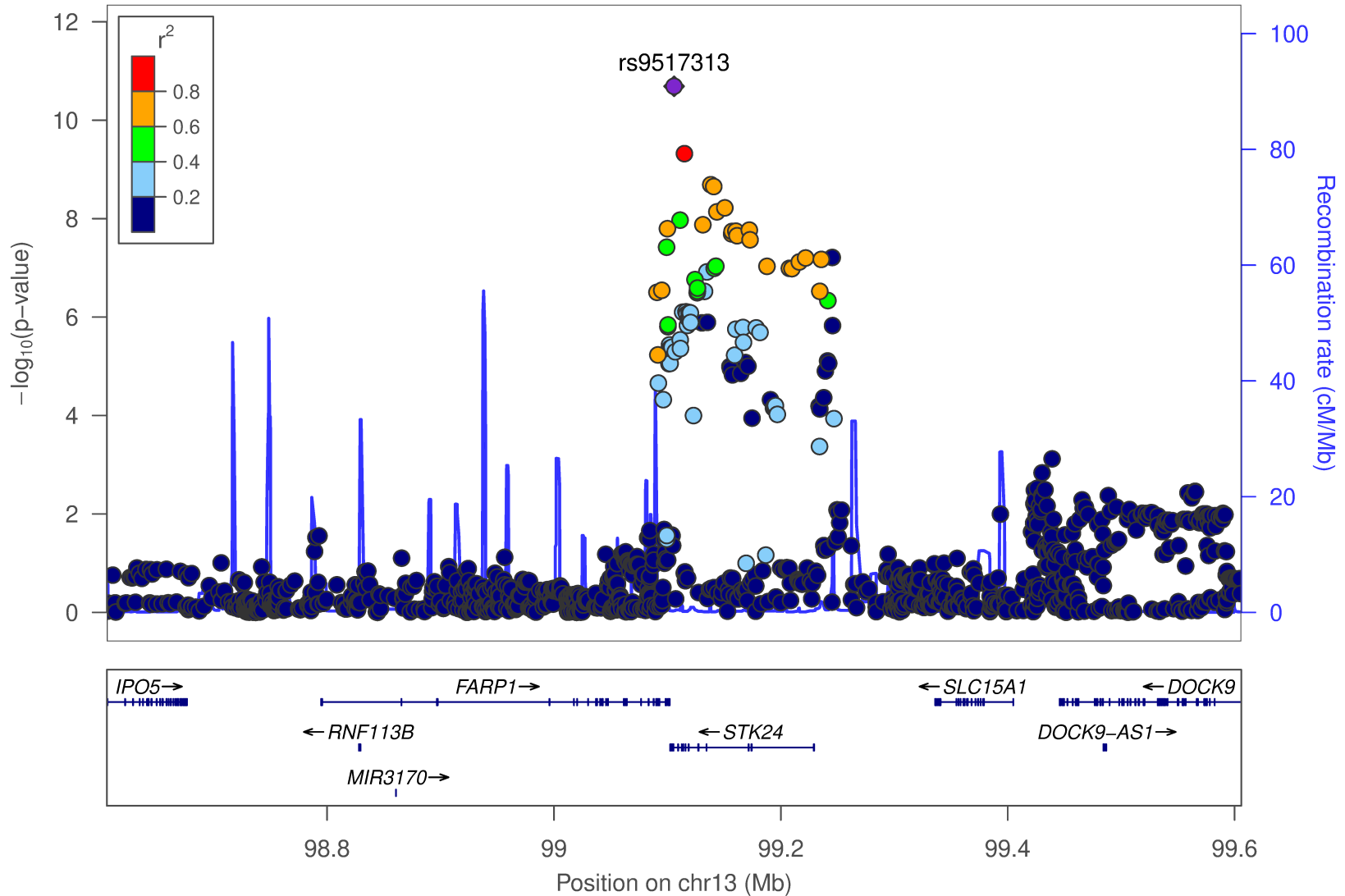
Plotted SNPs



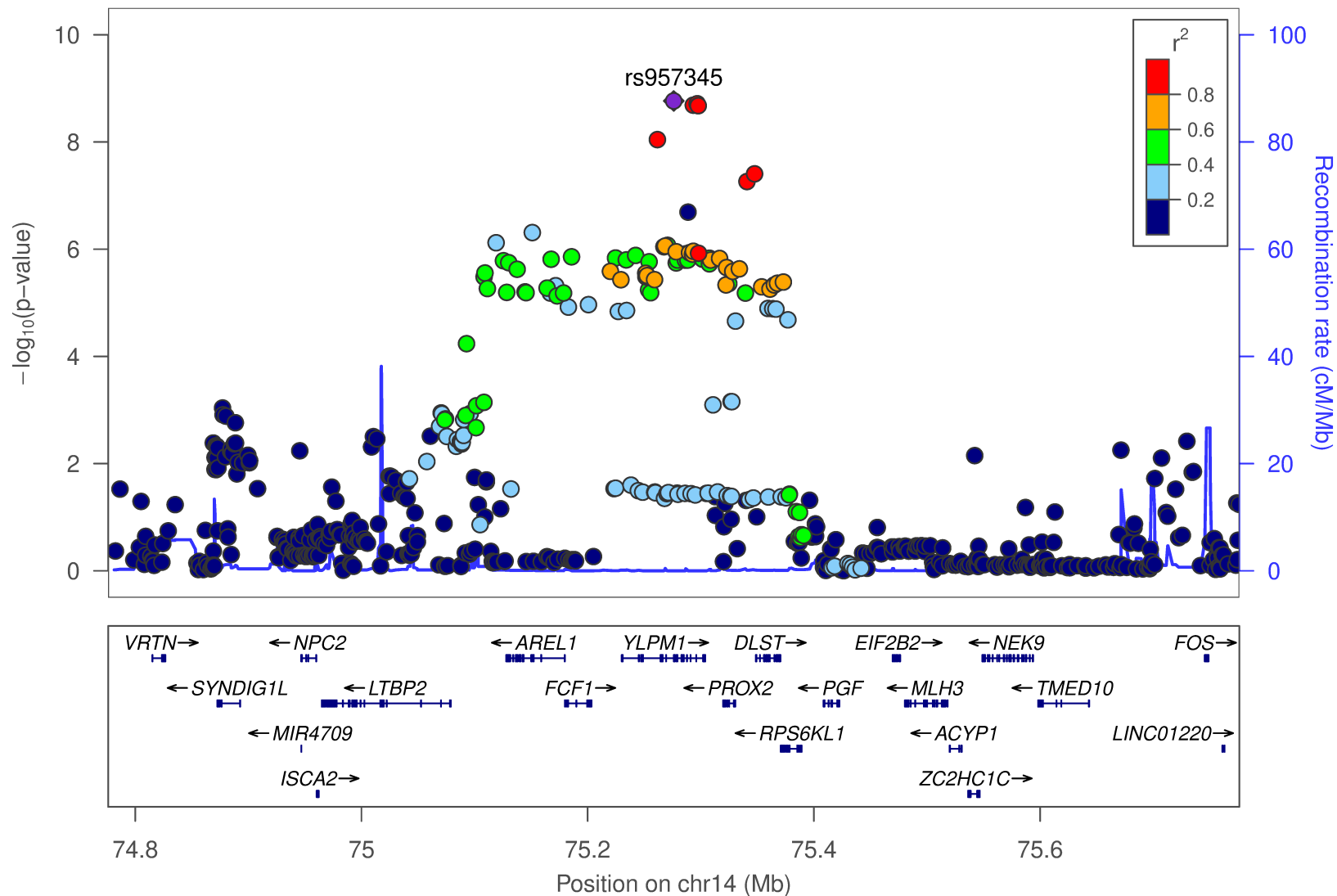
Plotted SNPs



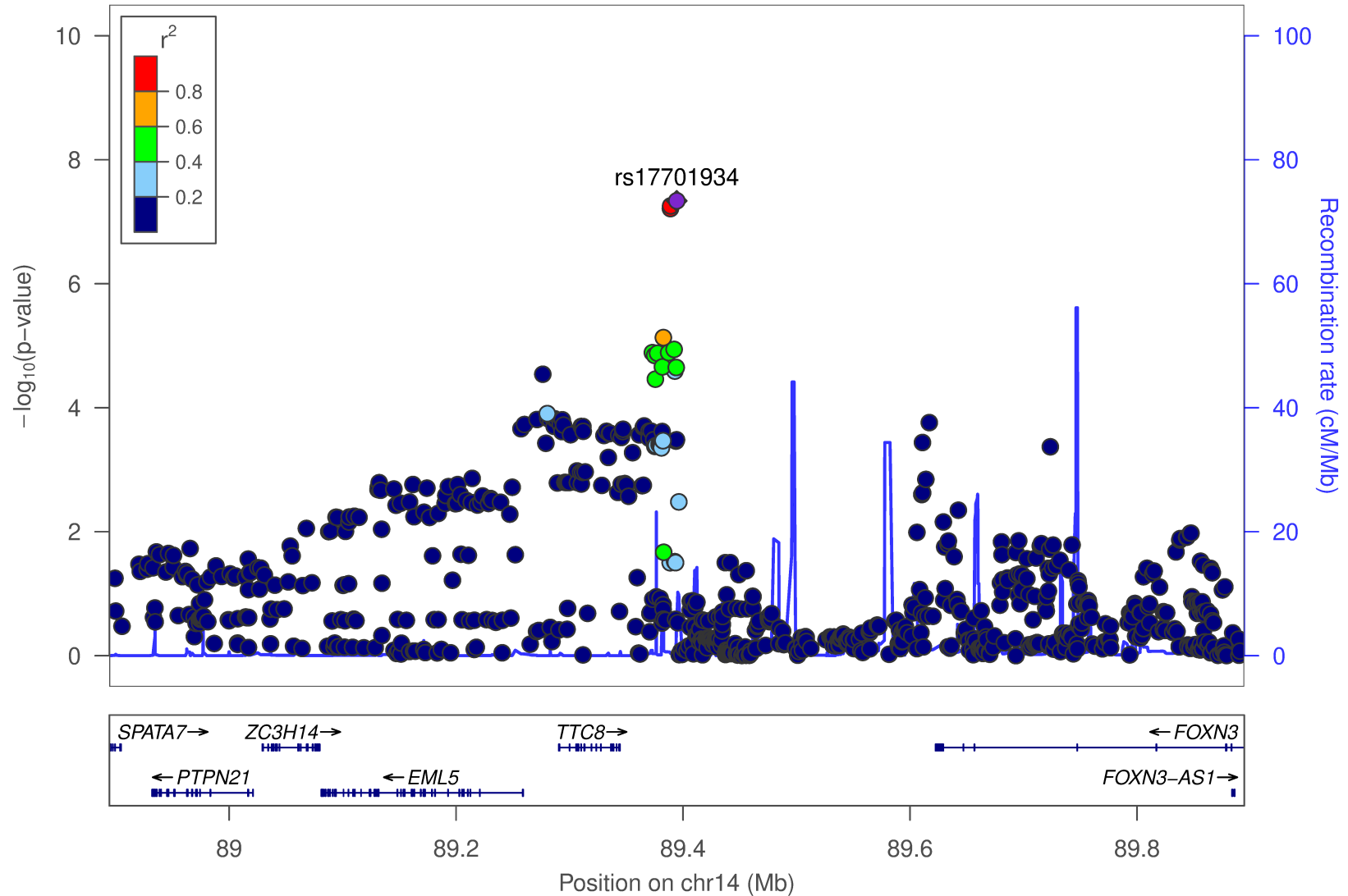
Plotted SNPs



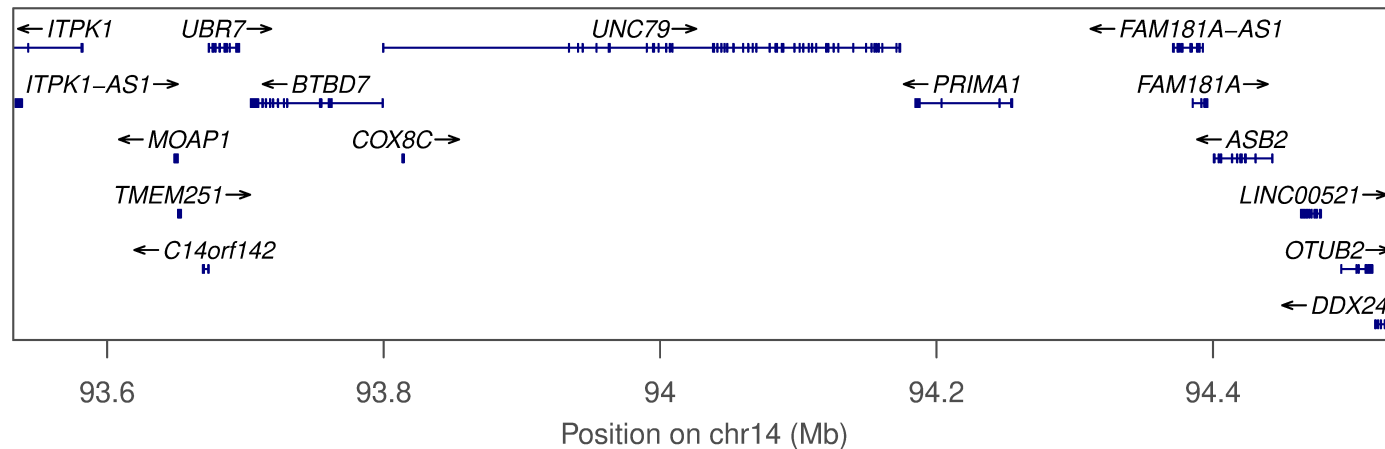
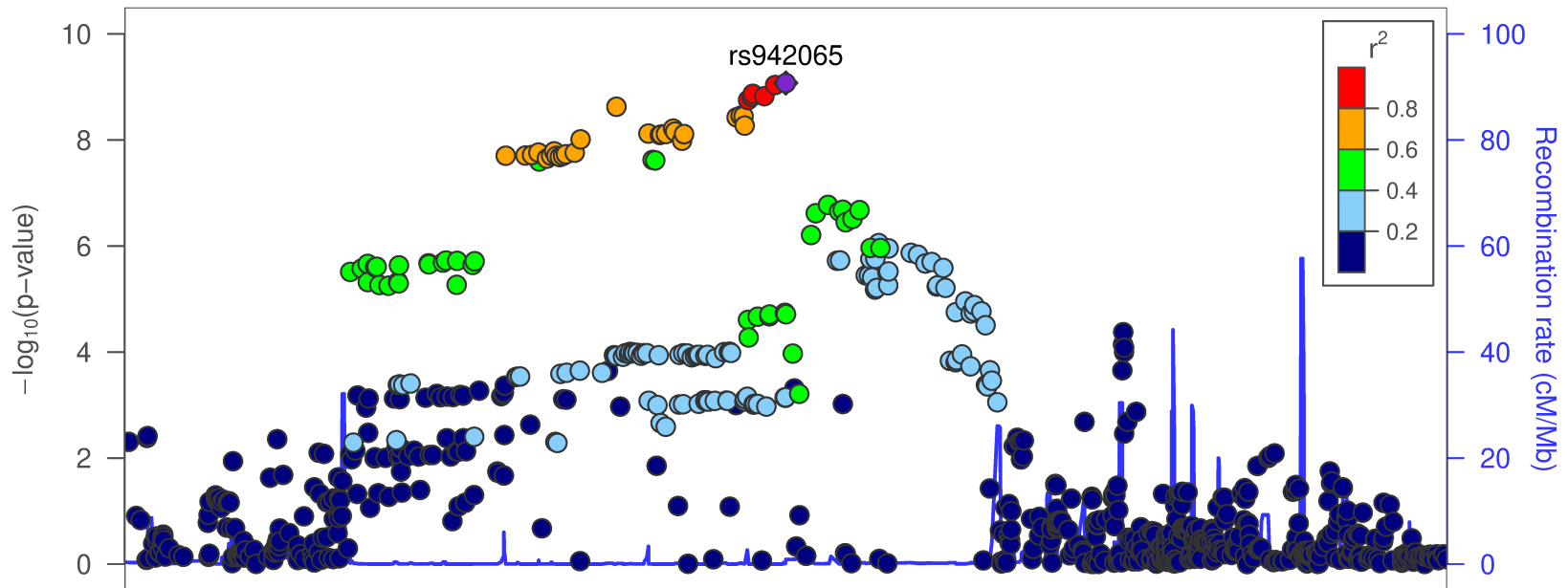
Plotted SNPs



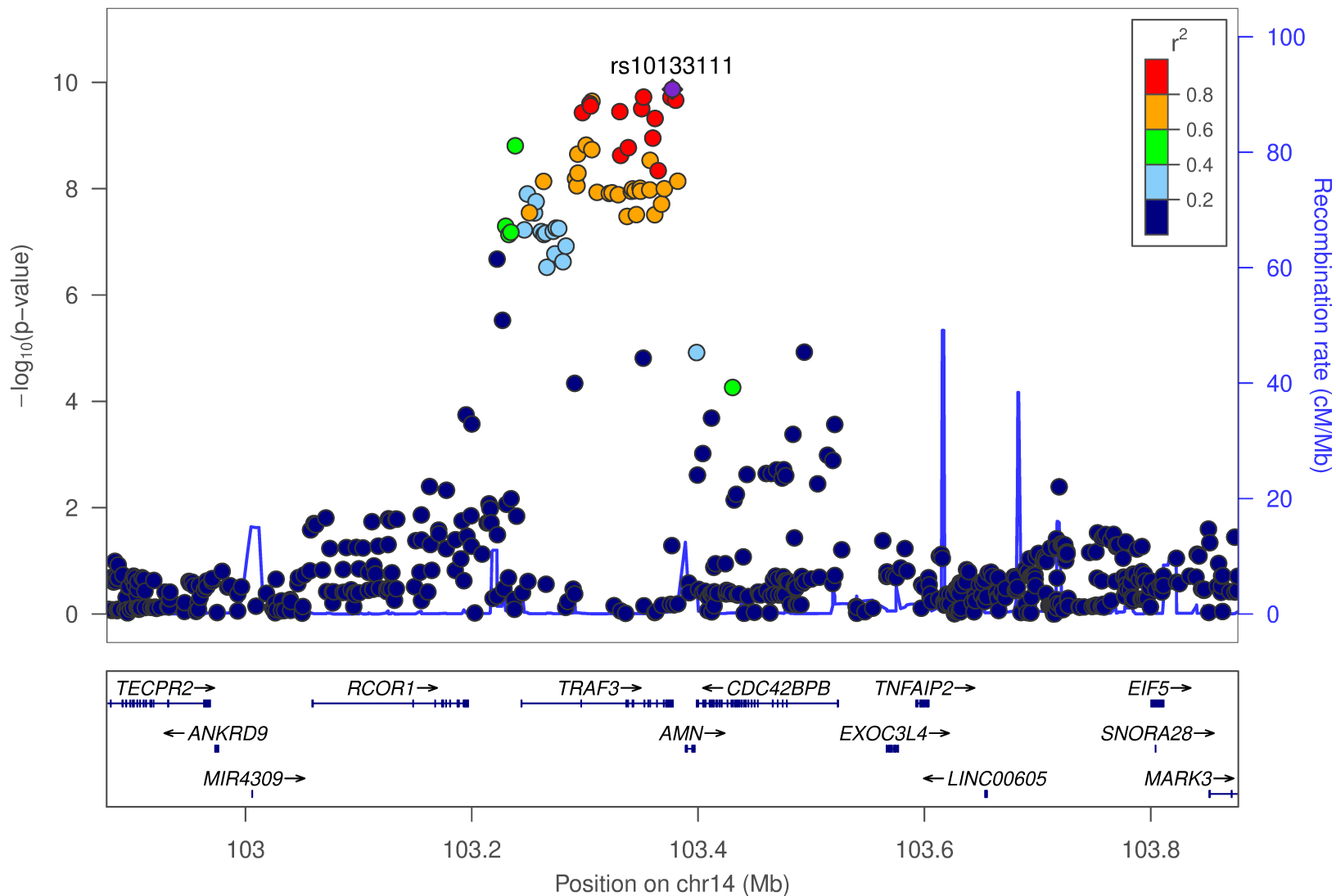
Plotted SNPs



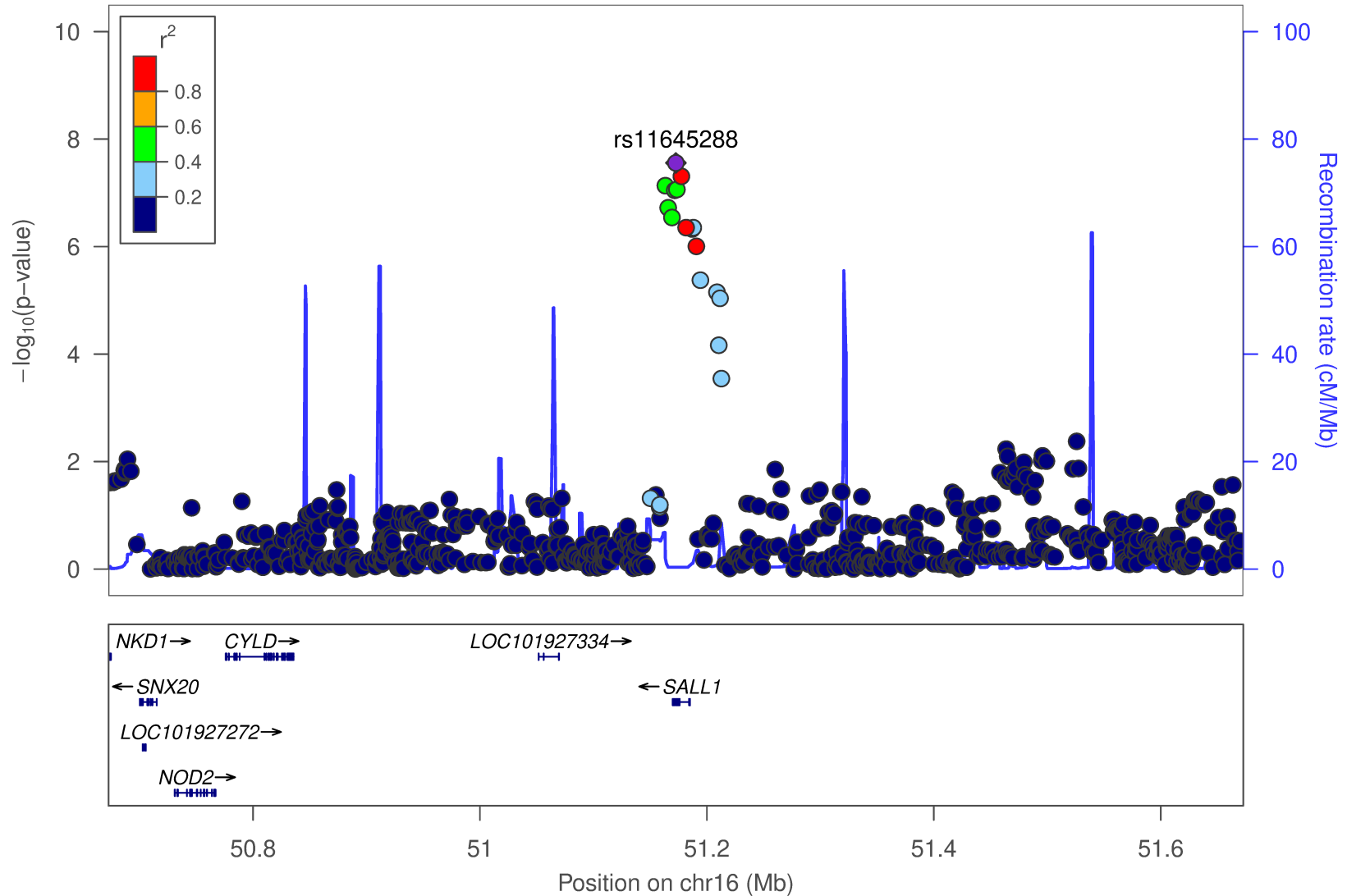
Plotted SNPs



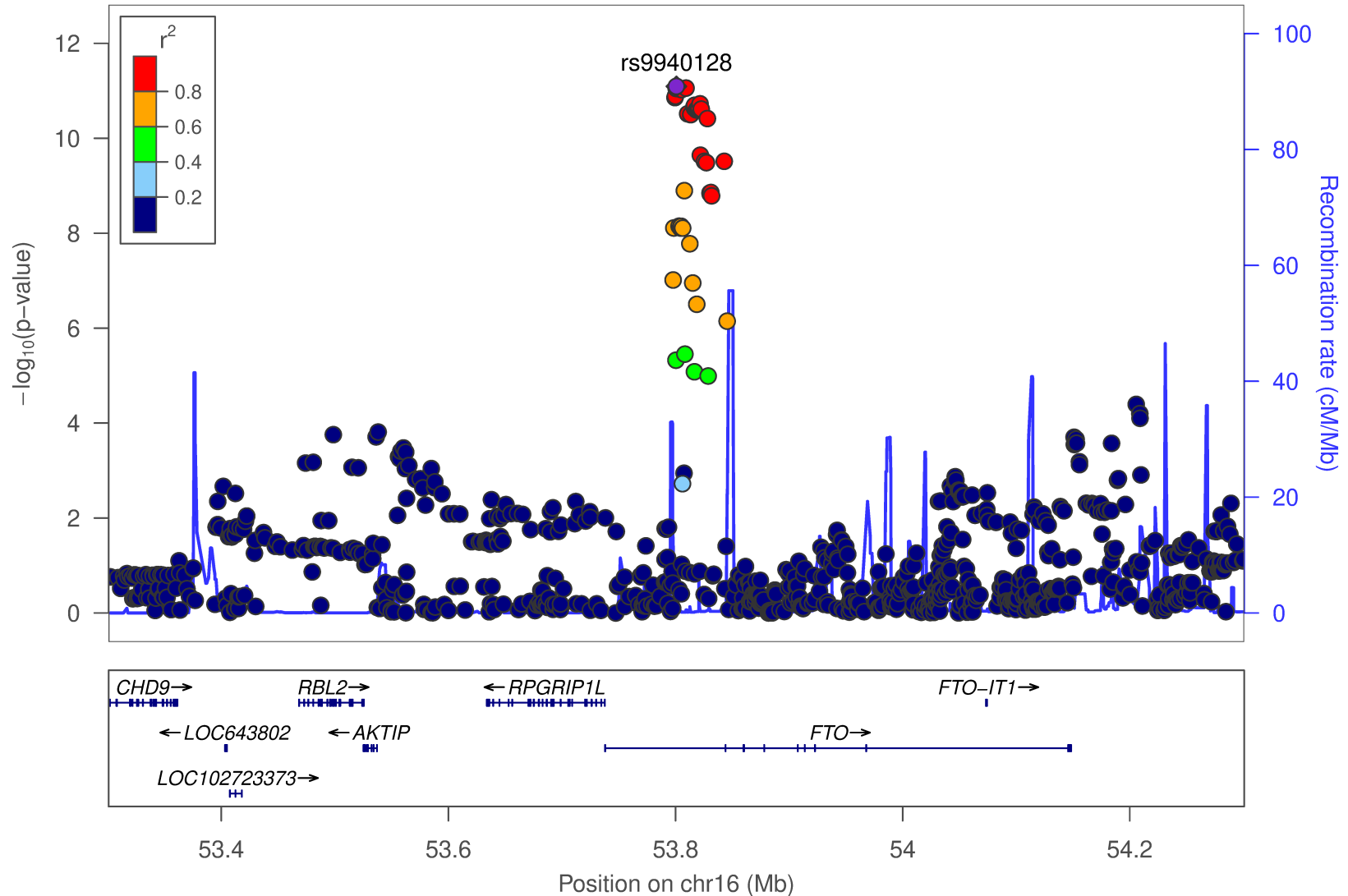
Plotted SNPs



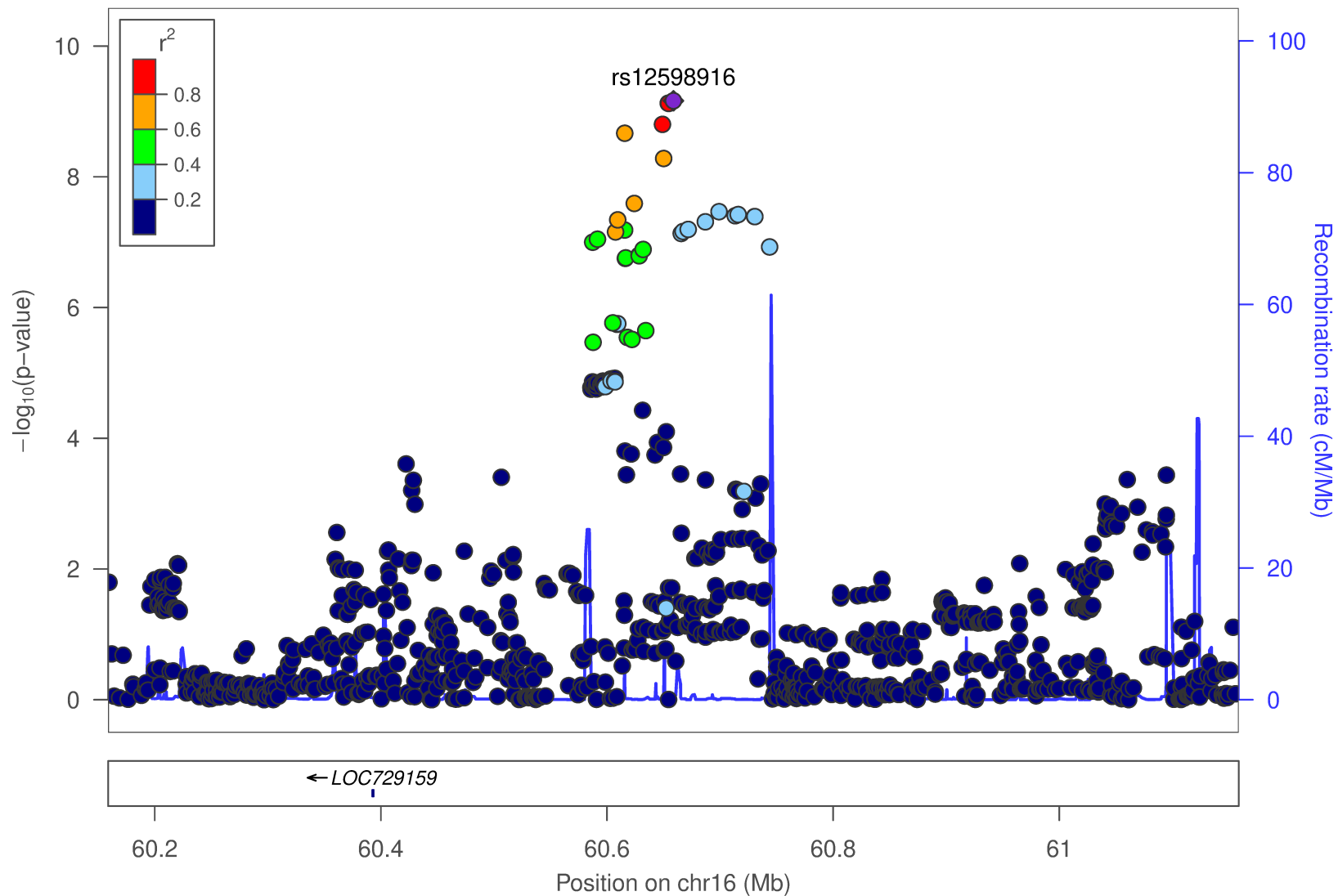
Plotted SNPs



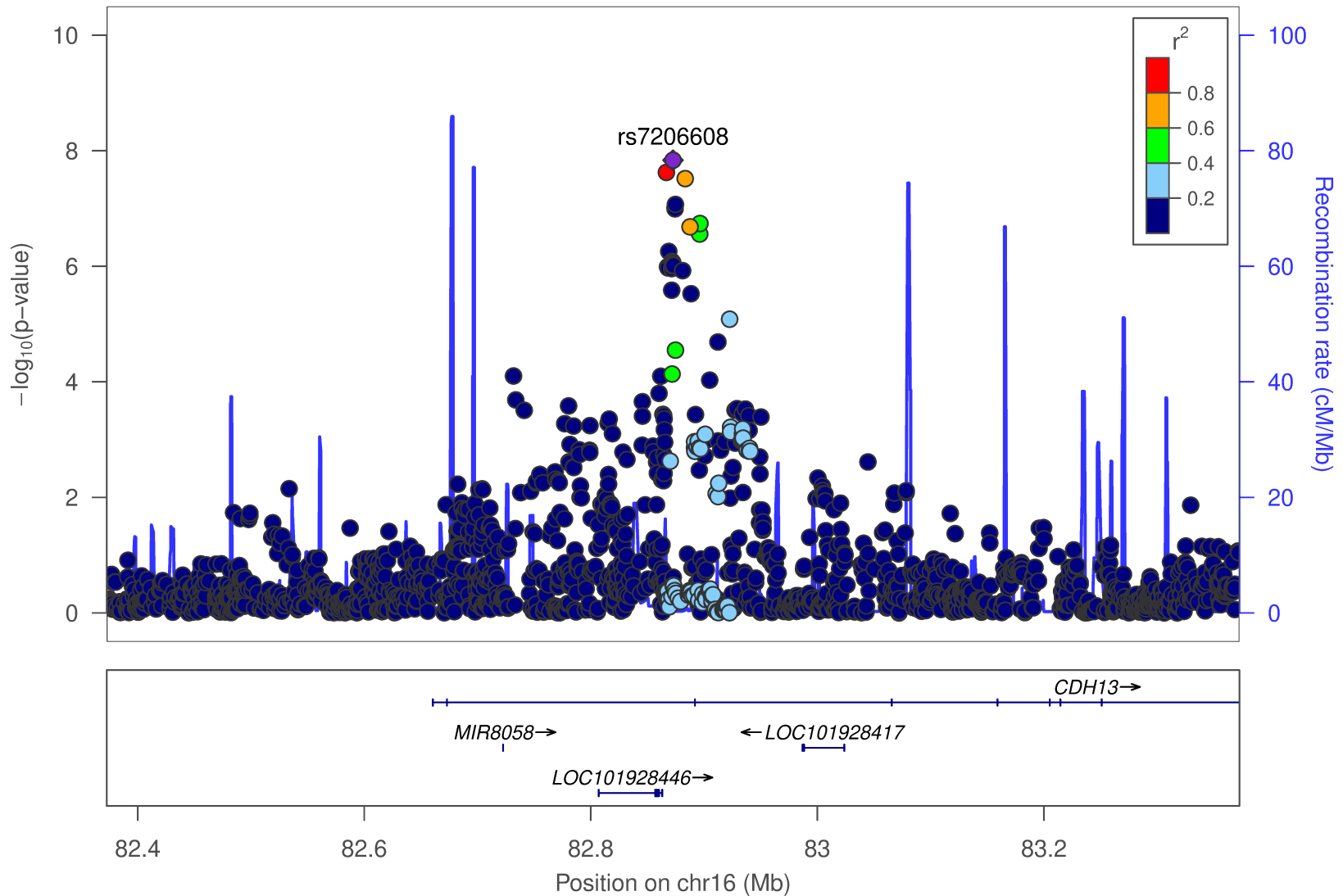
Plotted SNPs



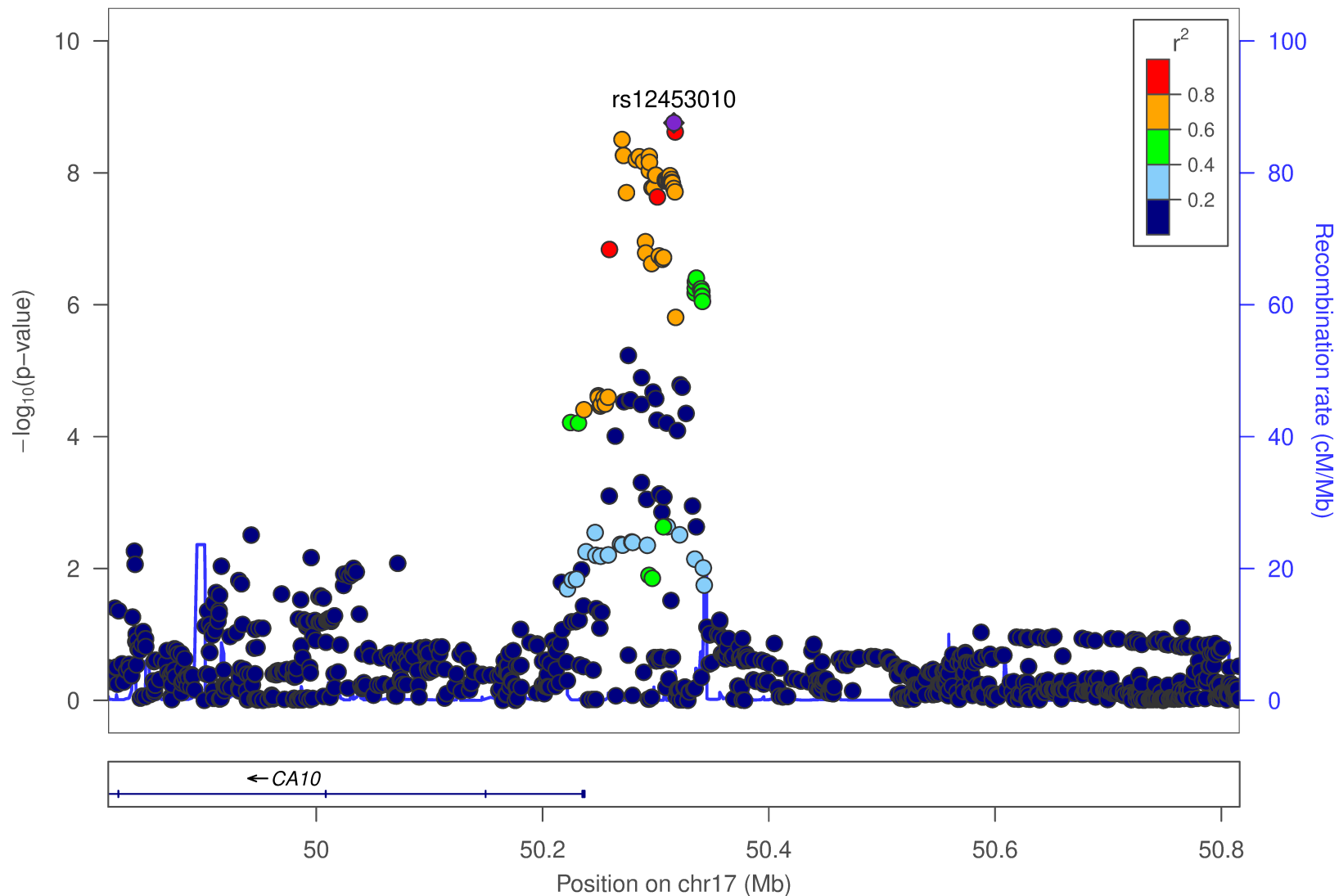
Plotted SNPs



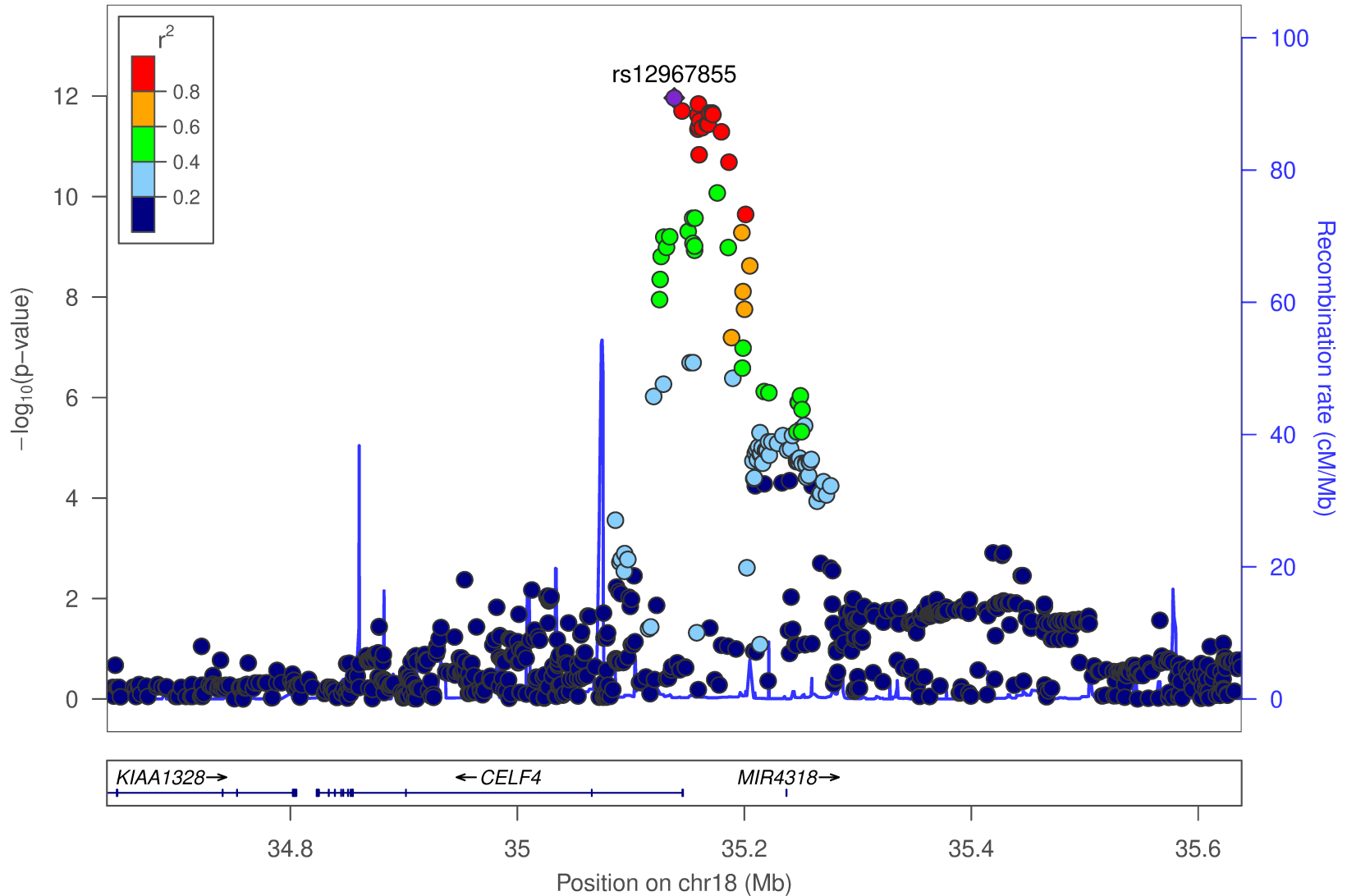
Plotted SNPs



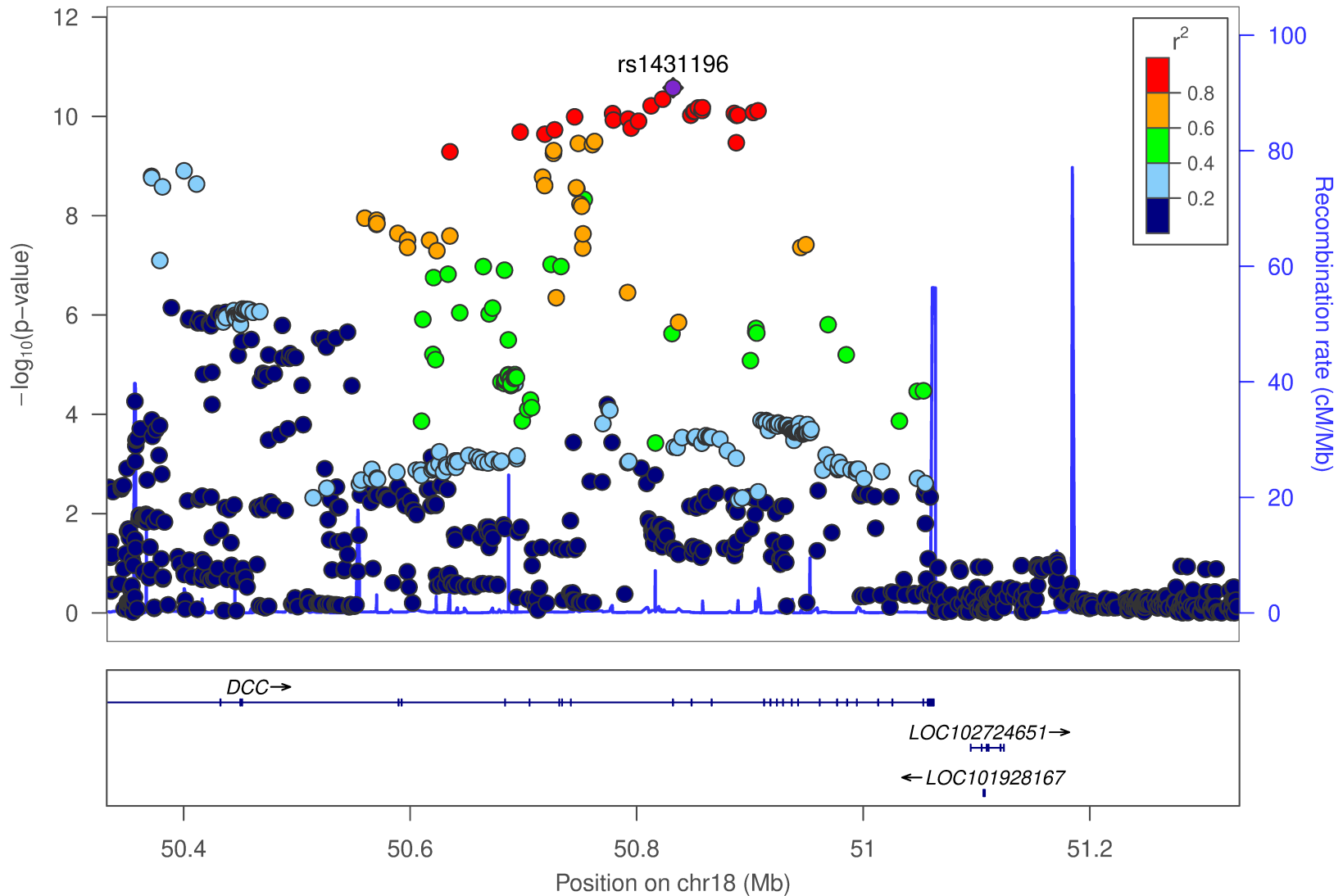
Plotted SNPs



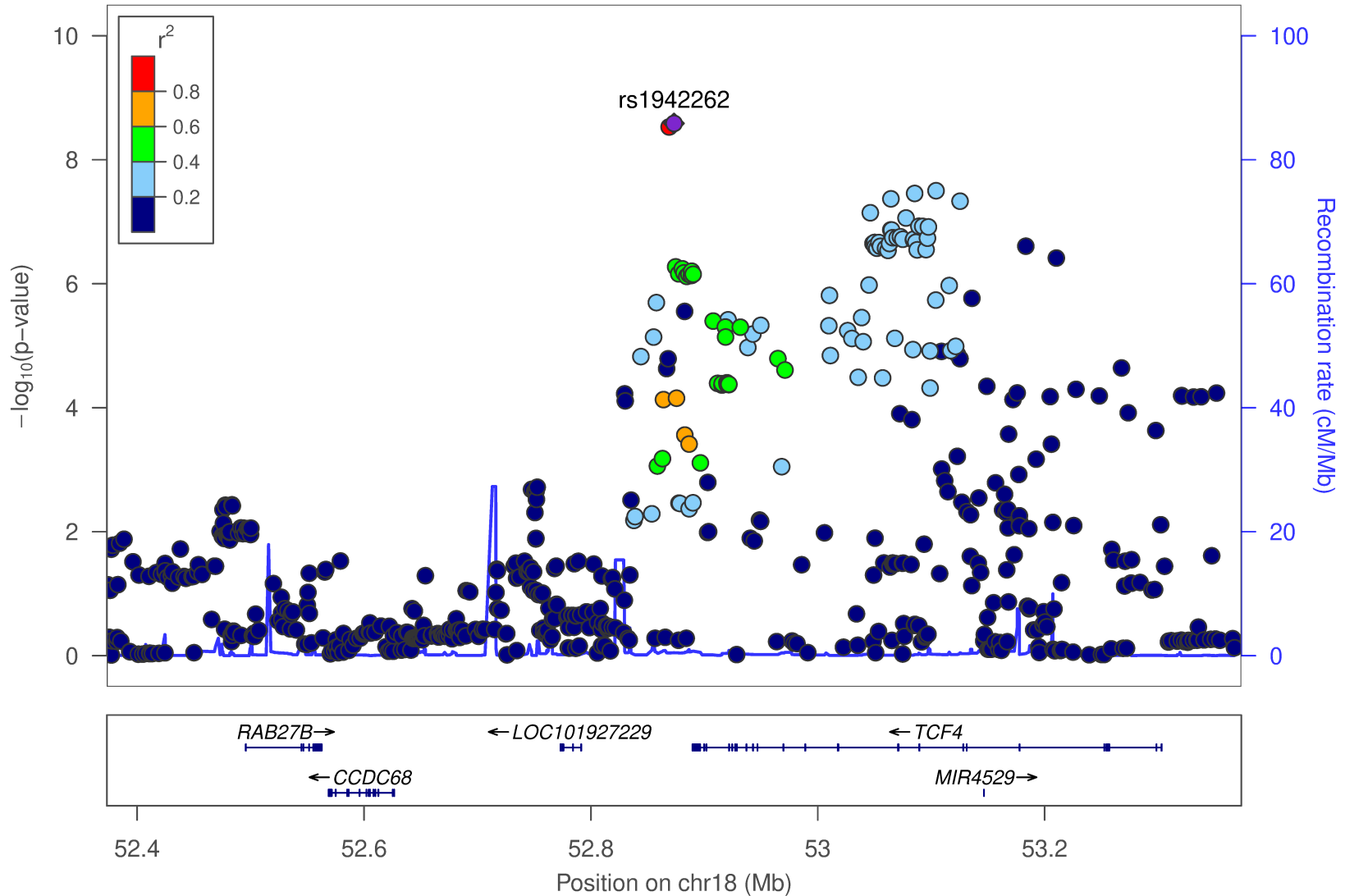
Plotted SNPs



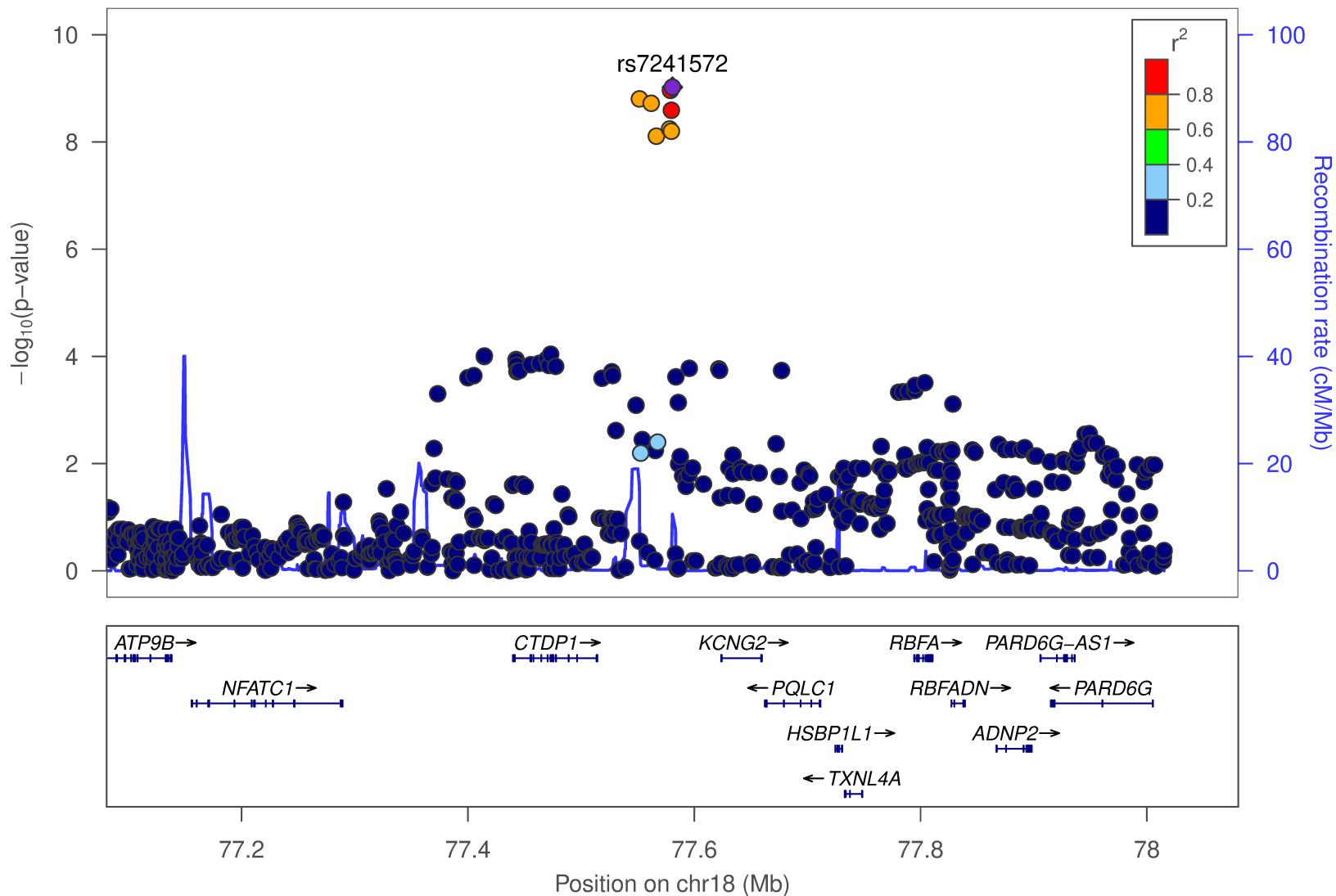
Plotted SNPs

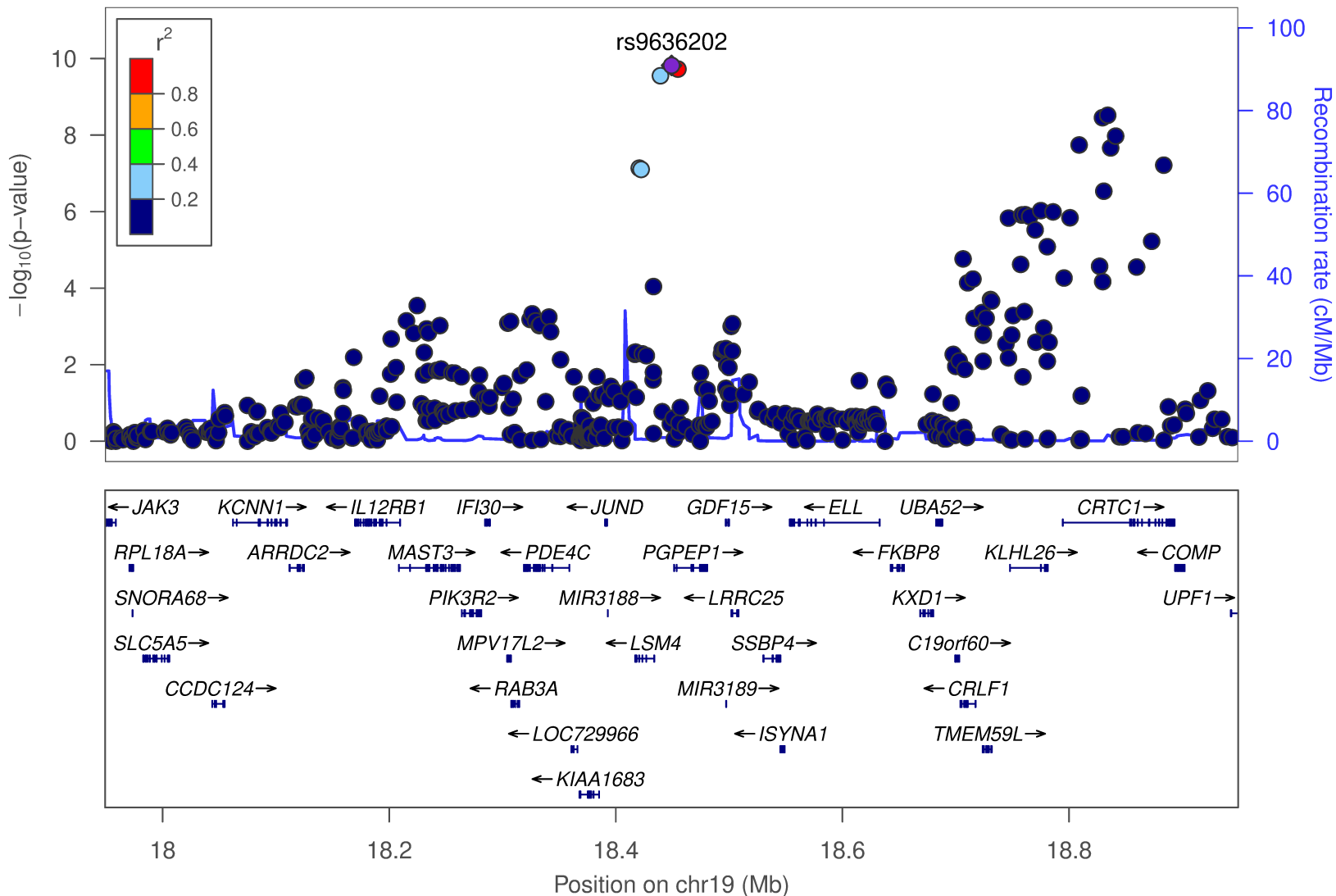


Plotted SNPs

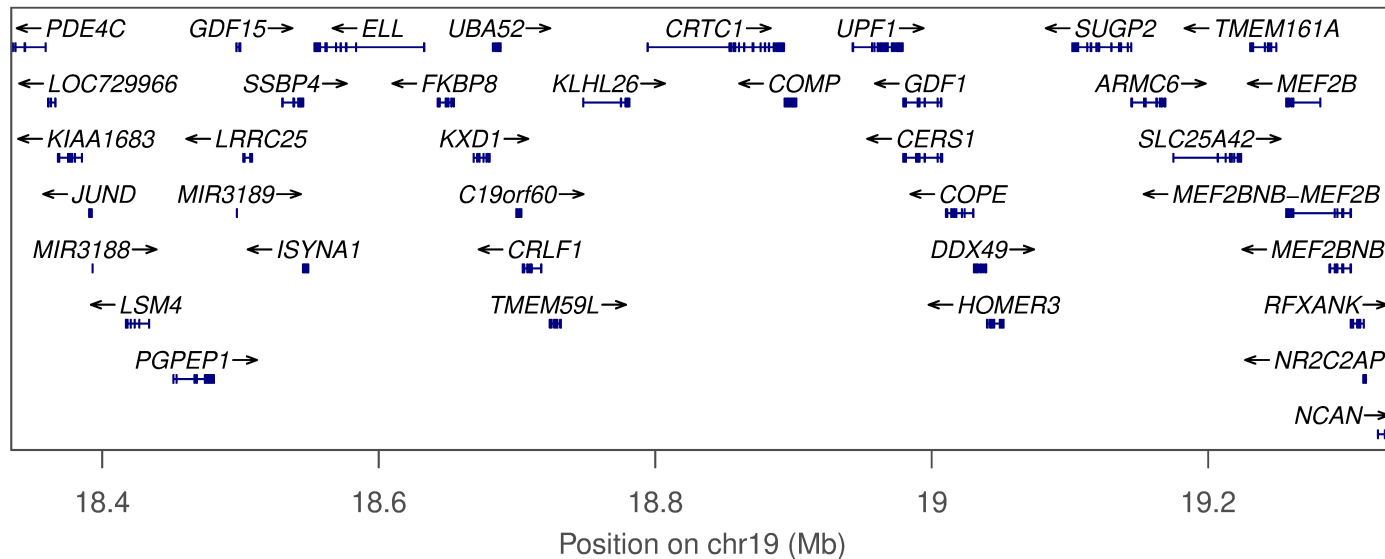
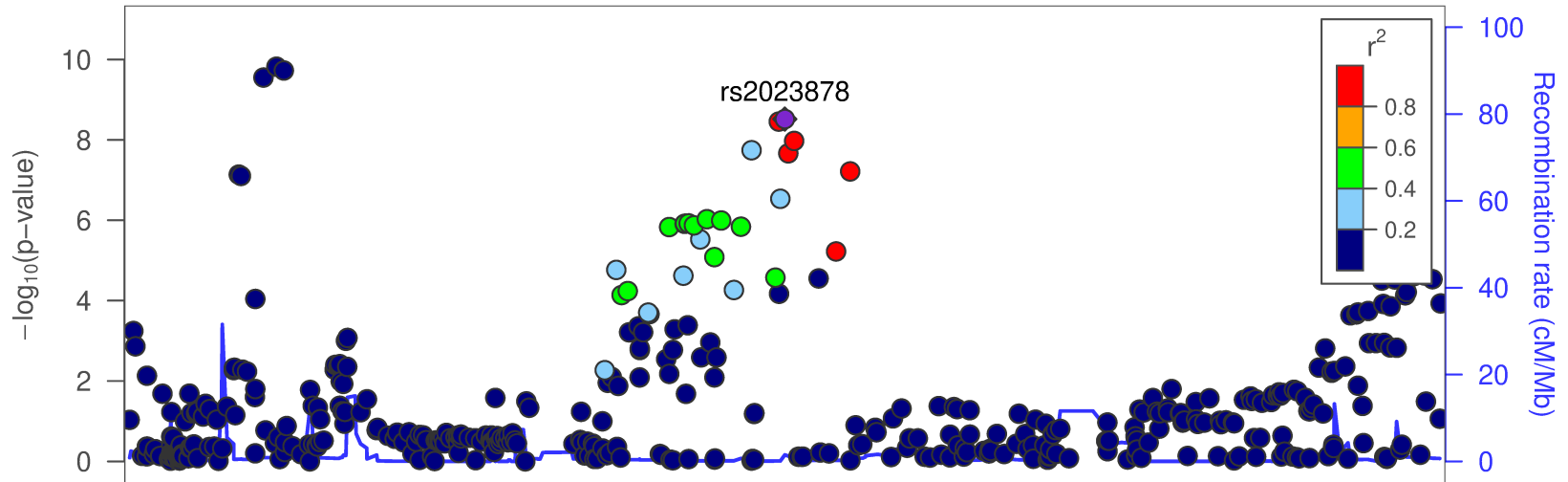


Plotted SNPs

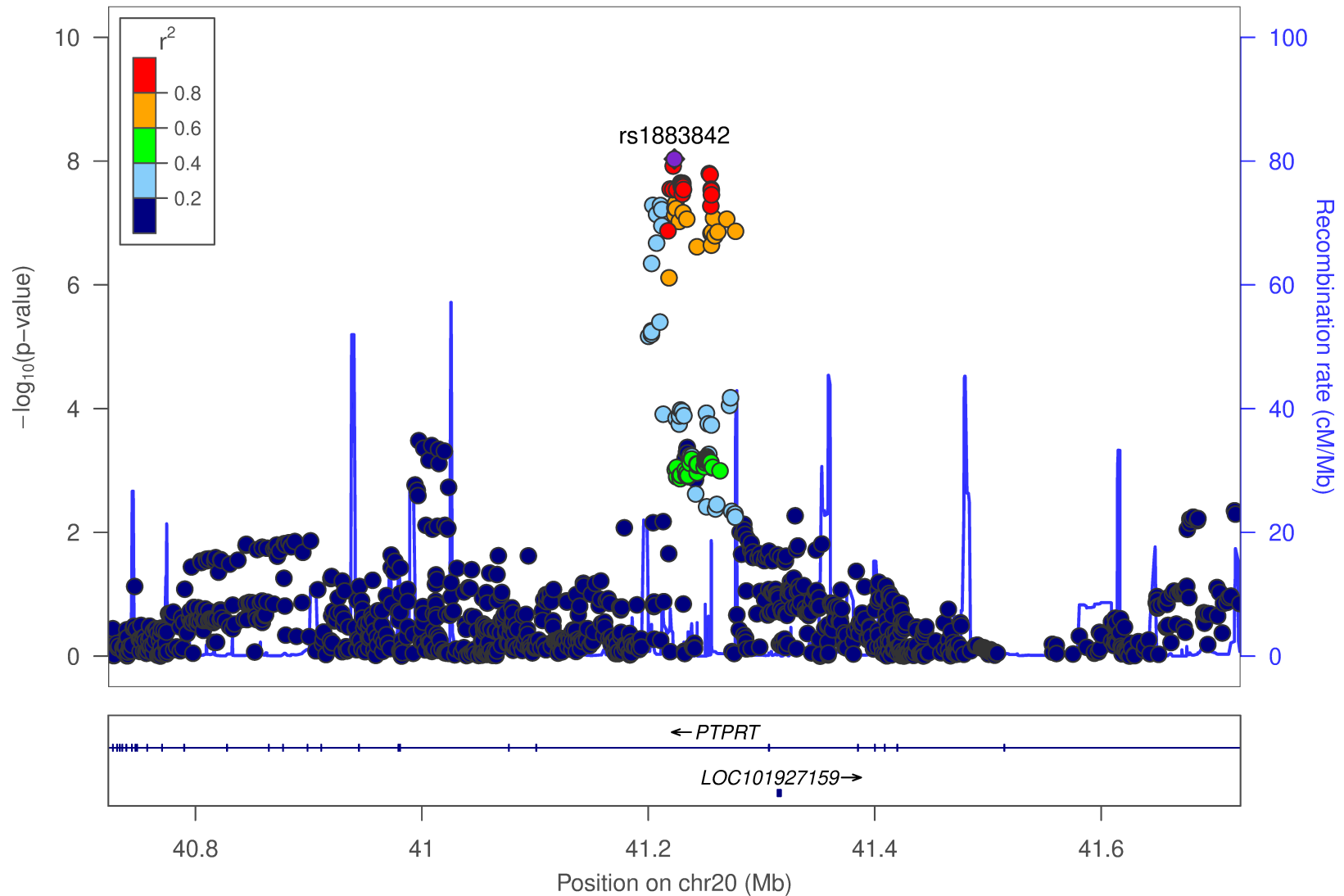




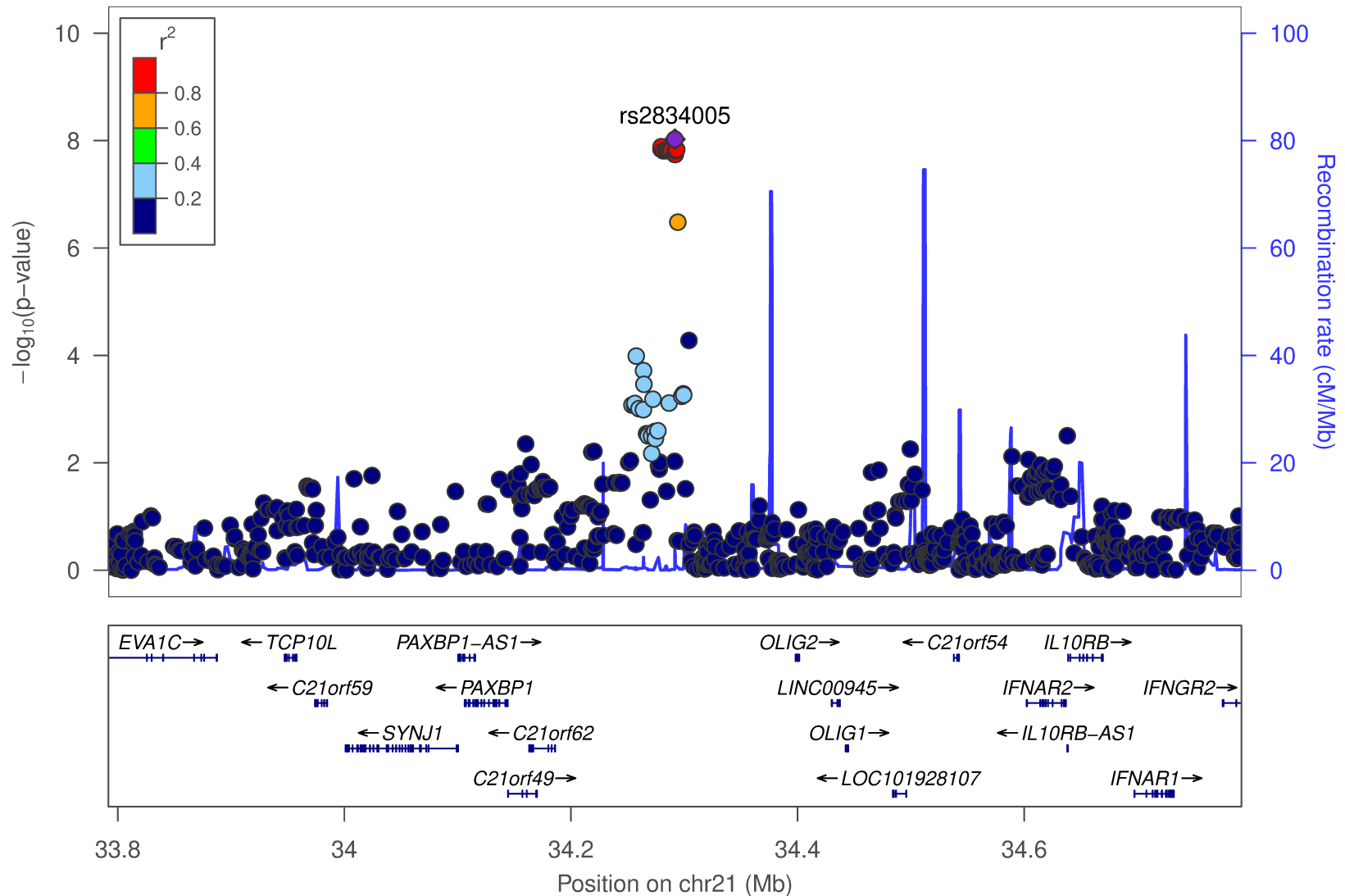
Plotted SNPs



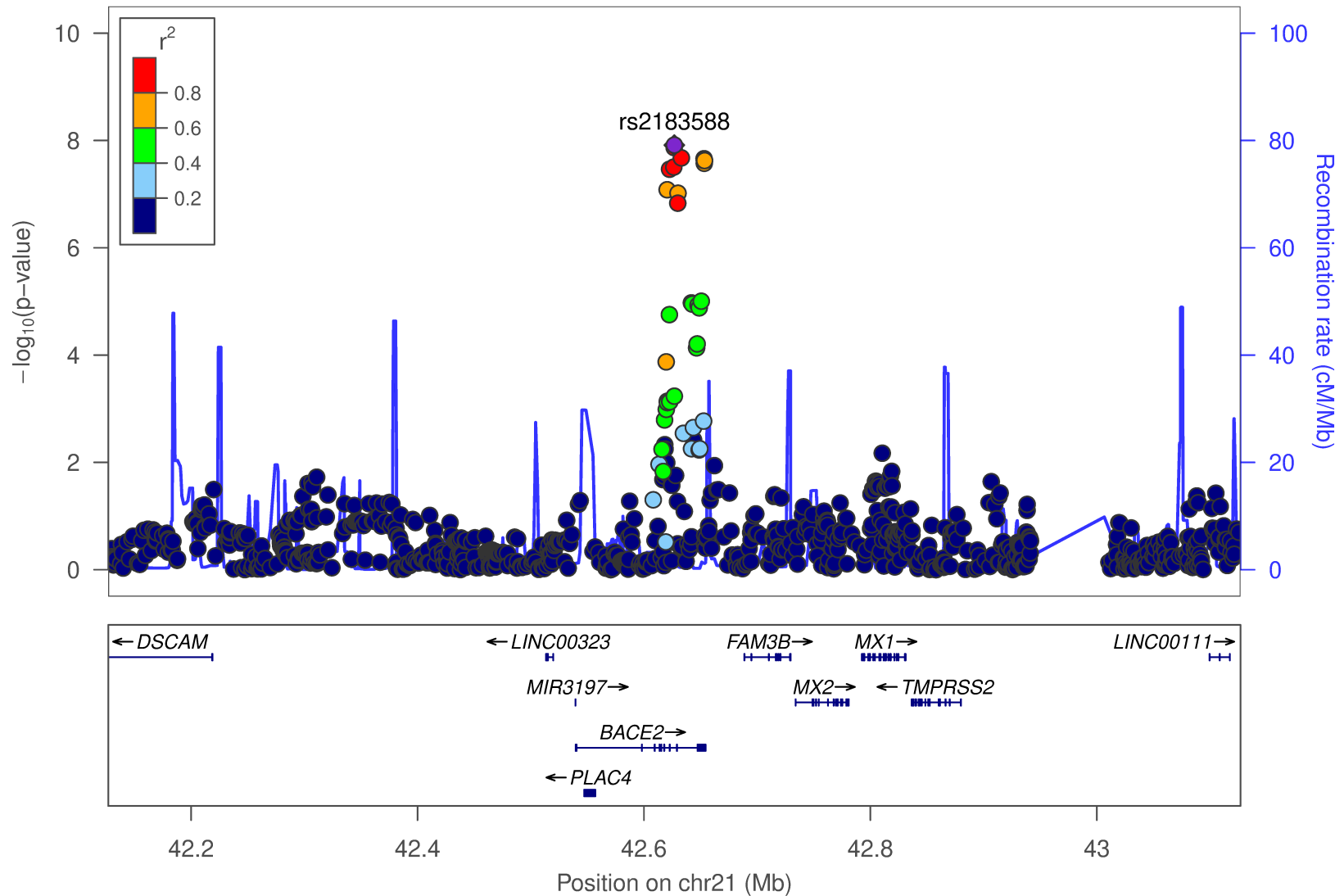
Plotted SNPs



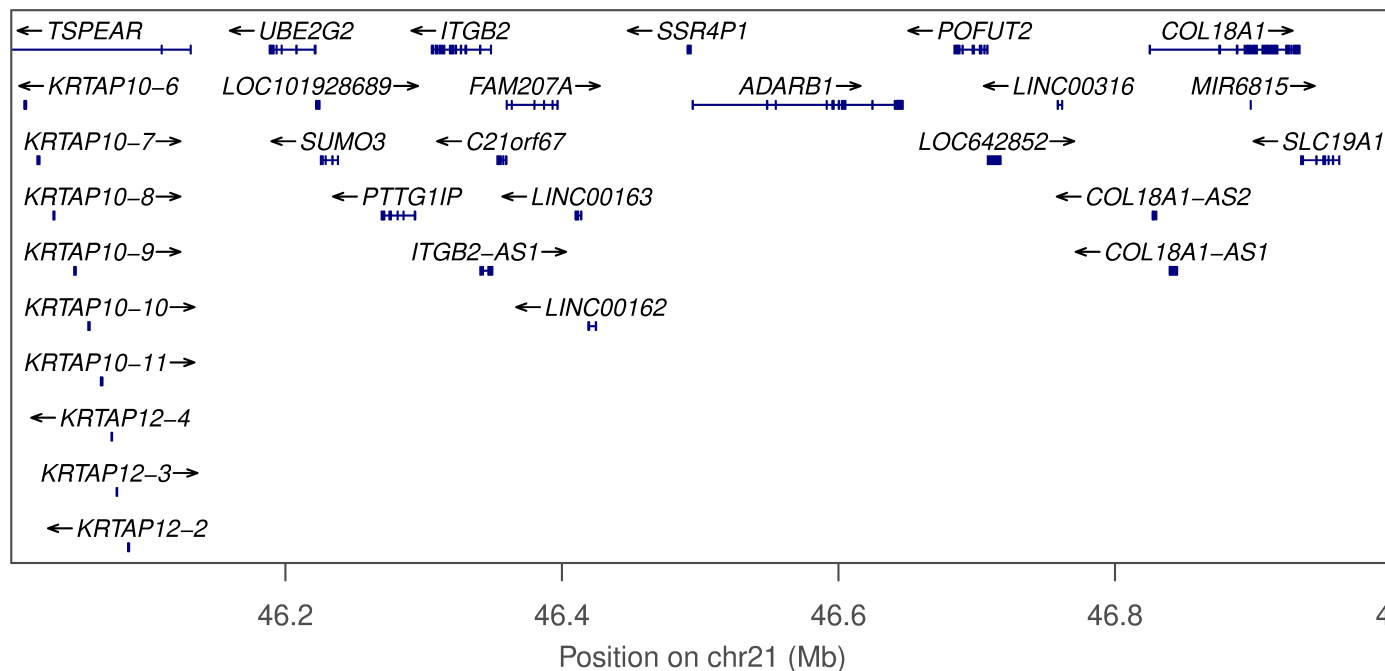
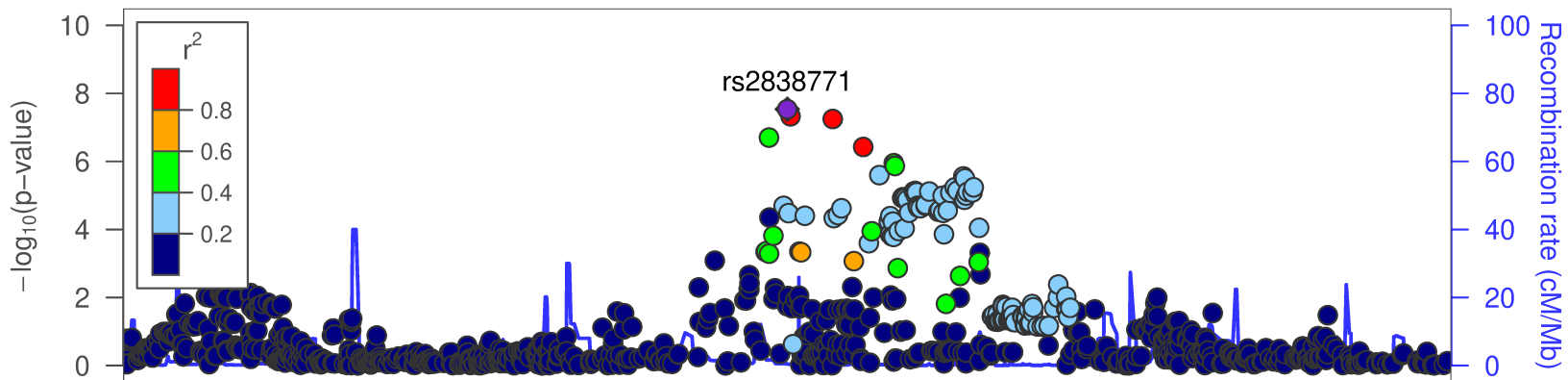
Plotted SNPs



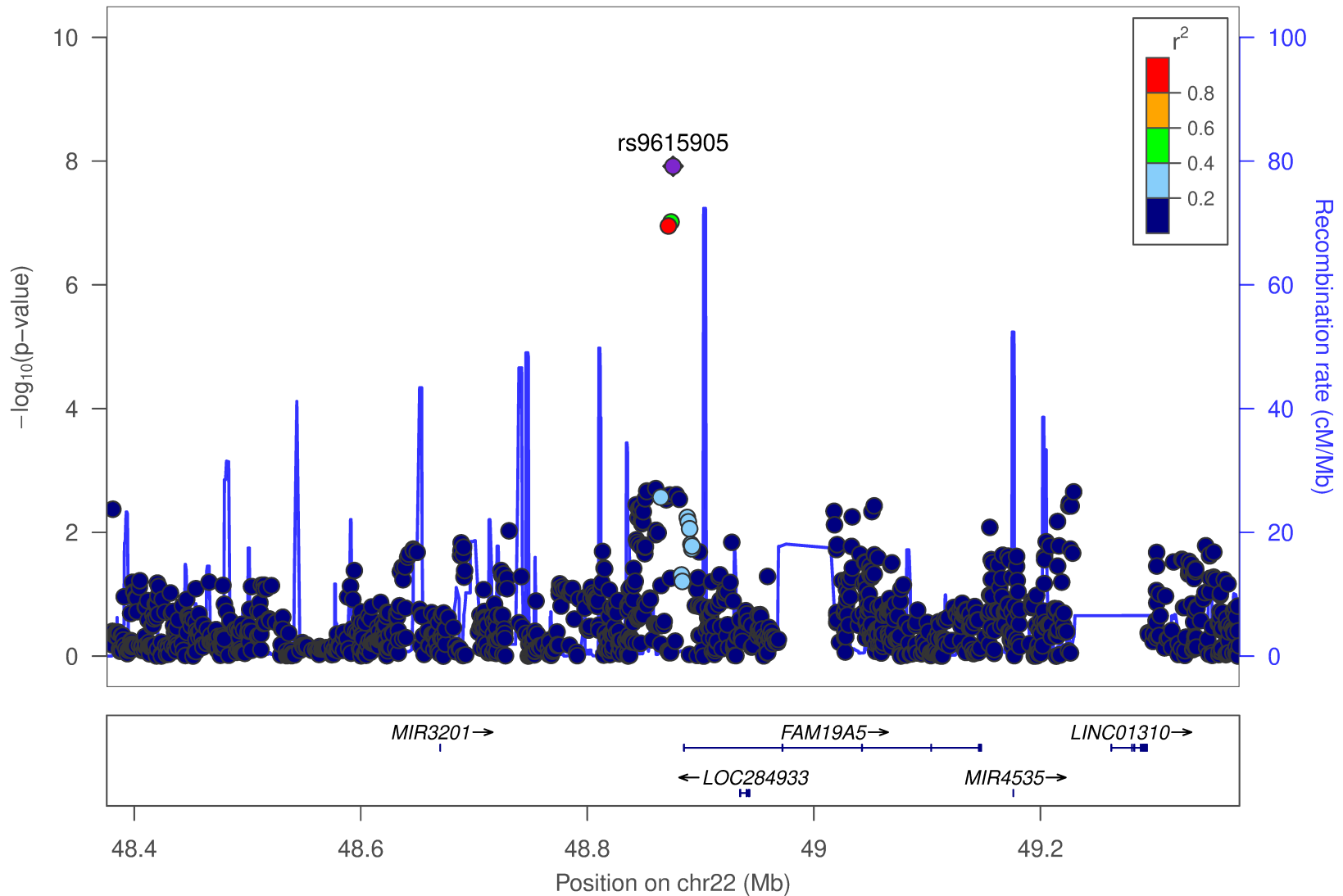
Plotted SNPs



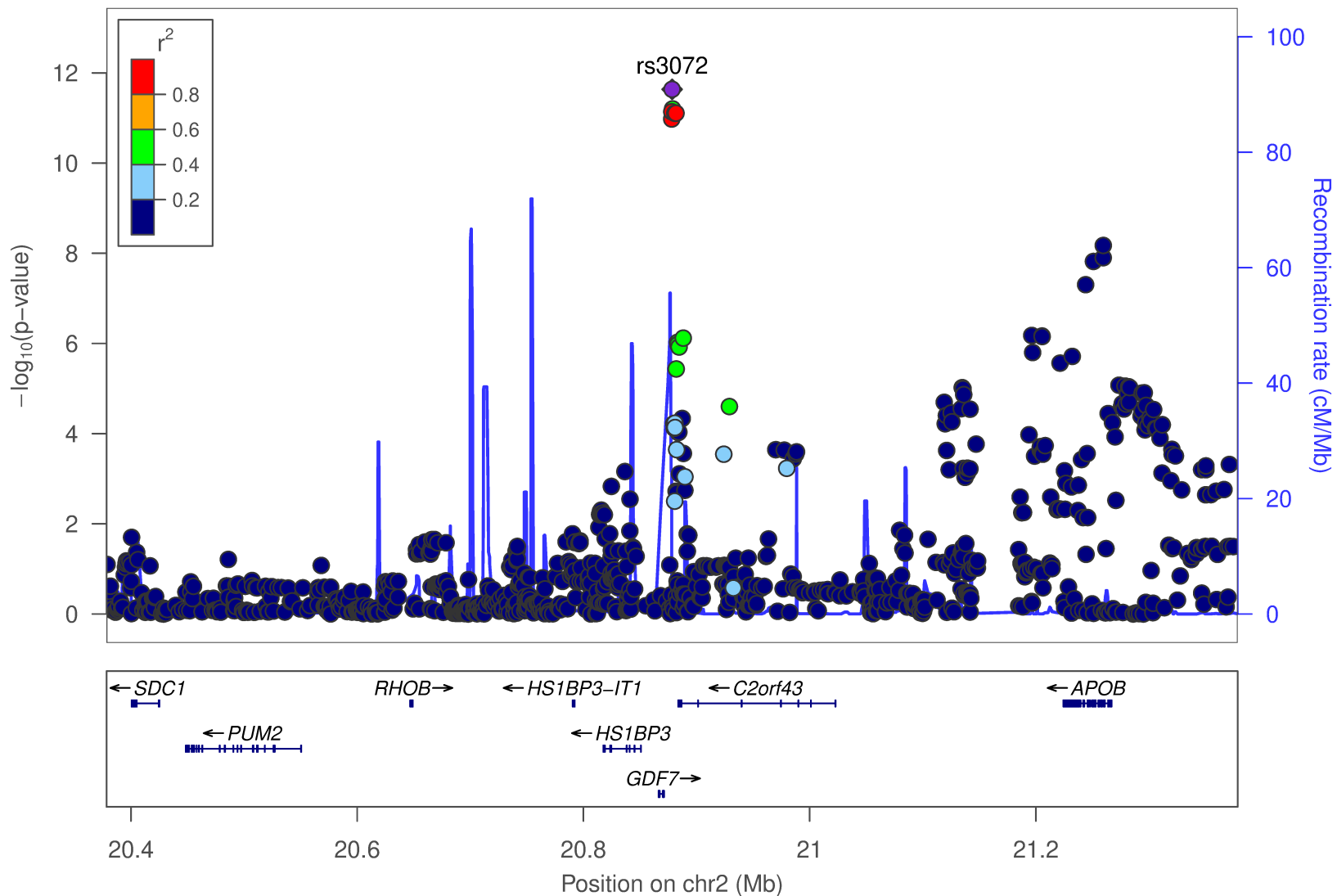
Plotted SNPs



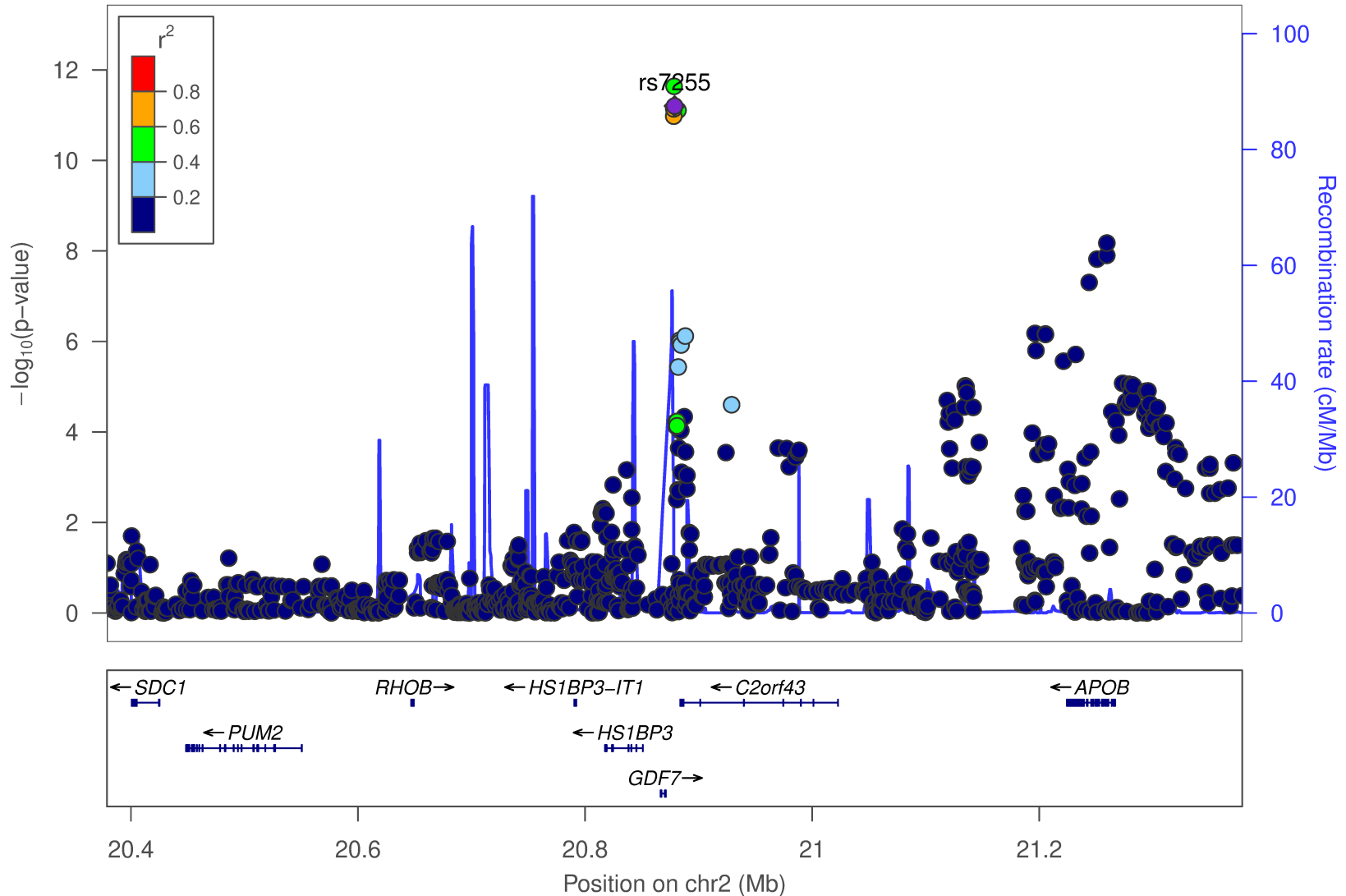
Plotted SNPs



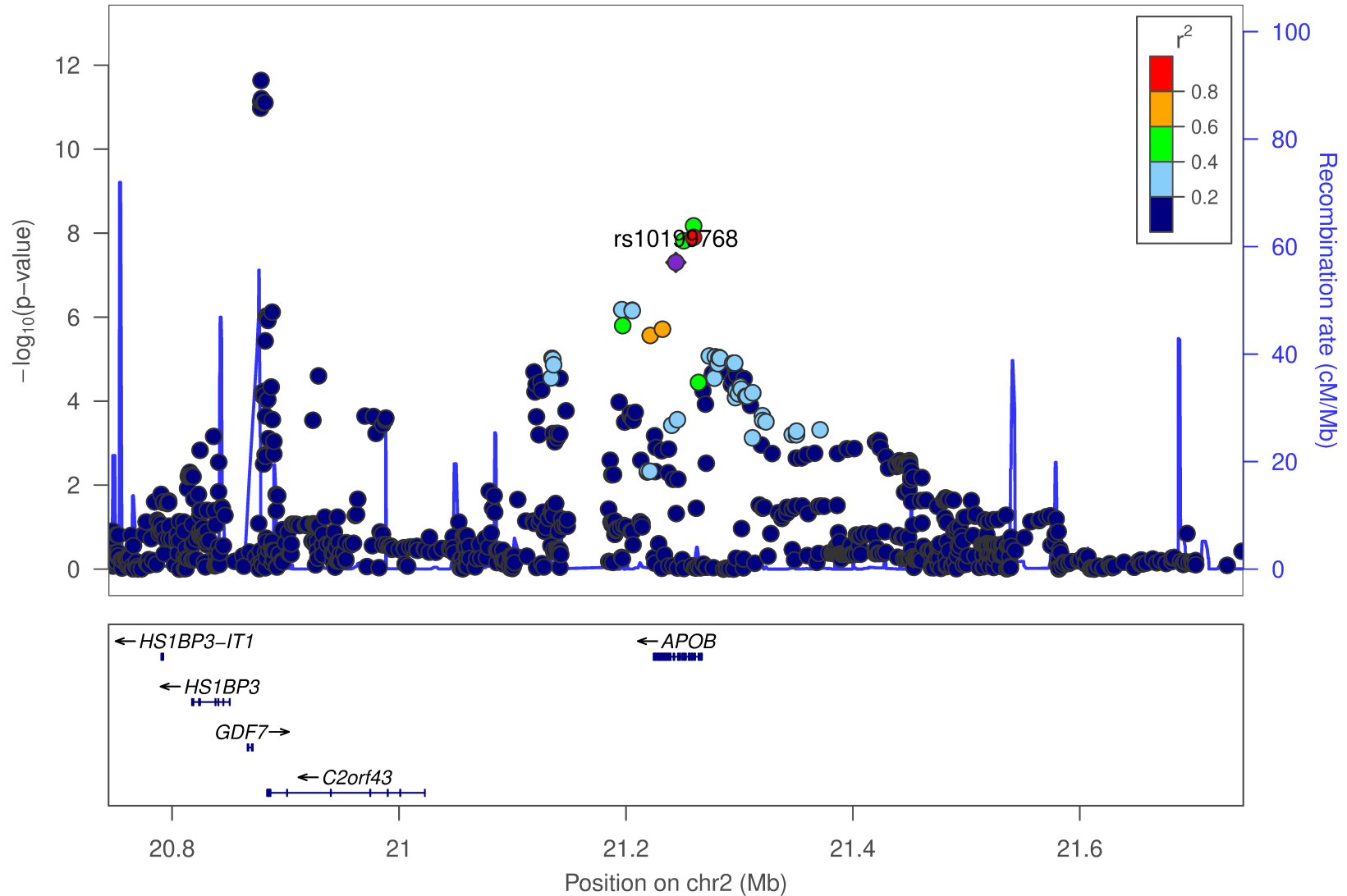
Plotted SNPs



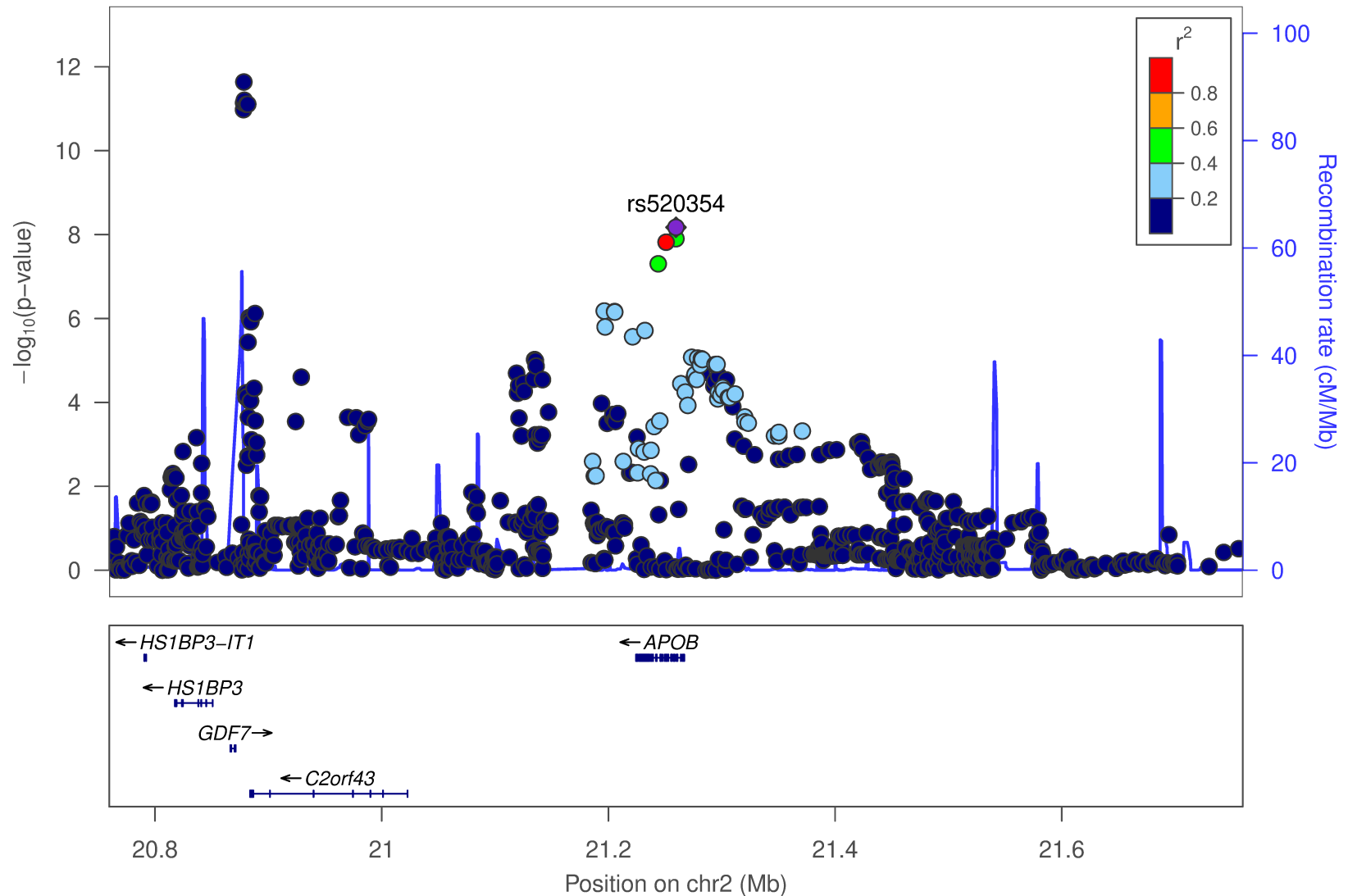
Plotted SNPs



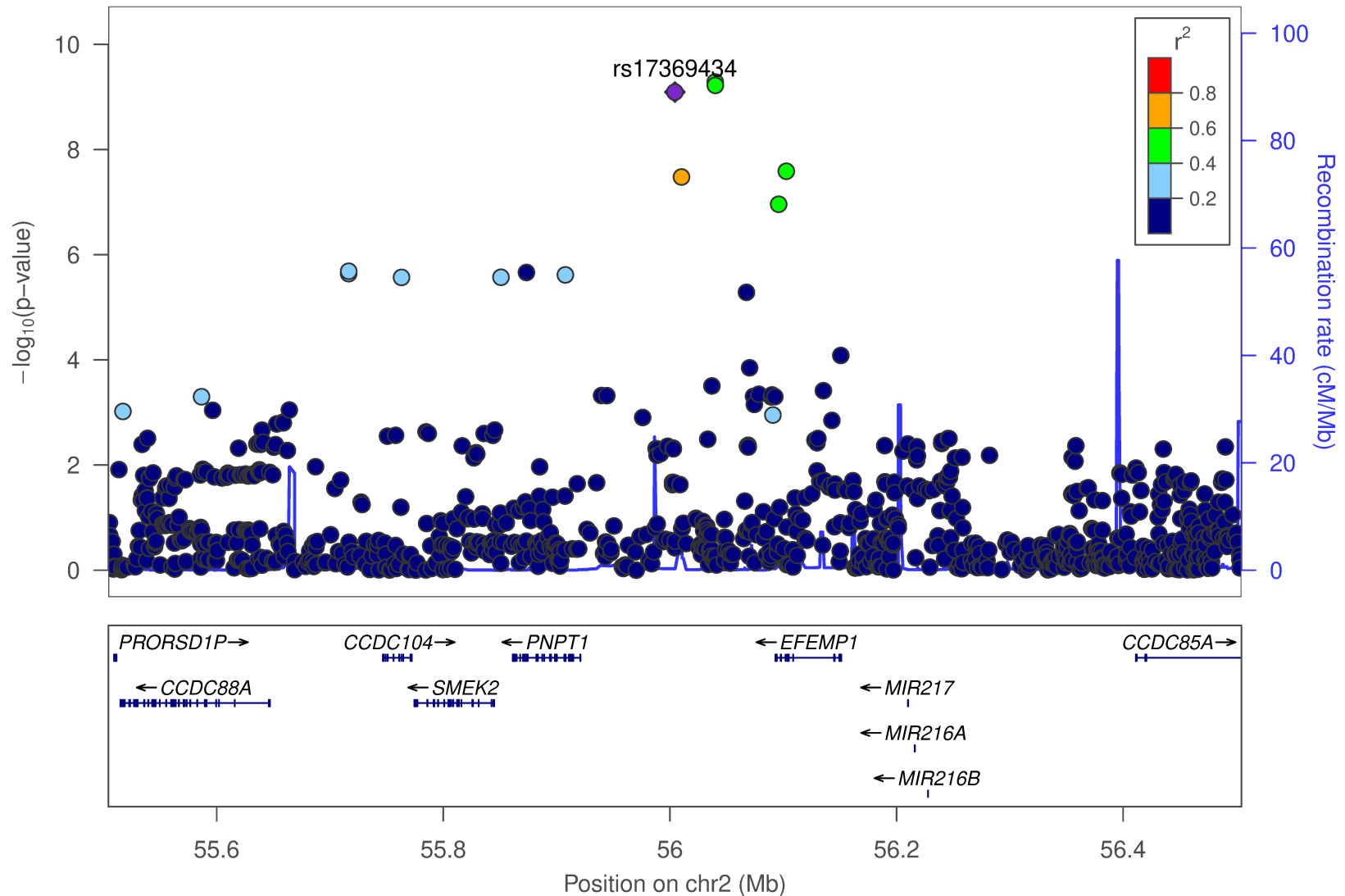
Plotted SNPs



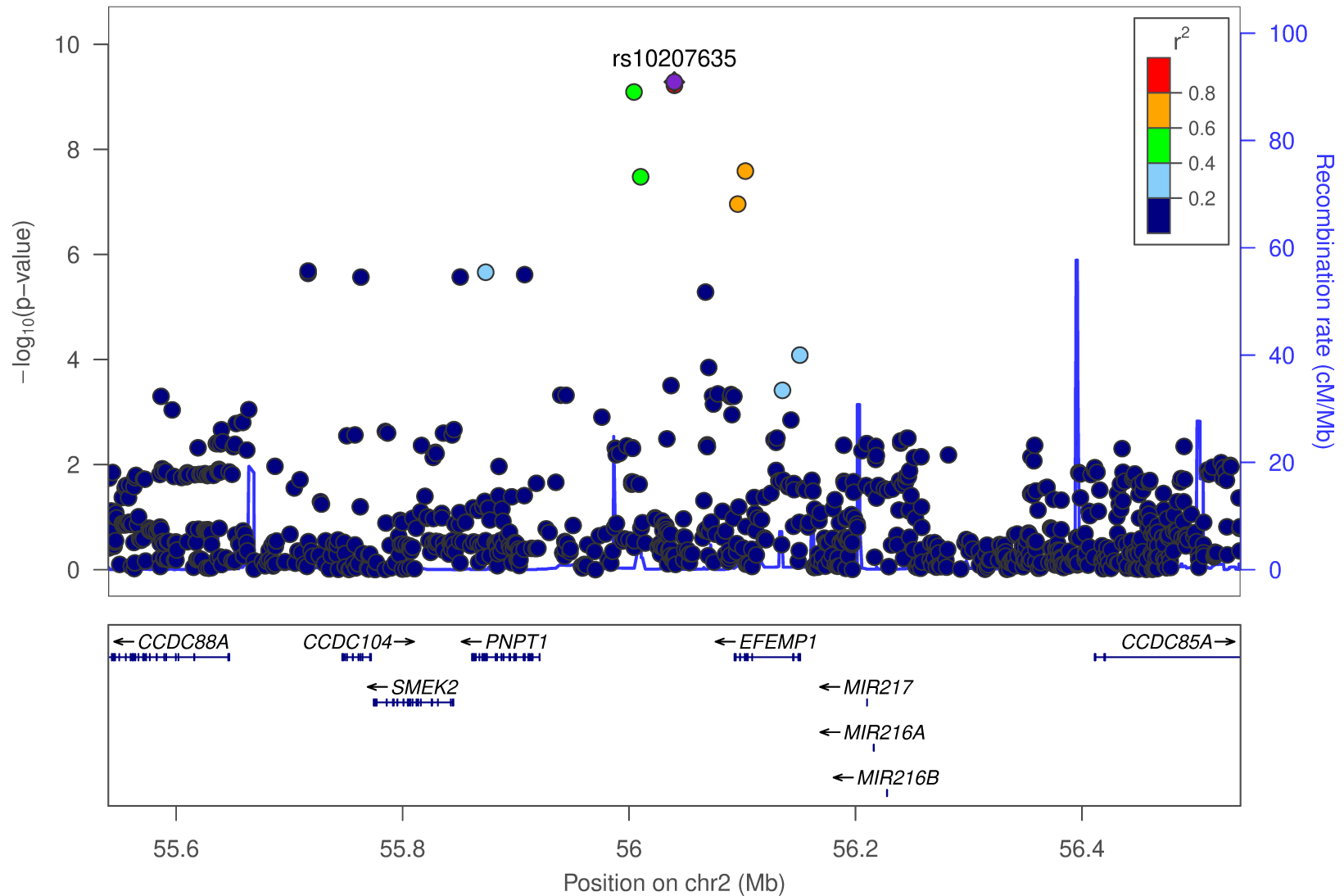
Plotted SNPs



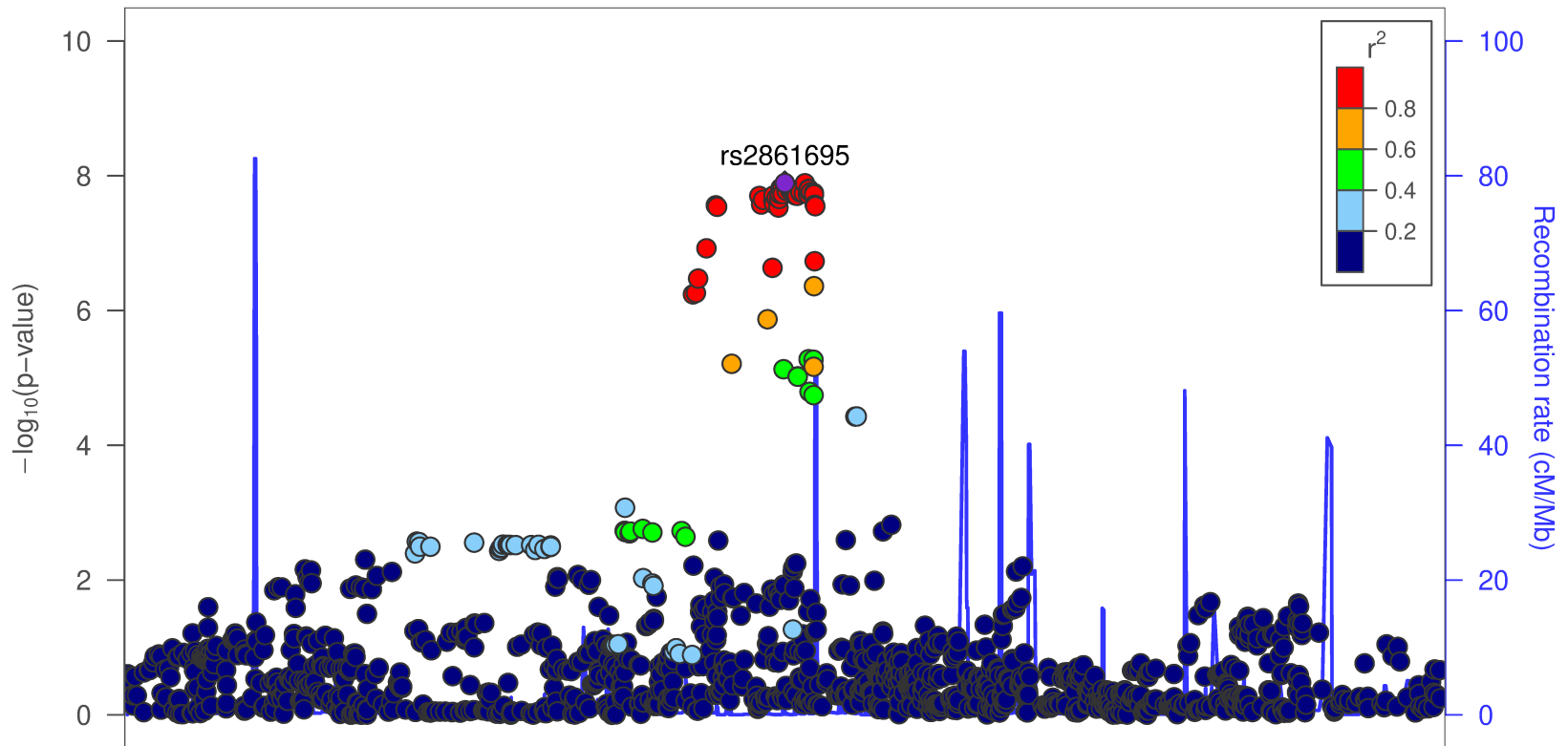
Plotted SNPs



Plotted SNPs



Plotted SNPs



67.4

67.6

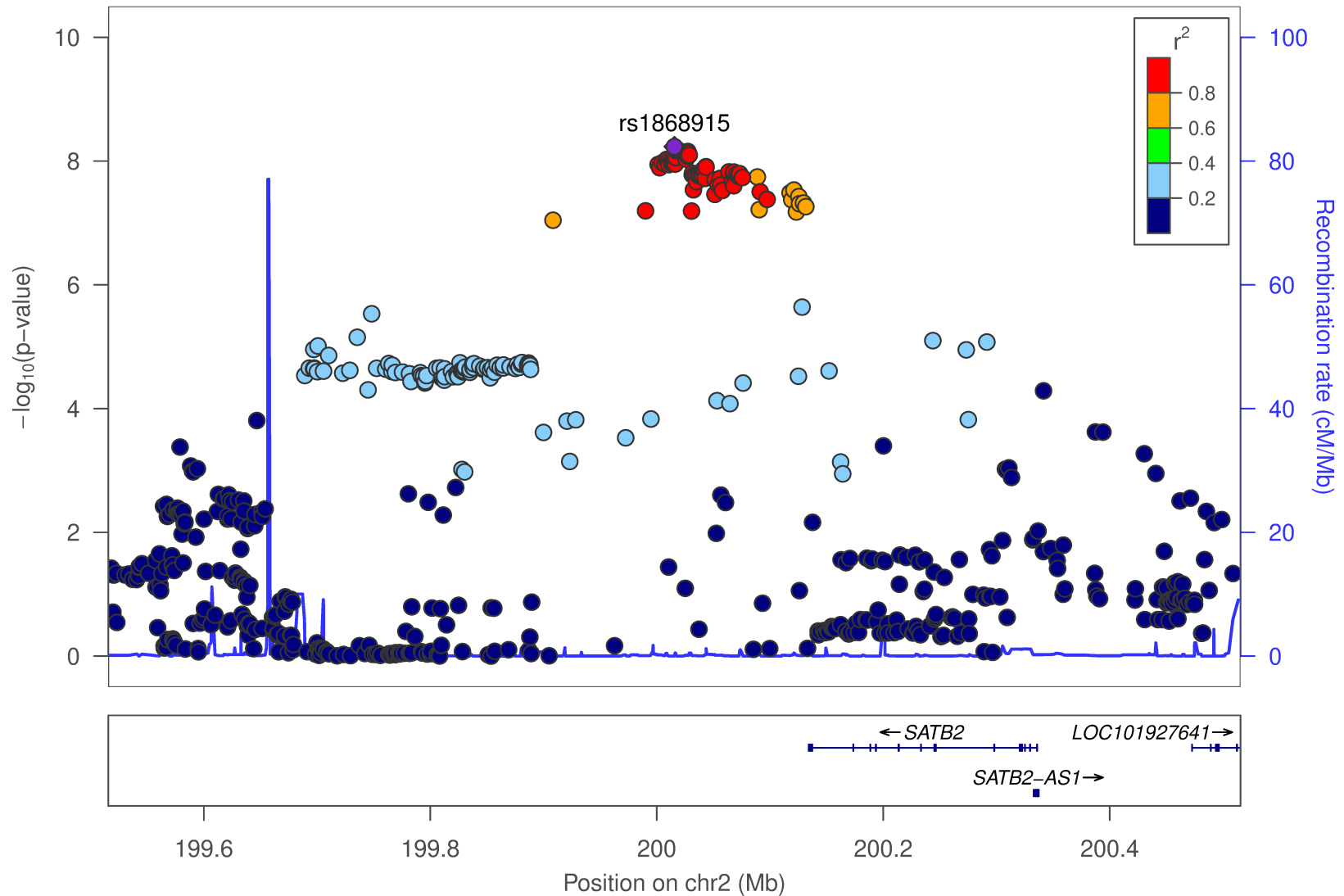
67.8

68

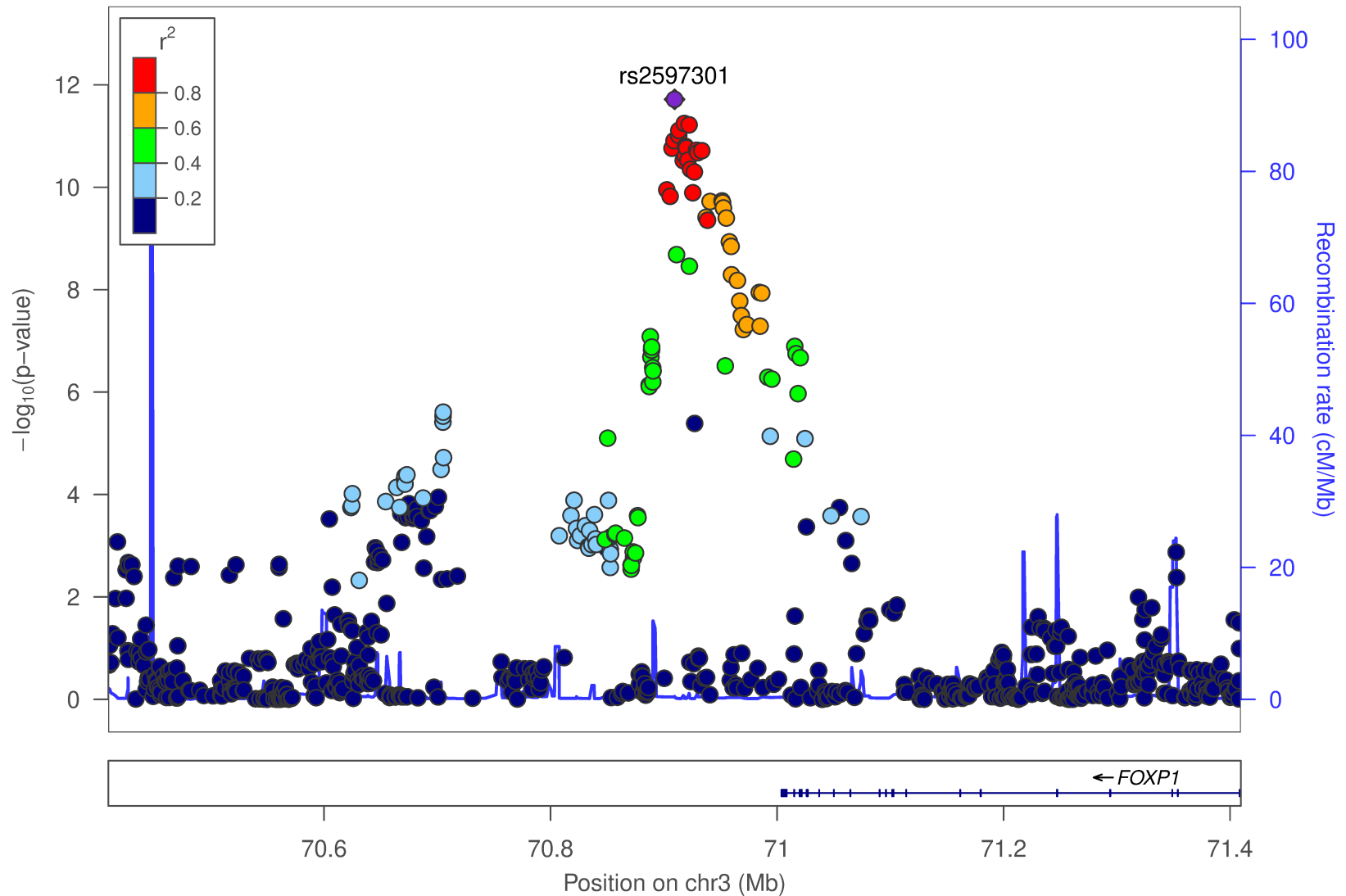
68.2

Position on chr2 (Mb)

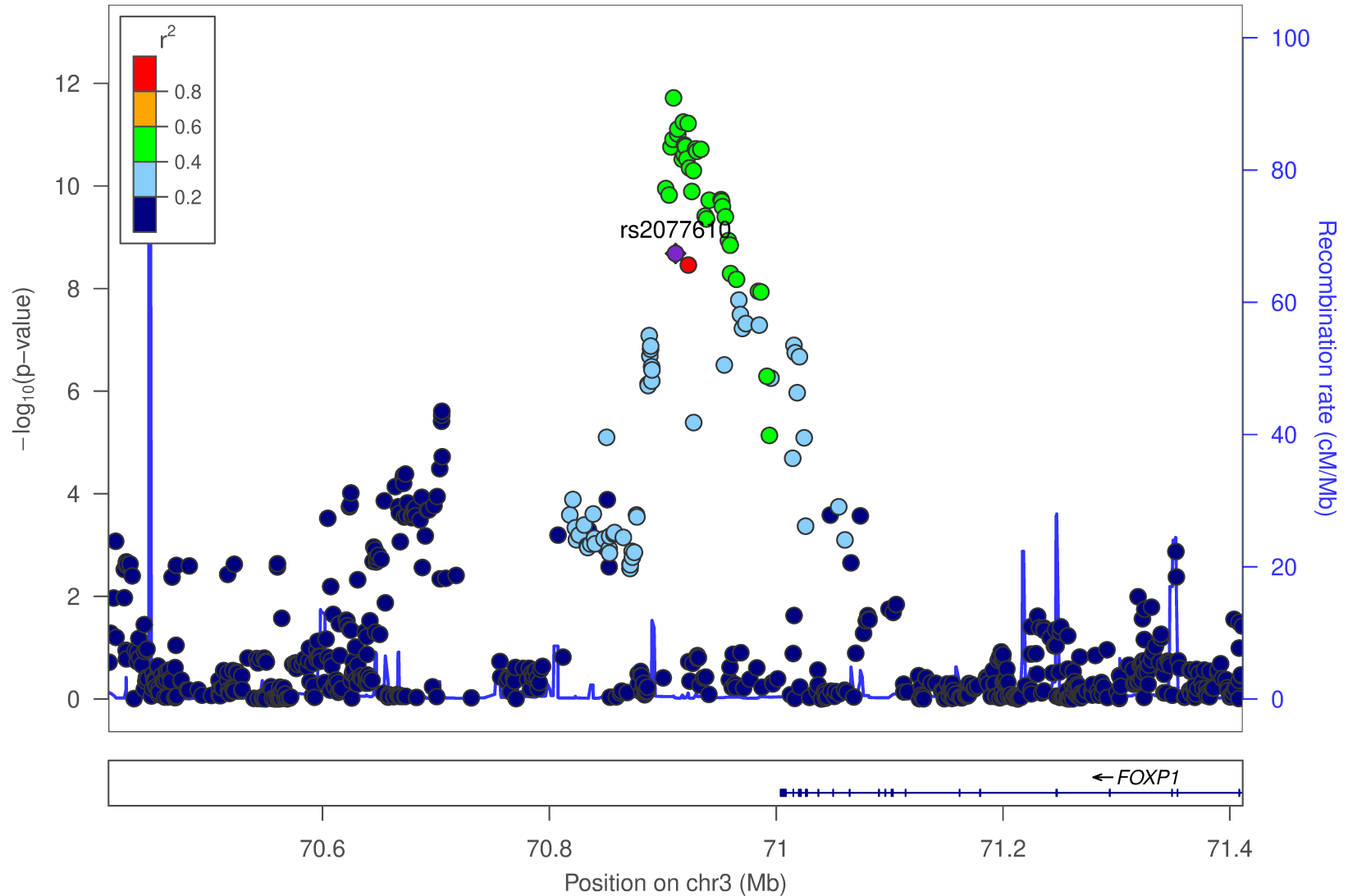
Plotted SNPs



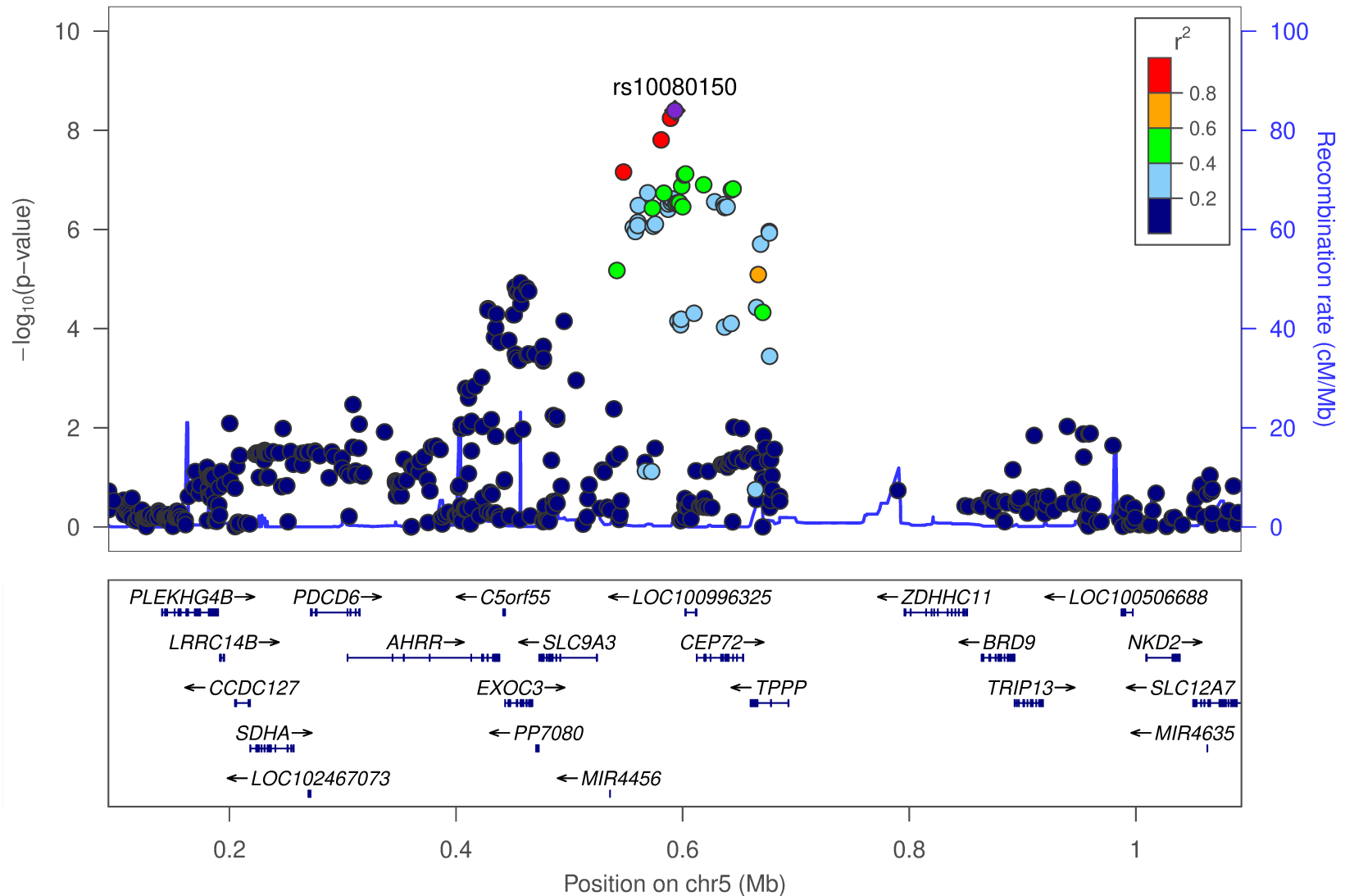
Plotted SNPs



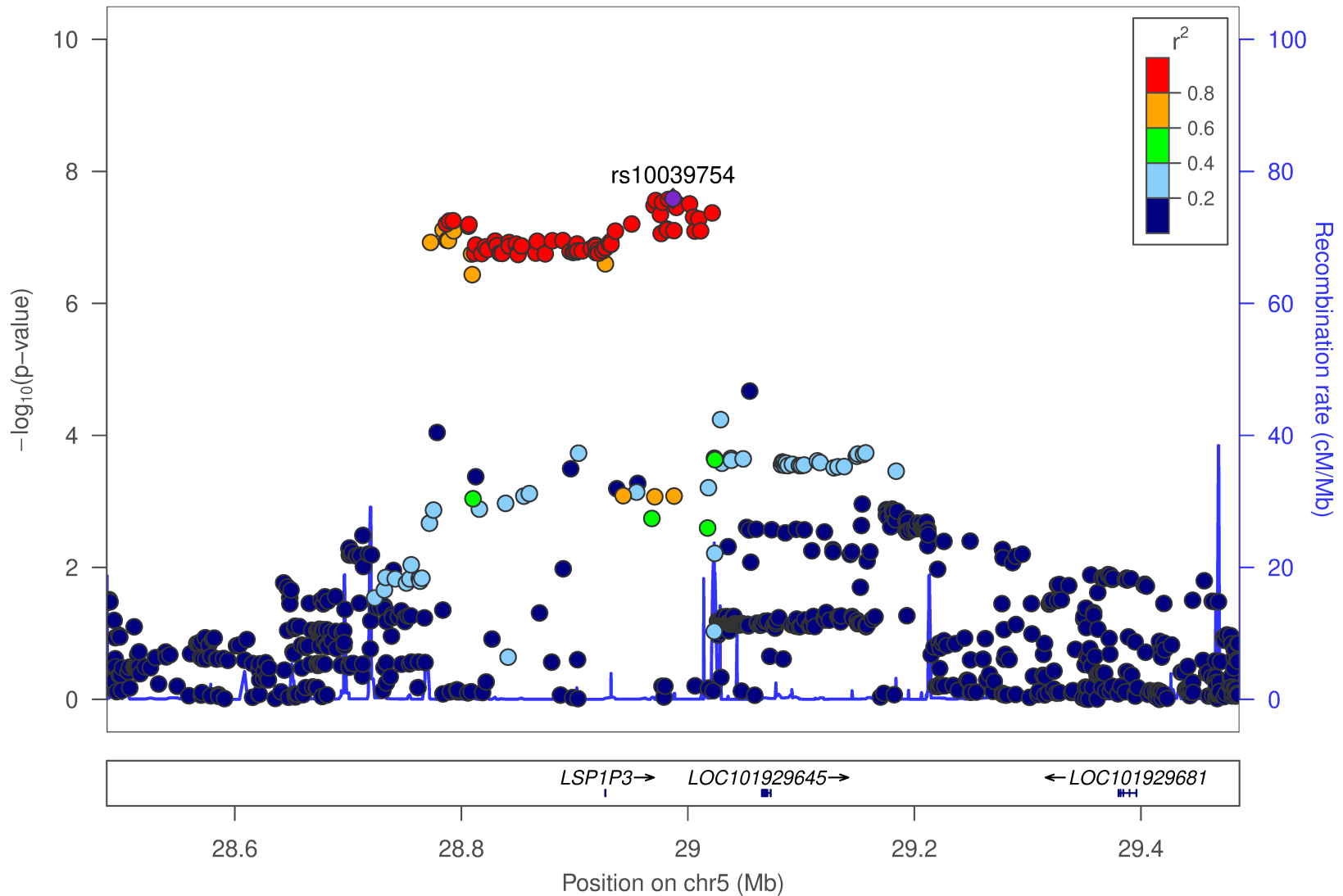
Plotted SNPs

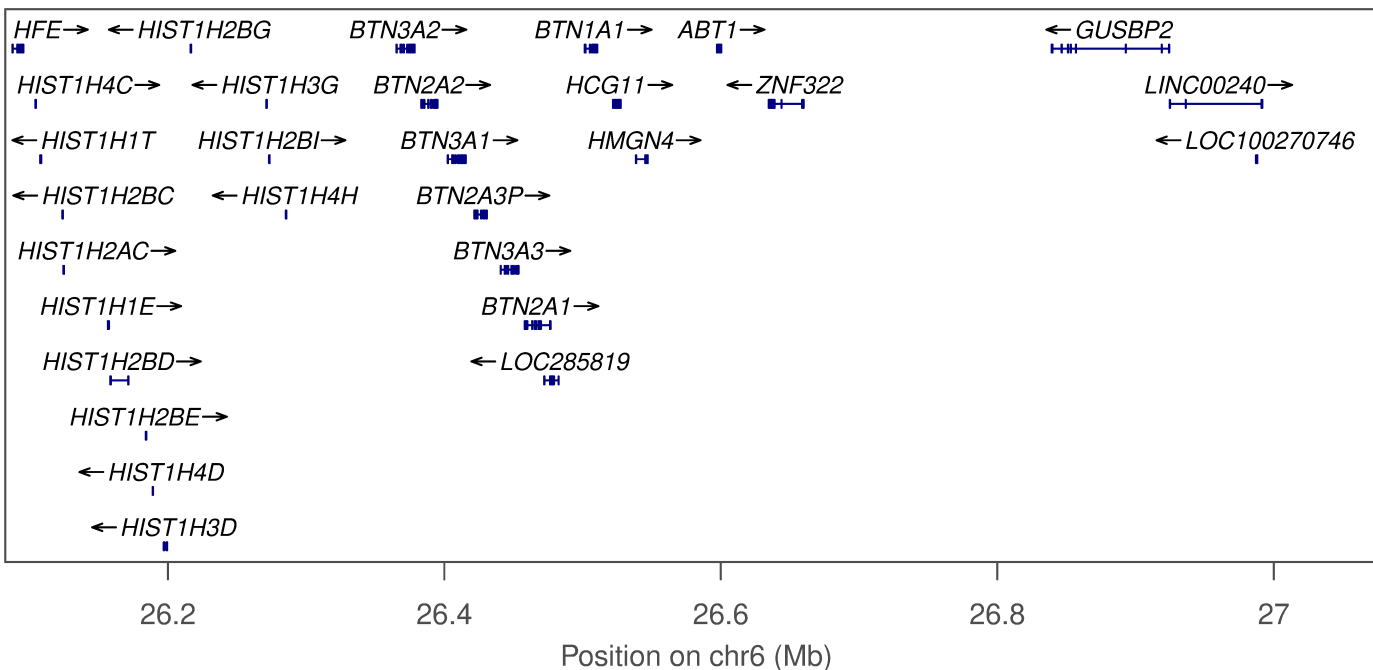
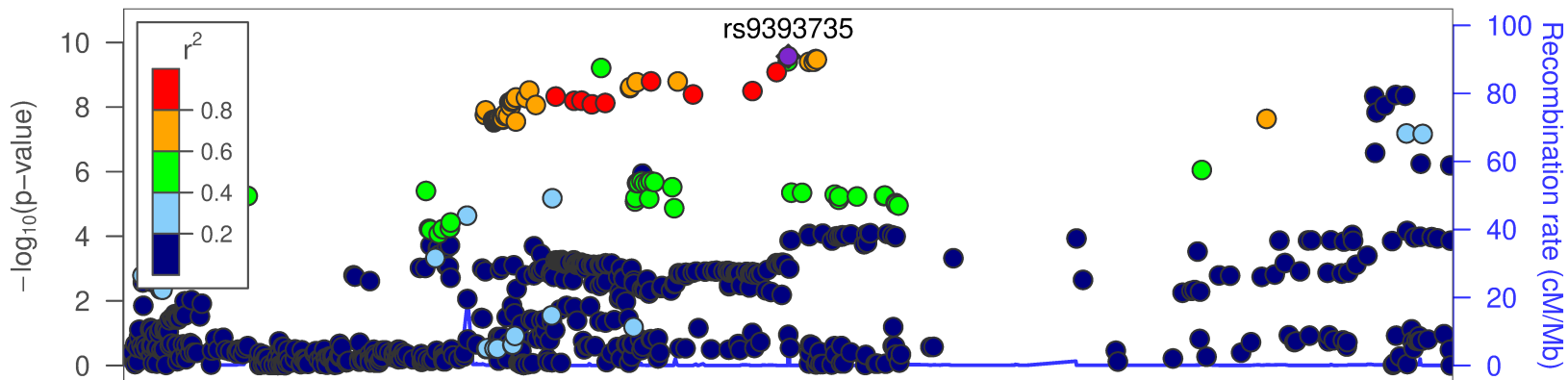


Plotted SNPs

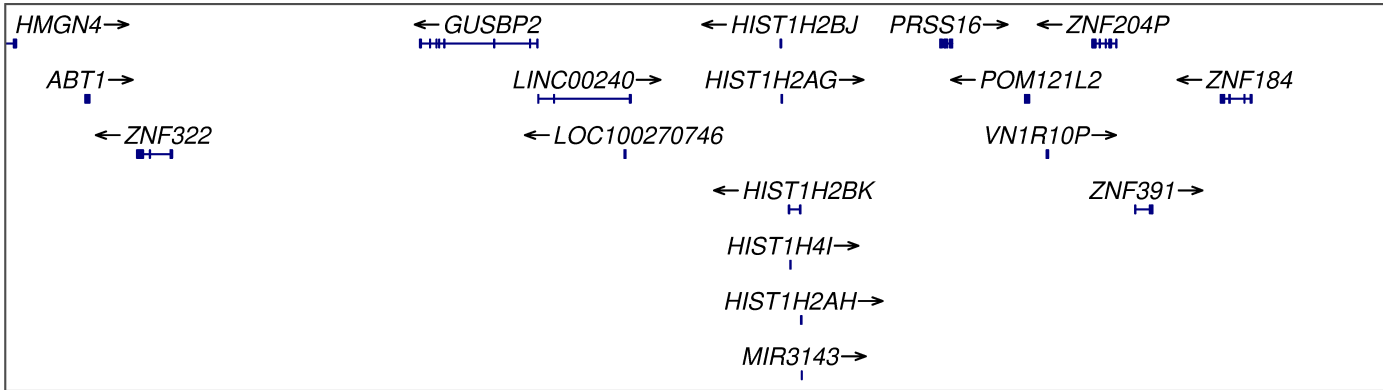
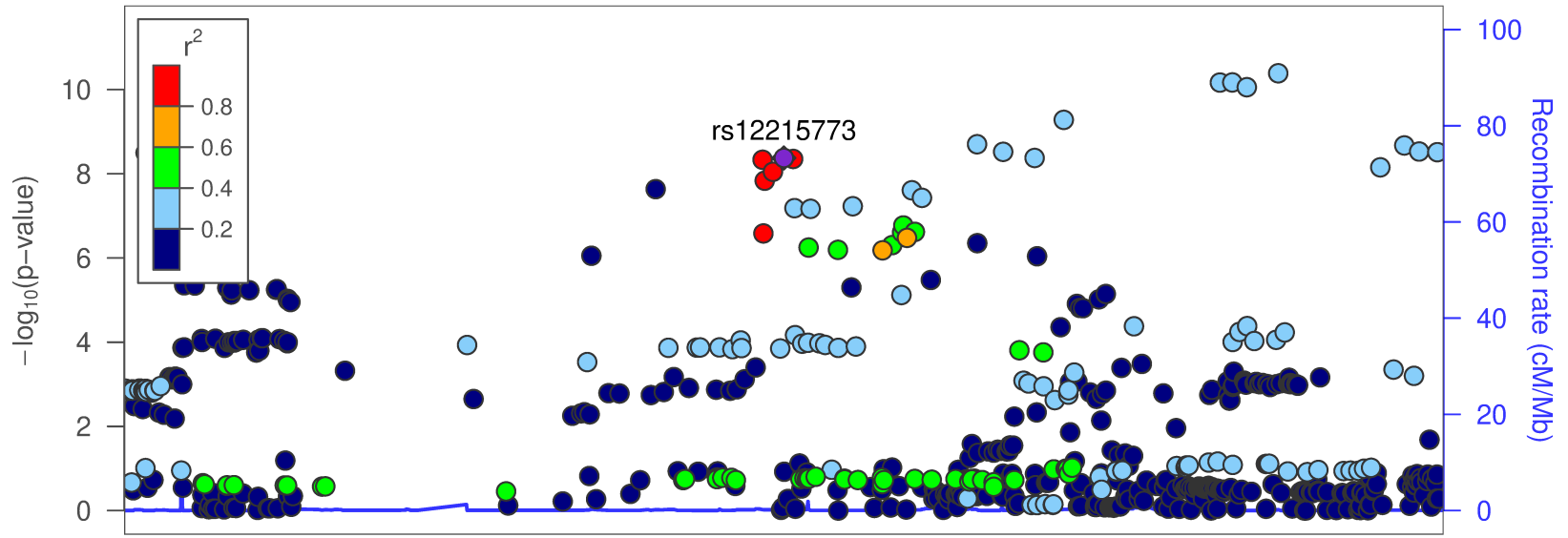


Plotted SNPs



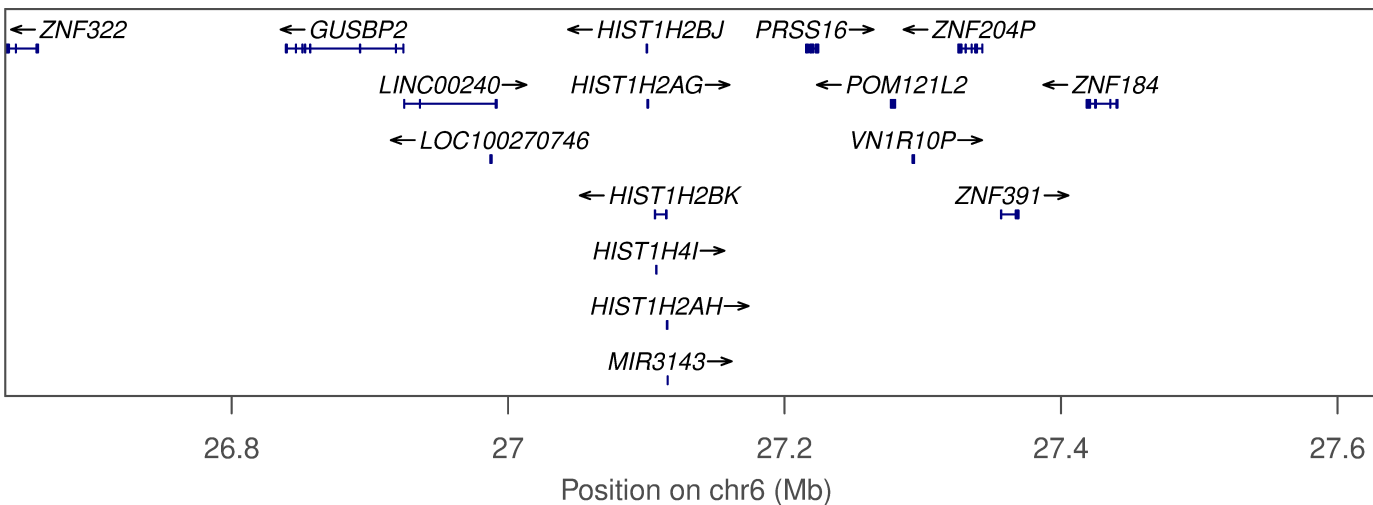
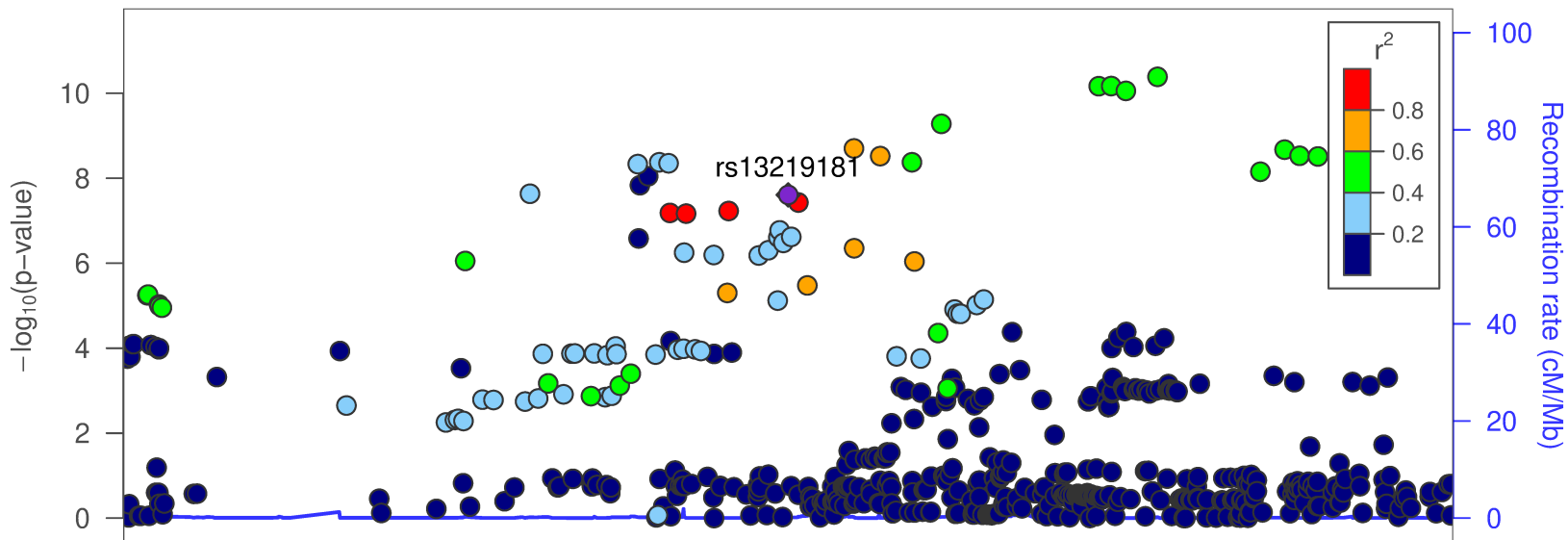


10 genes omitted

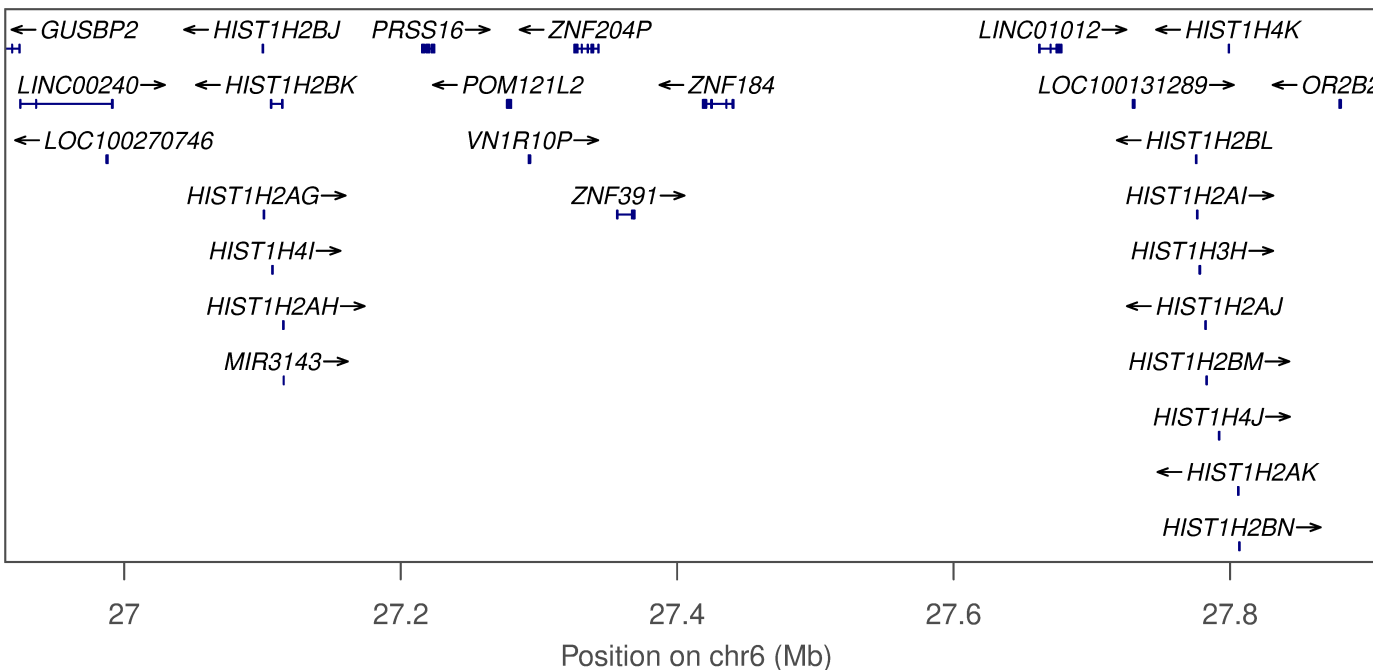
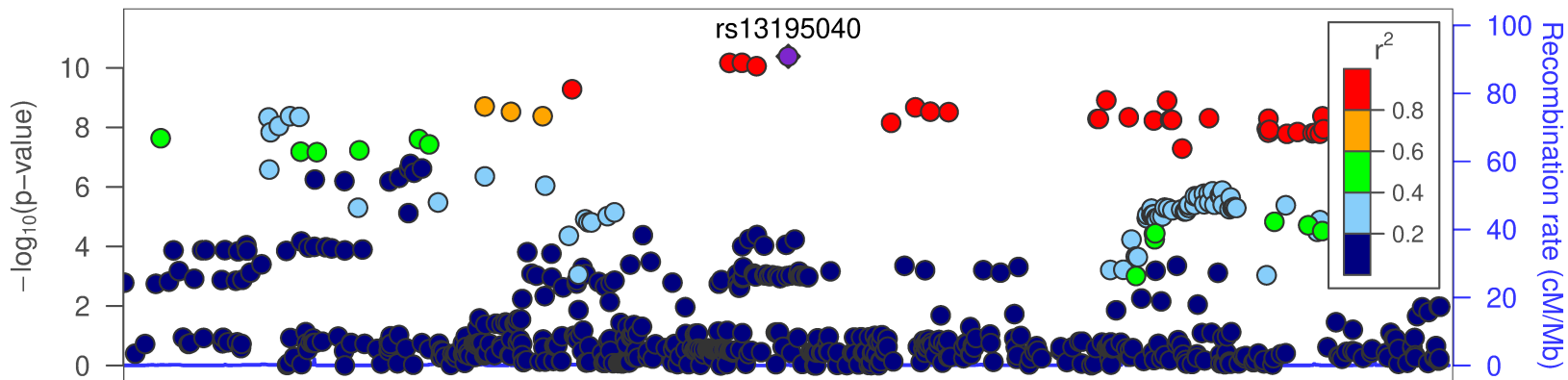


26.6 26.8 27 27.2 27.4

Position on chr6 (Mb)

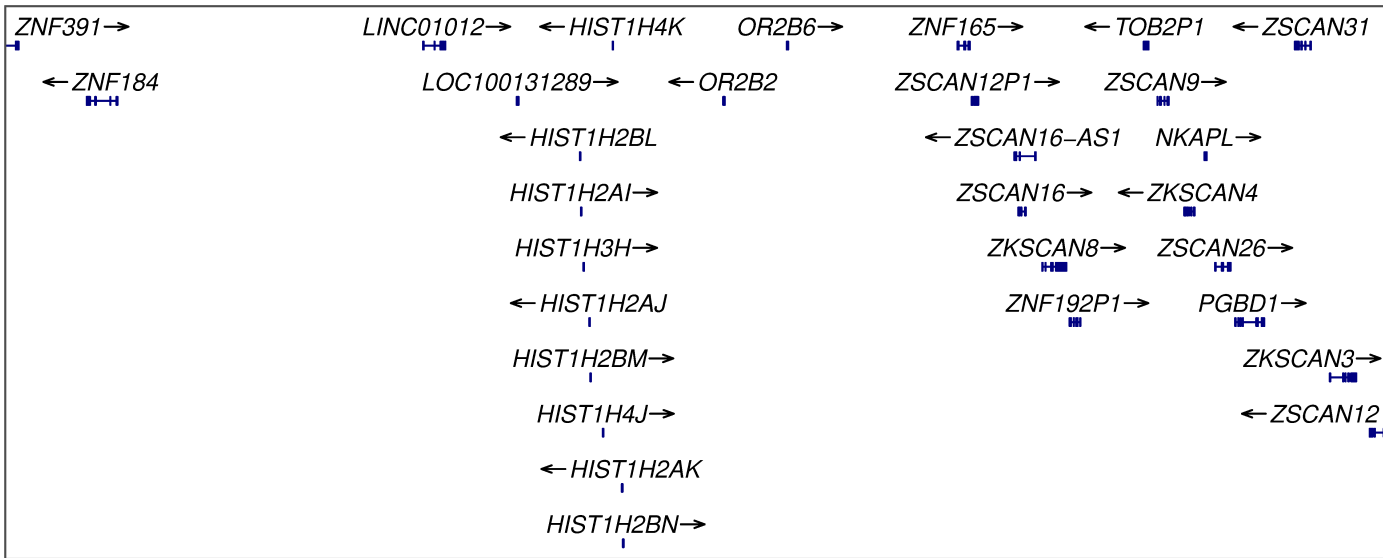
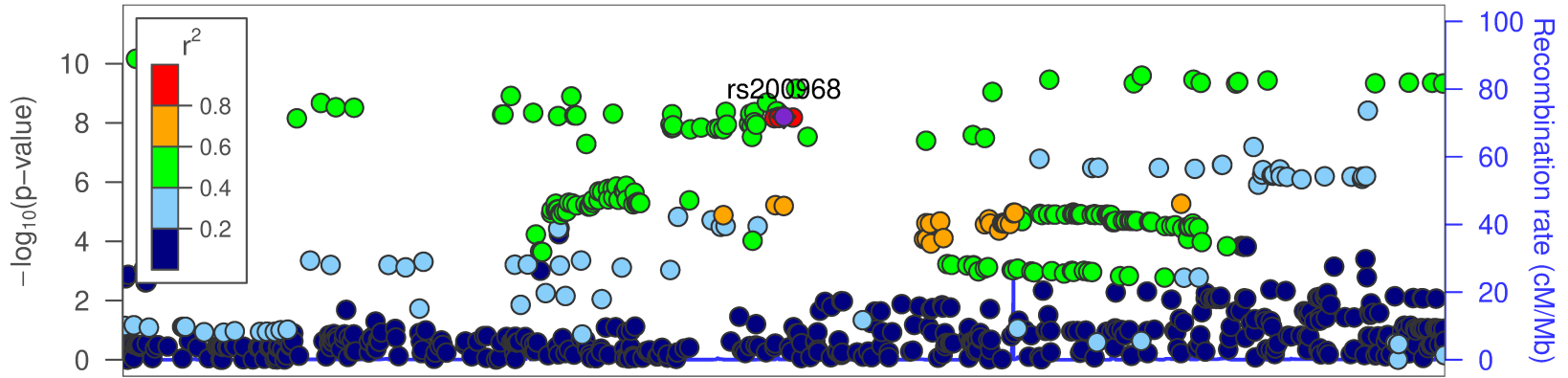


Plotted SNPs



7 genes omitted

Plotted SNPs

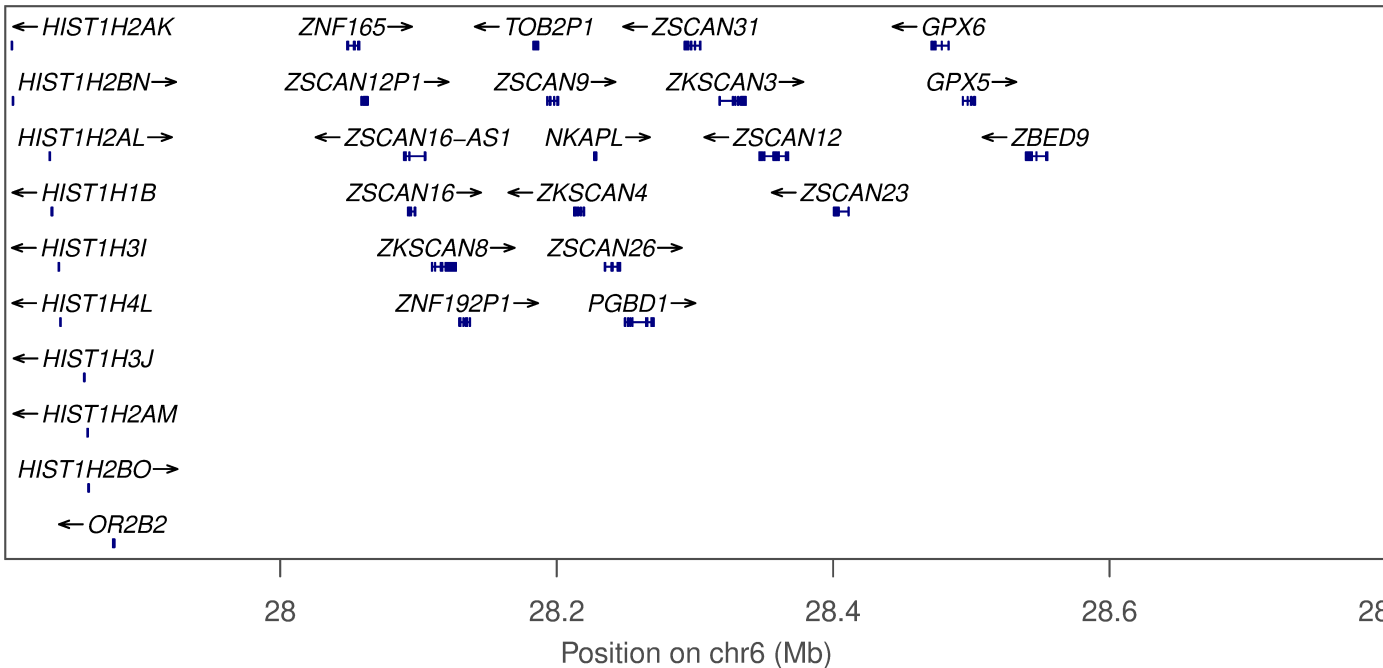
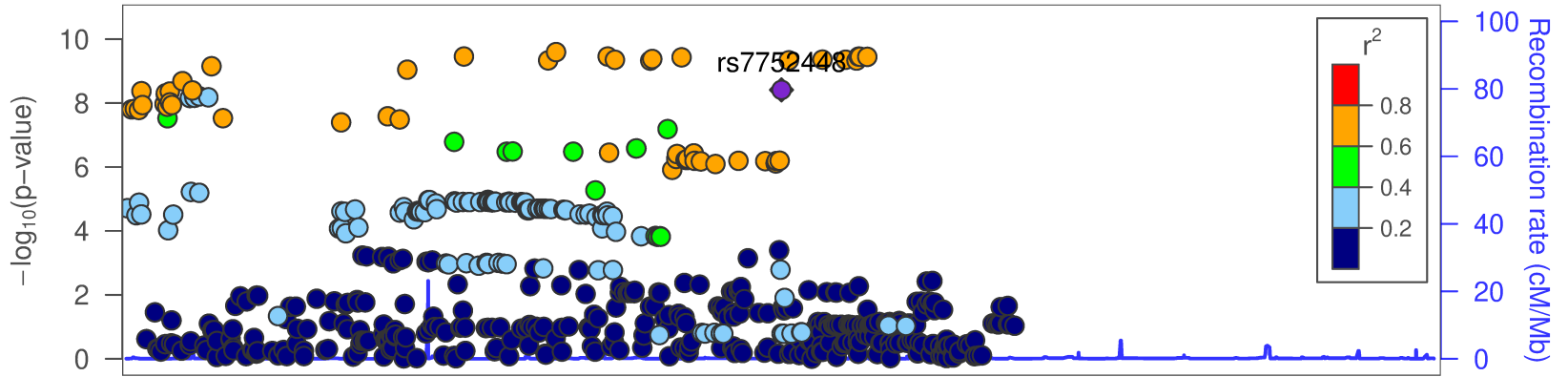


7 genes omitted

27.4 27.6 27.8 28 28.2

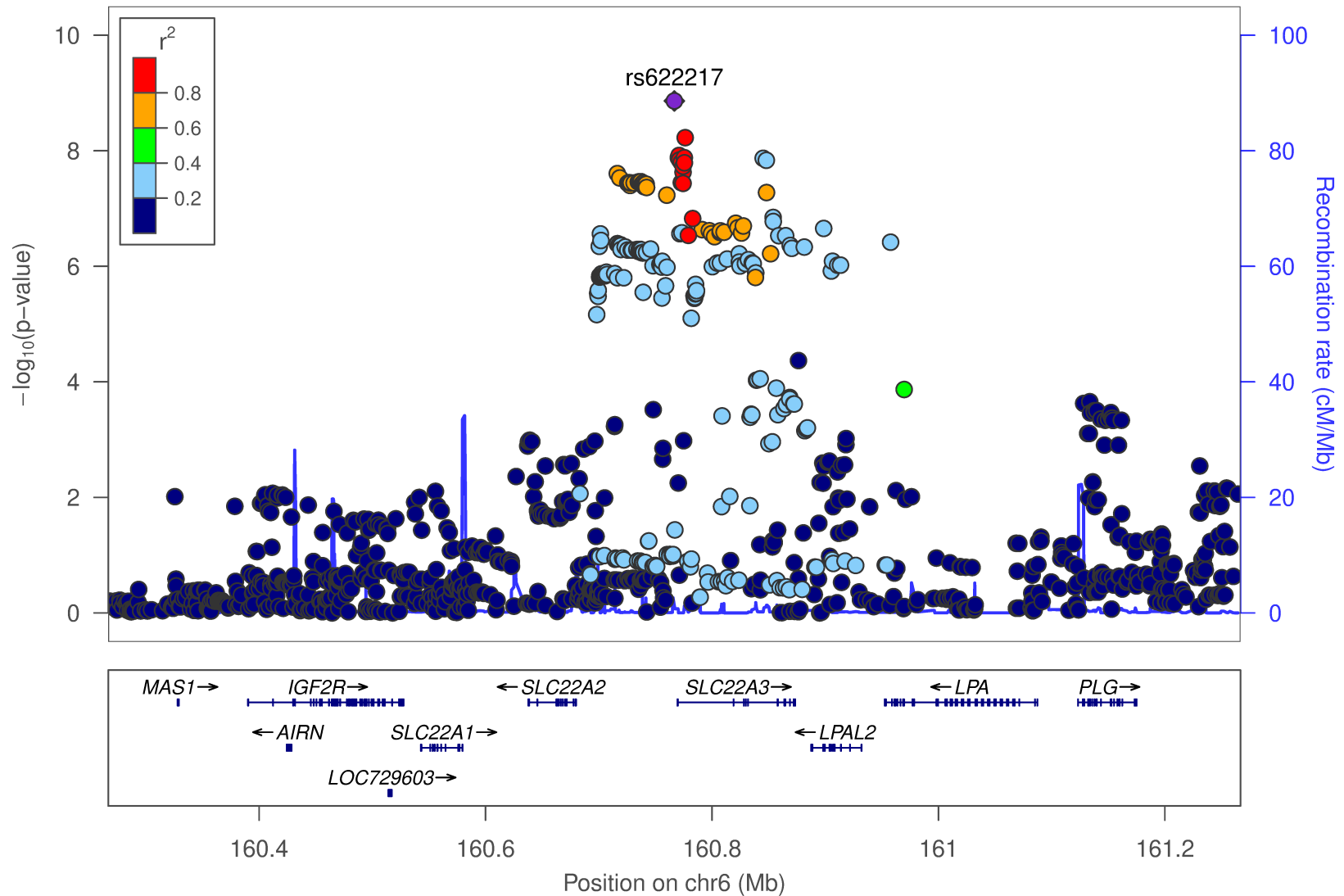
Position on chr6 (Mb)

Plotted SNPs

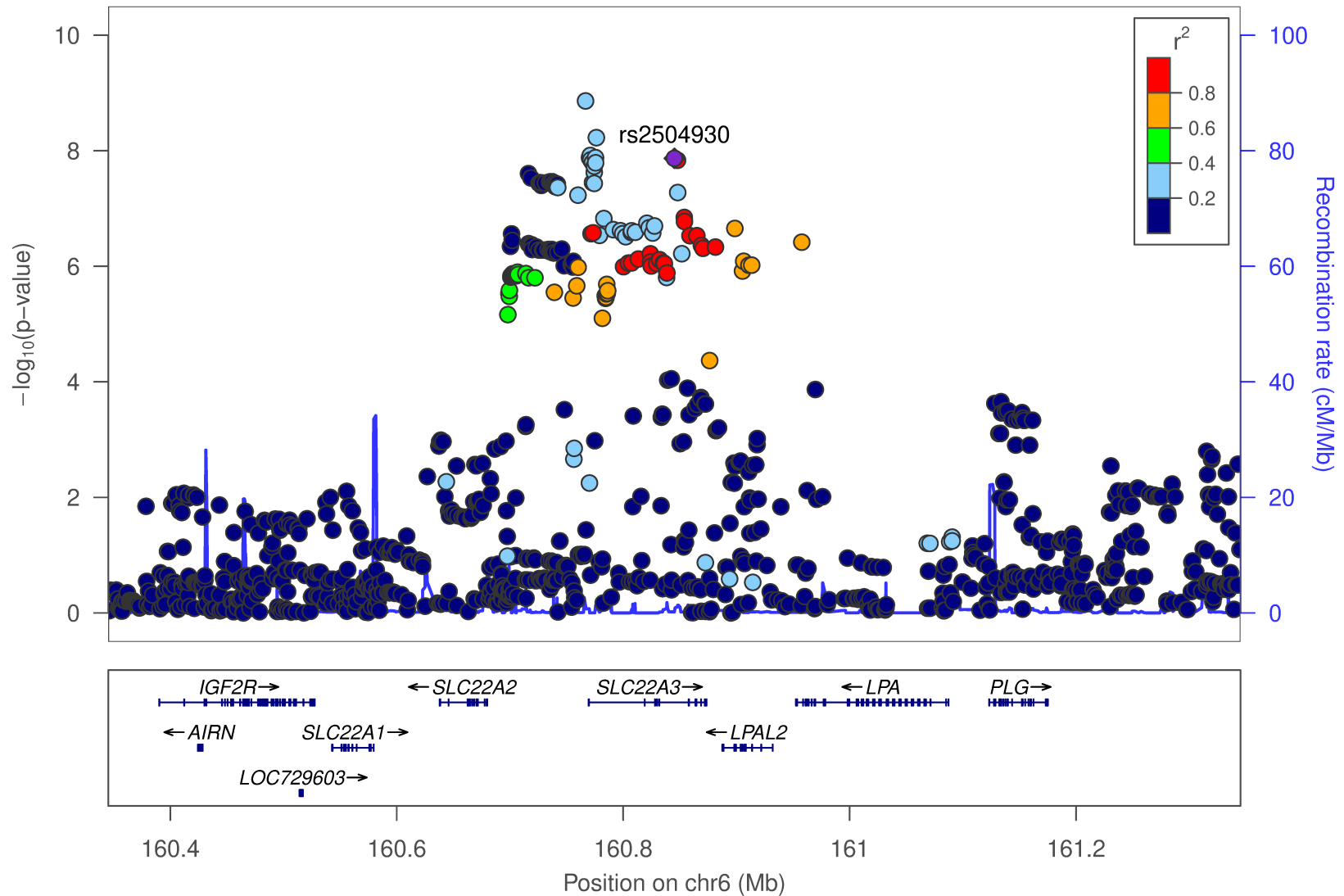


1 gene omitted

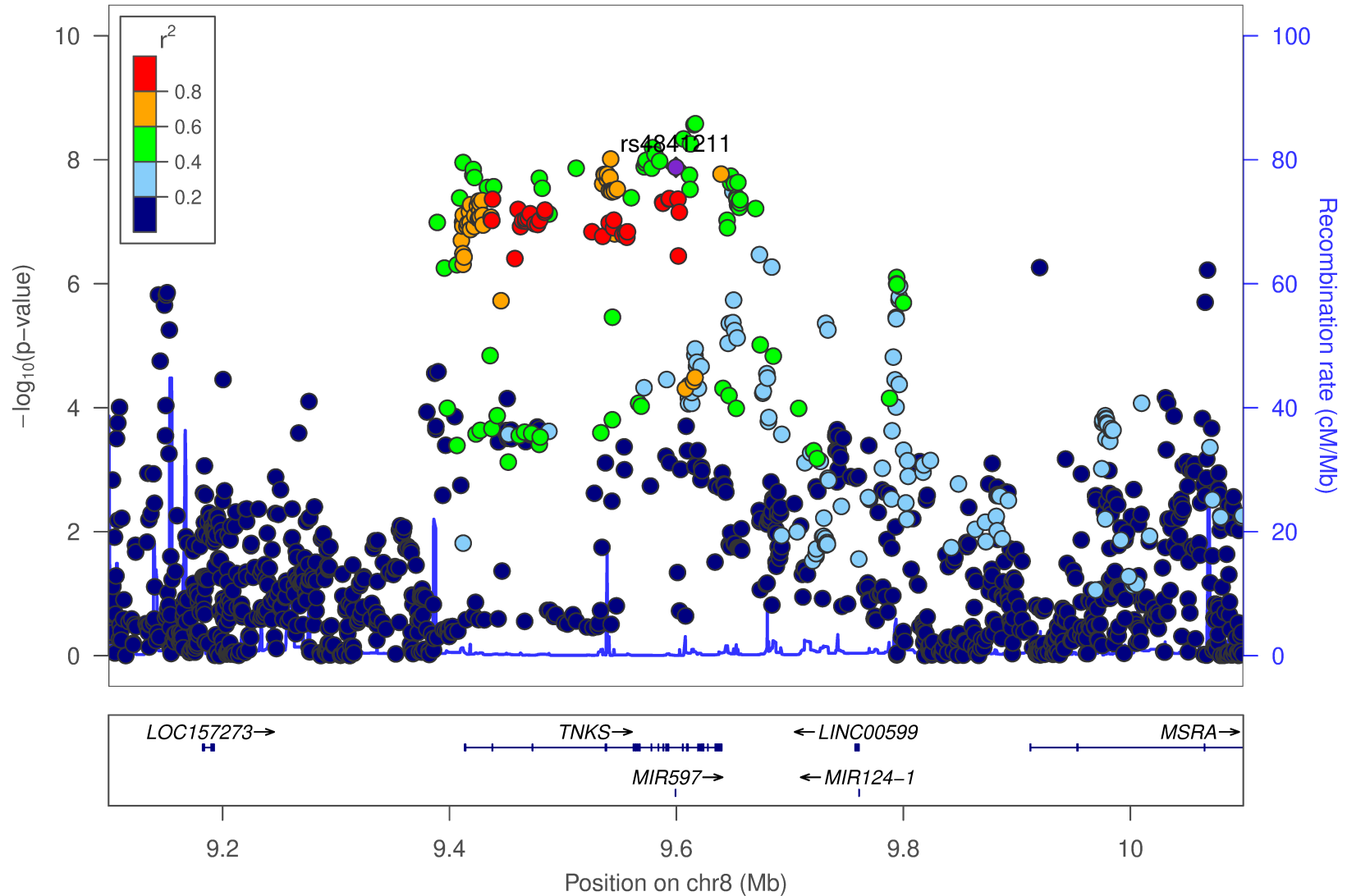
Plotted SNPs



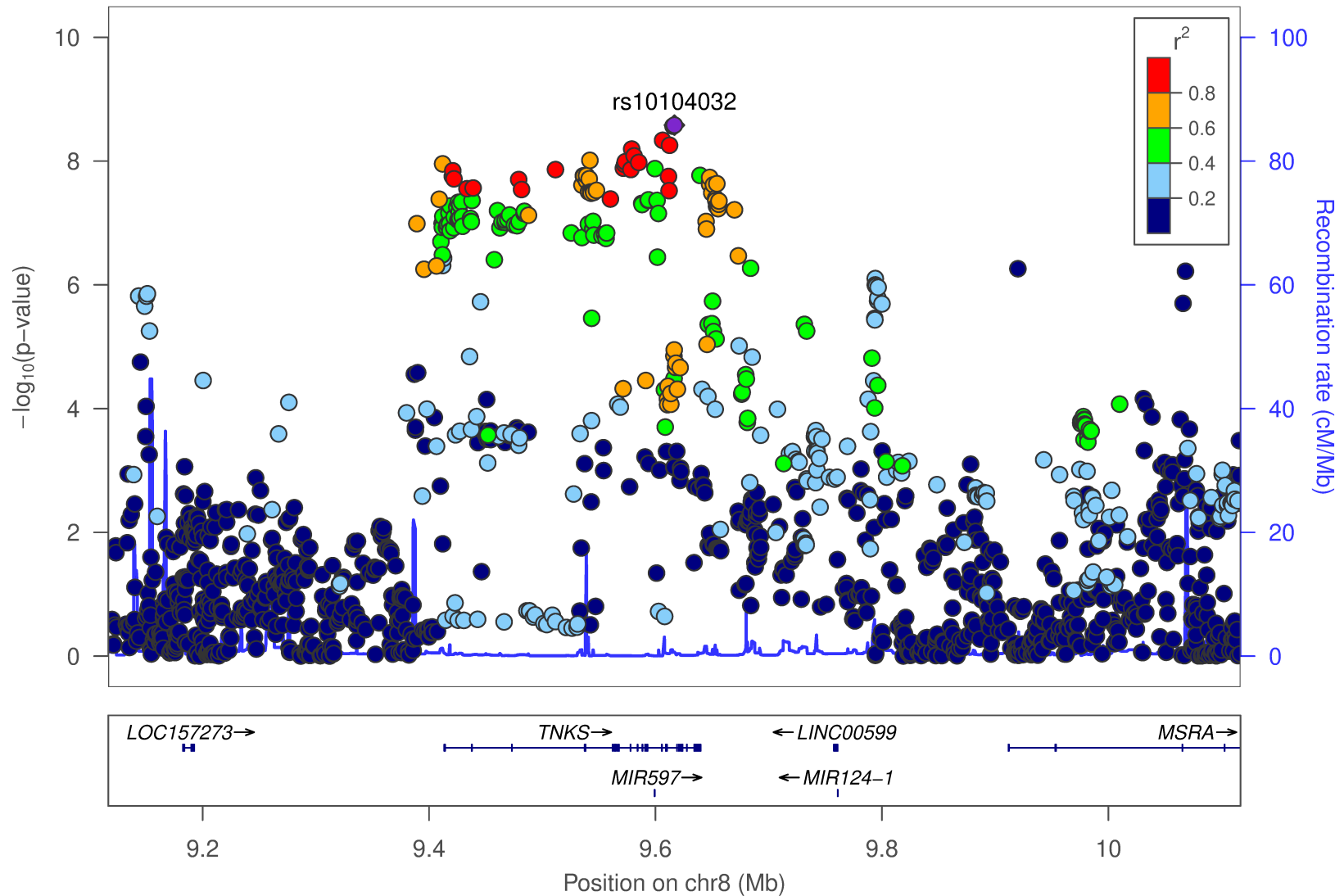
Plotted SNPs



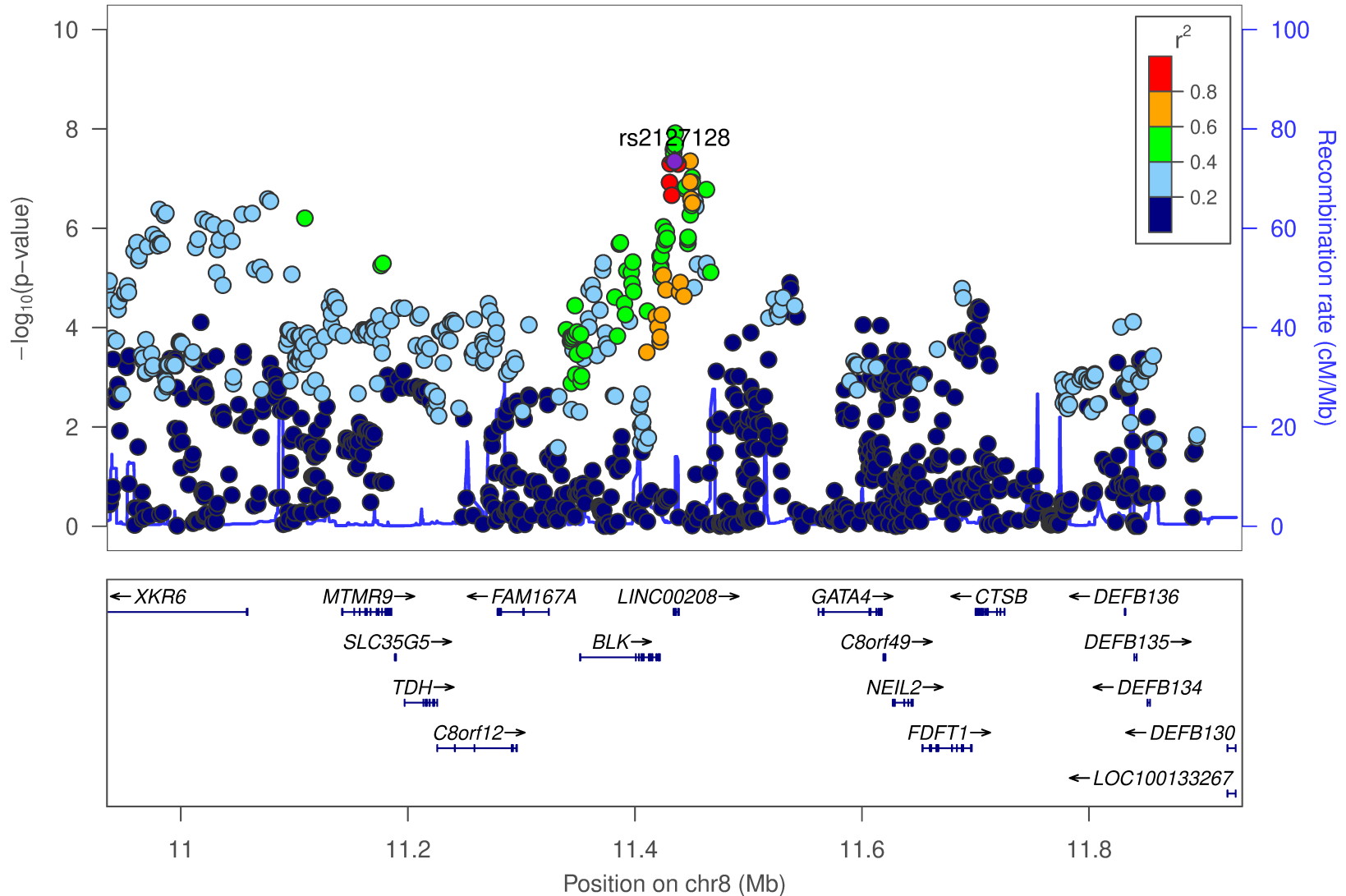
Plotted SNPs



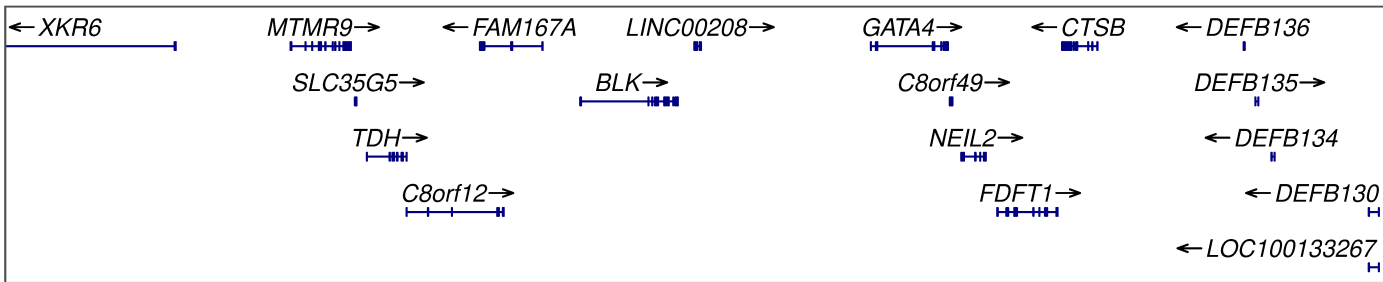
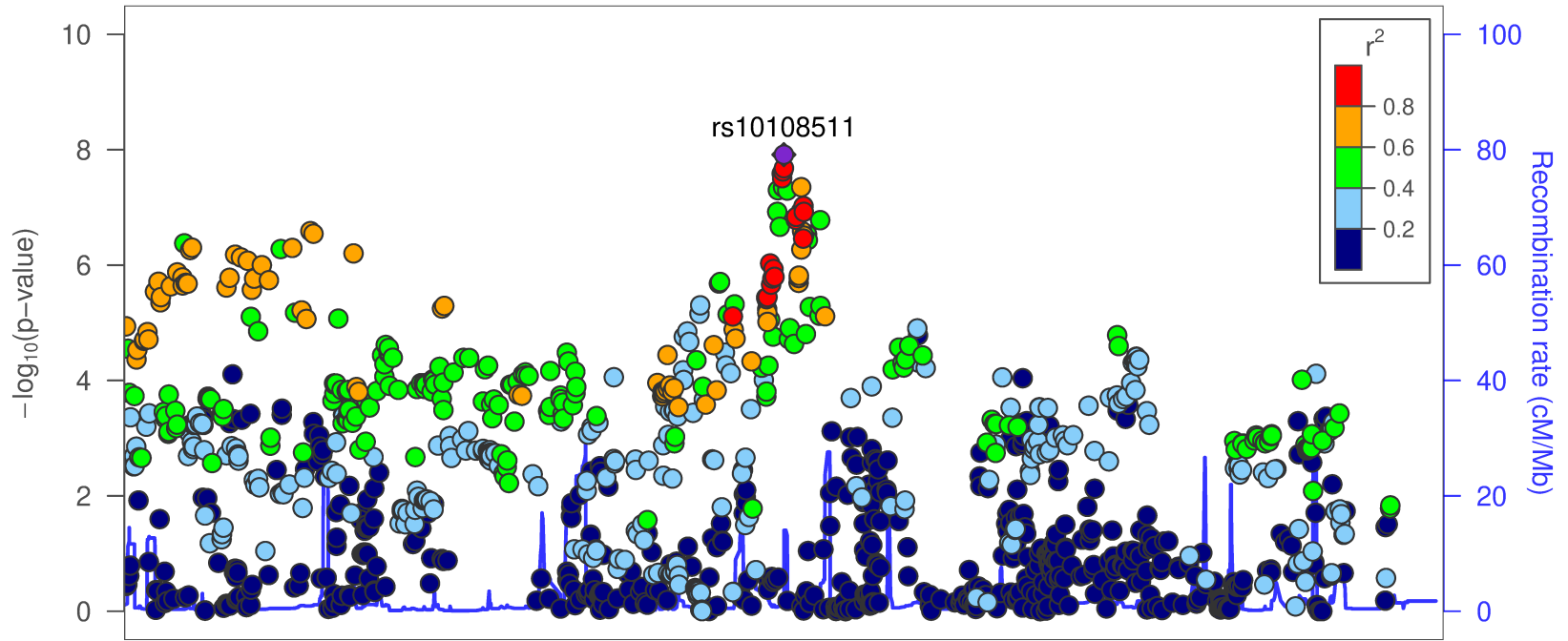
Plotted SNPs



Plotted SNPs



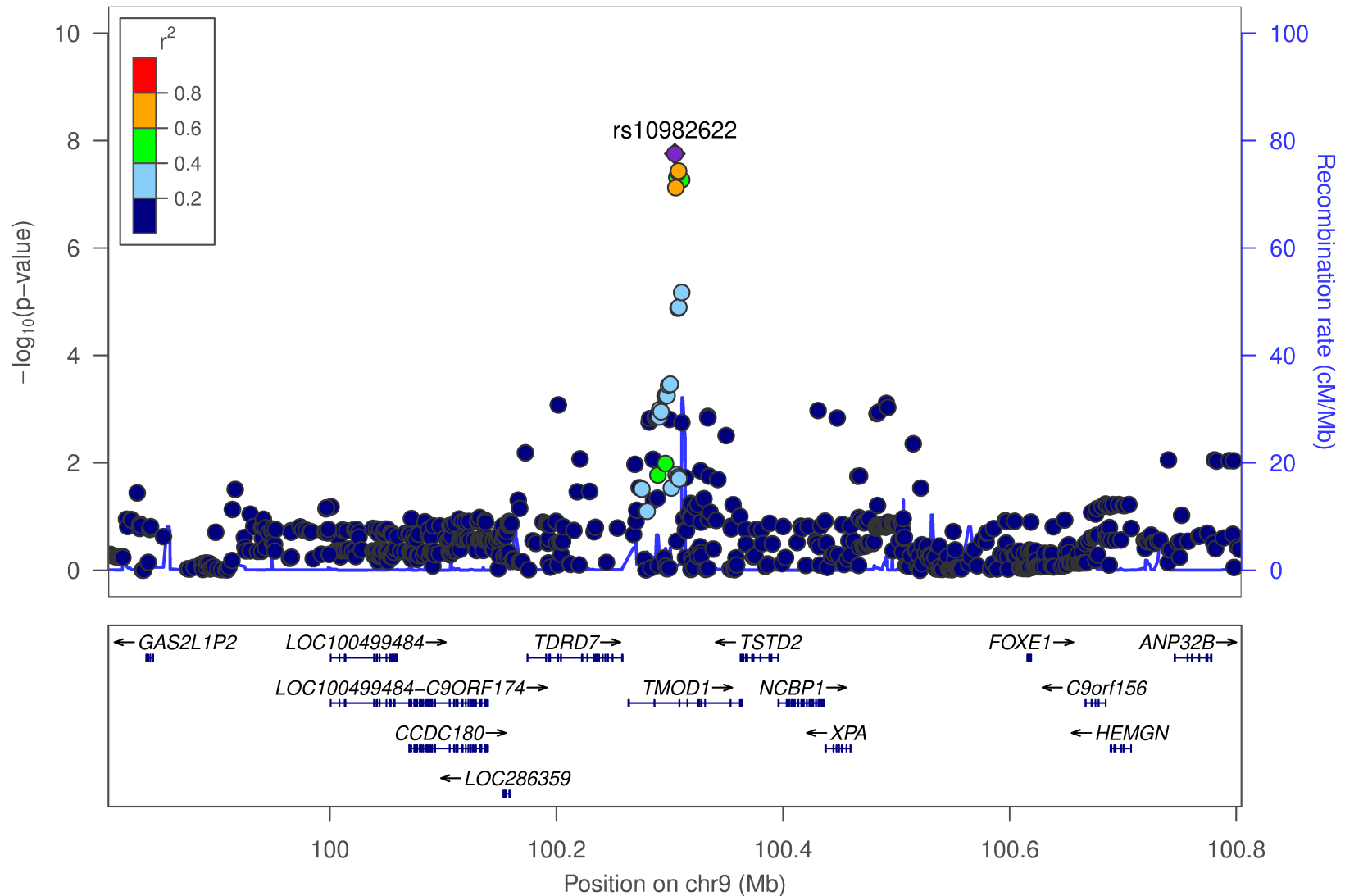
Plotted SNPs



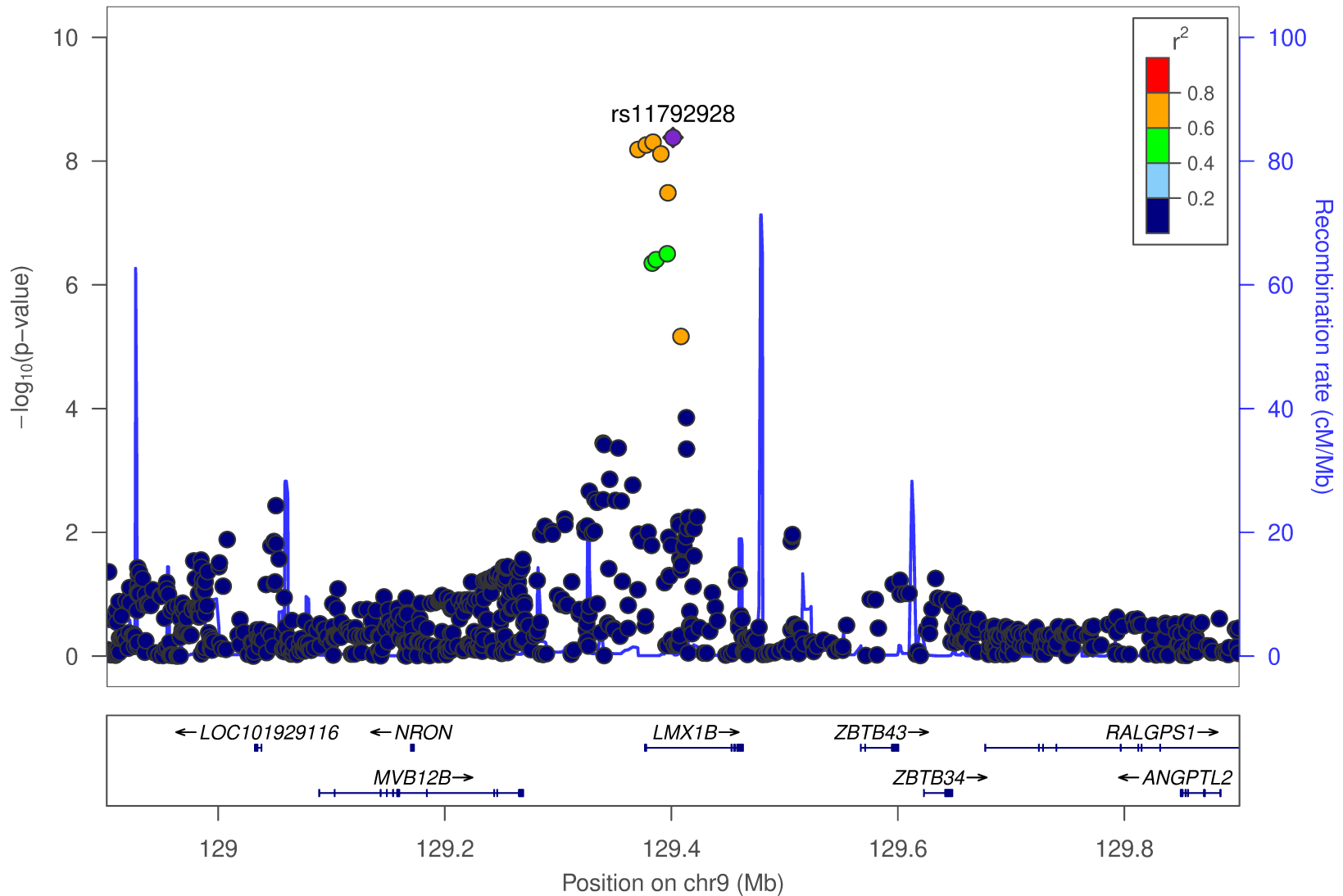
11 11.2 11.4 11.6 11.8

Position on chr8 (Mb)

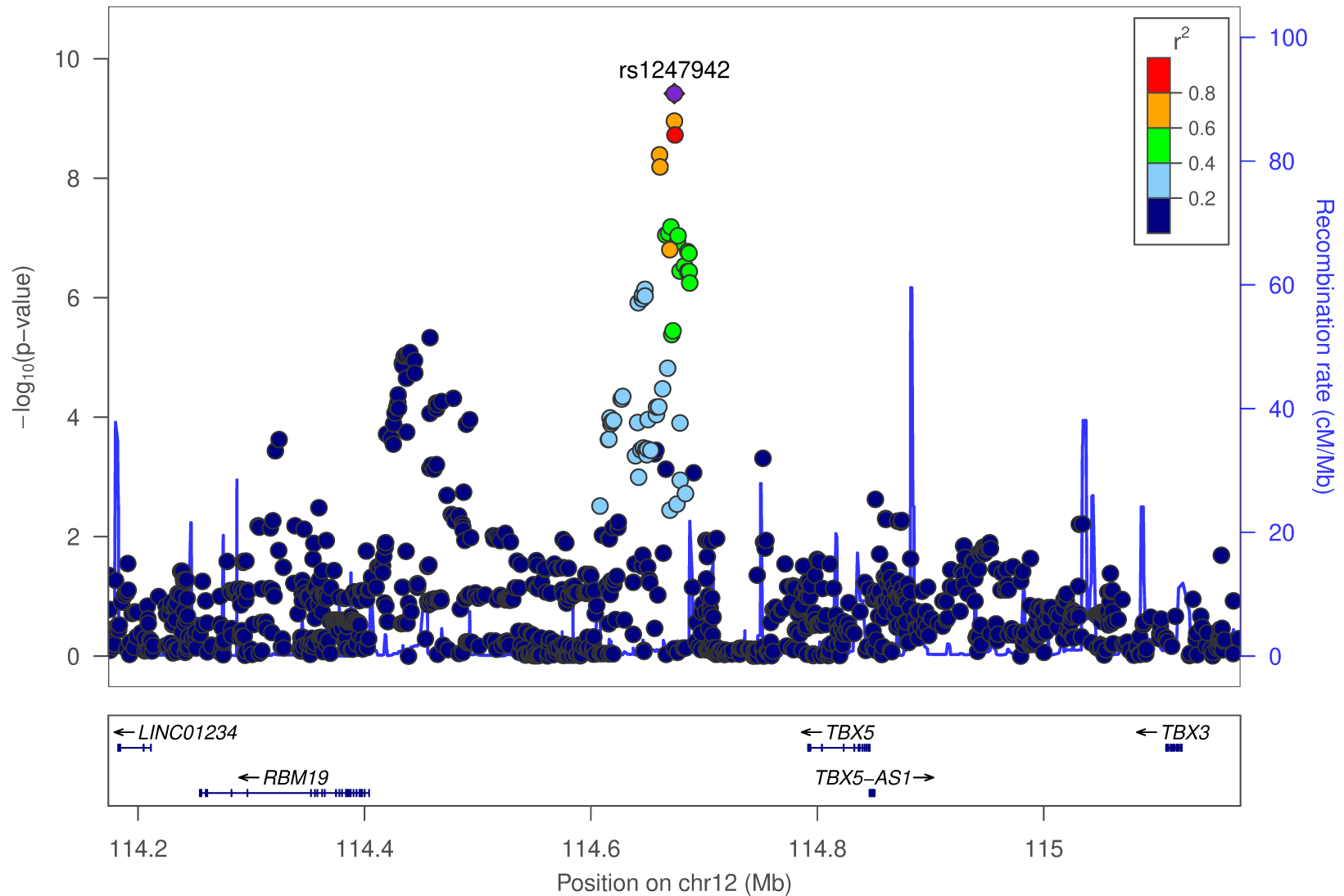
Plotted SNPs



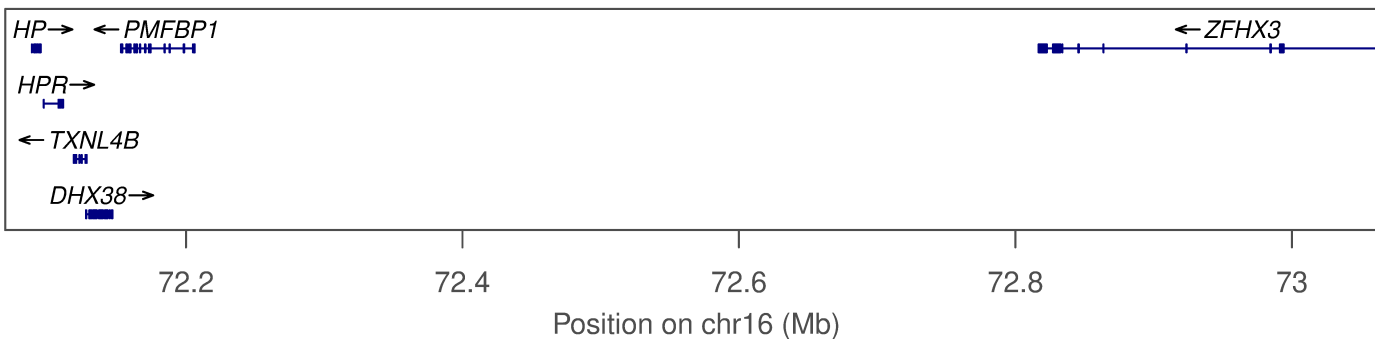
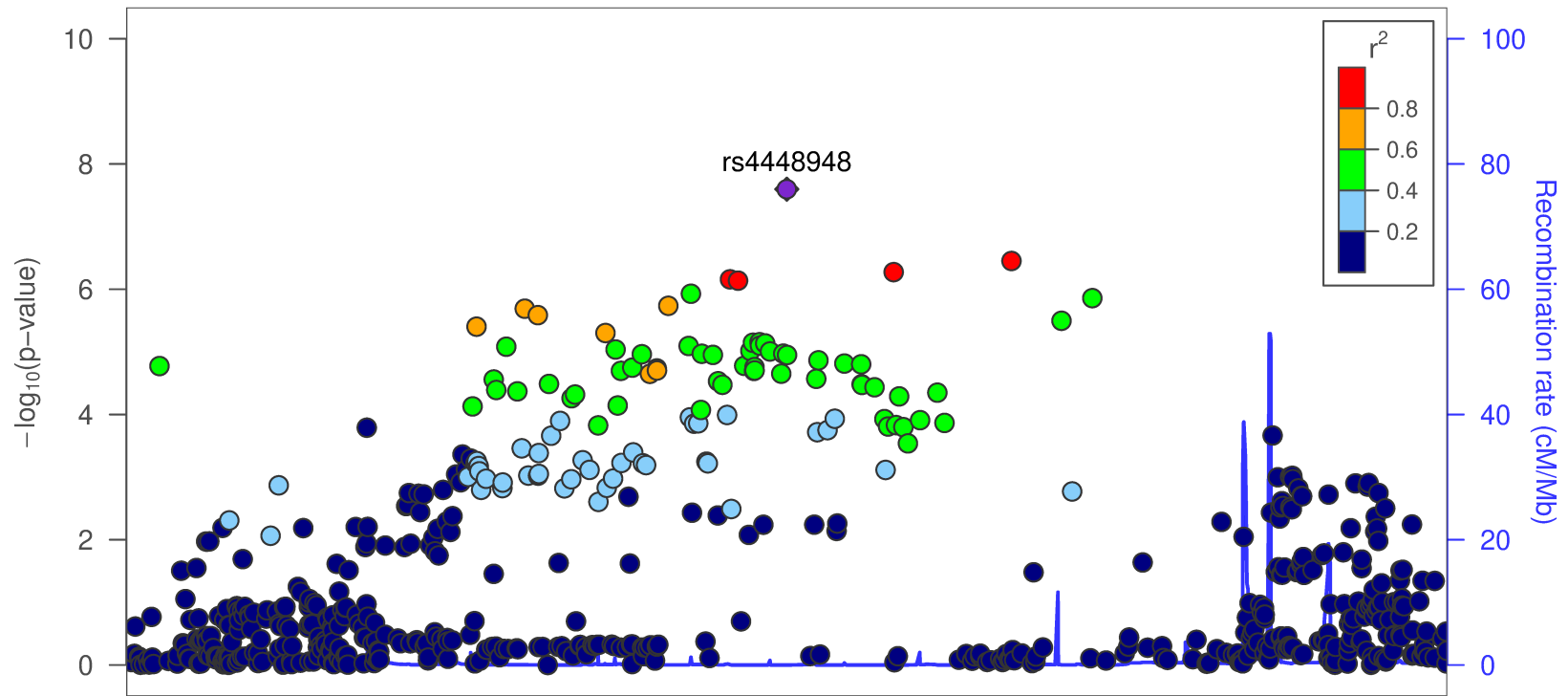
Plotted SNPs



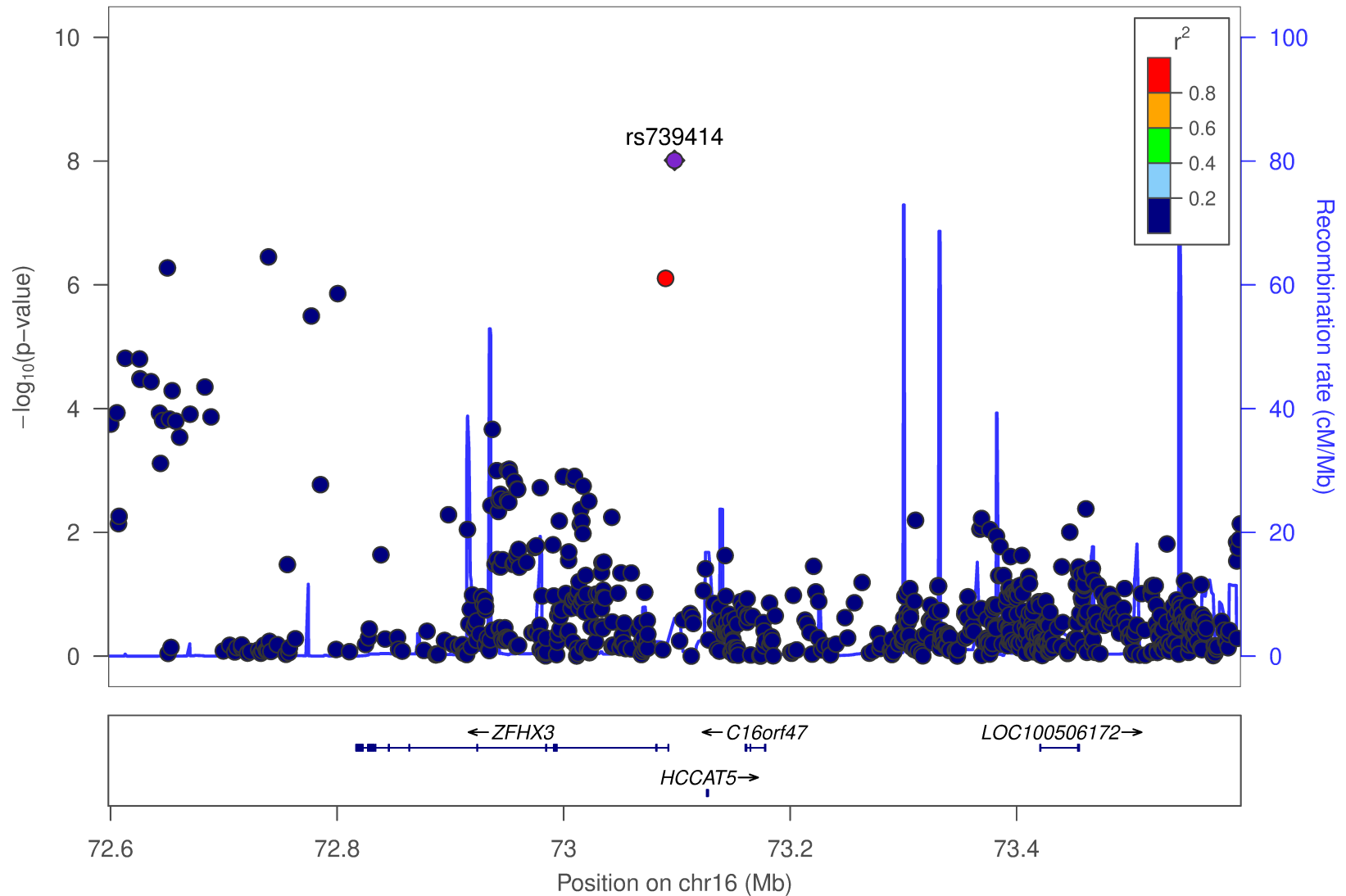
Plotted SNPs



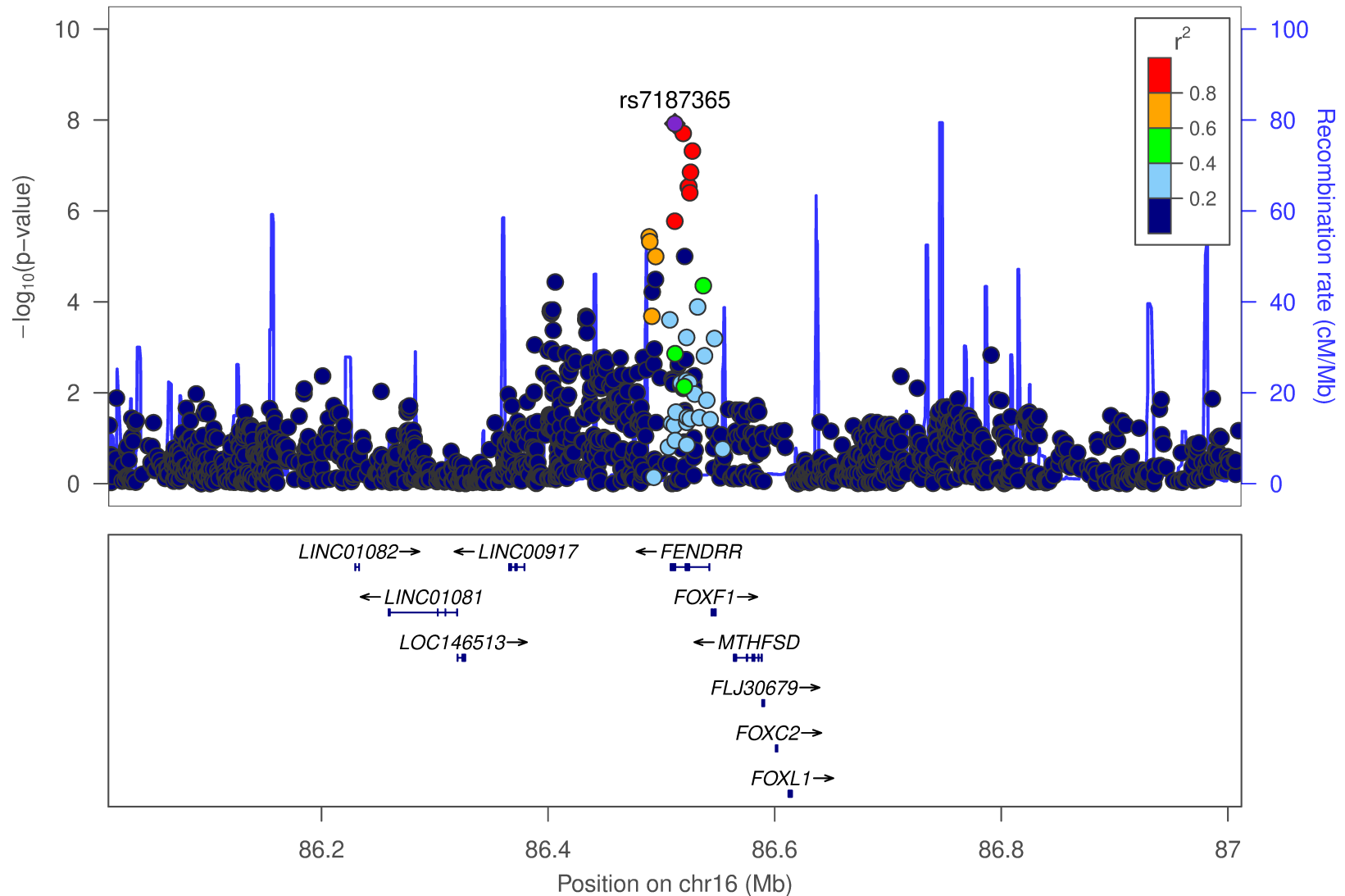
Plotted SNPs

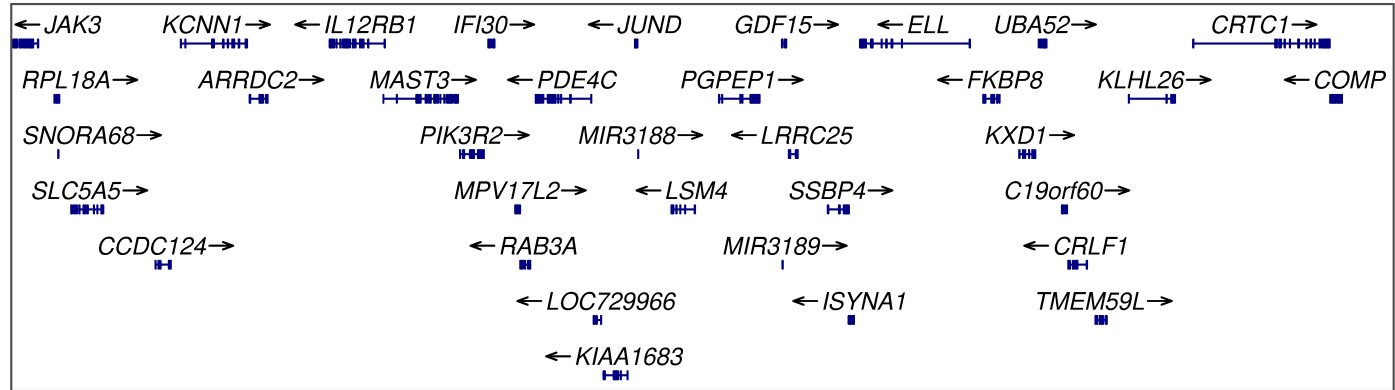
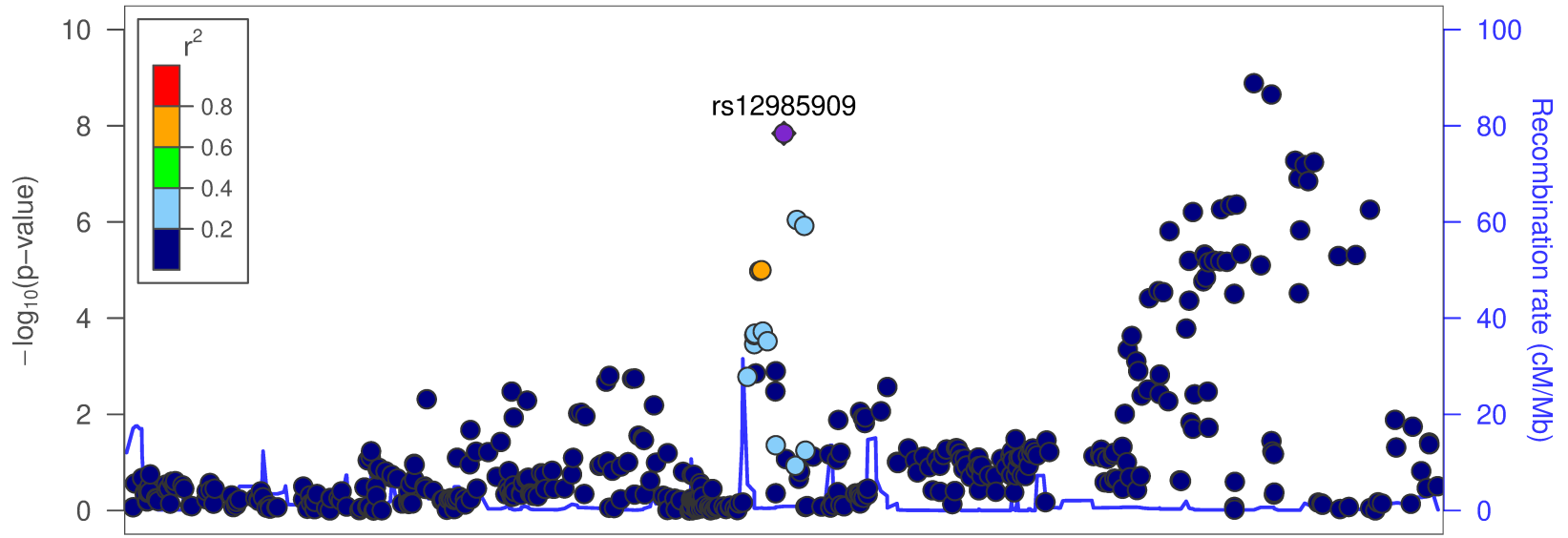


Plotted SNPs



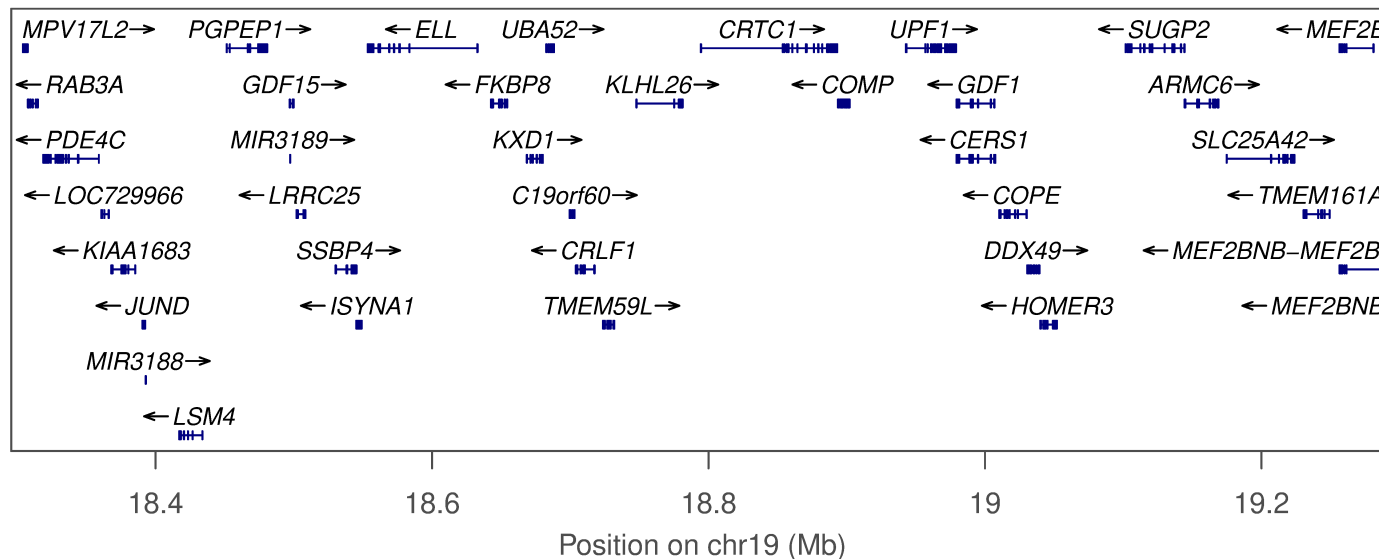
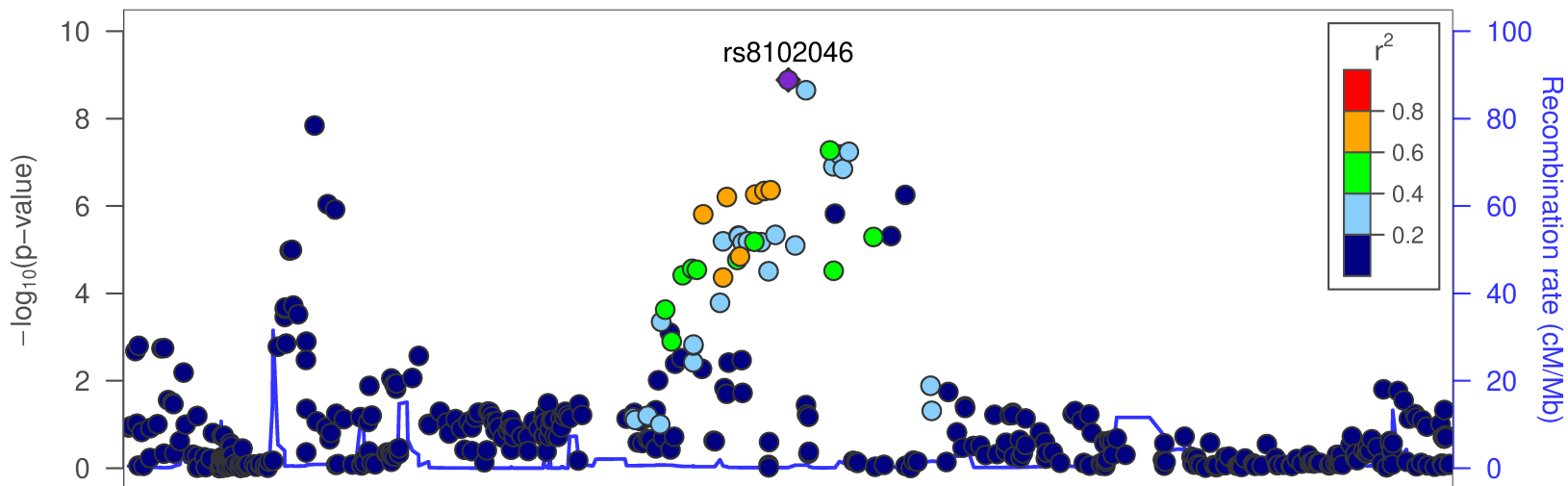
Plotted SNPs



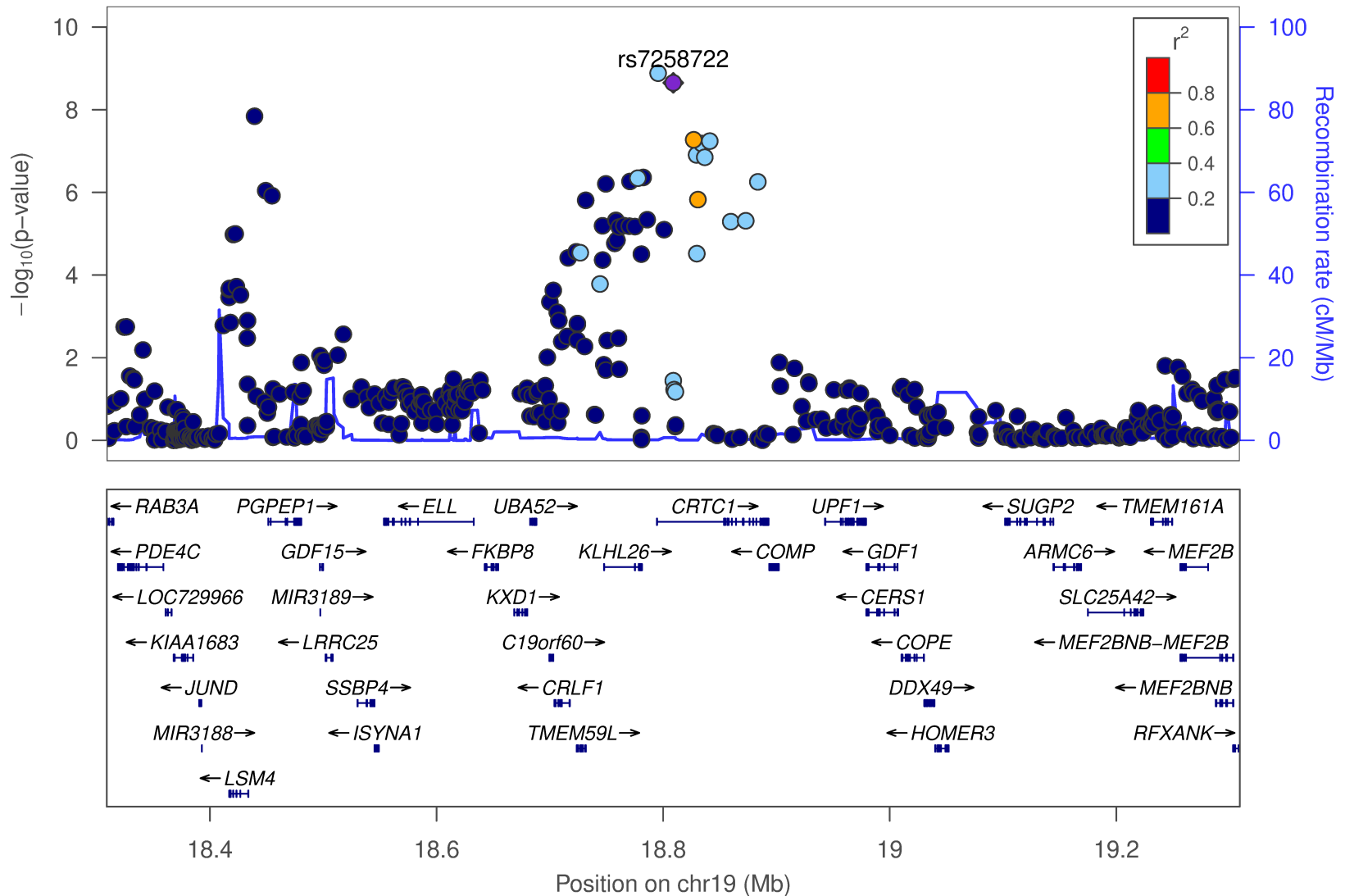


18 18.2 18.4 18.6 18.8

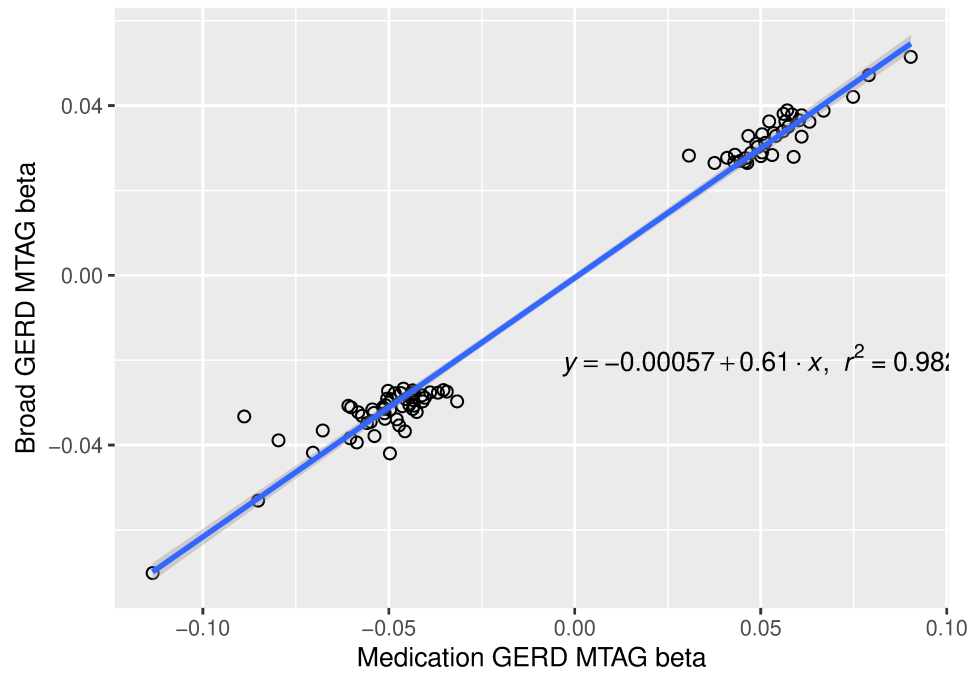
Position on chr19 (Mb)



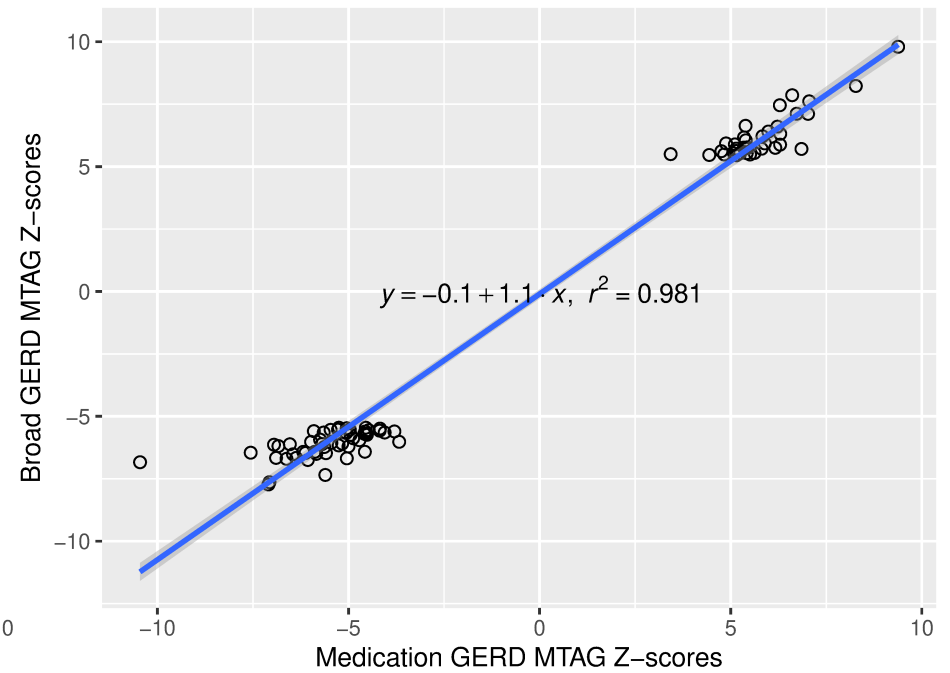
Plotted SNPs



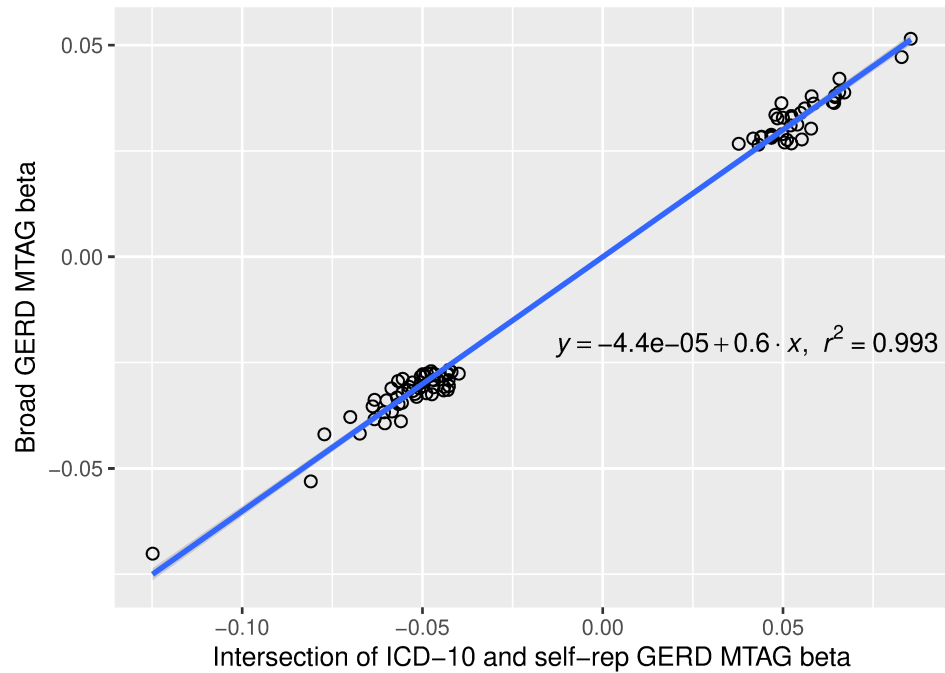
Panel (A) Comparison of MTAG GERD betas



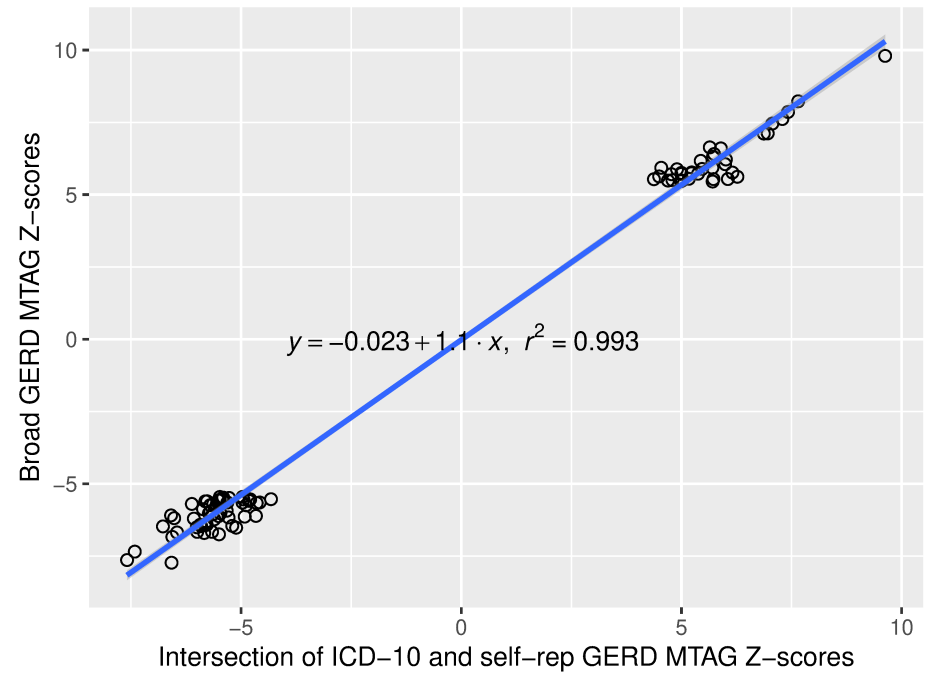
Panel (C) Comparison of MTAG GERD Z-scores



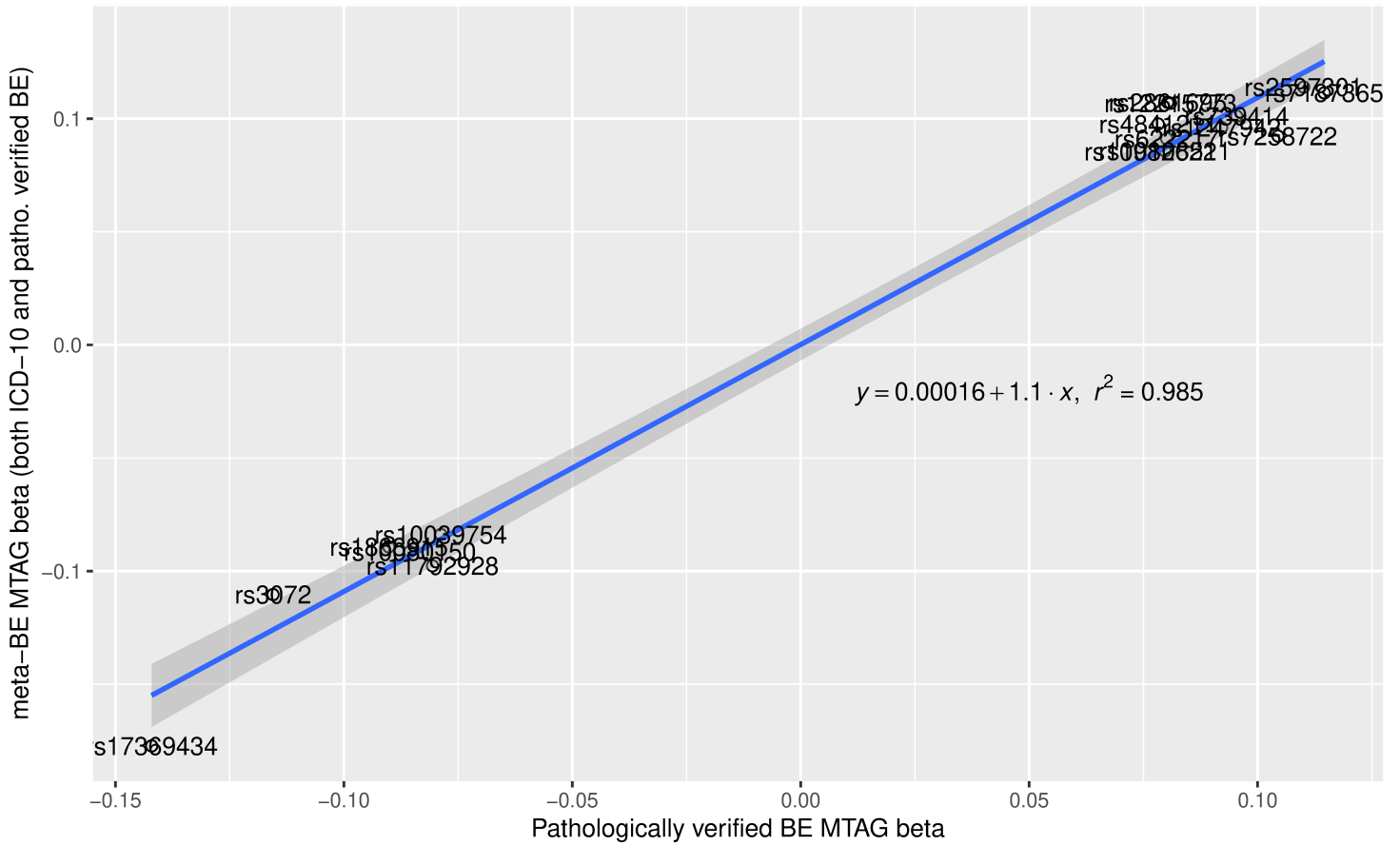
Panel (B) Comparison of MTAG GERD betas



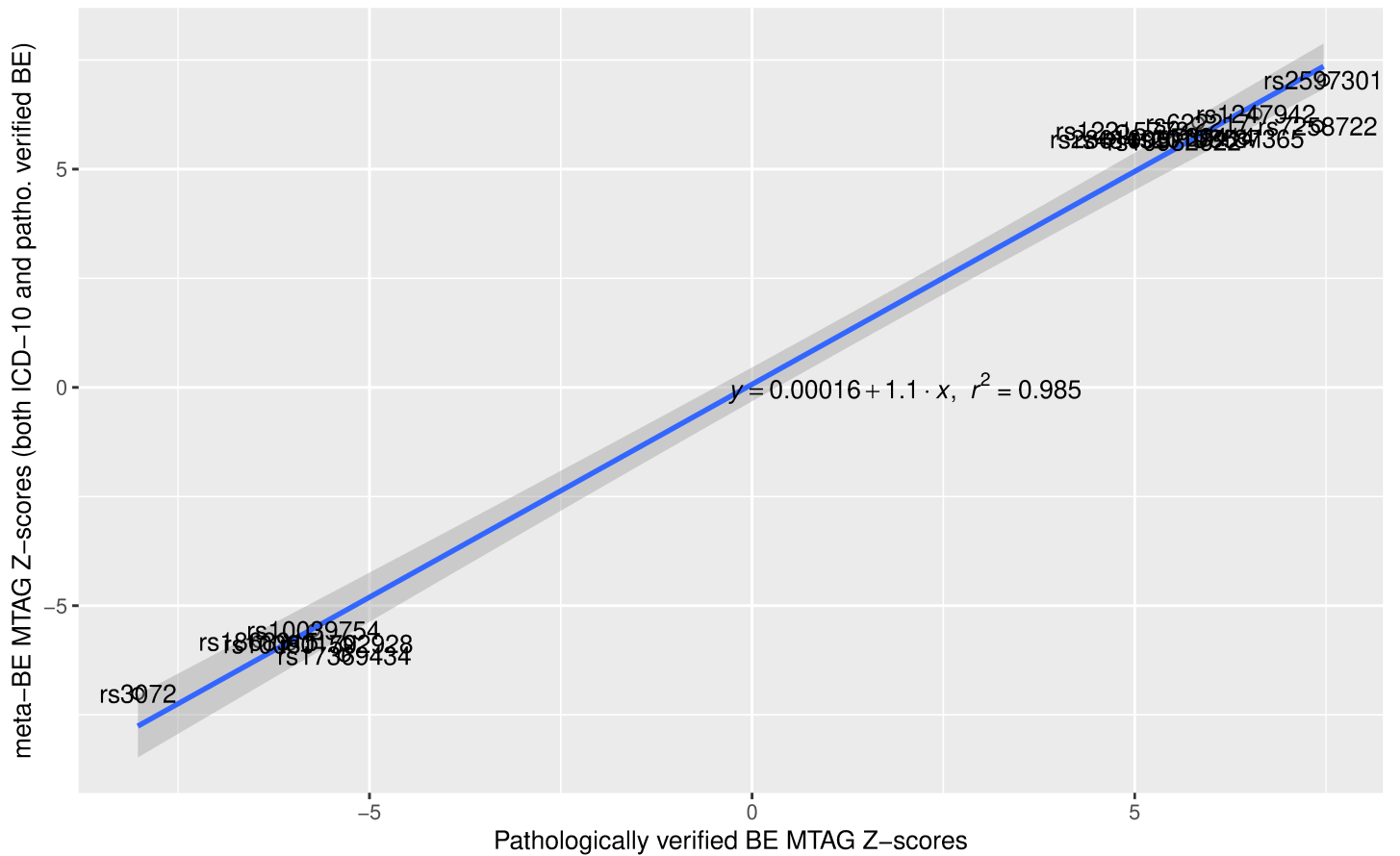
Panel (D) Comparison of MTAG GERD z-scores



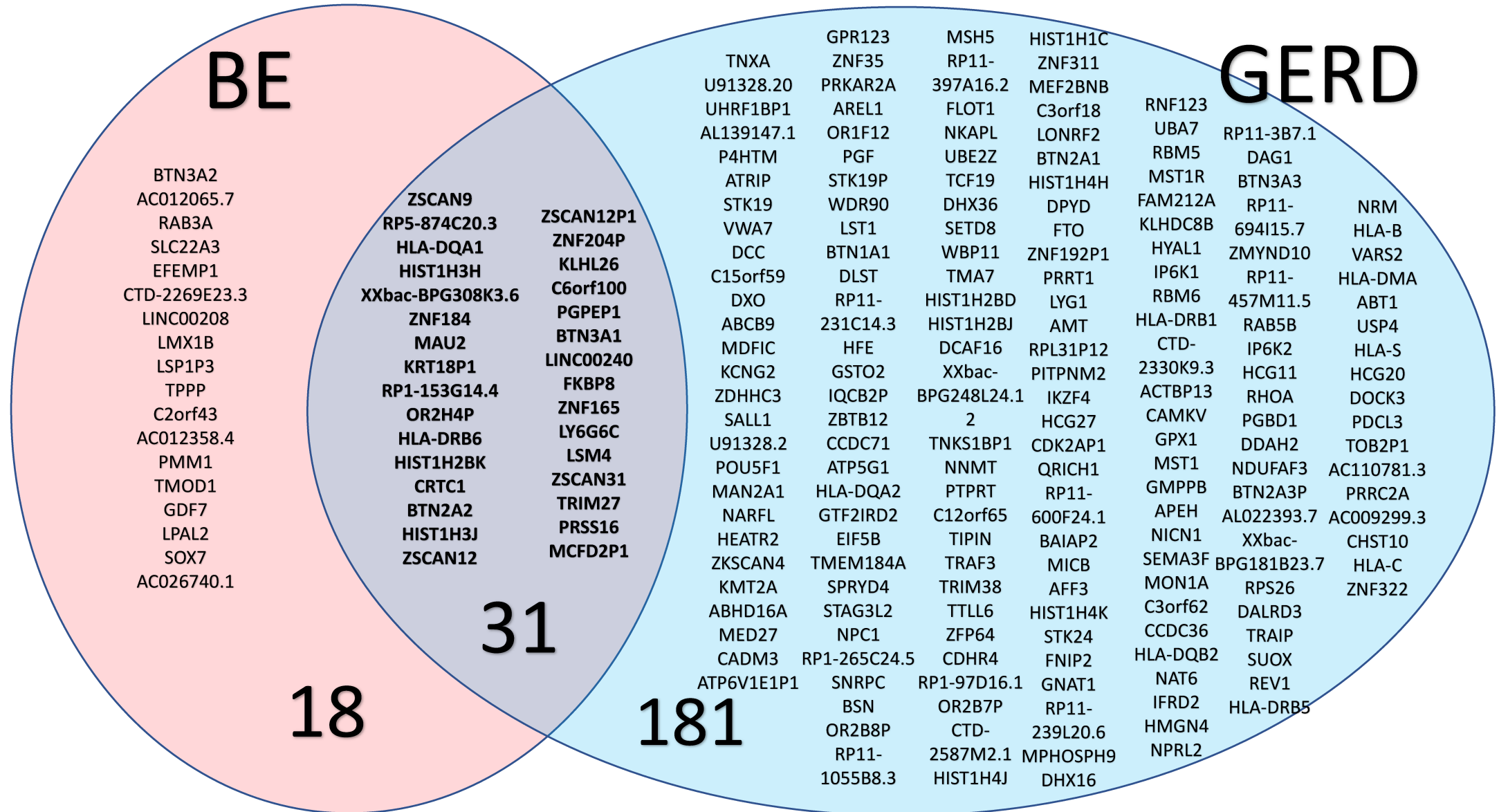
Panel (A) Comparison of MTAG BE beta estimates

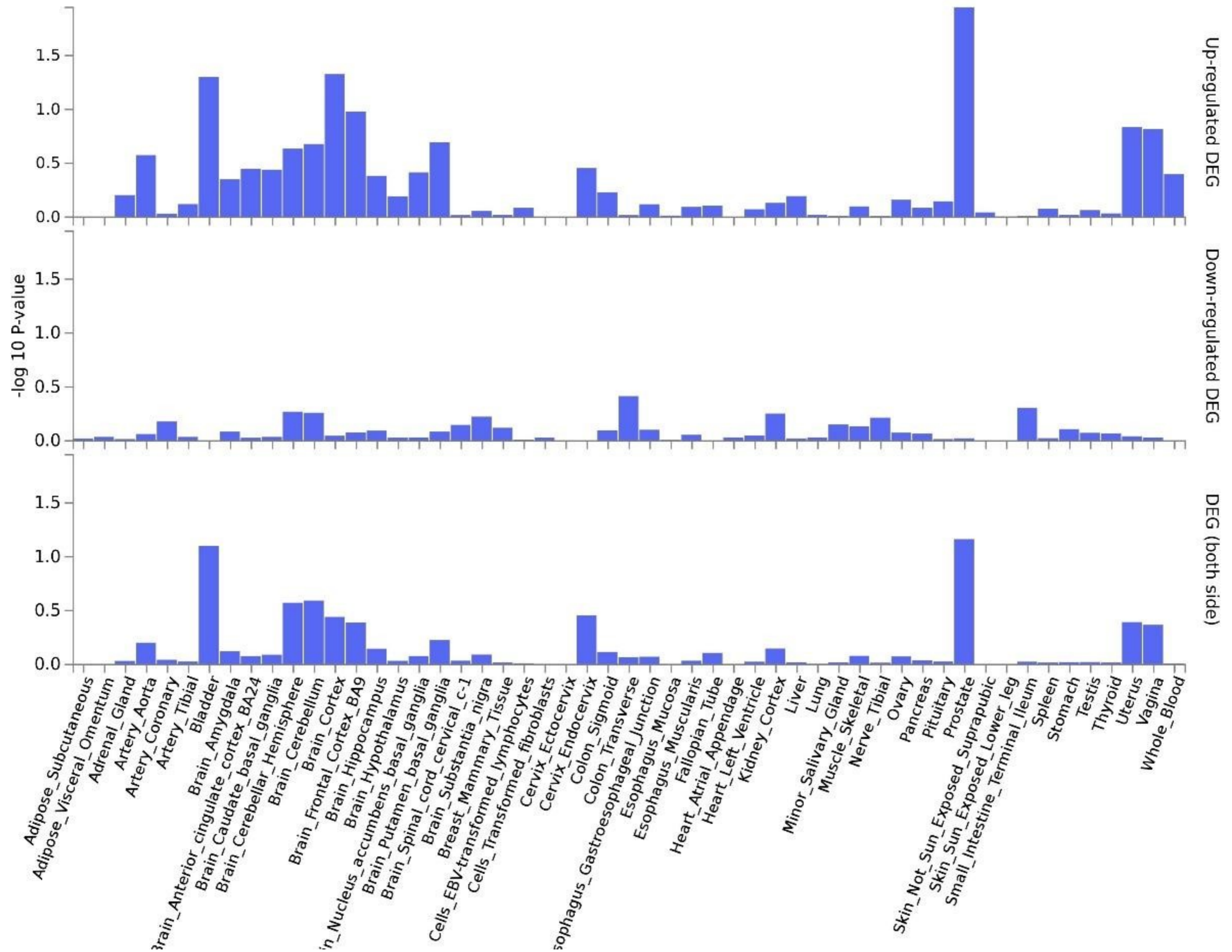


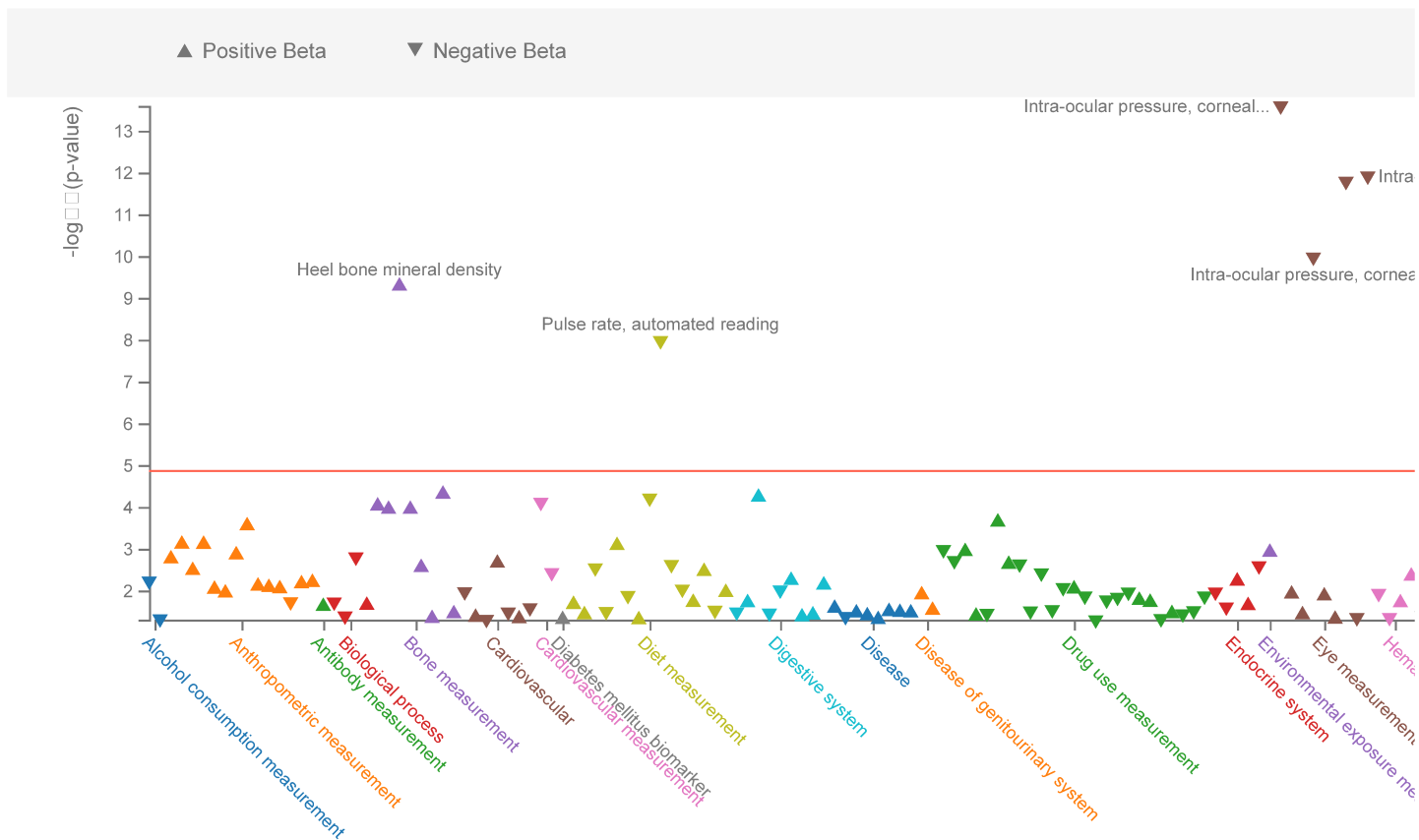
Panel (B) Comparison of MTAG BE Z-scores

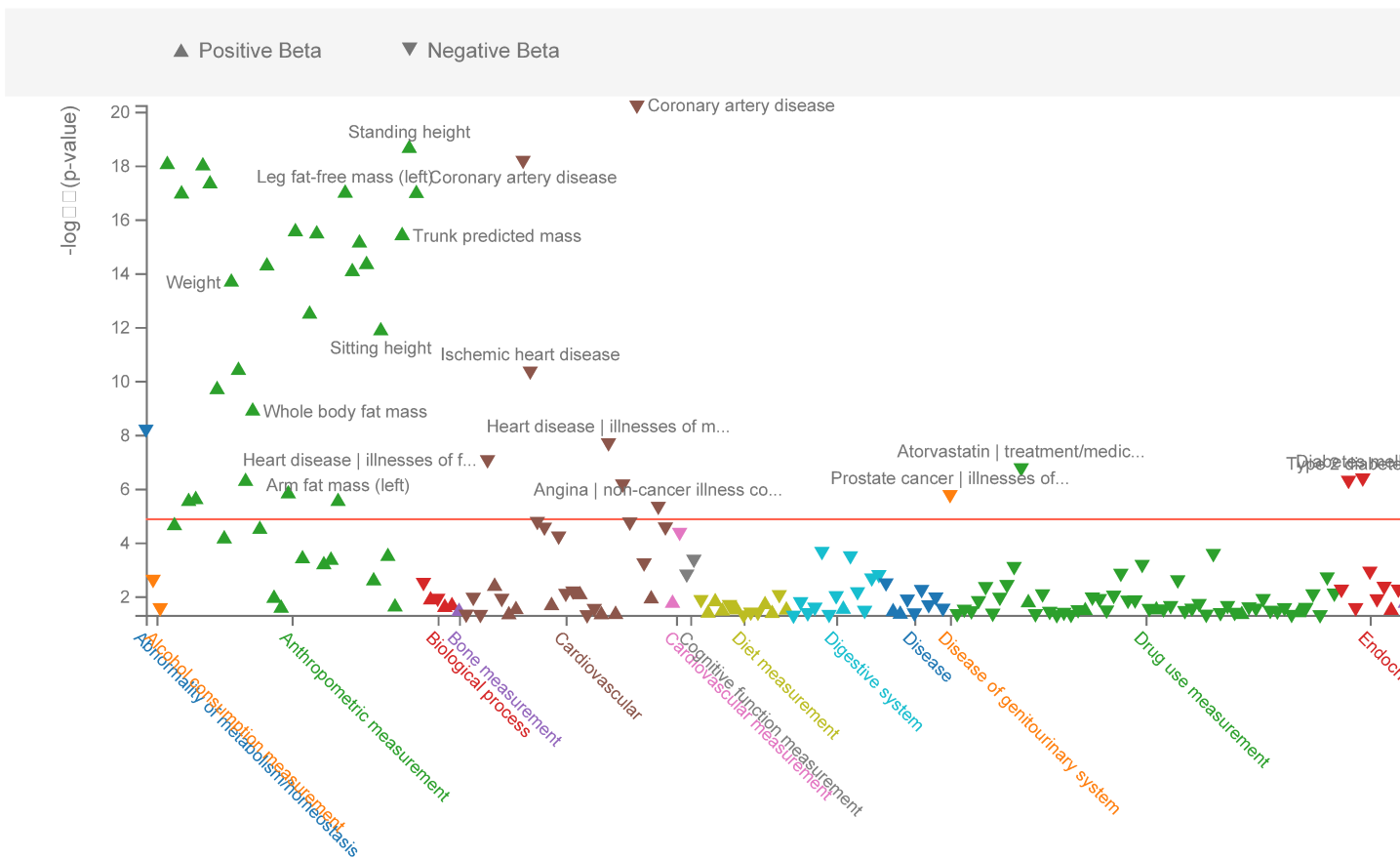


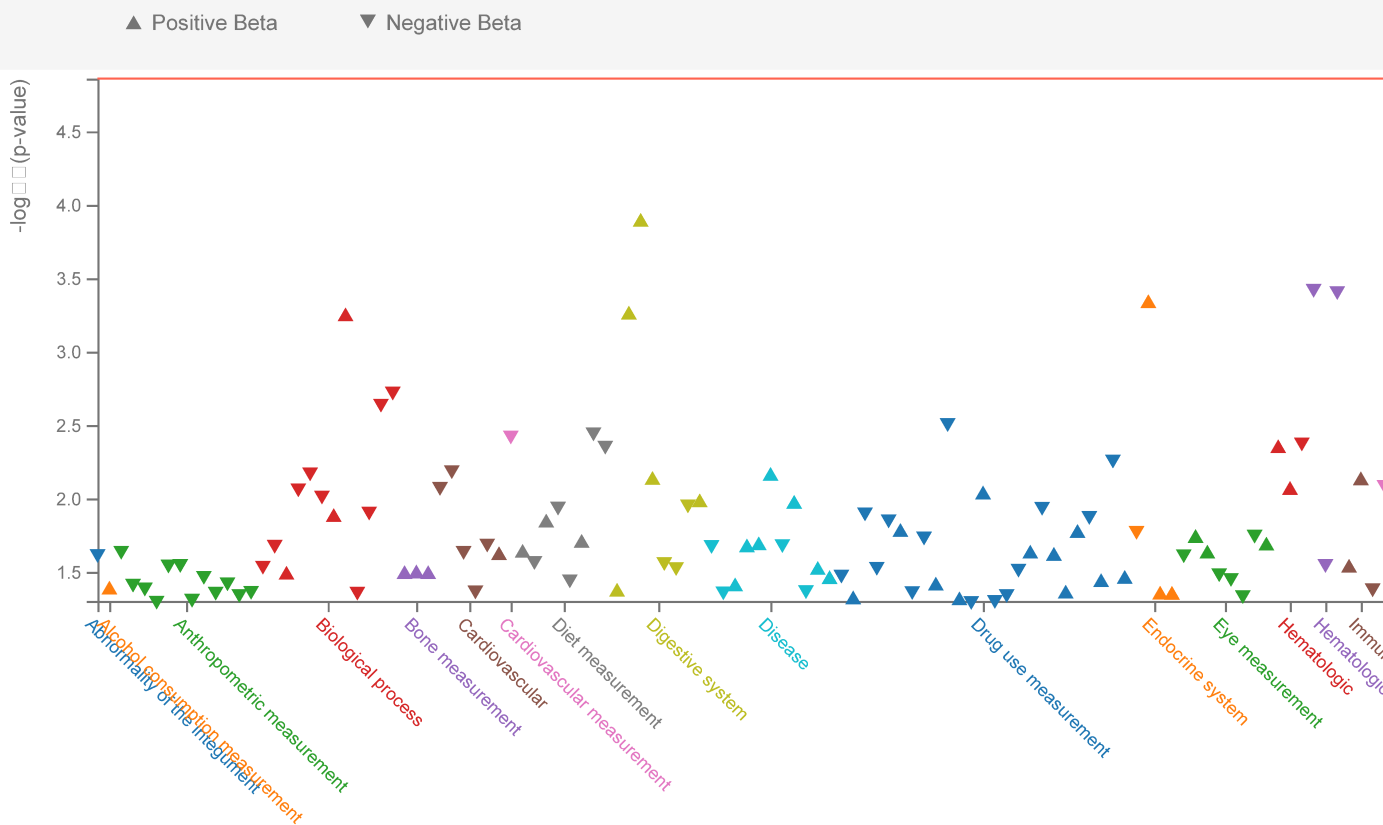
Putative genes identified with GERD and BE susceptibility from the MTAG model using multiXcan

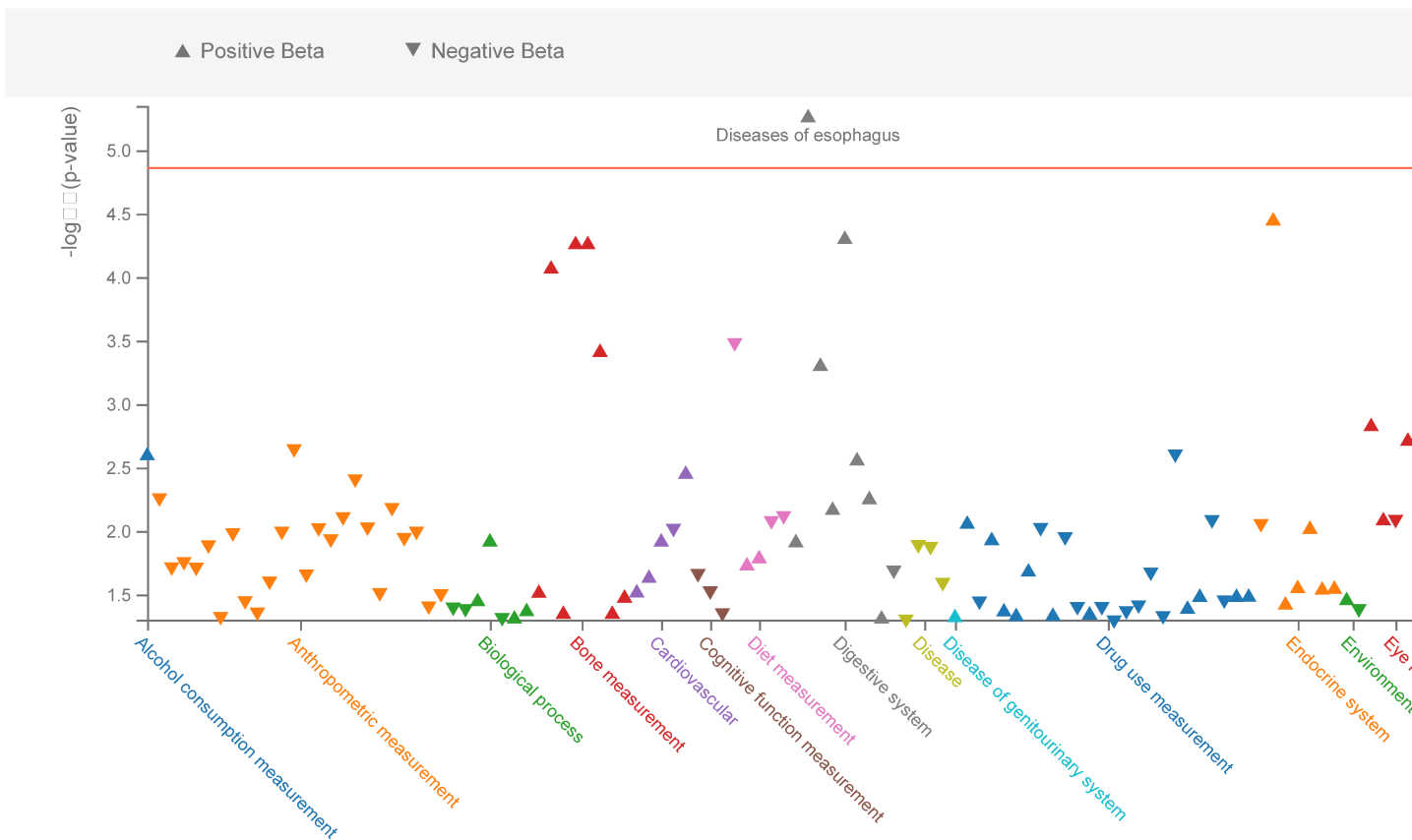


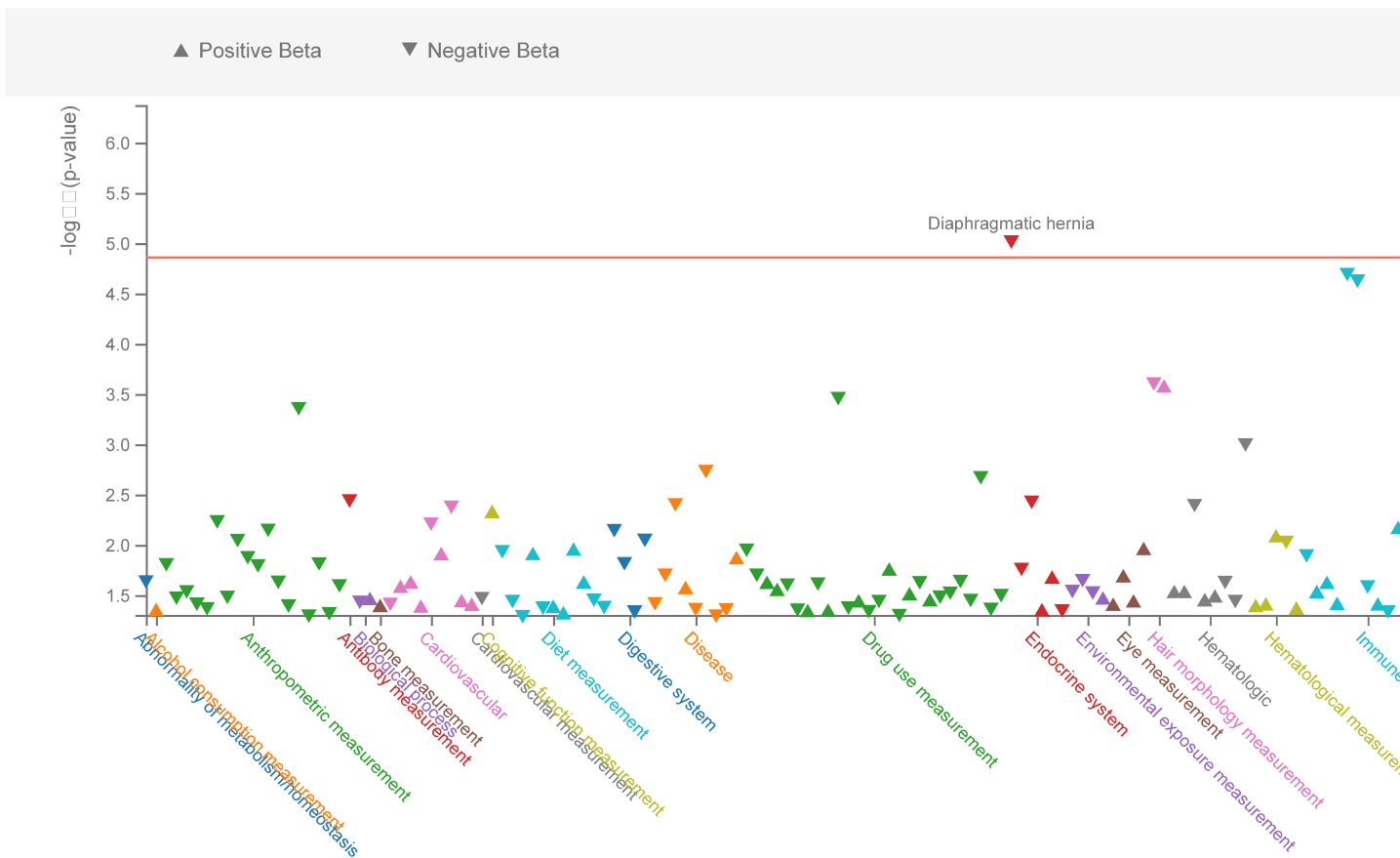


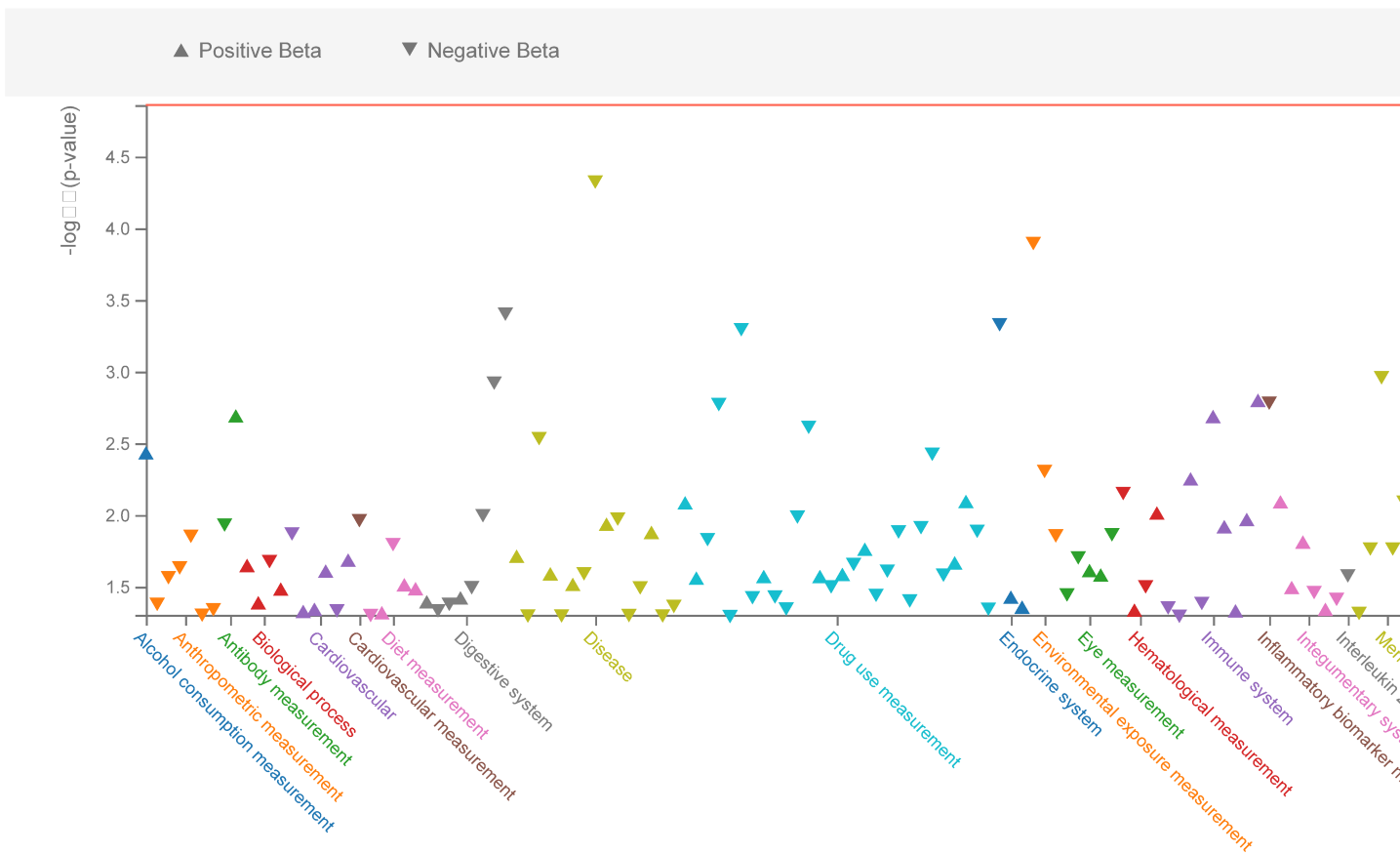


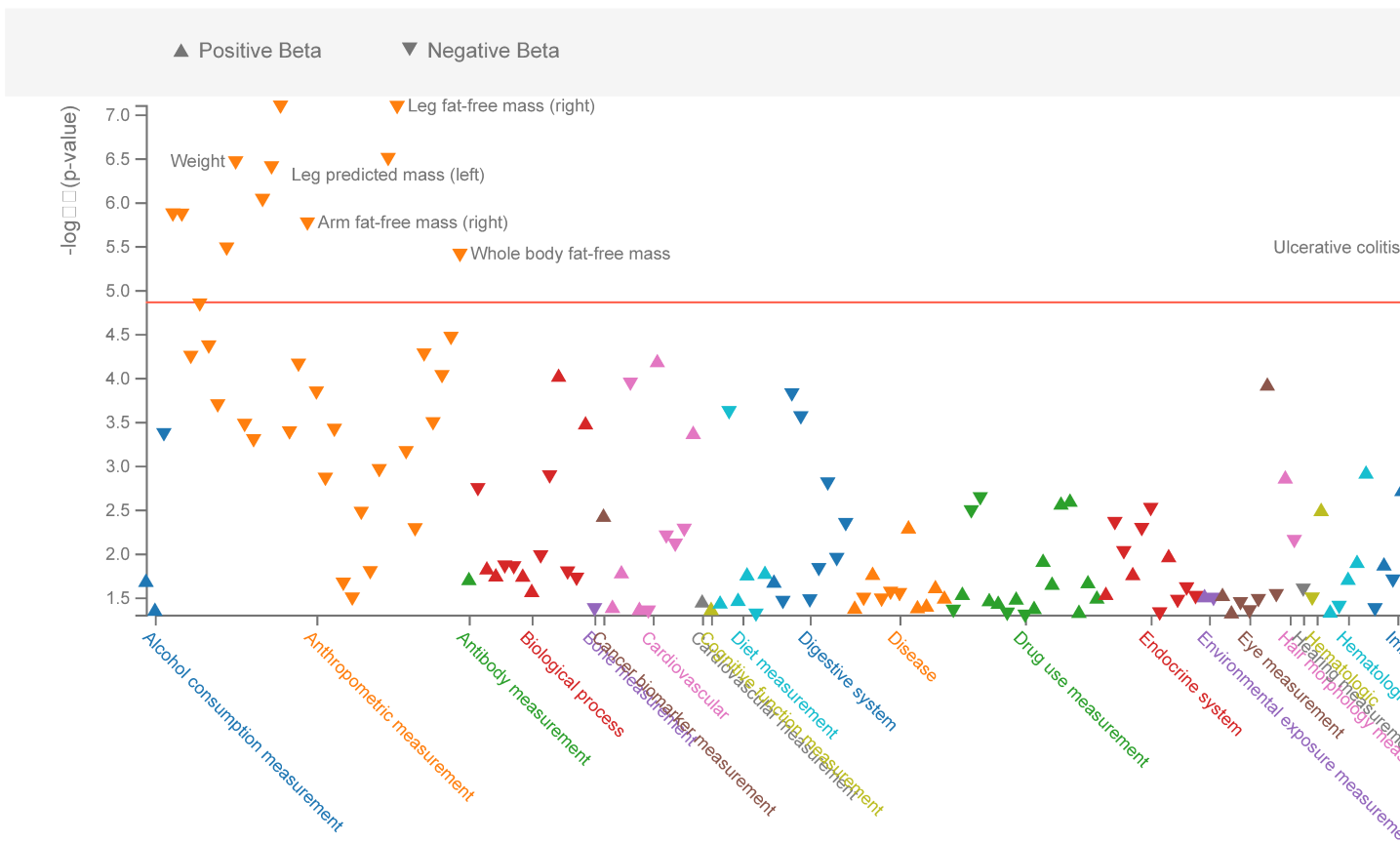


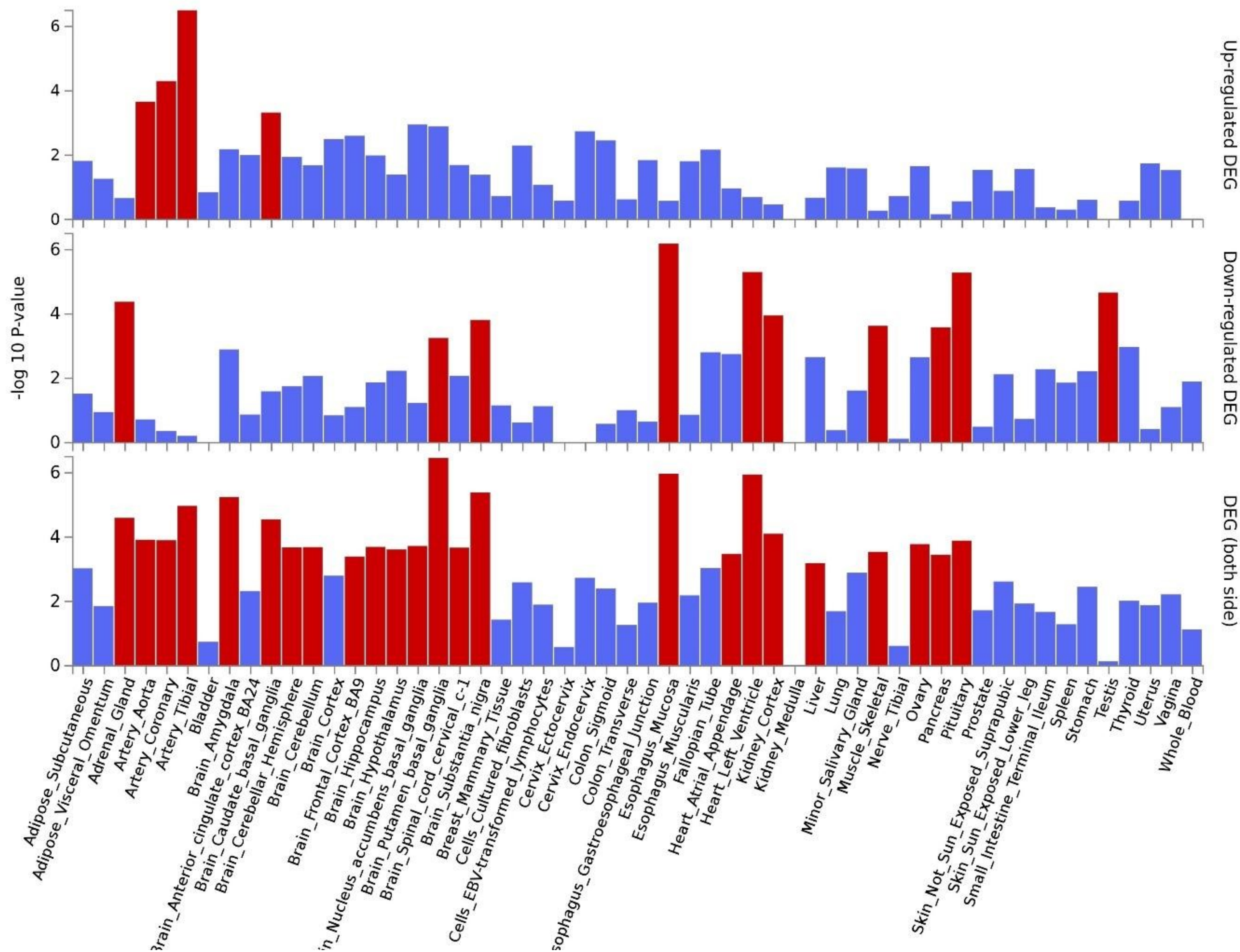


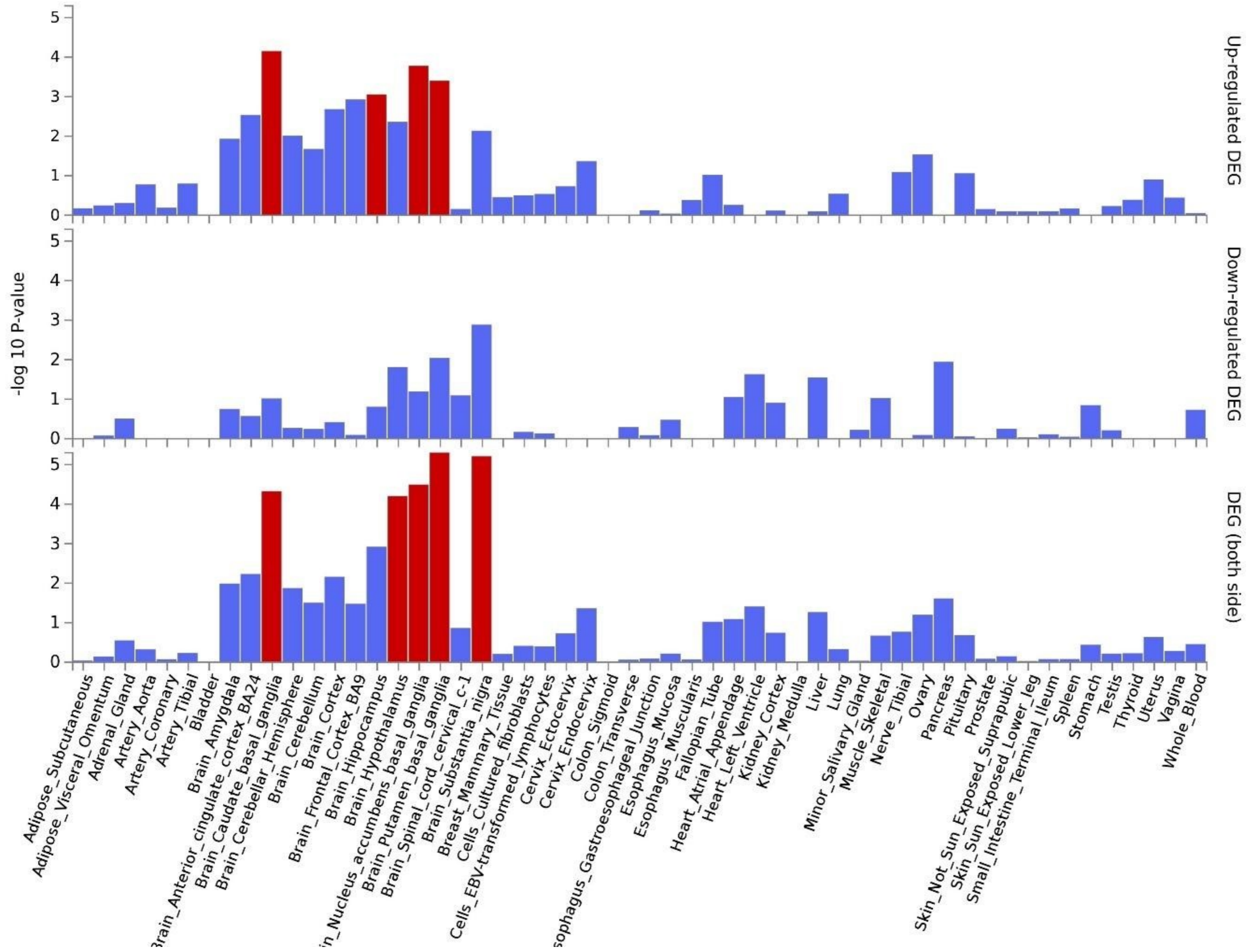


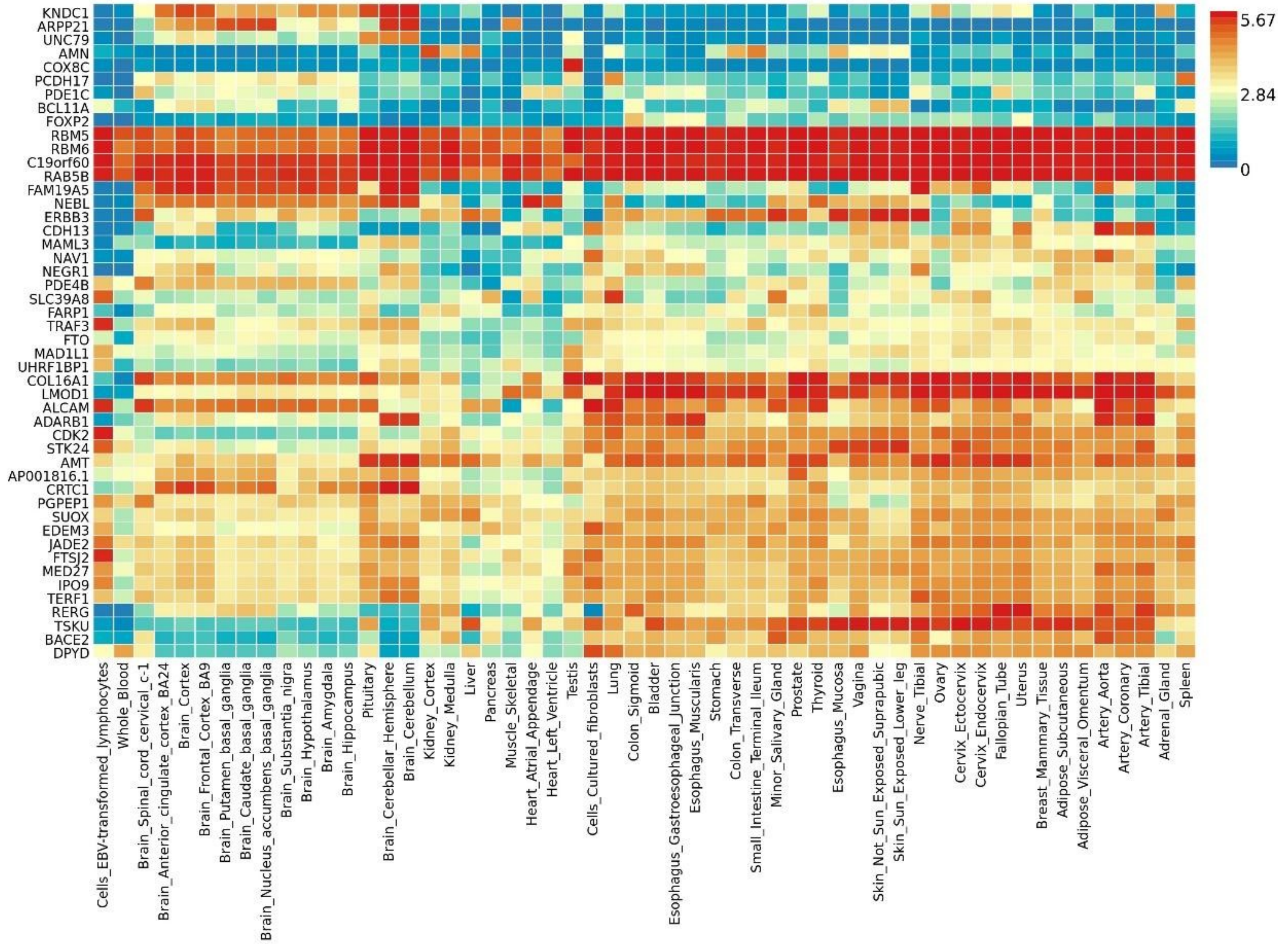


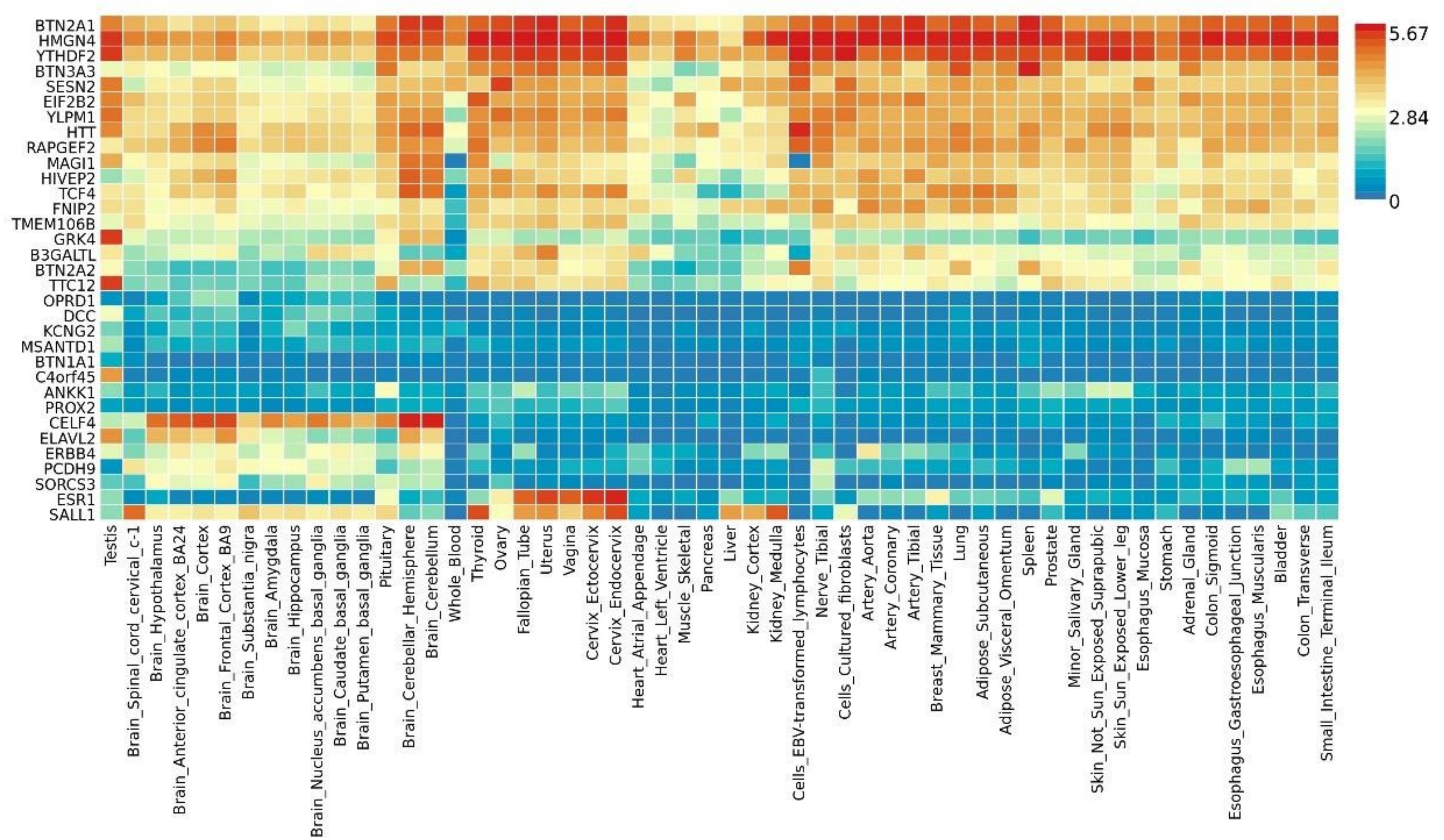




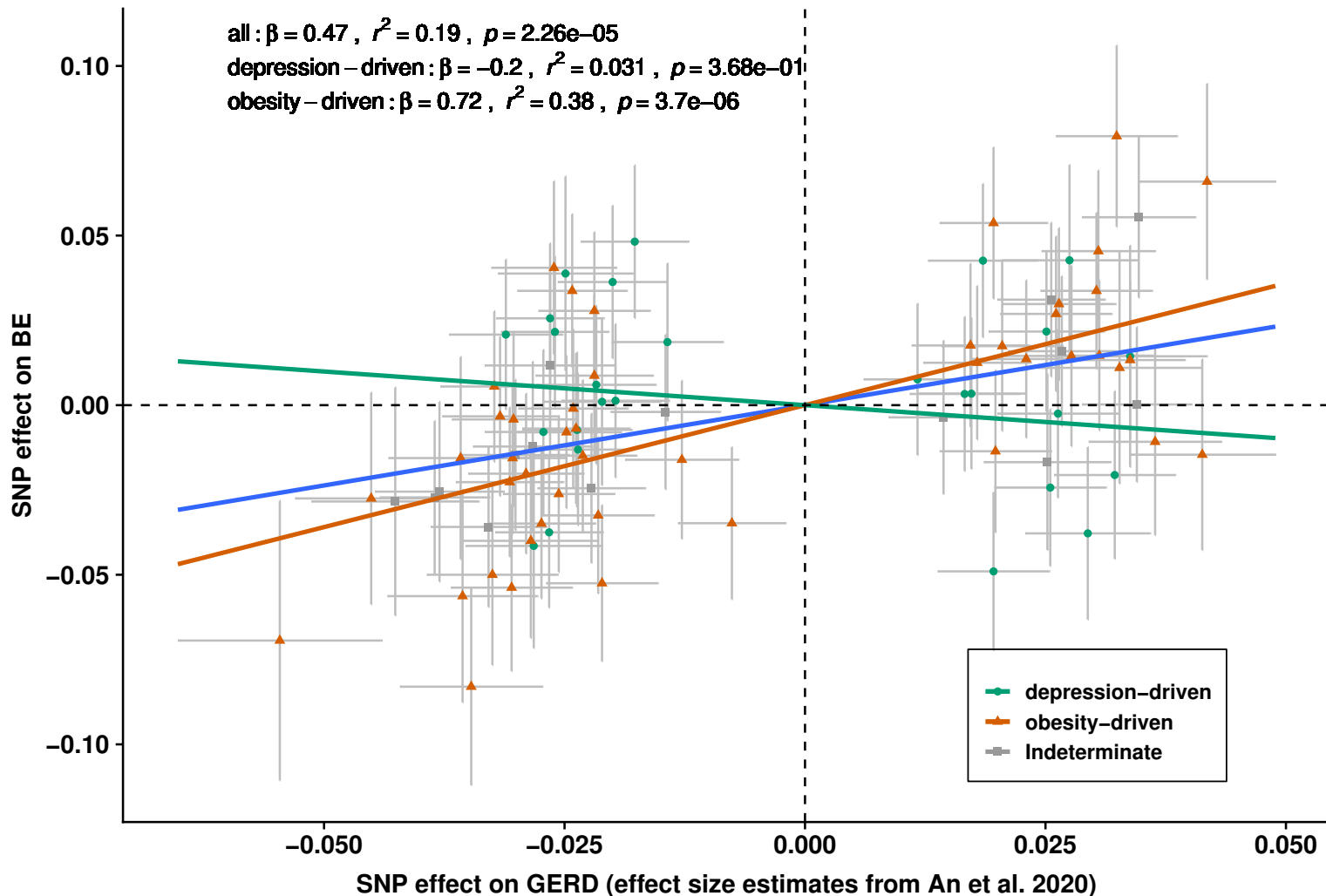








Genetic association between genome-wide significant MTAG GERD loci and risk of Barrett's Esophagus



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

