

# **Deciphering colorectal cancer genetics through multi-omic analysis of 100,204 cases and 154,587 controls of European and east Asian ancestries**

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## Supplementary Note

### **URLs**

BarcUVa-seq - <https://barcuvasseq.org/>

ENCODE ATAC-seq pipeline - <https://github.com/ENCODE-DCC/atac-seq-pipeline>

ENCODE histone ChIP-seq pipeline - <https://github.com/ENCODE-DCC/chip-seq-pipeline2>

Enrichr - <https://maayanlab.cloud/Enrichr/>

GCTA-COJO- <https://cnsgenomics.com/https://cnsgenomics.com/content/softwarecontent/software>

GENCODE 24 - [https://www.gencodegenes.org/human/release\\_24.html](https://www.gencodegenes.org/human/release_24.html)

GENESIS software - <https://github.com/yandorazhang/GENESIS>

GTEEx - <https://www.gtexportal.org/home/>

GTEEx Pipeline - <https://github.com/broadinstitute/gtex-pipeline>

LD Hub - <http://ldsc.broadinstitute.org/ldhub/>

META - [https://mathgen.stats.ox.ac.uk/genetics\\_software/meta/meta.html](https://mathgen.stats.ox.ac.uk/genetics_software/meta/meta.html)

Michigan Imputation Server - <https://imputationserver.sph.umich.edu/index.html>

Open Targets - <https://platform.opentargets.org/>

PredictDB, HakyImLab Team 2020 - <http://predictdb.org/>

pyGenomeTracks Python library - <https://pygenometracks.readthedocs.io>

The NHGRI-EBI Catalog of human genome-wide association studies - <https://www.ebi.ac.uk/gwas/>

The NIH Roadmap Epigenomics Mapping Consortium - <http://www.roadmapepigenomics.org/>

### ***GWAS patient and data sets***

We analyzed GWAS data from previously published GWAS (**Supplementary Table 1, Supplementary Table 3**), grouping participants into analytical units by study or genotyping platform<sup>1-4</sup>. Studies that contributed to more than one prior GWAS were analyzed only once in the current analysis. In total, there were 31 analytical units (17 from European descent populations and 14 from Asian descent populations), totaling 100,204 CRC cases and 154,587 controls. Comprehensive details on the subjects, genotyping and standard quality control (QC) procedures have been previously reported and are summarized in **Supplementary Table 1**. As reference for LD estimation, we made use of genotyping data from 6,684 unrelated East Asian samples genotyped with MEGA array (interindividual genetic relationships < 0.025, 453 from Aichi1, 162 from HCES1, 1,764 from HCES2, 832 from Korea\_NCC, 312 from Korea\_NCC2, 405 from Korea\_seoul, 1,833 from Shanghai4, 70 from SBCS1 (PMID: 32139696), 426 from SBCS2 (PMID: 32139696), 427 from the lung cancer Asian study cohort). To evaluate the polygenic risk score (PRS) based on all significant

GWAS loci we used independent studies not included in the discovery: the Genetic Epidemiology Research on Adult Health and Aging (GERA) cohort<sup>5,6</sup> for PRS evaluation in the European population (1,401 cases and 75,611 cohort participants) and several Asian studies (2,324 cases and 2,331 controls) as described before for PRS evaluation in the Asian population<sup>7</sup>. All study protocols were approved by the relevant Institutional Review Boards, and informed consent was obtained from all study participants in accordance with the Helsinki accord.

### ***Transcriptome and methylome samples and data***

INTERMPHEN study: 109 individuals of self-reported European ancestry undergoing colonoscopy<sup>8</sup>. Of these, 58% were males and average age was 58 years. Colorectal biopsies were obtained from the caecum, sigmoid colon, and rectum in each individual, together with an EDTA-venous blood sample. DNA and RNA were extracted and quantified using standard methodologies. 75bp paired-end RNA sequencing of samples was performed on an Illumina HiSeq4000 platform (Illumina Inc. San Diego, USA) to achieve a median of 50M reads per sample. Genotyping of DNA was performed using Illumina Infinium Human Core Exome arrays. Methylation profiling of caecal, sigmoid, and rectal samples from 89 of the 109 individuals was performed using Illumina EPIC methylation arrays on bisulfite modified DNA samples from histologically normal colorectal mucosa (n=267). Ethical approval for the study was obtained from the Oxfordshire Research Ethics Committee A and all participants provided informed written consent.

The Study of Colorectal Cancer in Scotland (SOCCS): SOCCS is a prospective study to identify genetic and environmental factors influencing CRC risk and survival outcome<sup>9</sup>. Histologically normal colorectal mucosa was sampled from a single site from freshly resected surgical specimens or through rectal biopsy from cancer, non-cancer patients, and healthy participants within SOCCS (n=221). Of these, 56% were males and average age was 62 years. Most of the individuals were of European ancestry (98%), with five participants showing evidence of admixture based on PCA plots. RNA was extracted and purified from histologically normal mucosa using A Ribopure kits (Applied Biosystems, Foster City, USA) according to the manufacturer's protocol. Paired-end RNA sequencing was performed in two batches on an Illumina HiSeq 4000 platform on 150bp and 75bp paired-end reads to achieve a median of 100M reads per sample. Epigenome-wide methylation analysis was performed for a subset of SOCCS samples (n=93, 55% males, mean age of 67). DNA was extracted from 93 histologically normal colonic mucosa samples using Qiagen (Qiagen, Hilden, Germany) DNeasy Blood and Tissue Kits according to the manufacturer's protocol. Genomic DNA was bisulfite modified using the Zymo EZ DNA Methylation Gold DNA methylation kit (ZymoResearch, Irvine, USA). Methylation analysis was performed using Illumina Infinium HumanMethylation450 (450K) BeadChip array (Illumina Inc). Genotyping of matched peripheral blood

DNA was conducted using Illumina OmniExpressExome8 or HumanOmni5 arrays. All participants provided informed written consent and the study was approved by the local (13/SS/0248) research ethics committees and National Health Service management (2014/0058).

BarcUVa-Seq: The BarcUVa-Seq (University of Barcelona and University of Virginia RNA sequencing project) data is based on 191 individuals (70 male, mean age = 60, and 93% of European ancestry) from the Barcelona province of Spain who had no personal history of CRC and underwent negative screening colonoscopies<sup>10</sup>. Mucosal biopsies from the ascending (n=68), transverse (n=47) and descending (n=76) colon were obtained together with peripheral blood samples. Total RNA was extracted using mirVana kits (Thermo Fisher Scientific) without miRNA enrichment. Libraries were prepared using Illumina TruSeq Stranded Total RNA Library Prep Gold kits, which include Ribo-Zero Plus rRNA Depletion kits for depletion of ribosomal RNA. Paired-end, 101bp or 51bp (depending on batch), RNA sequencing was performed using an Illumina HiSeq 2500 sequencer in High Output mode. Genotyping of lymphocytes was performed using the Illumina OncoArray 500K beadchip. The study protocol was approved by the Bellvitge University Hospital Ethics Committee (PR073/11 and PR286/15).

COLONOMICS: Methylation profiles of histologically normal colon tissue samples from the Colonomics cohort, which comprises both colon cancer patients and healthy individuals of European ancestry<sup>11</sup>. It included 128 samples from 128 individuals (85 males, mean age of 69), 92 adjacent to tumors from CRC patients and 36 from healthy individuals. DNA was extracted with phenol-chloroform and quantified by Nanodrop (Thermo Scientific, Wilmington, DE). Bisulfite conversion of DNA (200-500 ng) was performed using Illumina Infinium Assays (EZ DNA methylation kit. Zymo Research. Cat. No. D5004), and samples were profiled using Illumina Infinium HumanMethylation450 BeadChips. DNA genotyping was performed using Affymetrix Genome-Wide Human SNP 6.0 arrays. The study protocol was approved by the Bellvitge University Hospital Ethics Committee (PR074/11).

GTex v8: This included data from 368 samples derived from colonic mucosa and underlying muscularis propria ("*Colon Transverse*"), as well as an additional 14,833 samples from 48 other tissues. eQTL data and gene models for S-PrediXcan and S-MultiXcan analyses were retrieved from the PredictDB resources repository (<http://predictdb.org/>)<sup>12,13</sup>. DGN: Whole blood data from 922 samples from the Depression Genes and Networks (DGN) cohort<sup>14</sup> was obtained from the PredictDB website.

No participants were compensated to participate in the presented studies.

### ***Regional GWAS association plots***

To examine overlap between the reported CRC association signals and CRC-relevant regulatory genomic annotations, we used the pyGenomeTracks Python library<sup>15</sup> to plot genomic data tracks displaying

epigenomic annotations for histologically normal colonic crypt epithelium and colonic mucosa tissue, and diverse CRC cell lines or CRC tissue<sup>1</sup>. Specifically, we examined overlap between the lead variant(s) or variants in linkage disequilibrium ( $r^2 \geq 0.8$ ) with the lead variant and active enhancer regions identified by histone marks H3K27ac and H3K4me1 along with active regulatory regions identified by accessible chromatin identified through DNase I hypersensitive sites (DHSs) and ATAC-seq. ChIP-seq data were processed with the ENCODE histone ChIP-seq pipeline, and DHS and ATAC-seq data were processed with the ENCODE ATAC-seq pipeline. Peak calls visualized in pyGenomeTracks are optimal overlap peak calls.

### ***Pathway analysis***

We used Data-driven Expression-Prioritized Integration for Complex Traits (DEPICT)<sup>16</sup> to predict gene targets based on gene functions that are shared across genome-wide significant risk loci, as well as those associated at  $P < 10^{-5}$  as advocated to mitigate against type II error.

### ***Drugability analysis***

Drug target information were obtained through the Open Targets platform (21.04 version). The drug tractability data is based on the Open Targets Tractability pipeline (version 2)<sup>17</sup>. Briefly, the pipeline assigns genes to tractability buckets based on evidence from diverse sources, including the Druggable Genome, ChEMBL, PDB, DrugEBility, UniProt, PROTAC, and Gene Ontology. Depending on the quality of the data, the gene is annotated with a tractability score, from strongest to weakest: "Clinical\_Precedence", "Discovery\_Precedence", "Predicted\_Tractable". Data were accessed via OncoEnrichR<sup>18</sup>.

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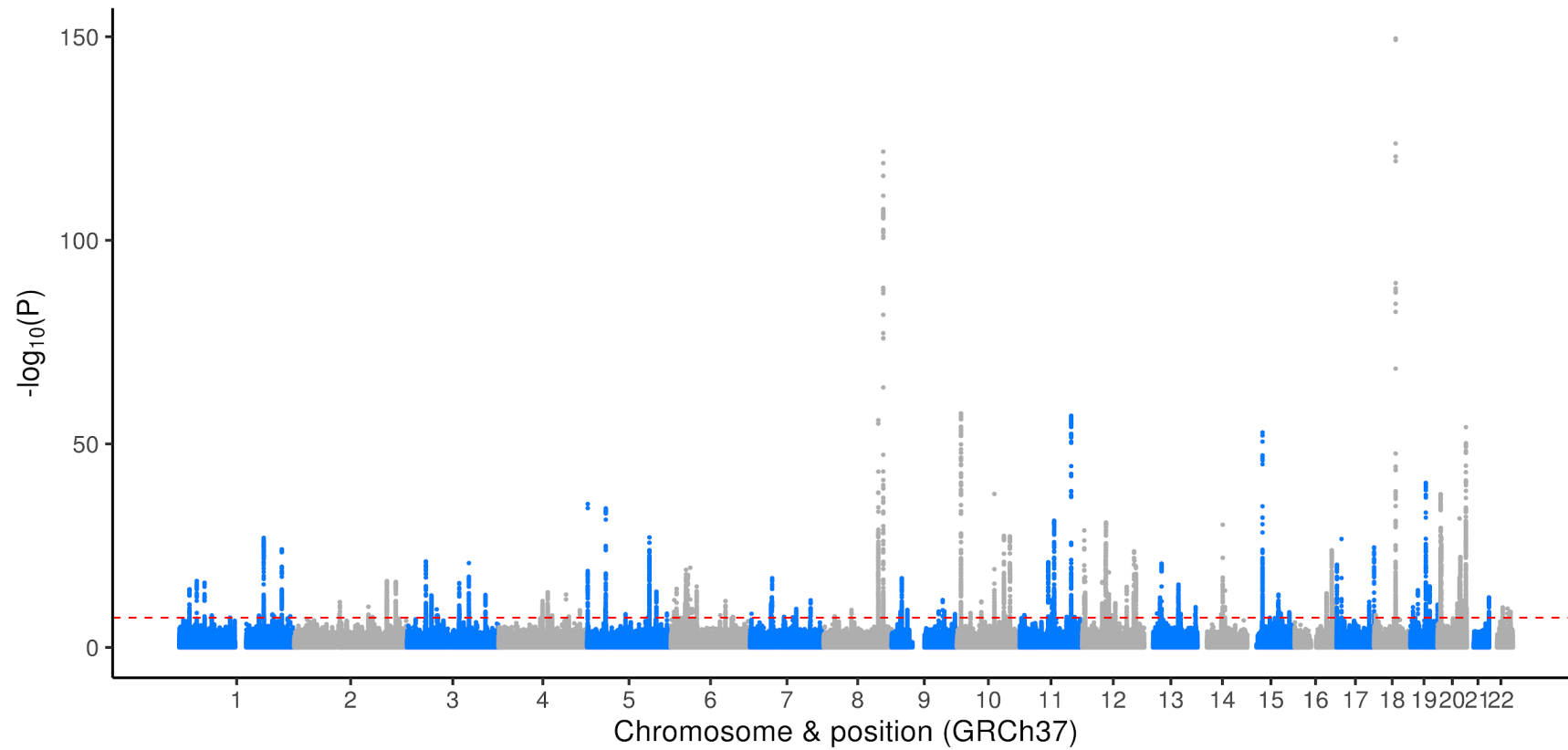
SELECT: We thank the research and clinical staff at the sites that participated on SELECT study, without whom the trial would not have been successful. We are also grateful to the 35,533 dedicated men who participated in SELECT.

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<http://www.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Short%20List.pdf>

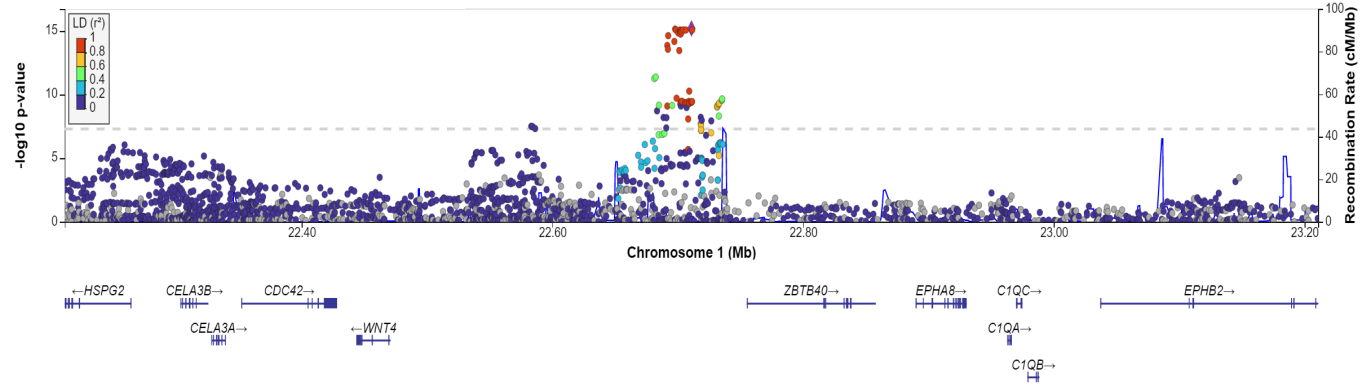
**Supplementary Figure 1: Manhattan plot showing all lead SNPs independently associated with colorectal cancer risk at  $P < 5 \times 10^{-8}$ . The red line indicates the genome-wide significance threshold. The x-axis represents the chromosomal positions and the y-axis represents the  $-\log_{10} P$ -values of the SNPs. P-values obtained from the meta-analysis.**



**Supplementary Figure 2: Regional association plots for the new colorectal cancer risk loci reaching genome-wide significance ( $P < 5 \times 10^{-8}$ ).**  
P-values obtained from the meta-analysis.

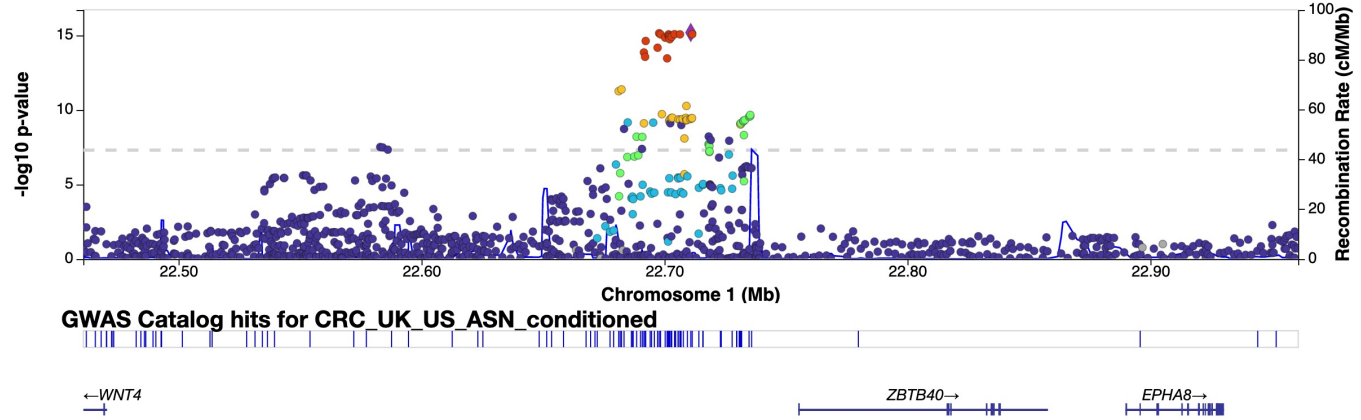
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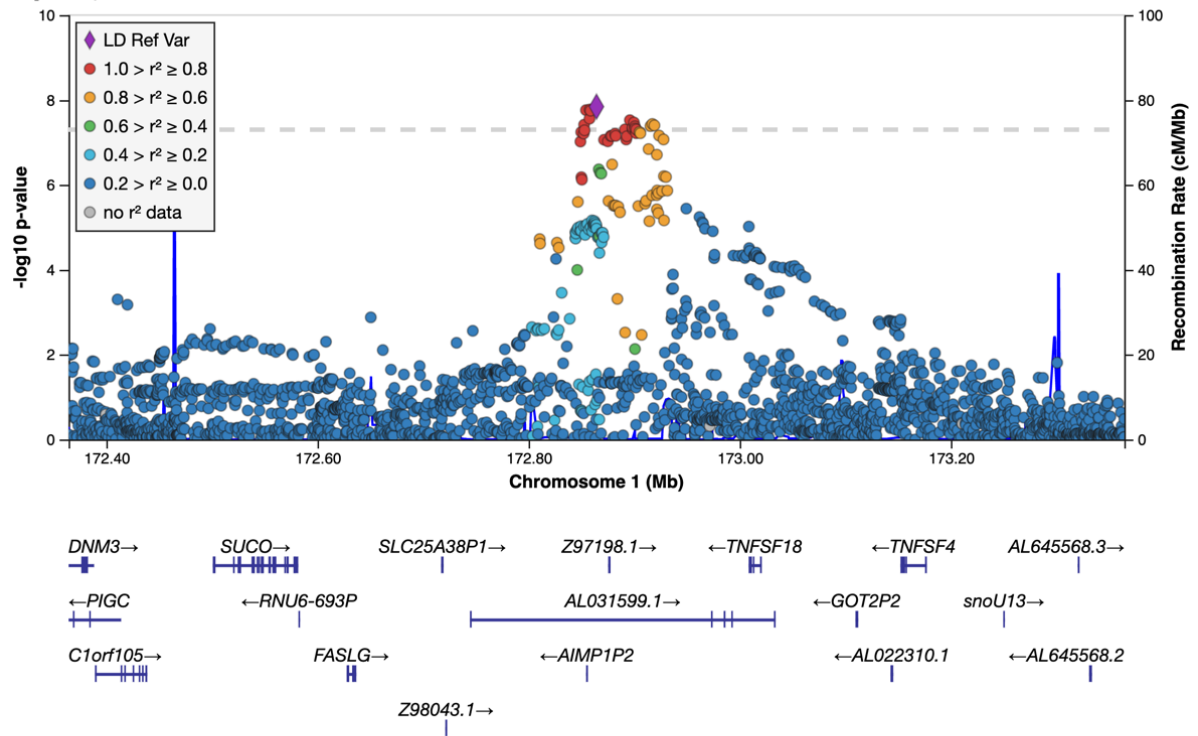
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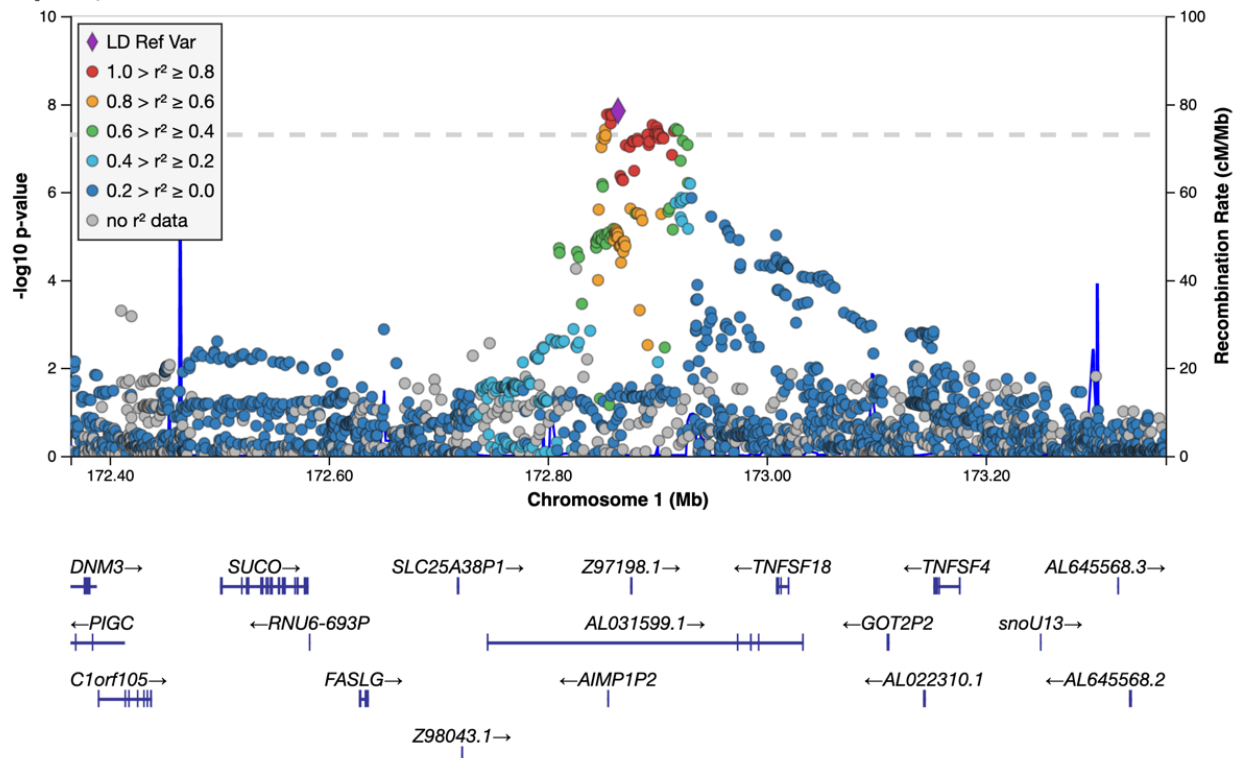
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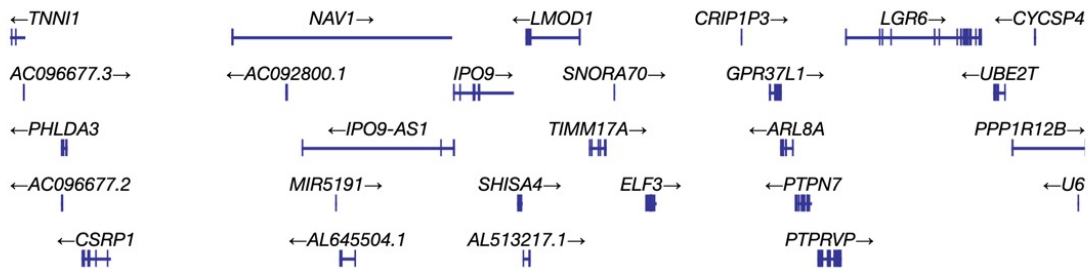
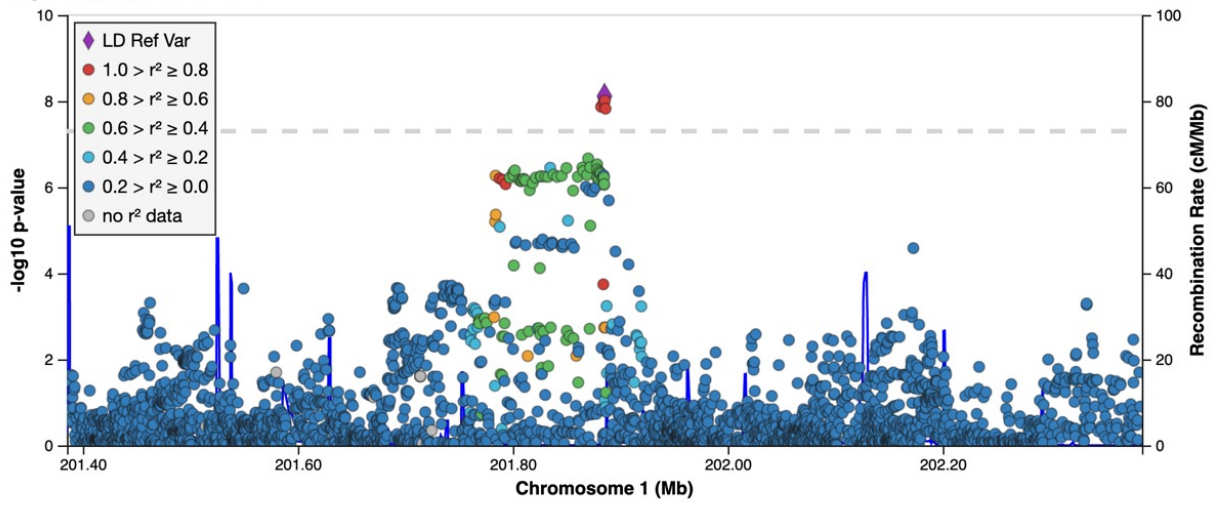
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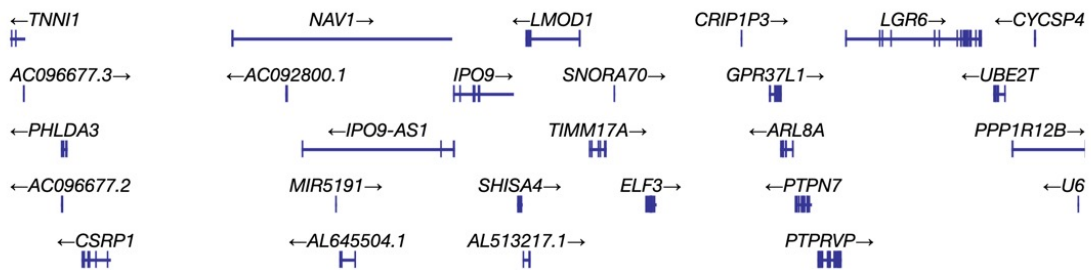
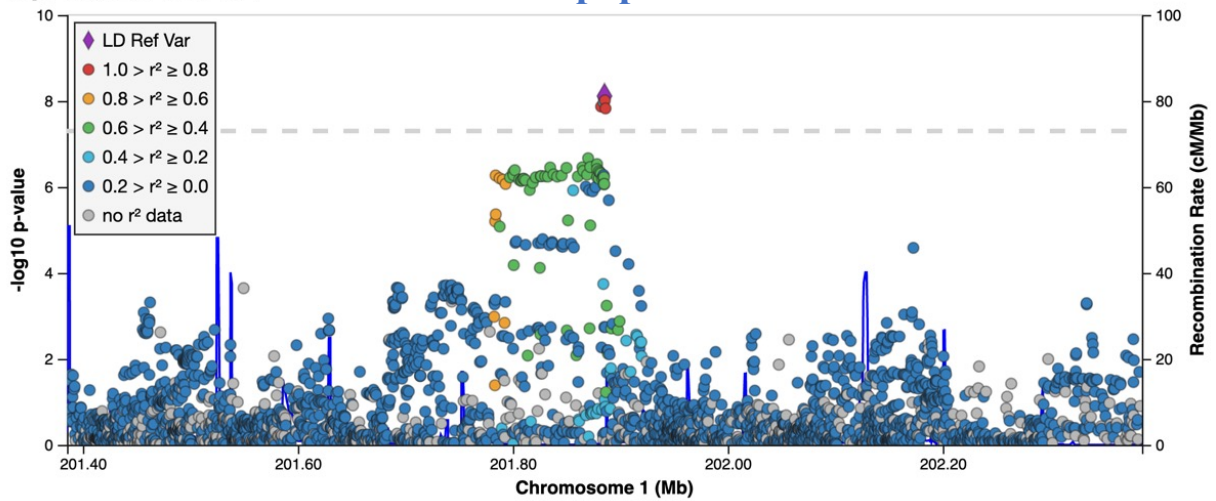
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1q32.1, rs12137232



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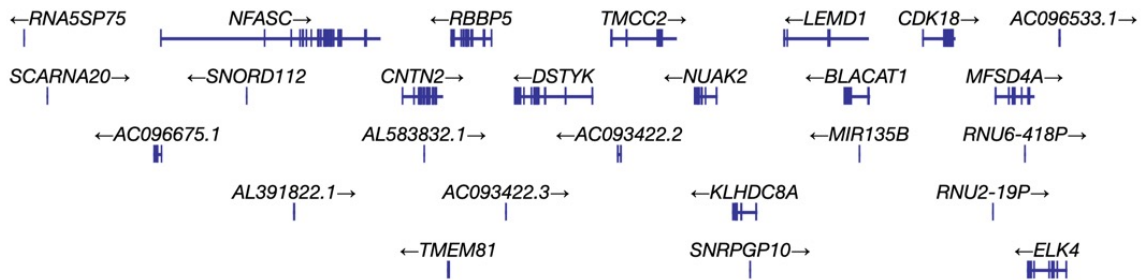
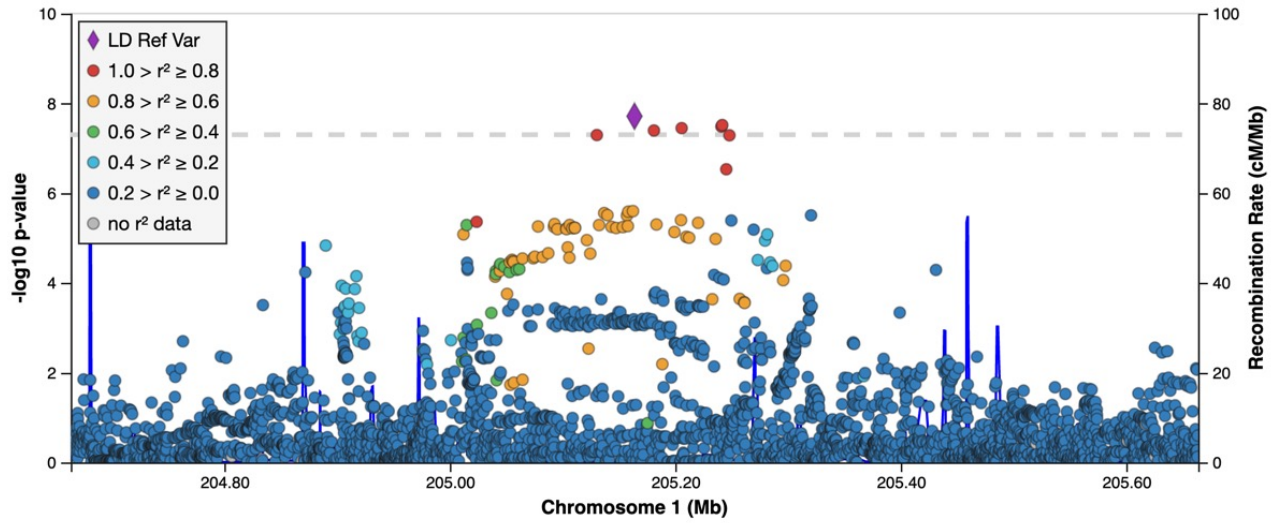
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1q32.1, rs12078075

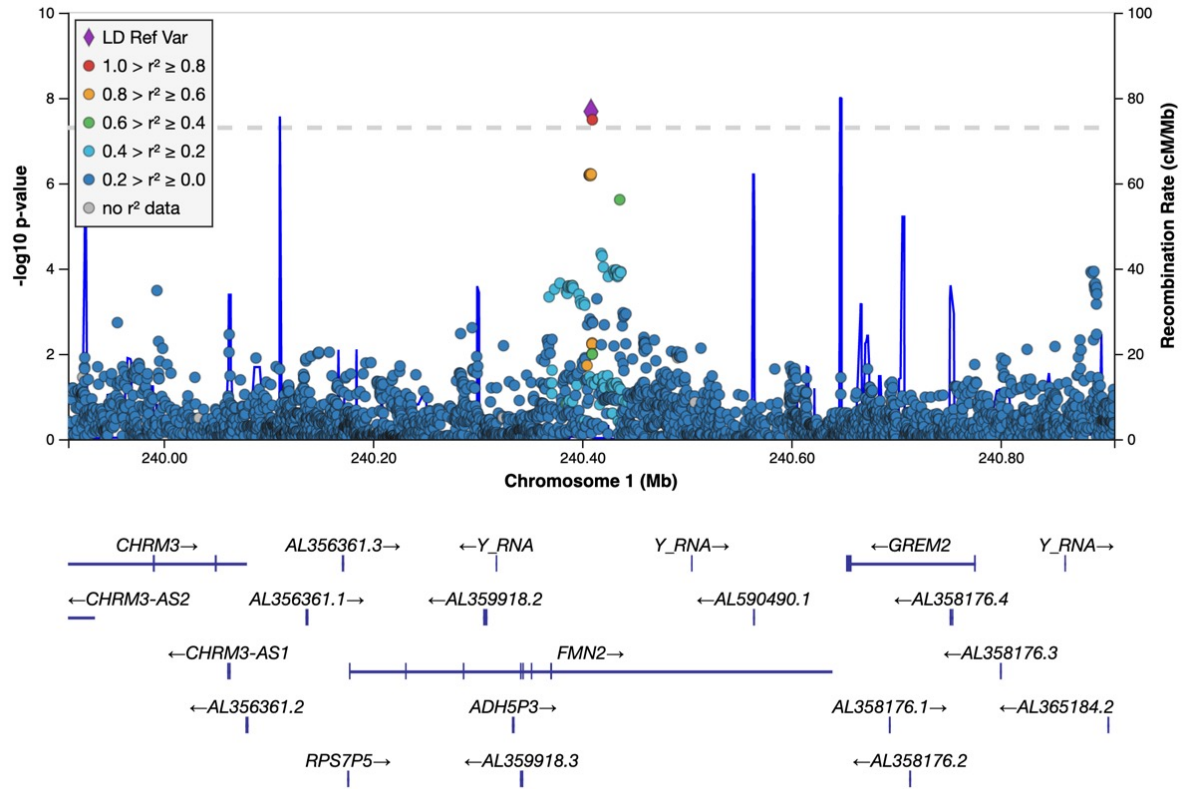


## LD reference population: EAS

rs12078075 is monoallelic in the EAS population

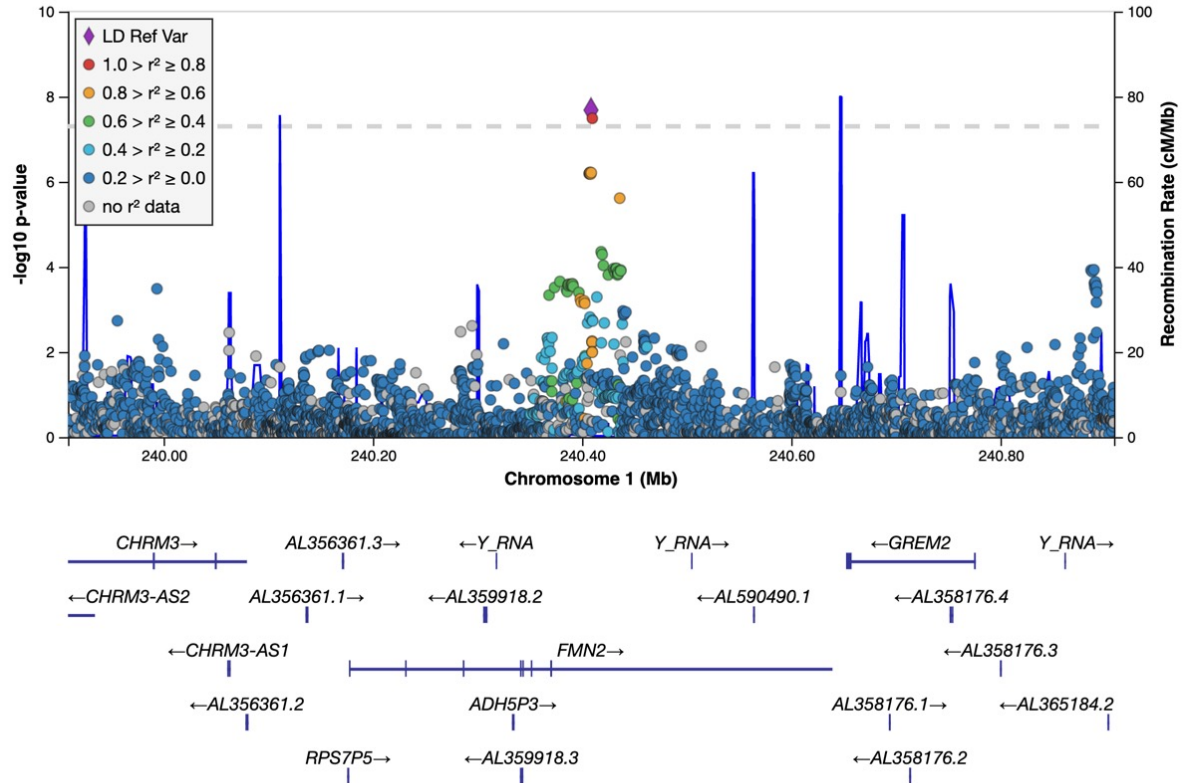
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1q43, rs2078095



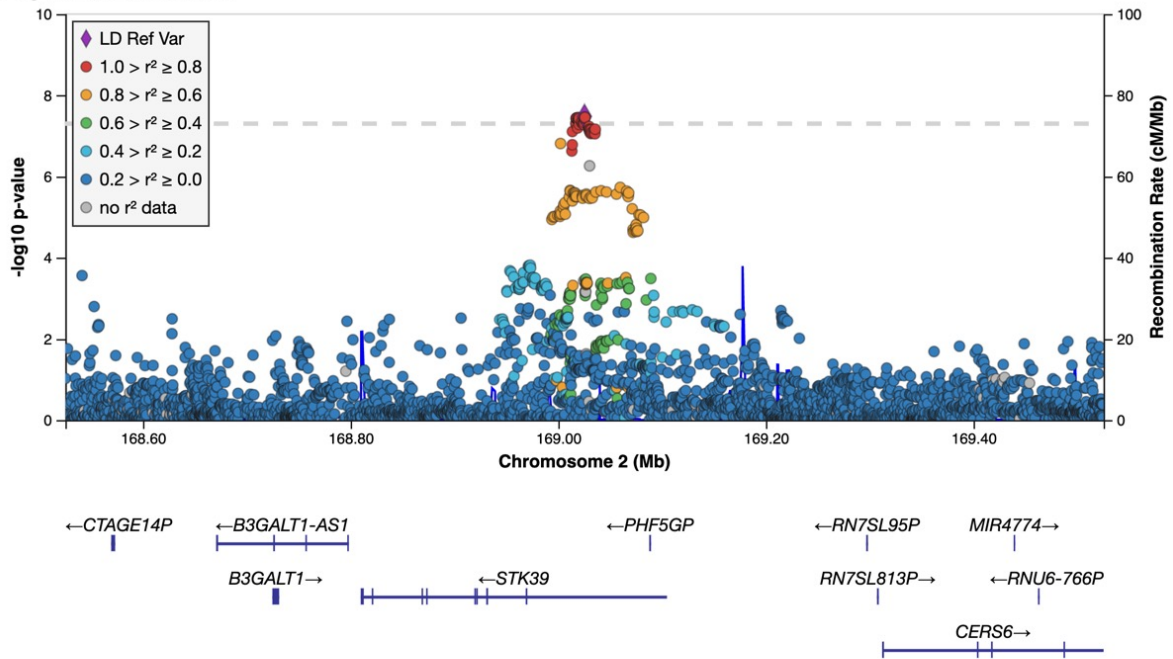
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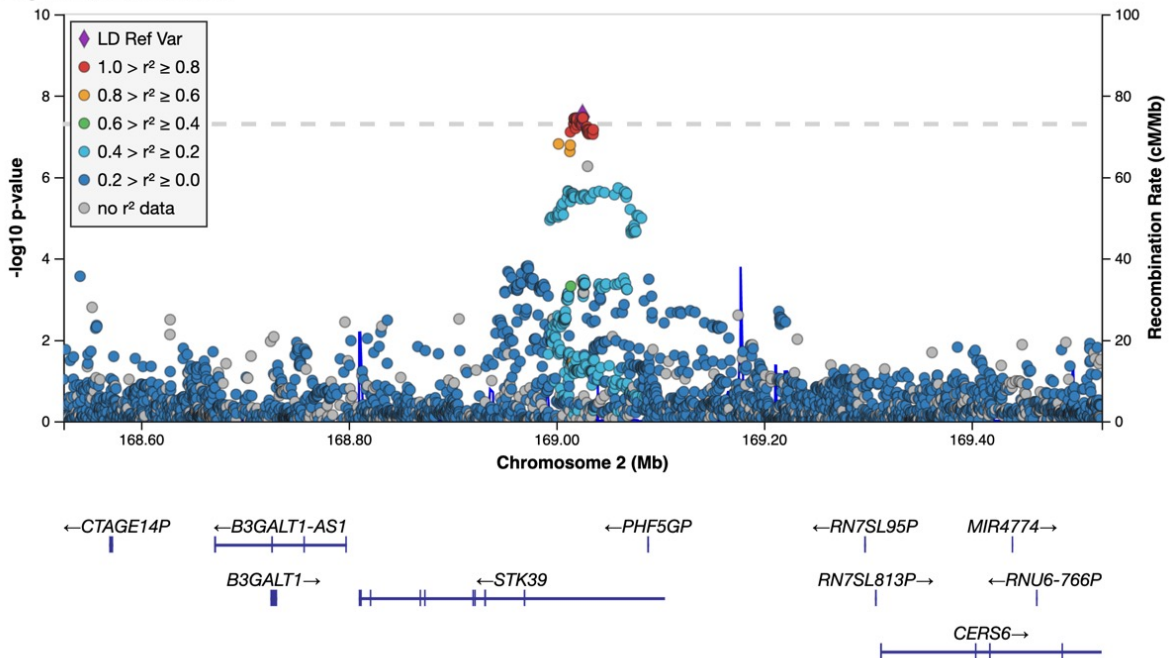
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2q24.3, rs4668039



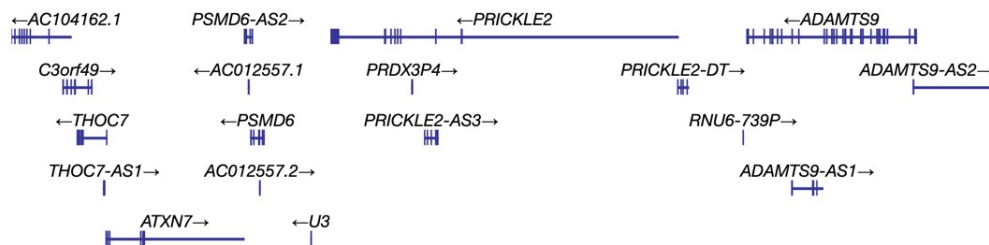
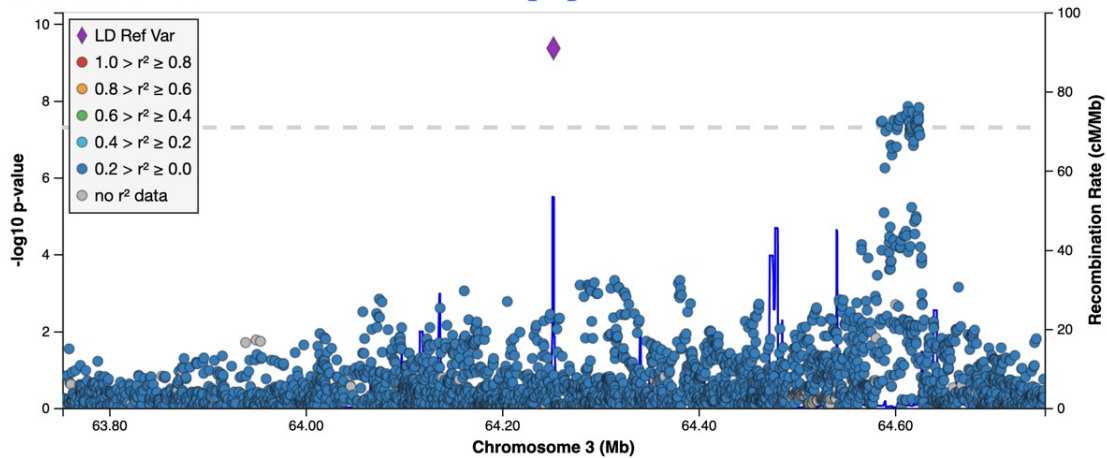
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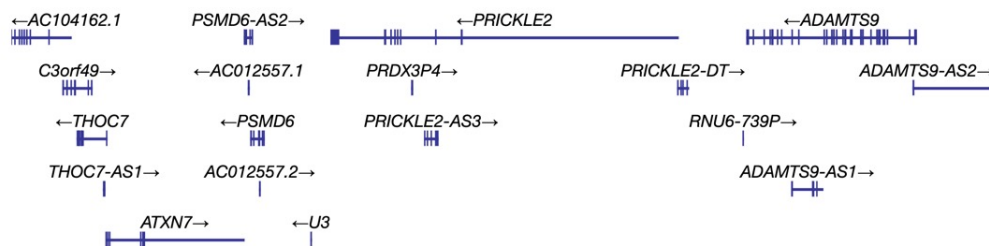
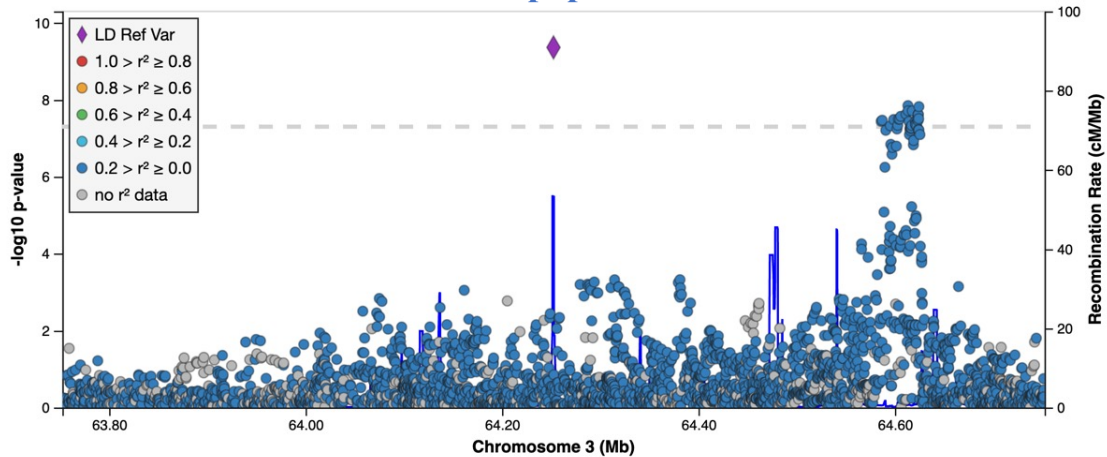
3p14.1, rs704417

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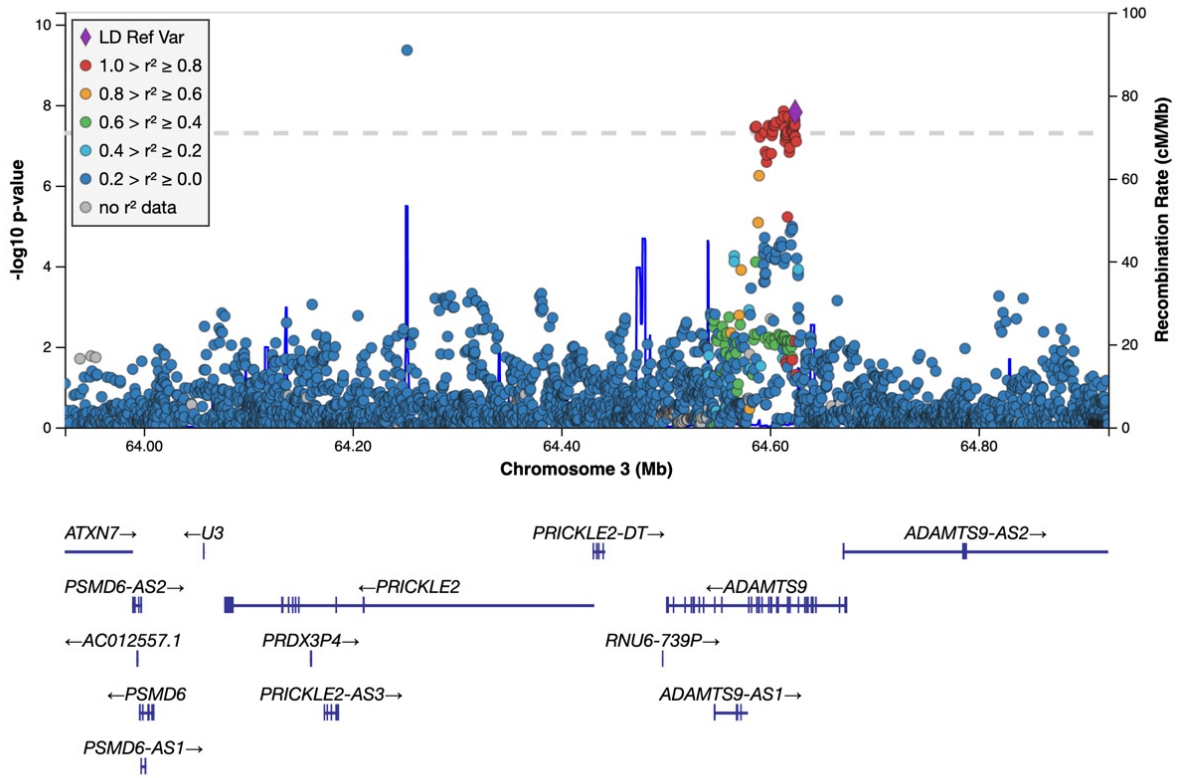
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### LD reference population: EAS



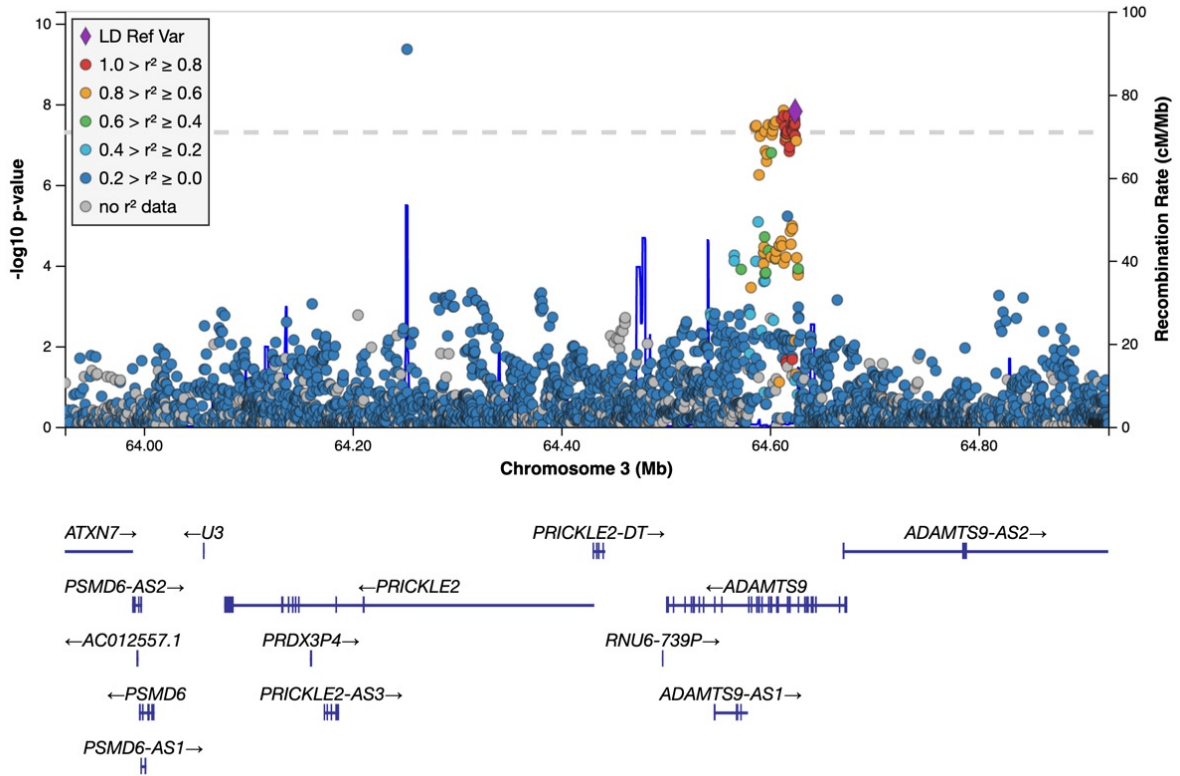
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3p14.1, rs7623129



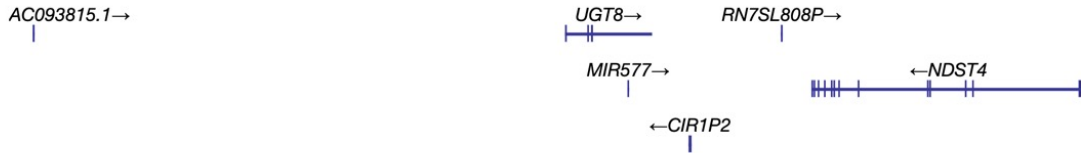
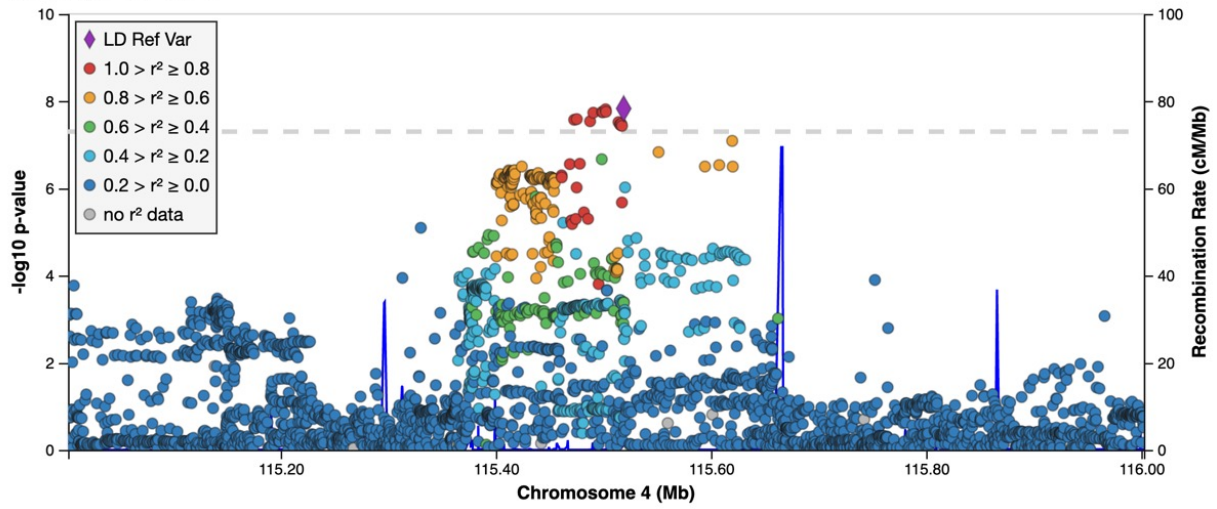
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3p14.1, rs7623129



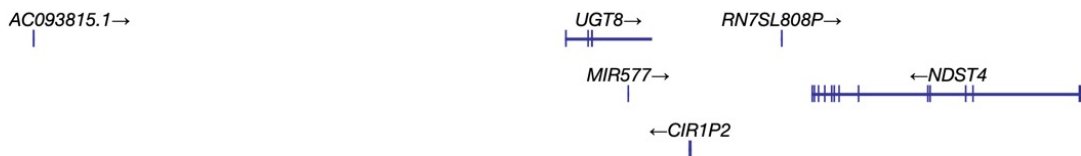
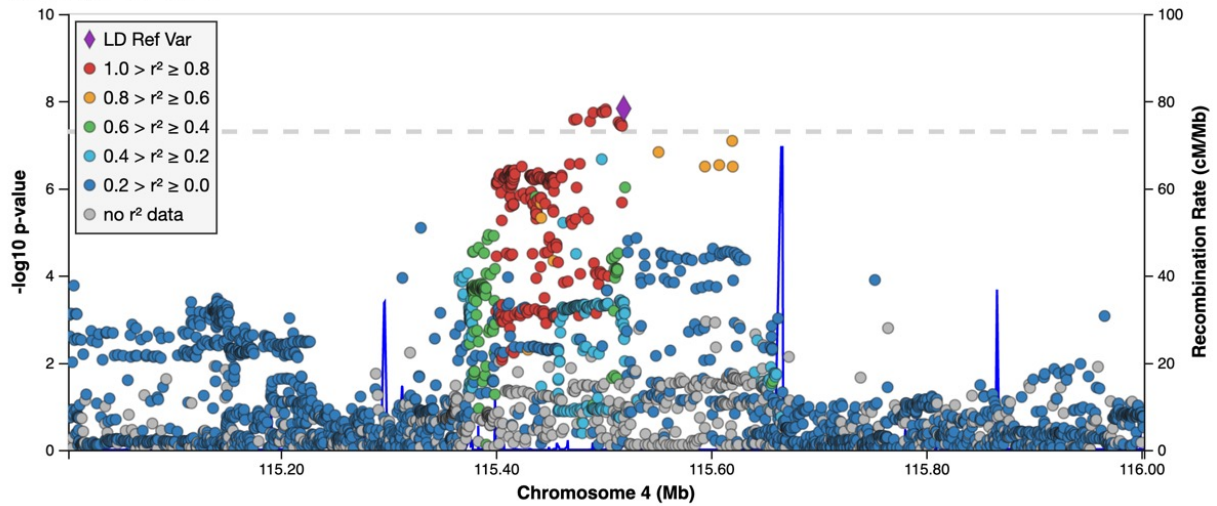
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4q26, rs2388976



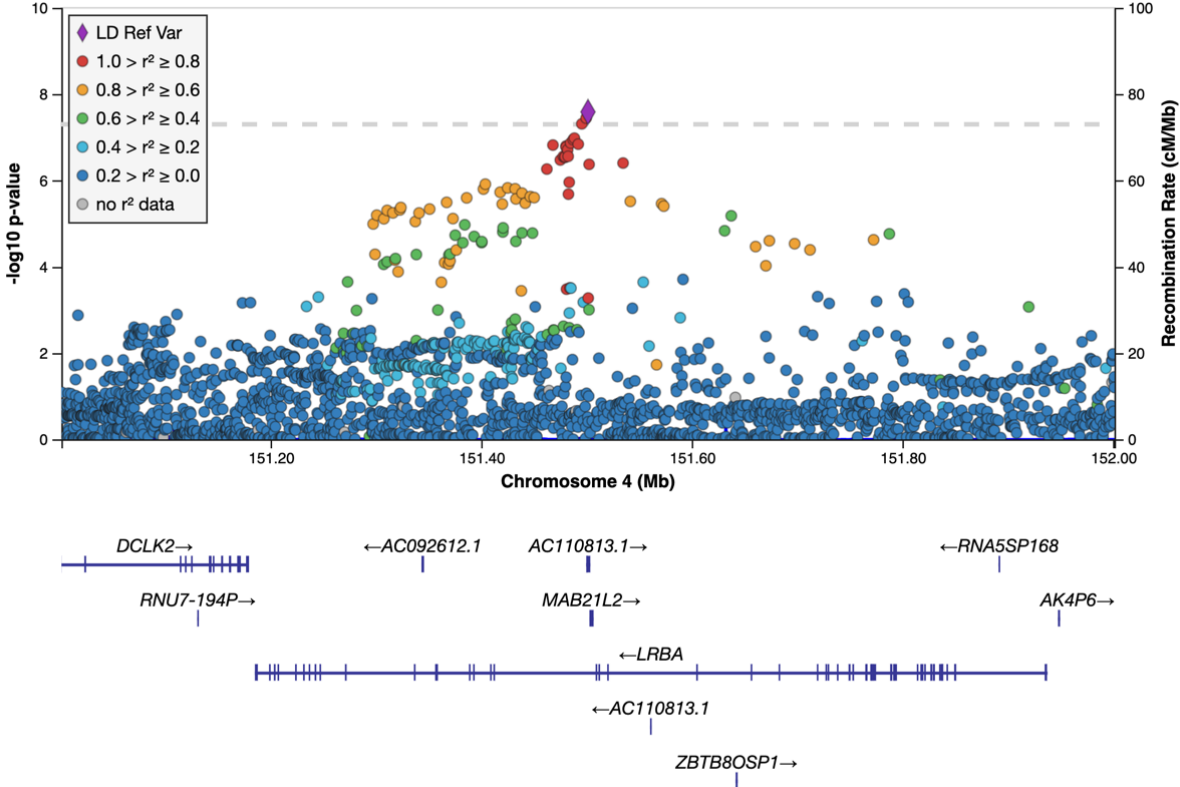
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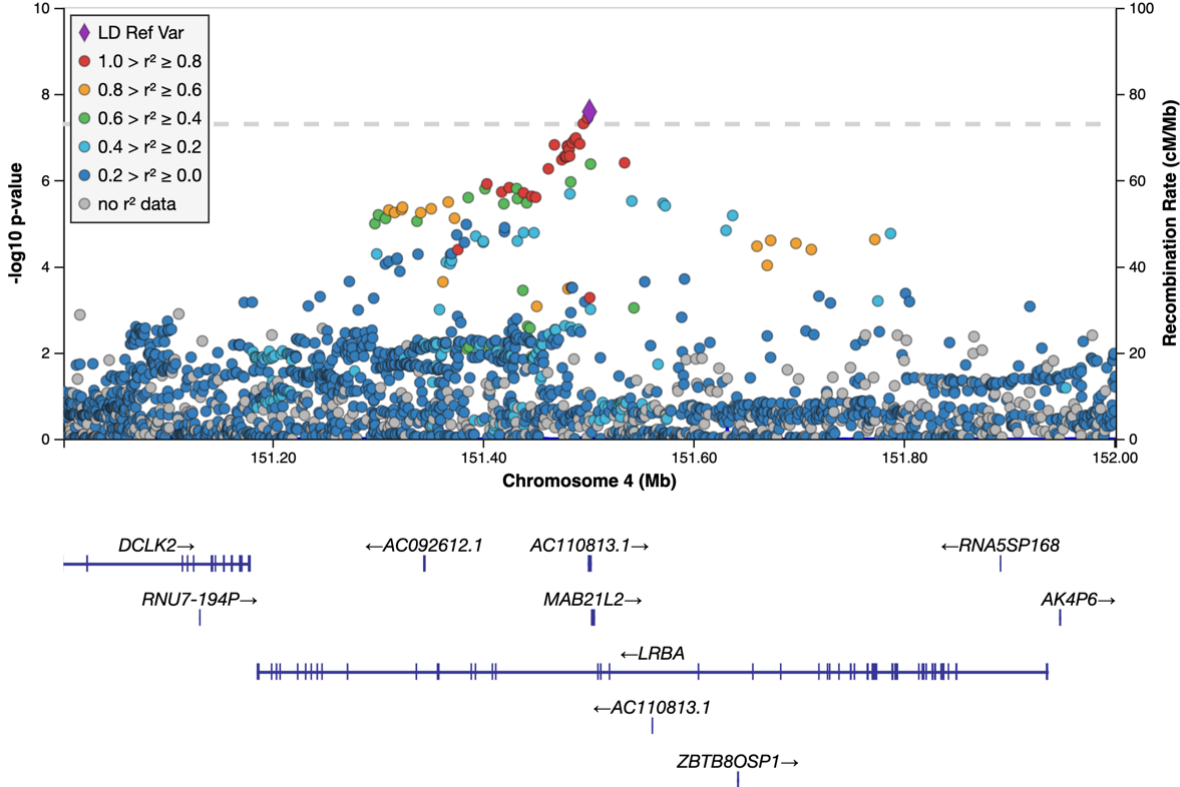
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4q31.3, rs10006803



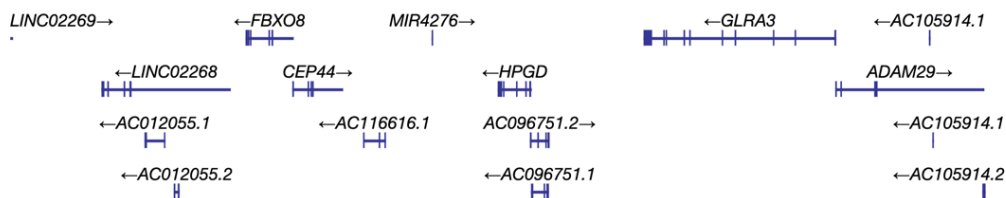
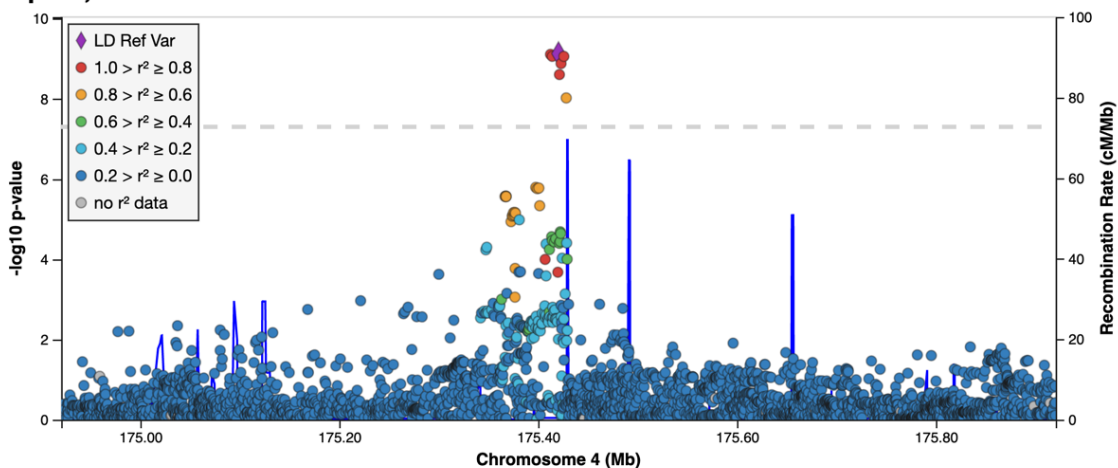
4q31.3, rs10006803

# LD reference population: EAS



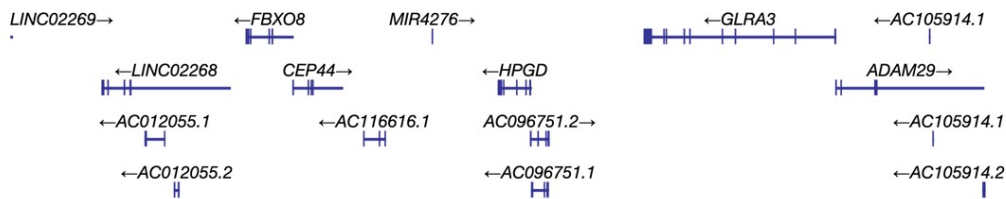
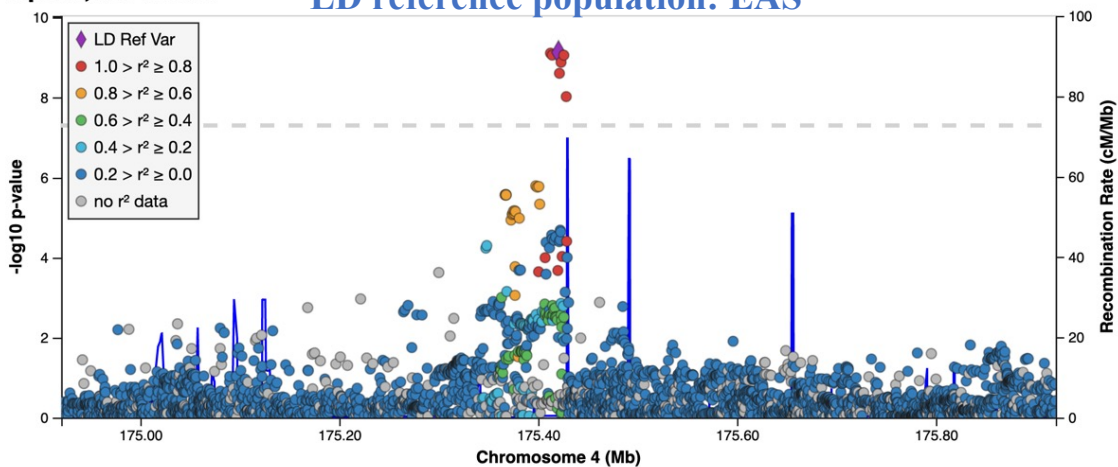
4q34.1, rs1426947

### LD reference population: EUR



4q34.1, rs1426947

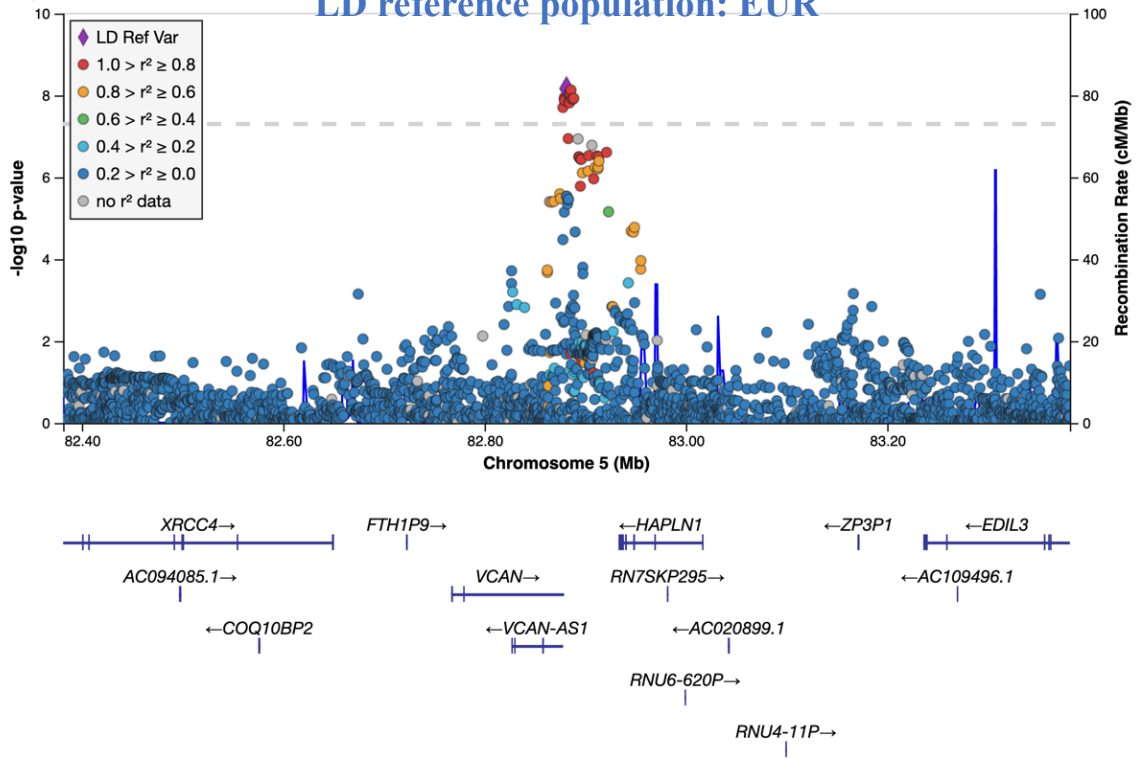
### LD reference population: EAS





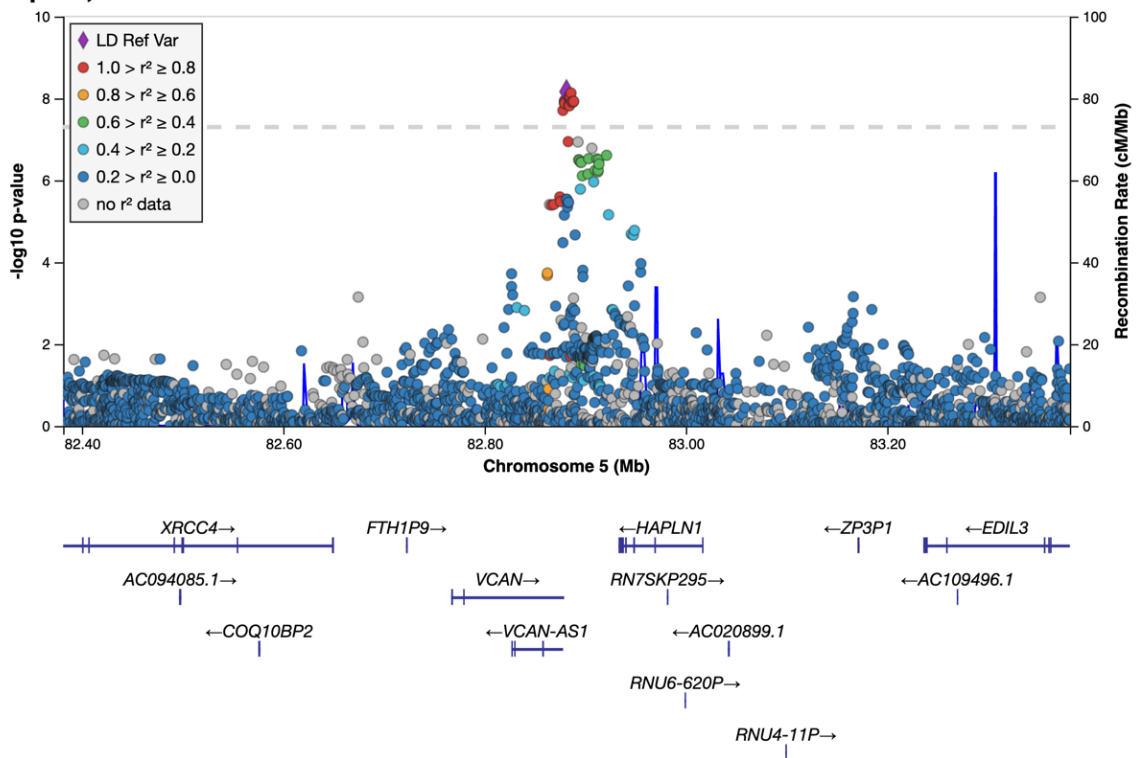
5q14.3, rs3930345

### LD reference population: EUR



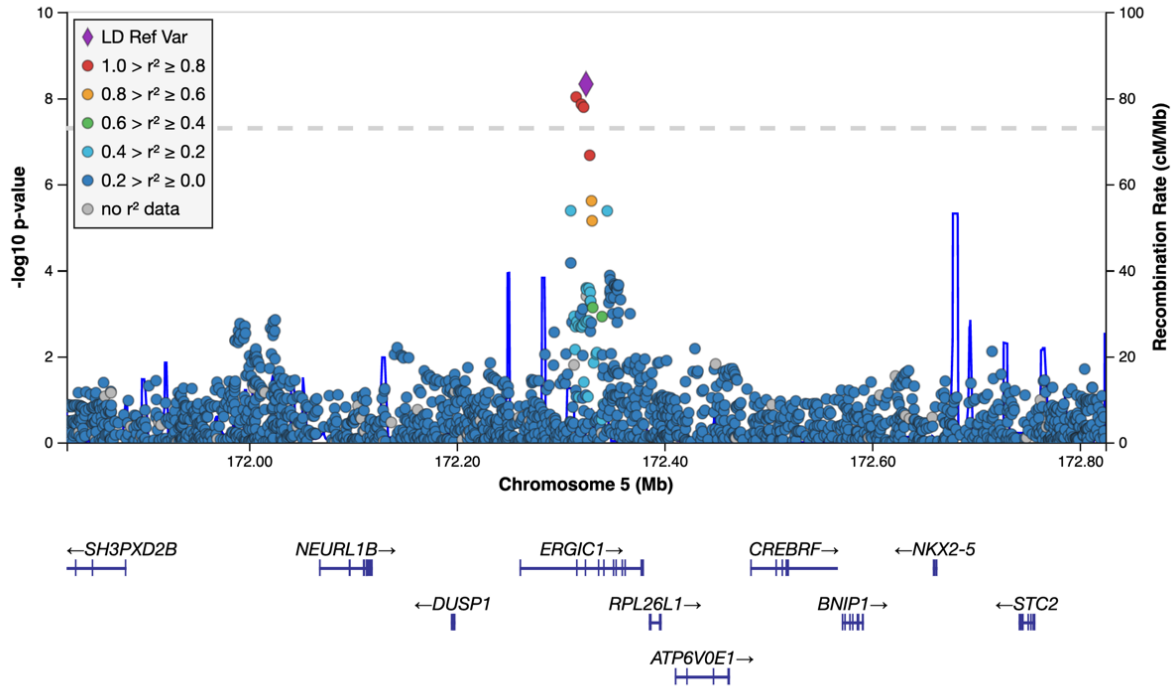
5q14.3, rs3930345

### LD reference population: EAS



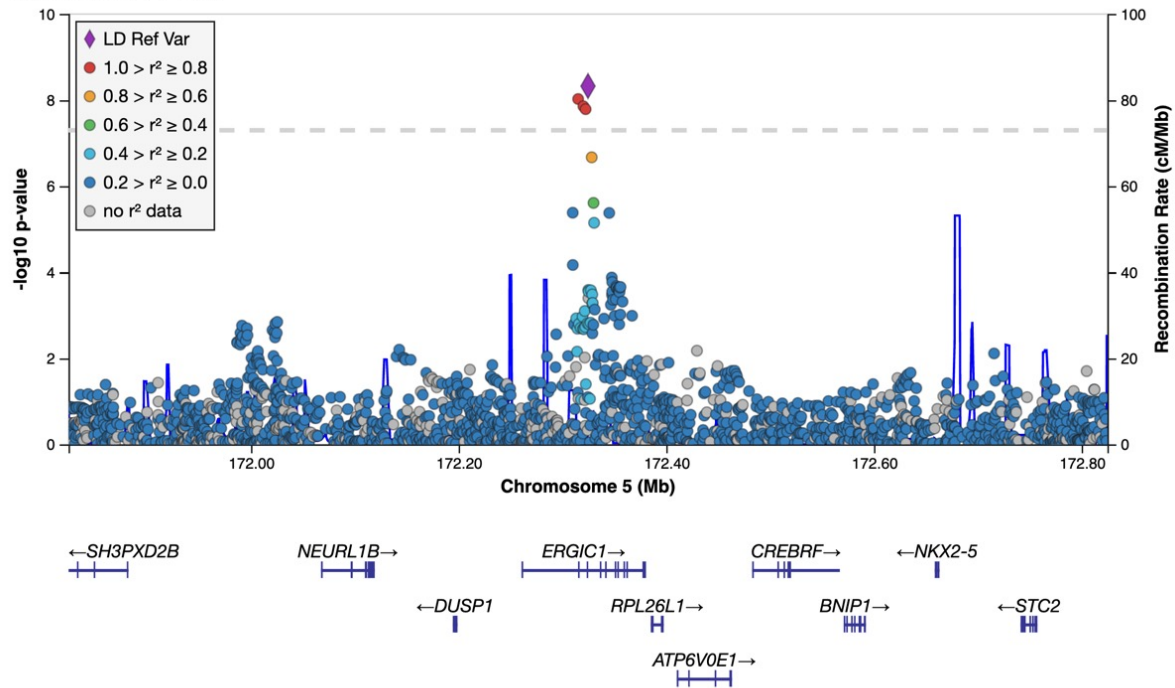
## LD reference population: EUR

5q35.1, rs472959



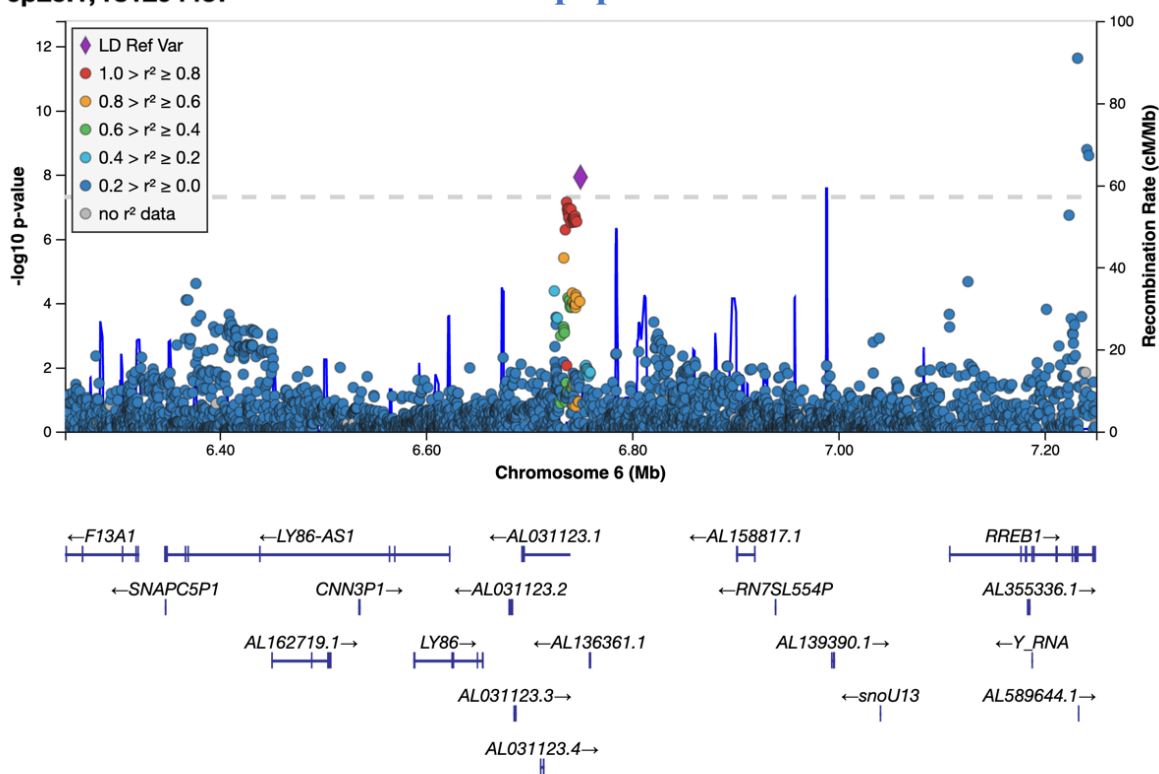
## LD reference population: EAS

5q35.1, rs472959



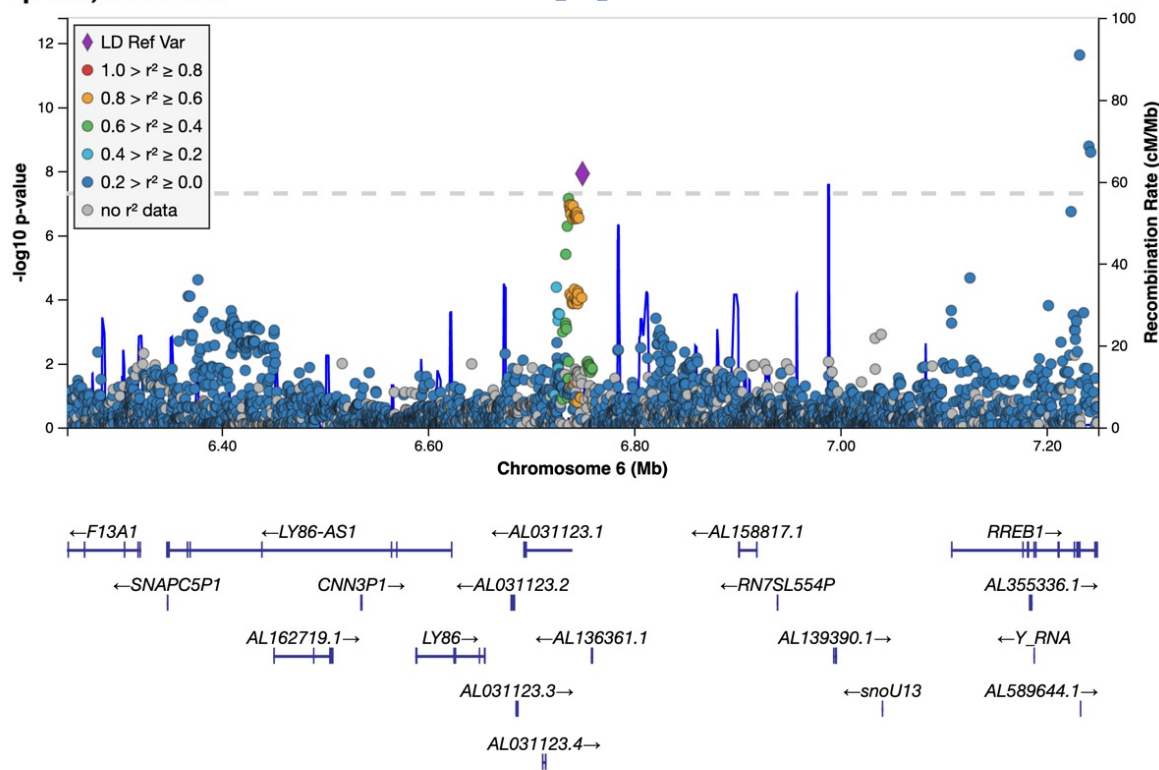
6p25.1, rs1294437

### LD reference population: EUR



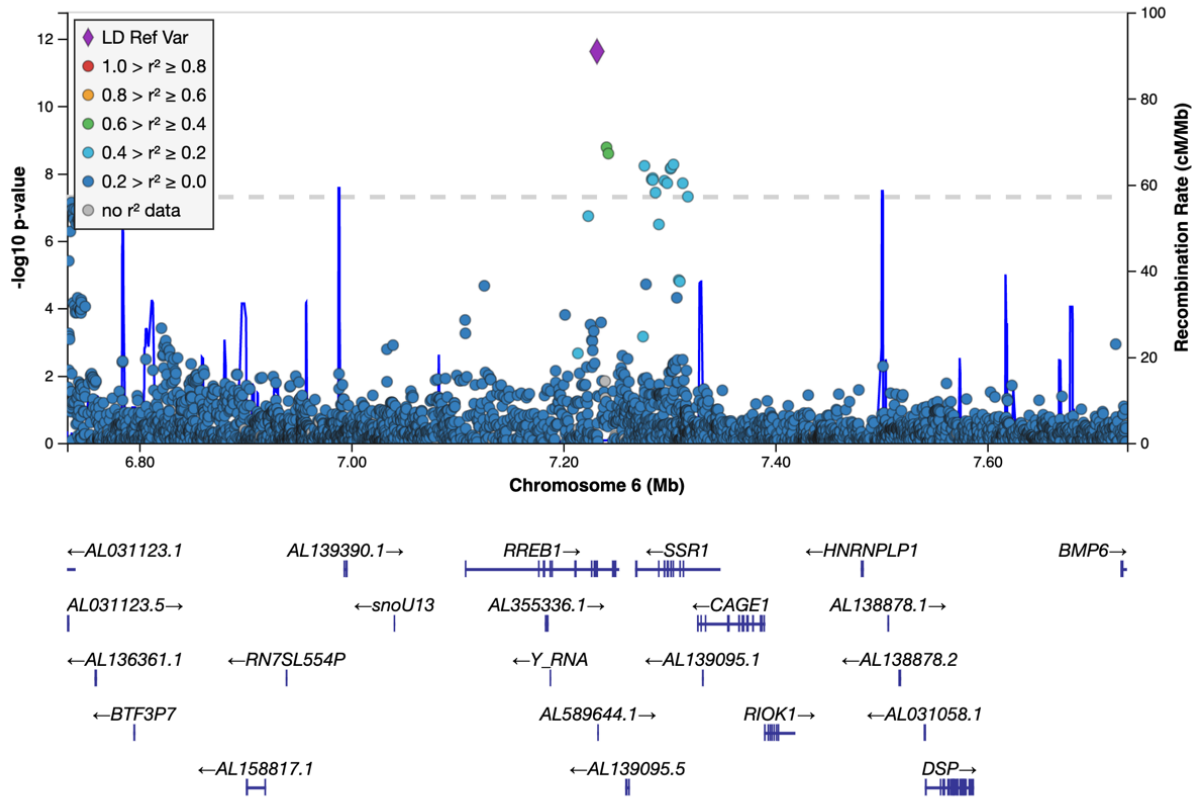
6p25.1, rs1294437

### LD reference population: EAS



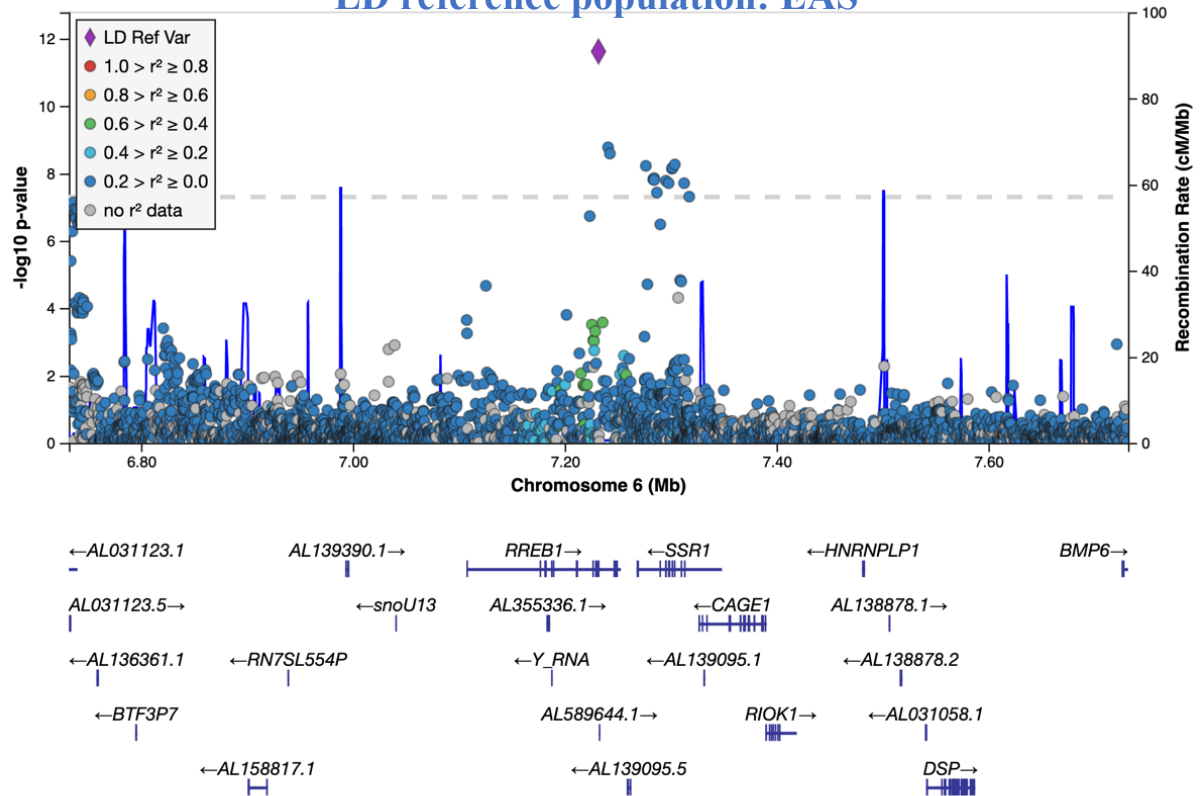
## LD reference population: EUR

6p24.3, rs9379084

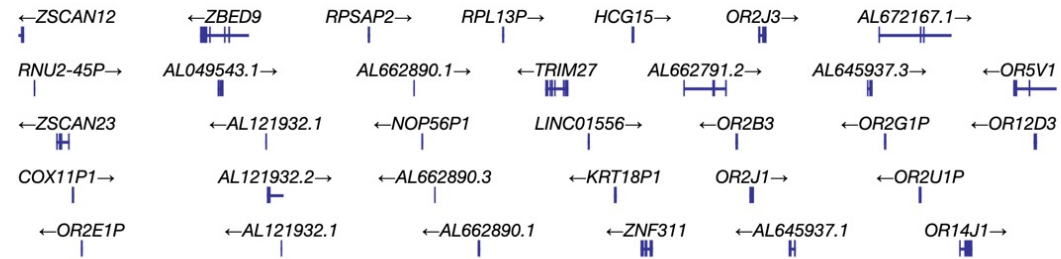
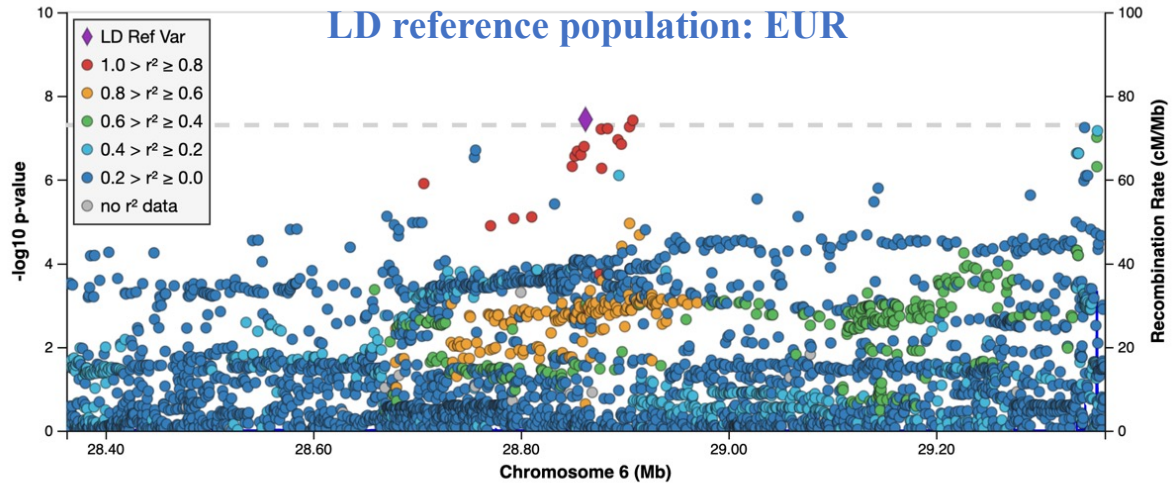


6p24.3, rs9379084

## LD reference population: EAS

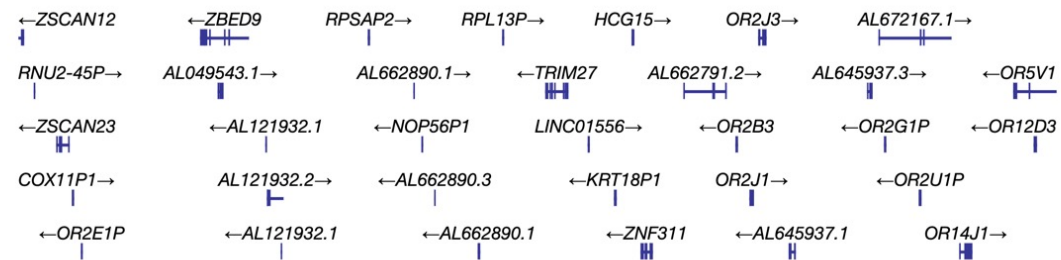
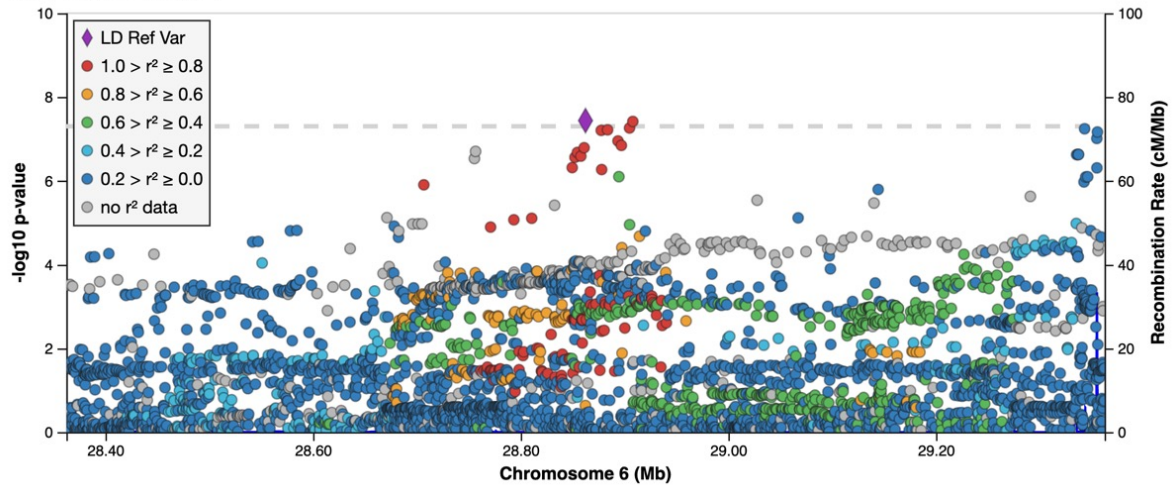


6p22.1, rs209142



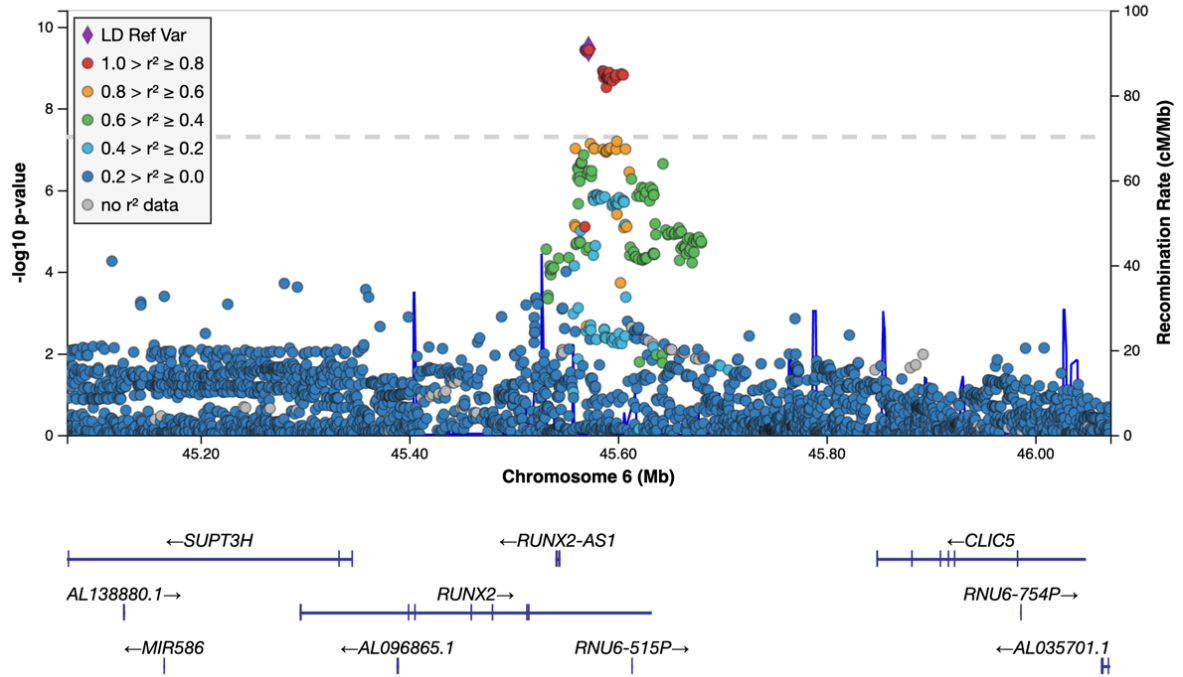
LD reference population: EAS

6p22.1, rs209142



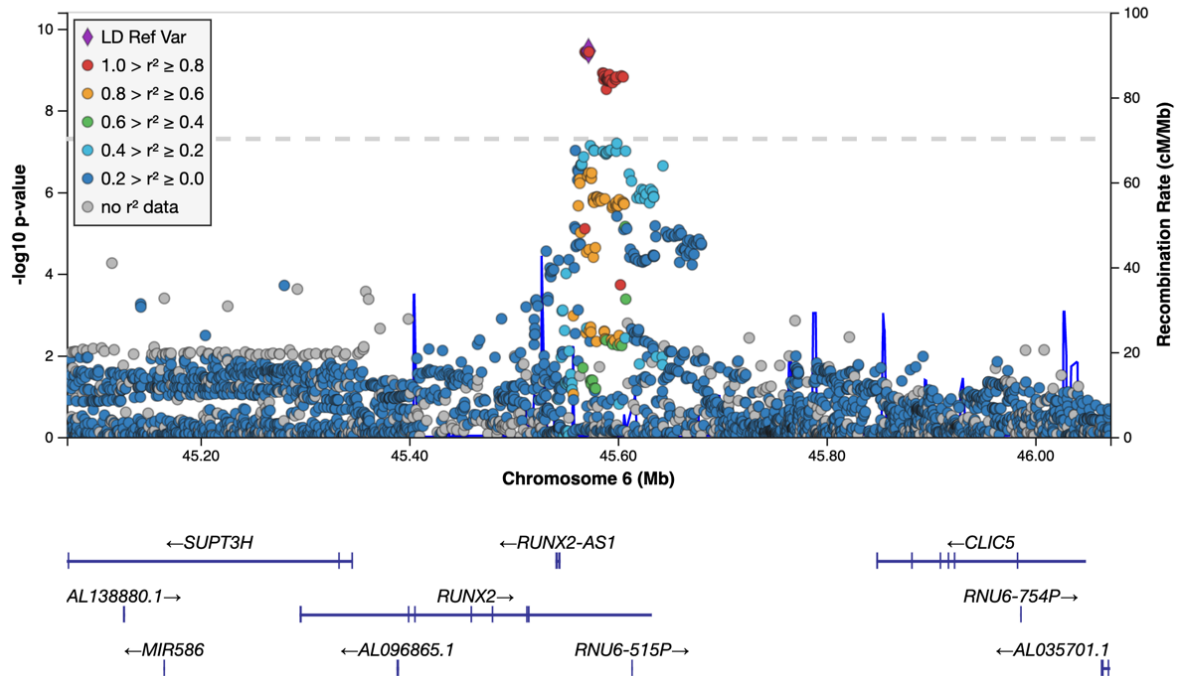
## LD reference population: EUR

6p21.1, rs57939401



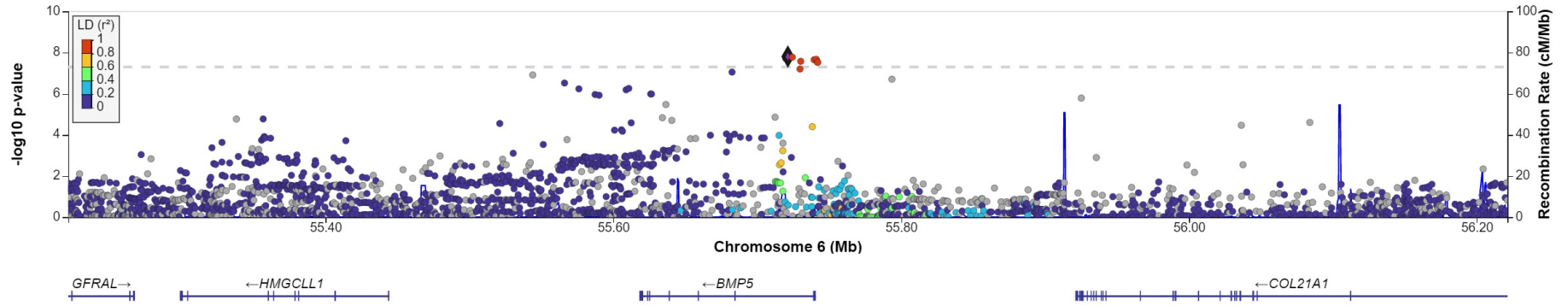
## LD reference population: EAS

6p21.1, rs57939401



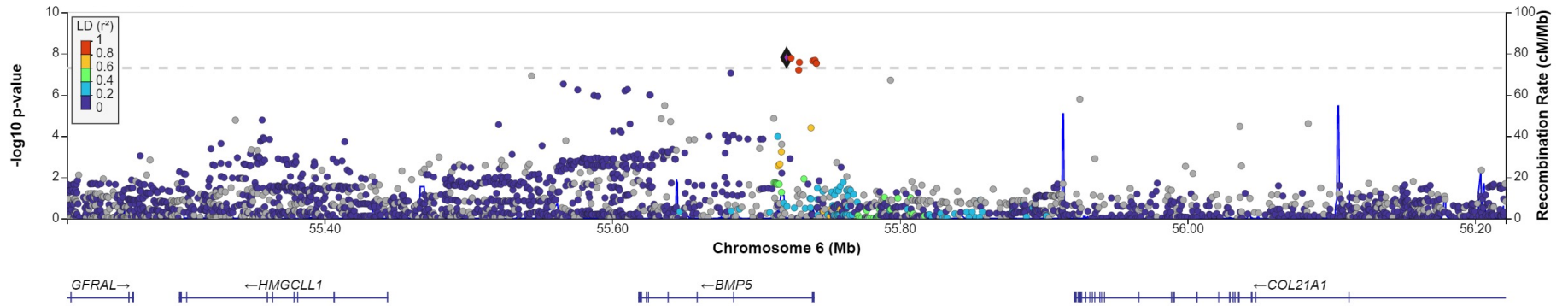
### LD reference population: EUR

6p12.1, rs6912214



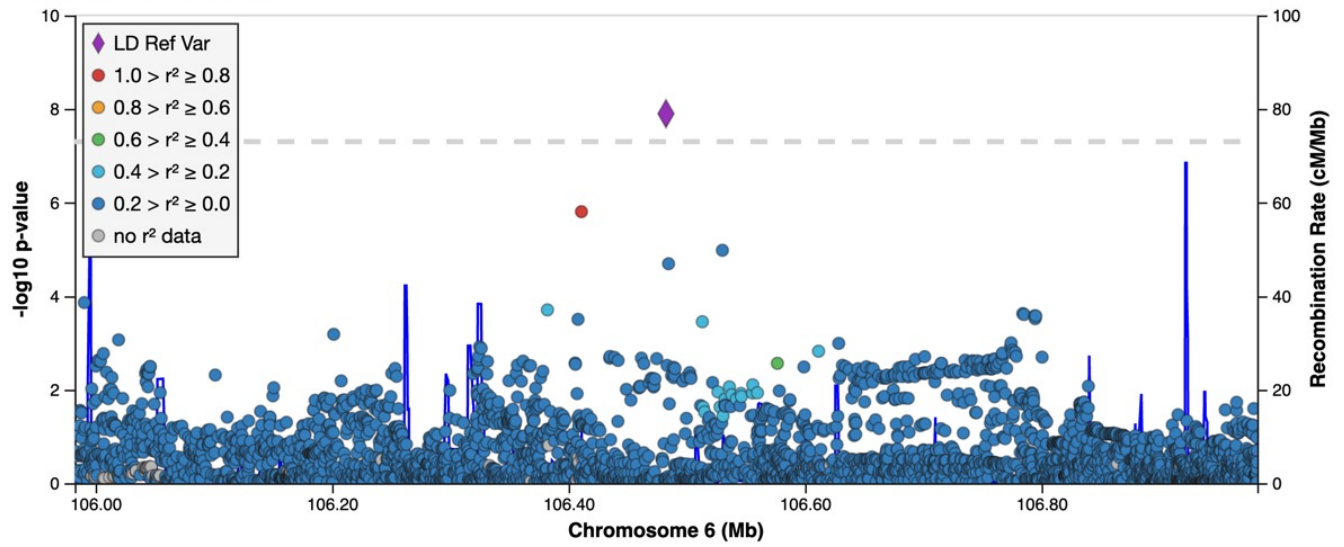
### LD reference population: EAS

6p12.1, rs6912214



## LD reference population: EUR

6q21, rs145997965



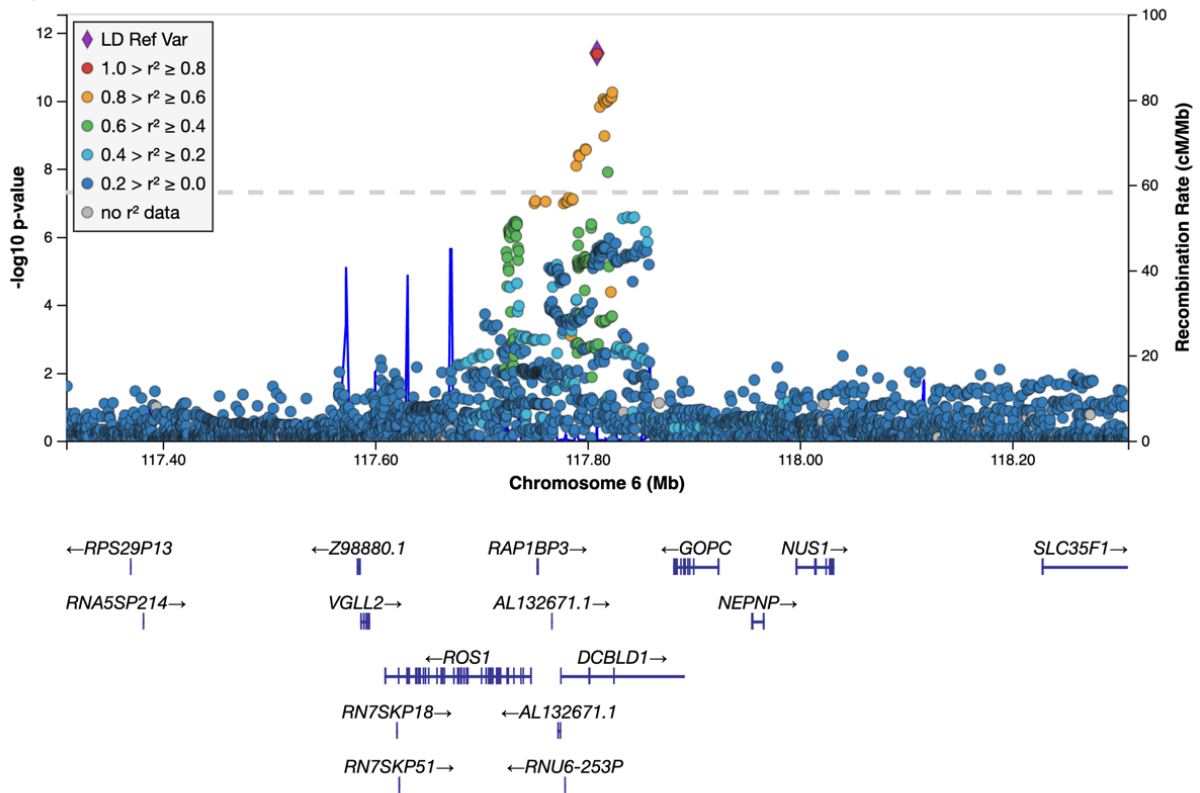
## LD reference population: EAS

rs145997965 is monoallelic in the EAS population



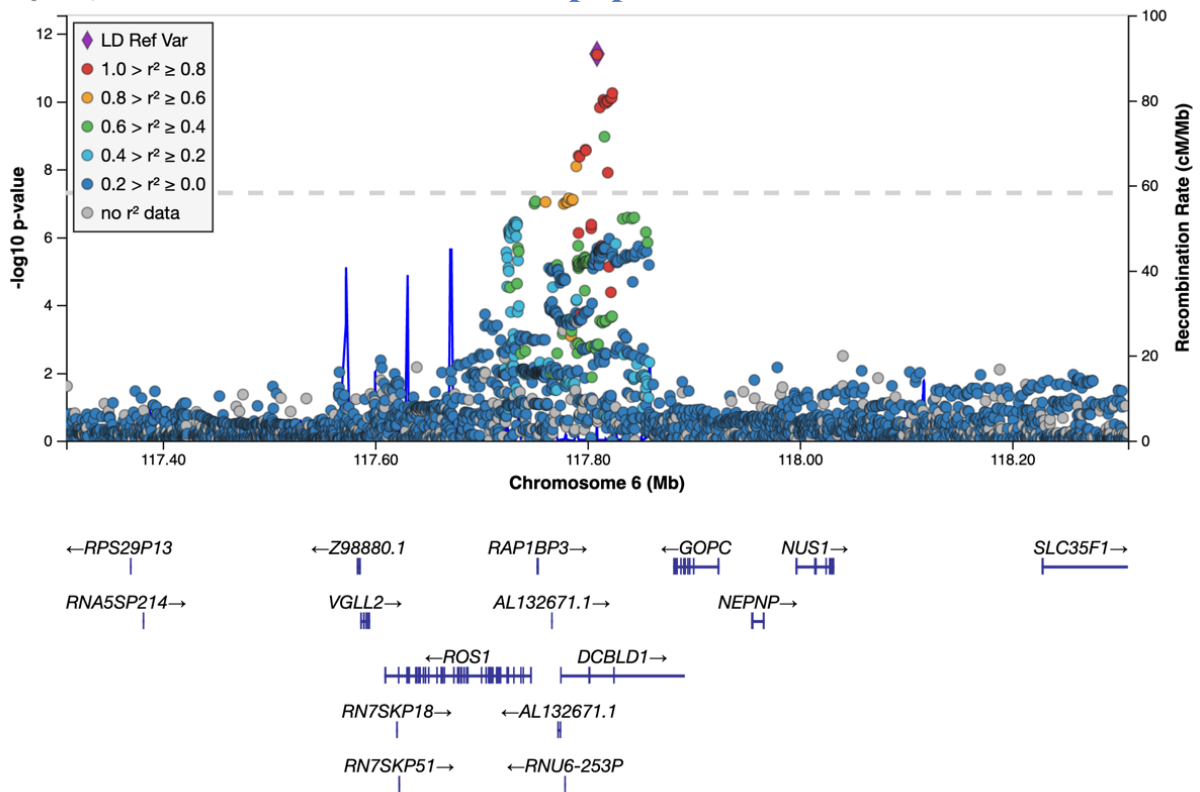
6q22.1, rs6911915

### LD reference population: EUR



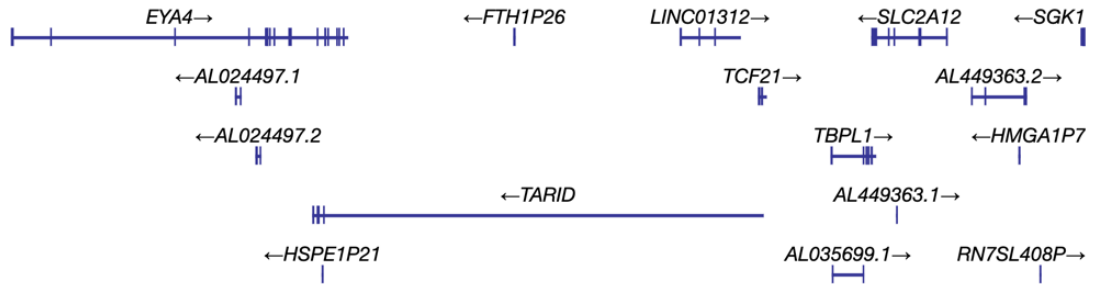
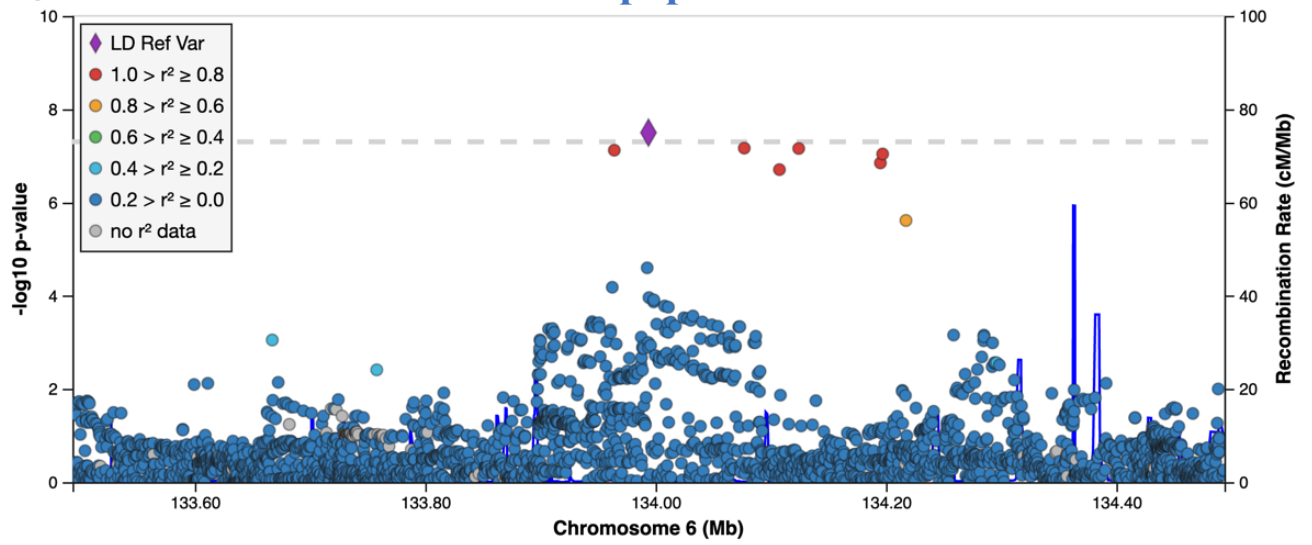
6q22.1, rs6911915

### LD reference population: EAS



6q23.2, rs151127921

## LD reference population: EUR

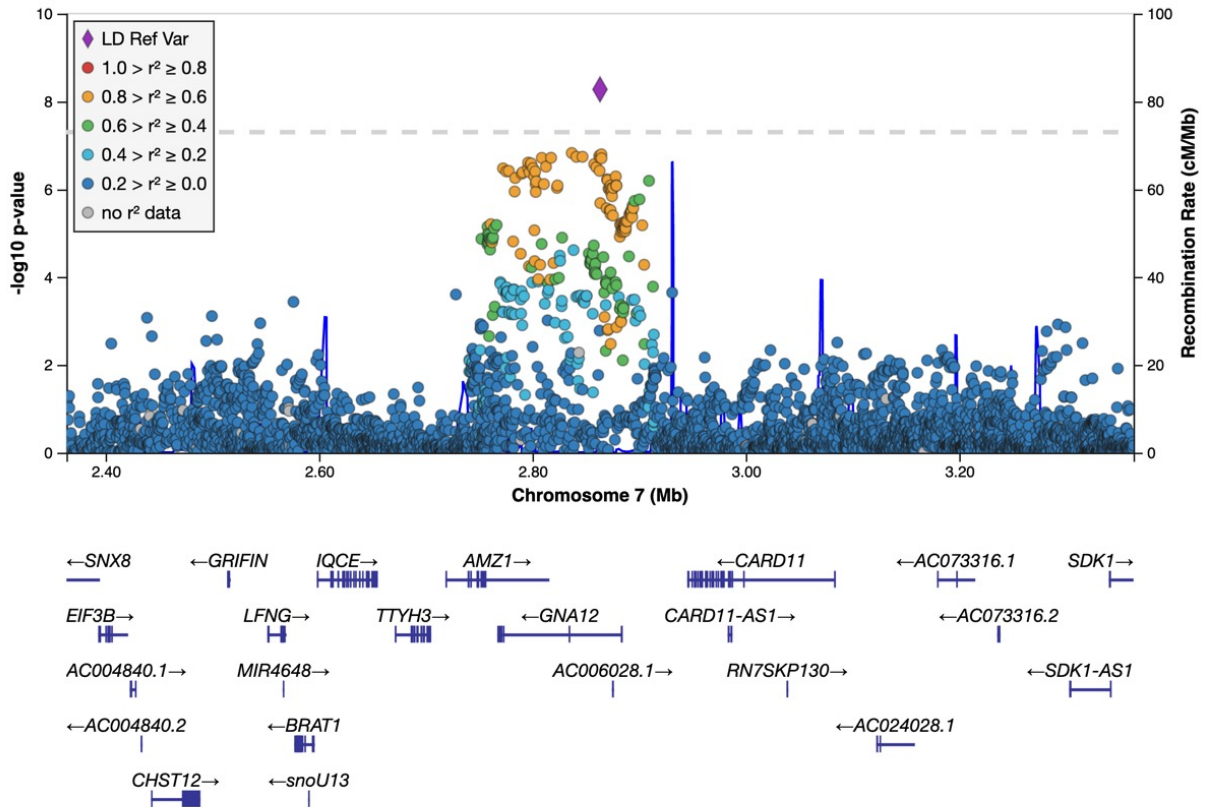


## LD reference population: EAS

rs151127921 is monoallelic in the EAS population

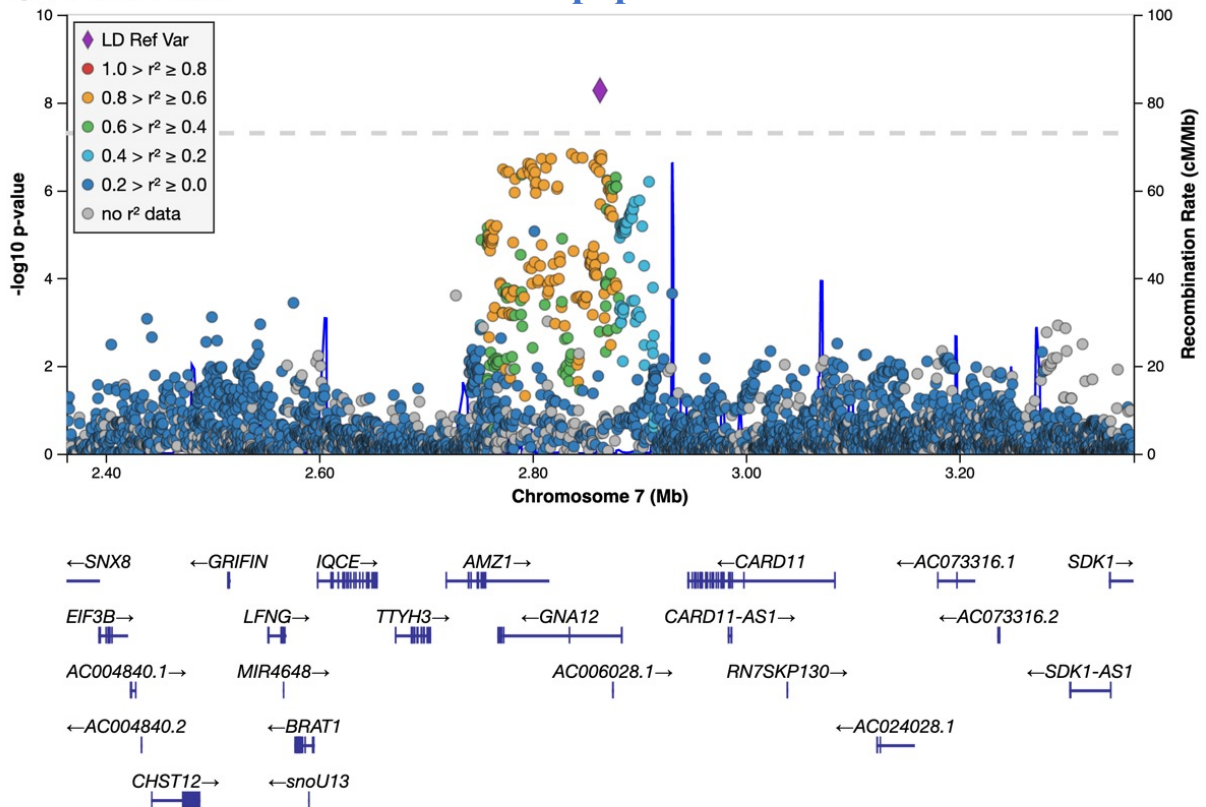
## LD reference population: EUR

7p22.2, rs1182197



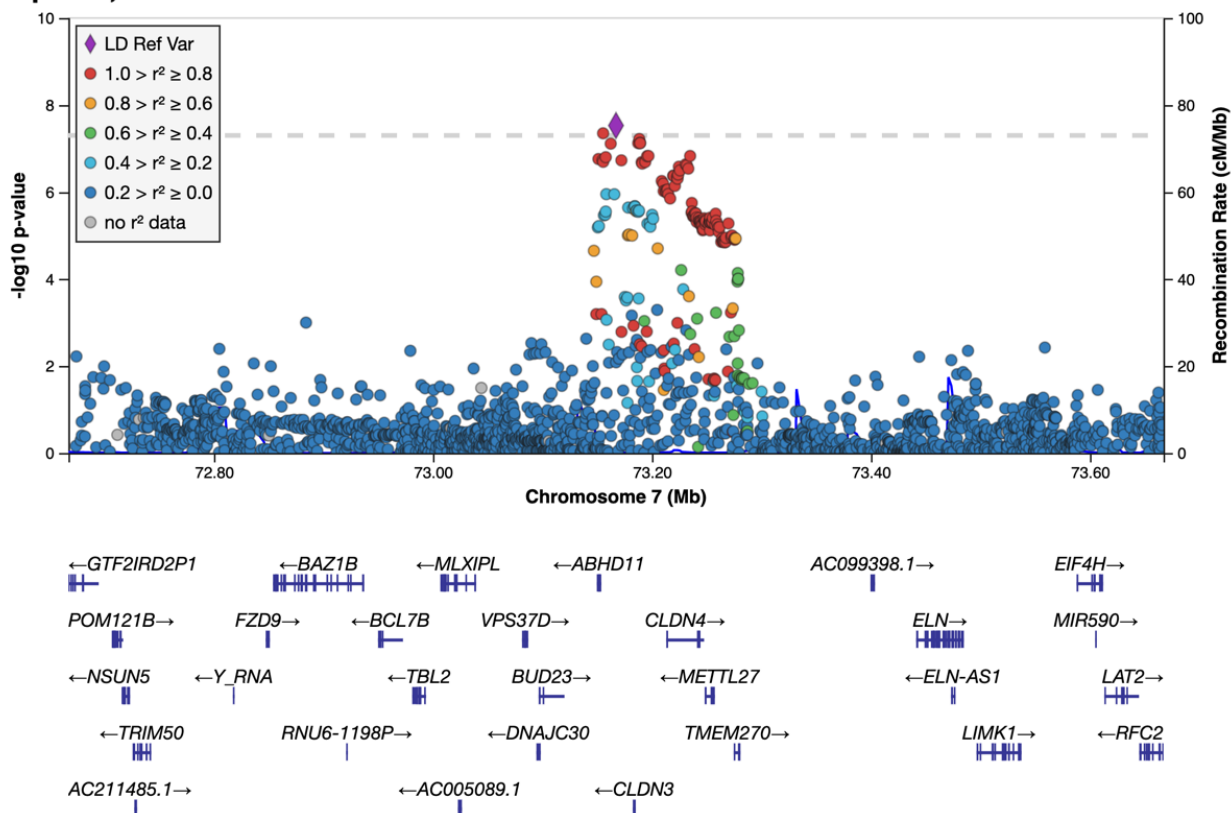
## LD reference population: EAS

7p22.2, rs1182197



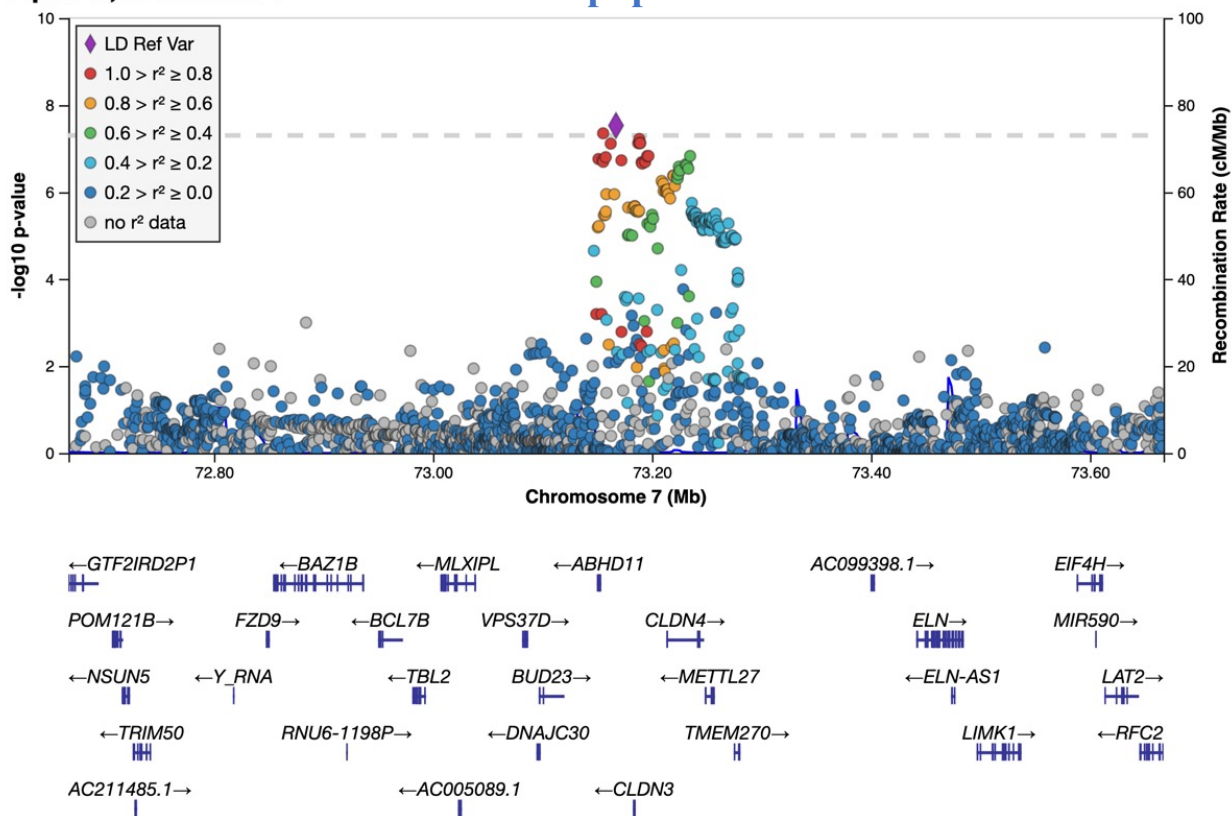
## LD reference population: EUR

7q11.23, rs12539962



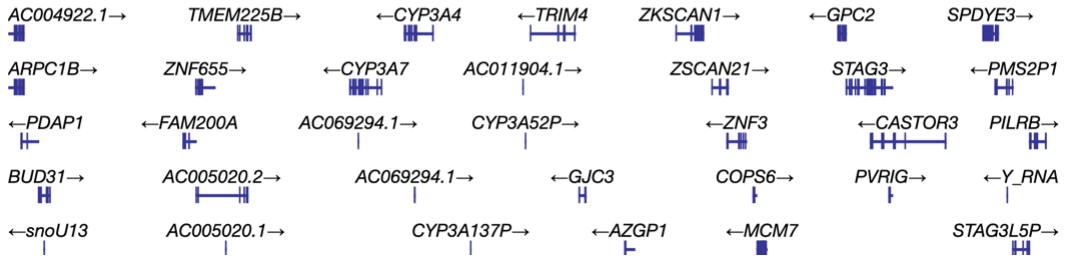
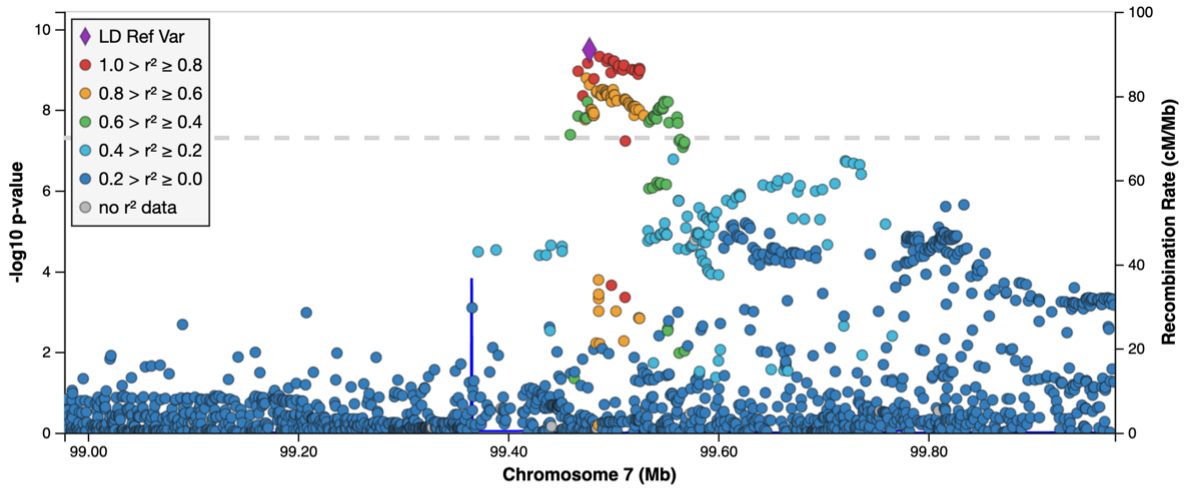
## LD reference population: EAS

7q11.23, rs12539962



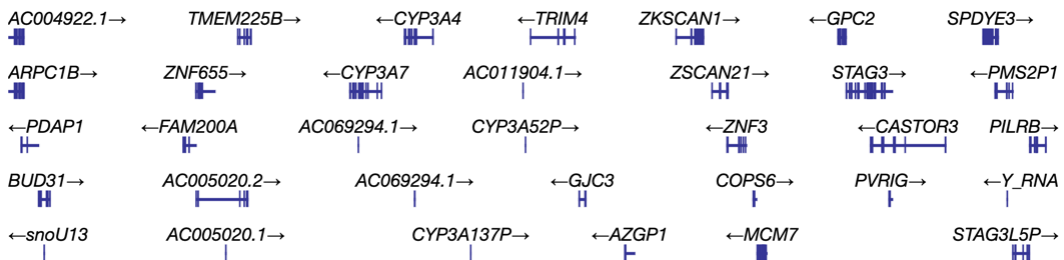
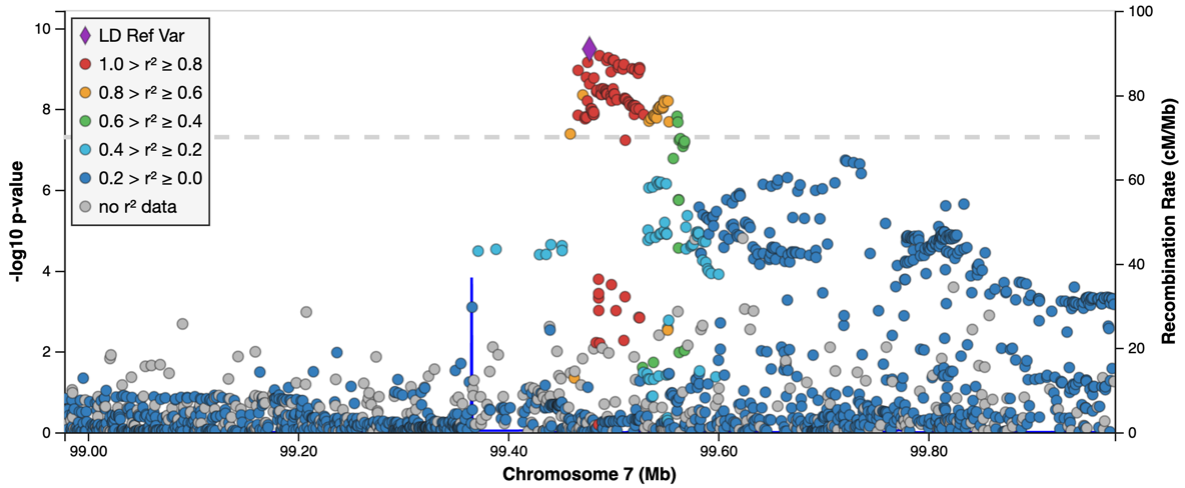
## LD reference population: EUR

7q22.1, rs2527927



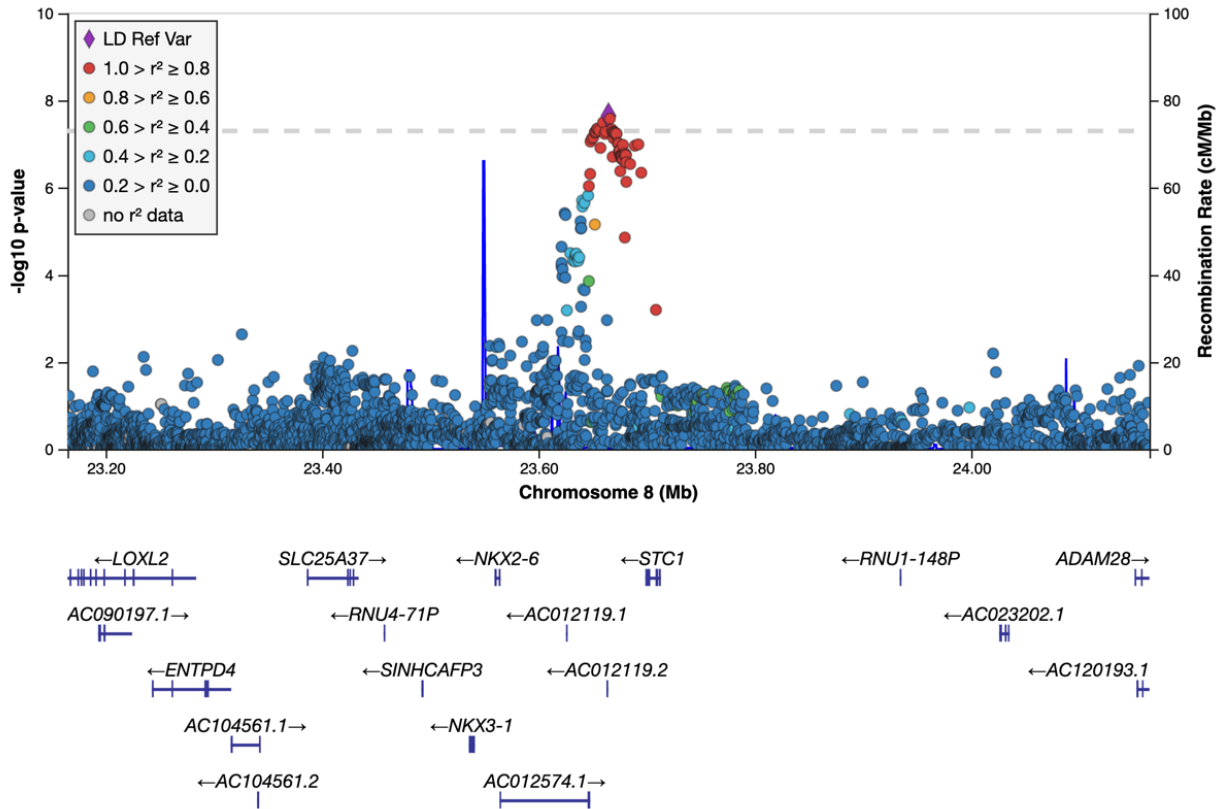
7q22.1, rs2527927

## LD reference population: EAS



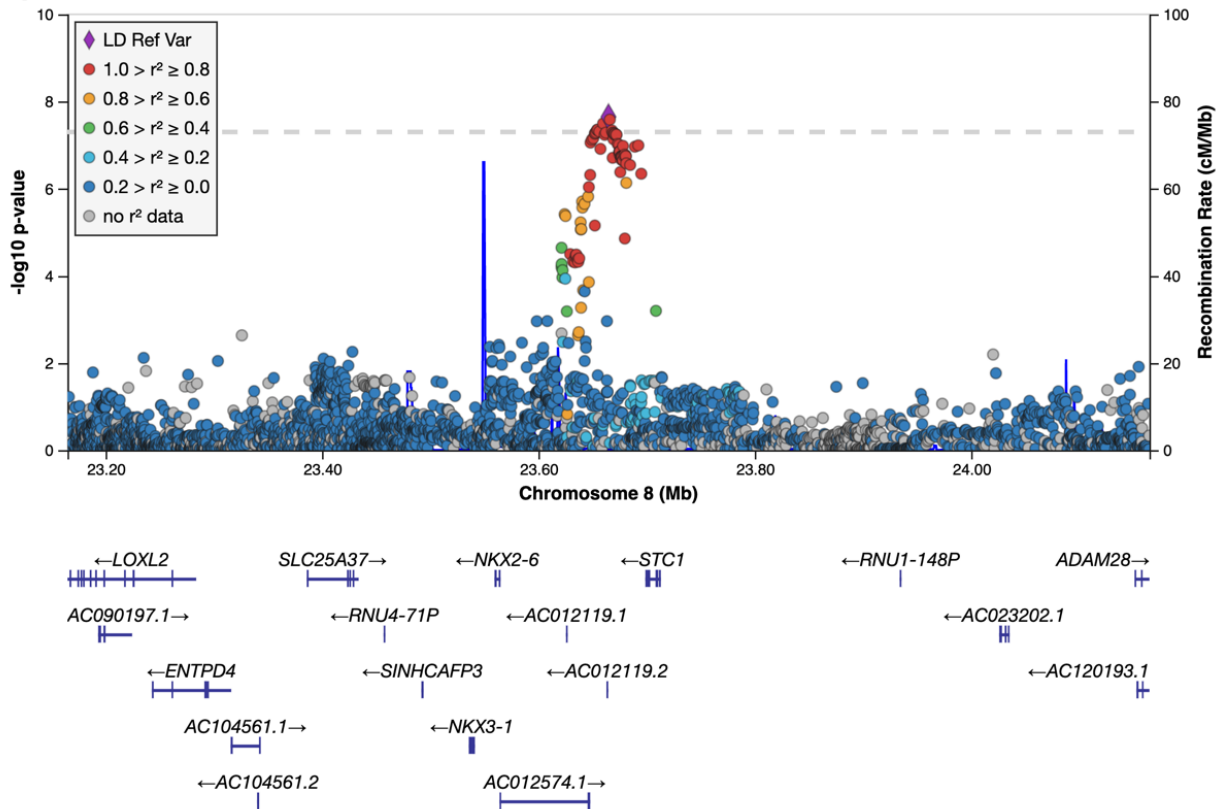
## LD reference population: EUR

8p21.2, rs60911071



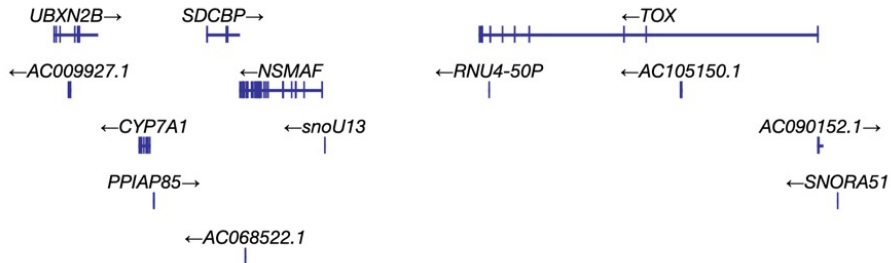
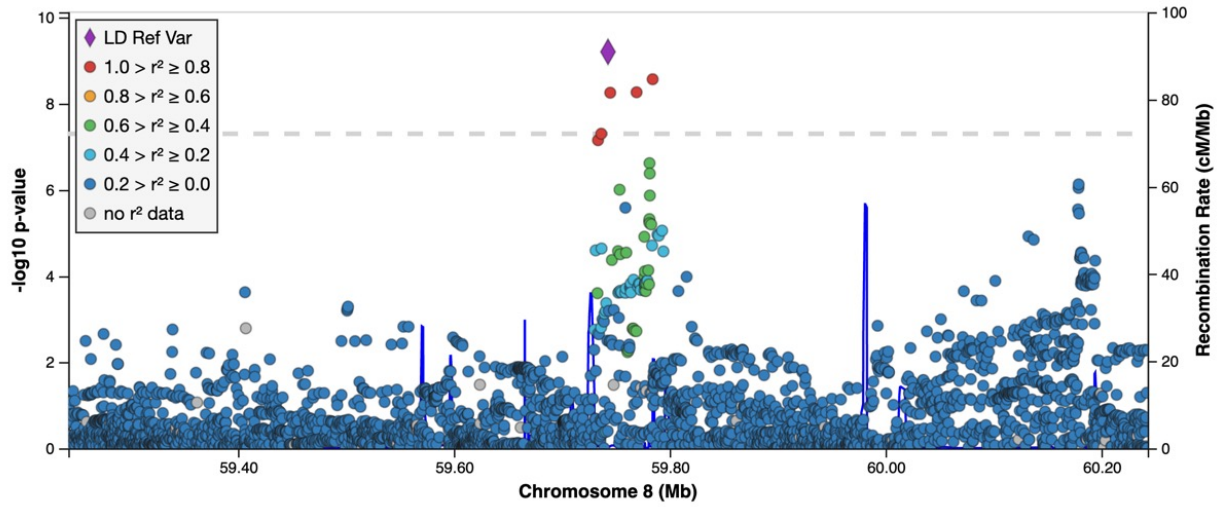
## LD reference population: EAS

8p21.2, rs60911071



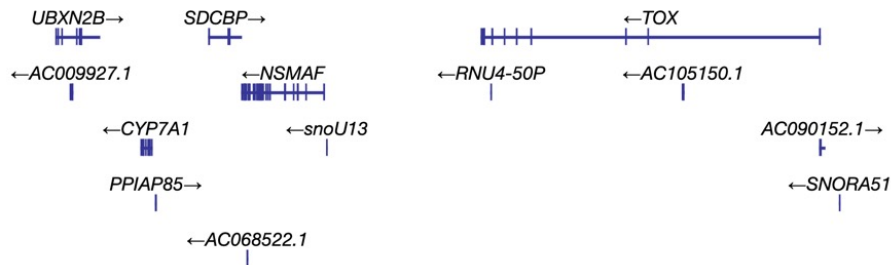
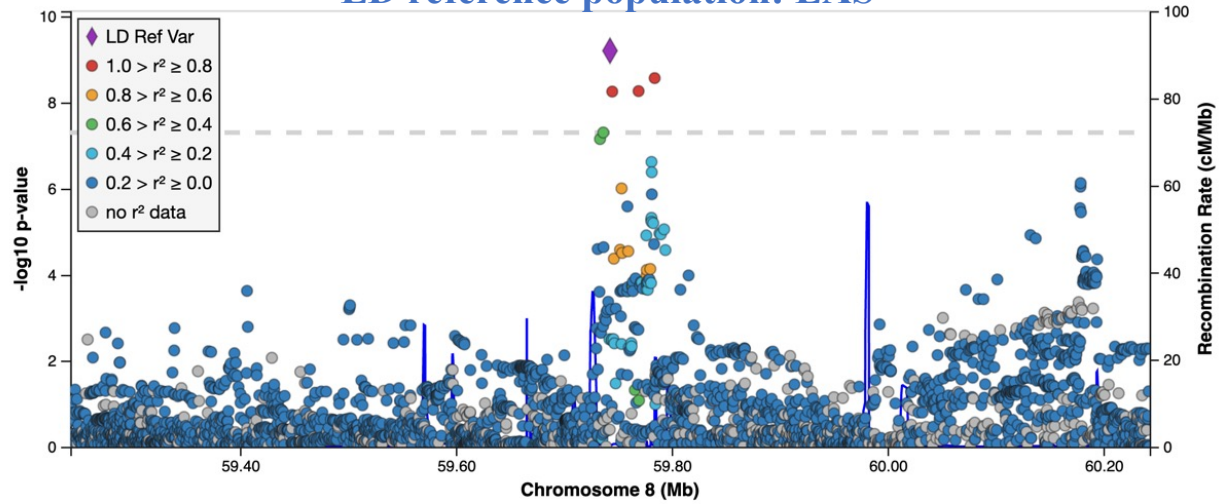
## LD reference population: EUR

8q12.1, rs826732



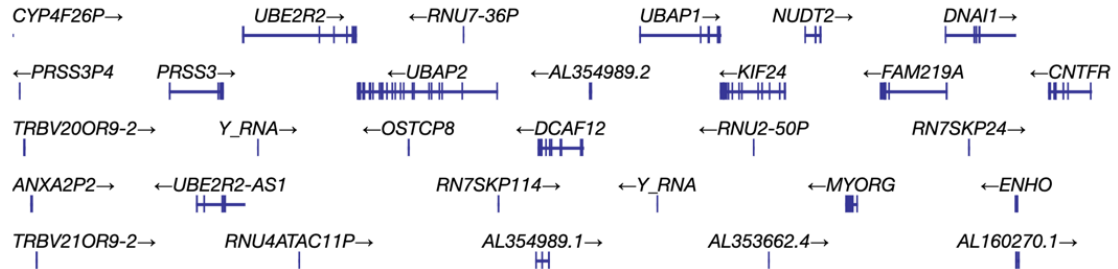
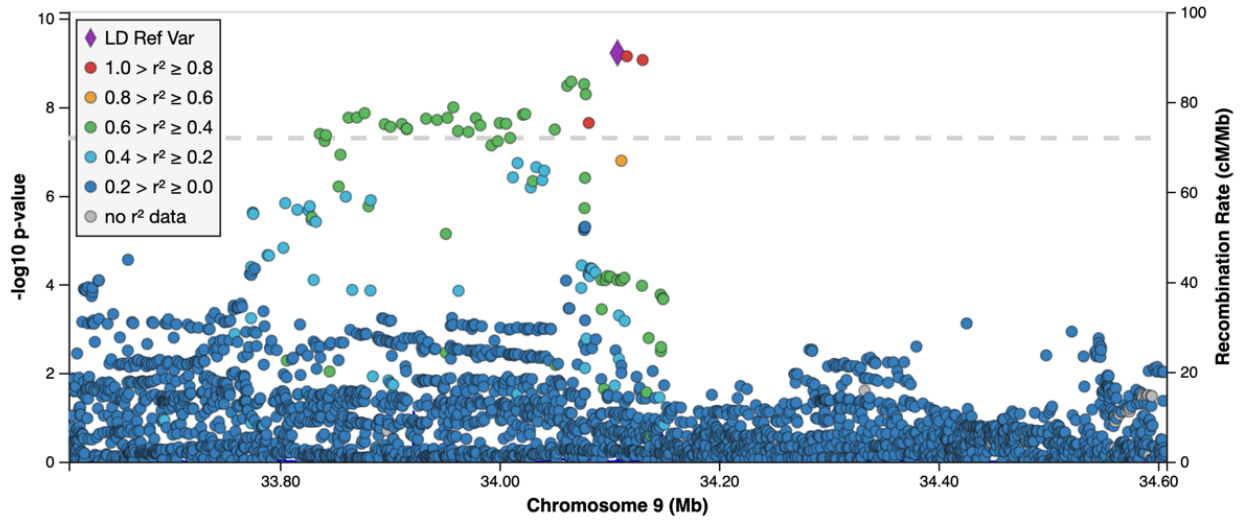
8q12.1, rs826732

## LD reference population: EAS



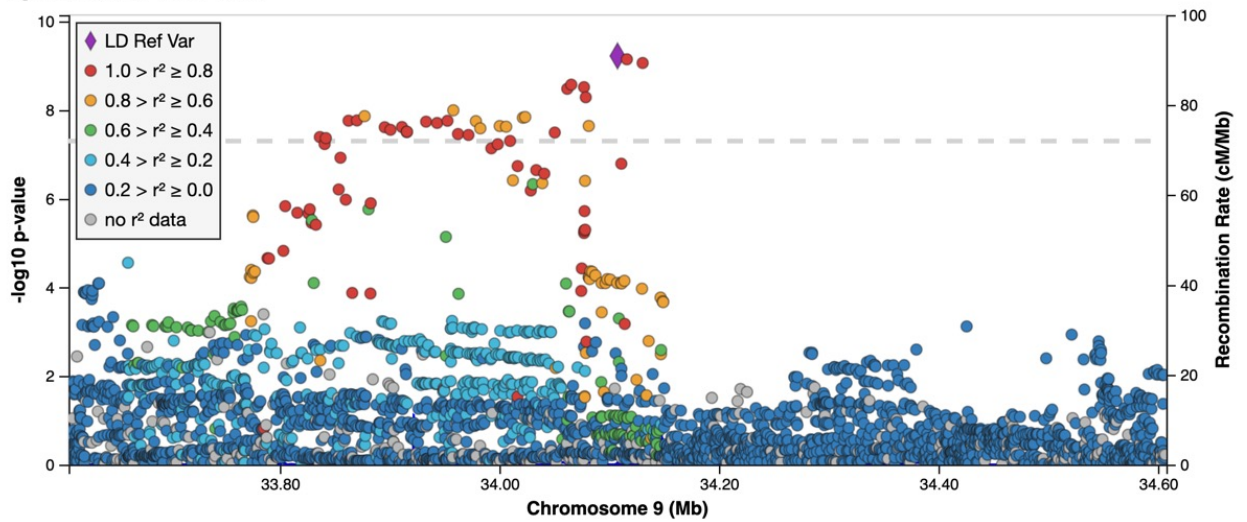
## LD reference population: EUR

9p13.3, rs11557154



## LD reference population: EAS

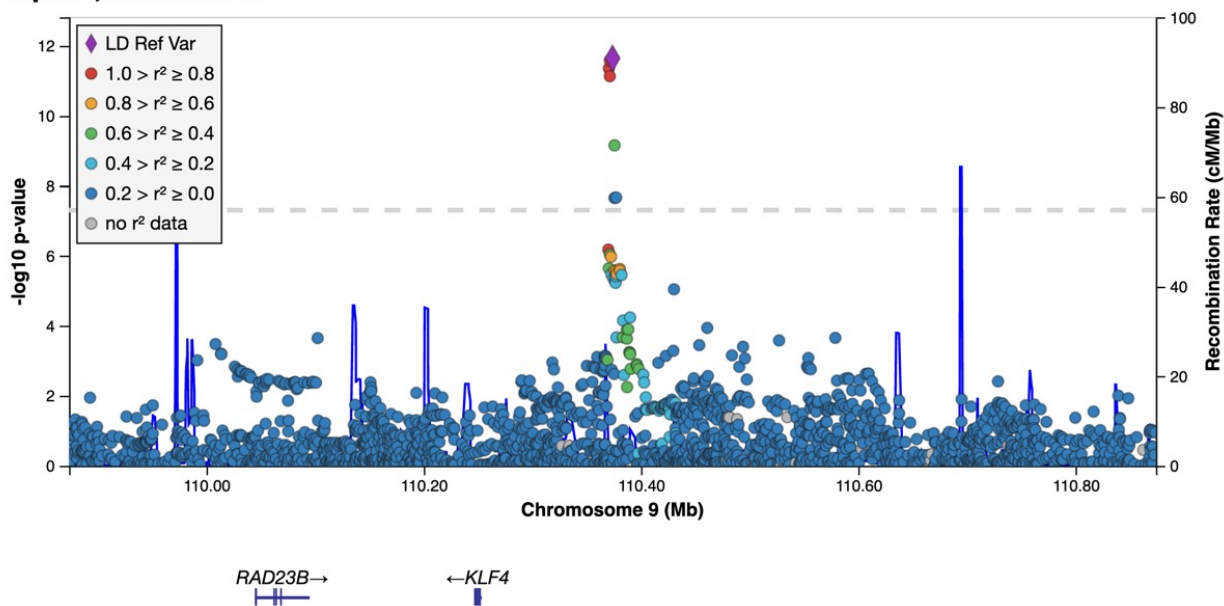
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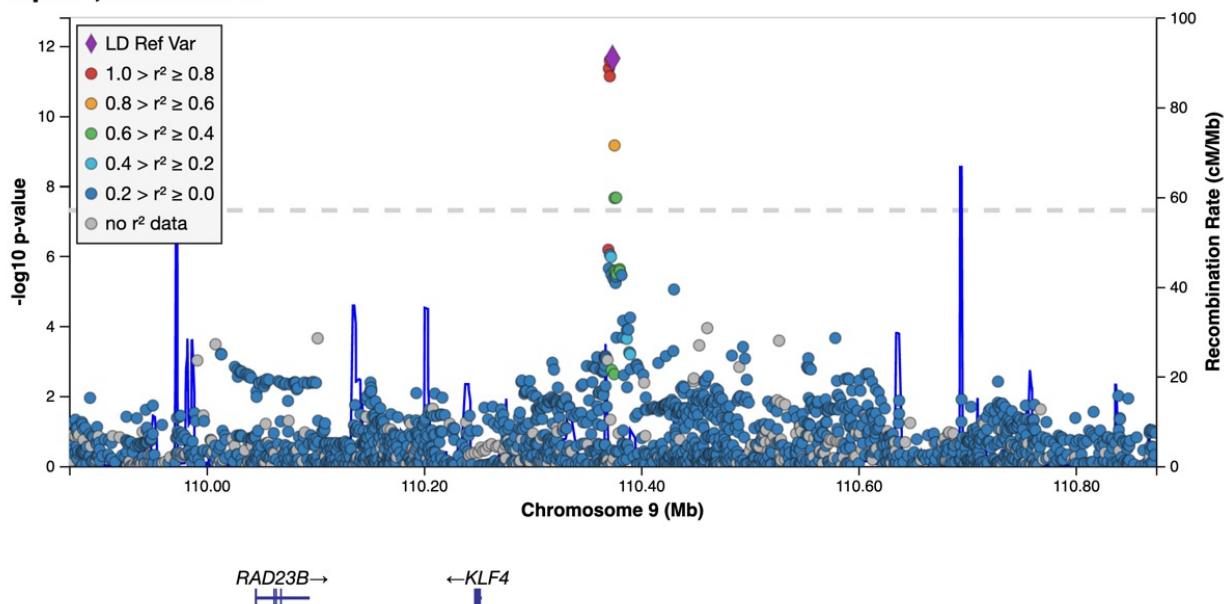
## LD reference population: EUR

9q31.2, rs10978941



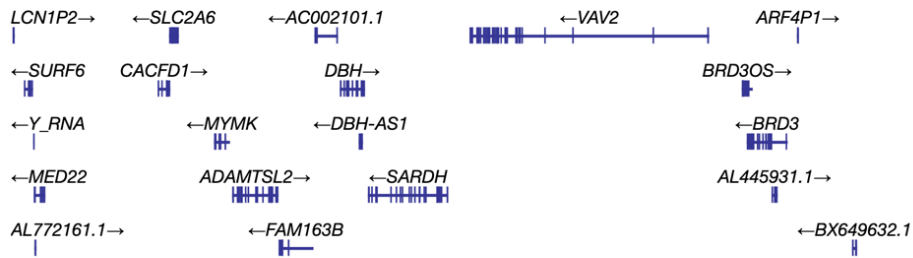
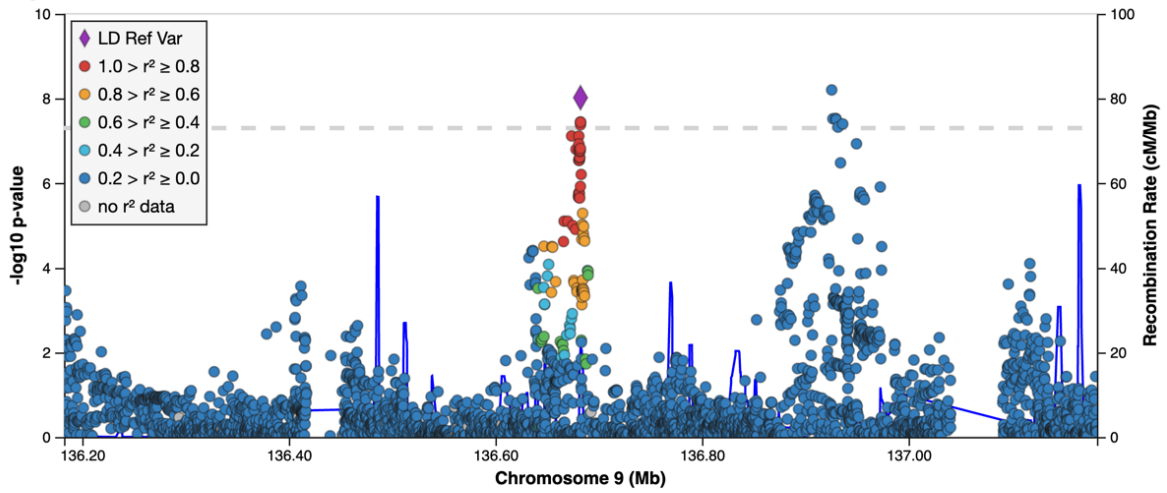
## LD reference population: EAS

9q31.2, rs10978941



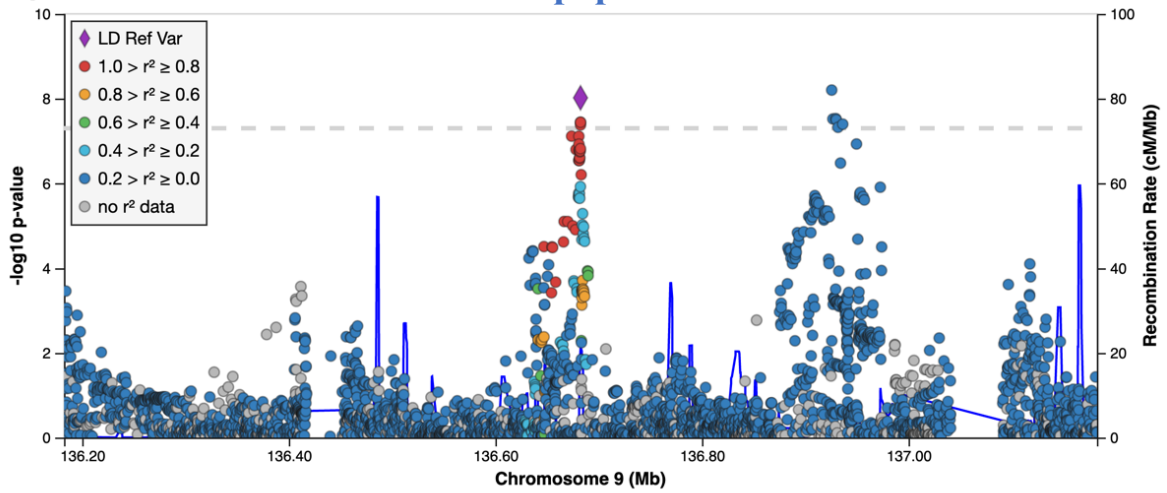
## LD reference population: EUR

9q34.2, rs7038489



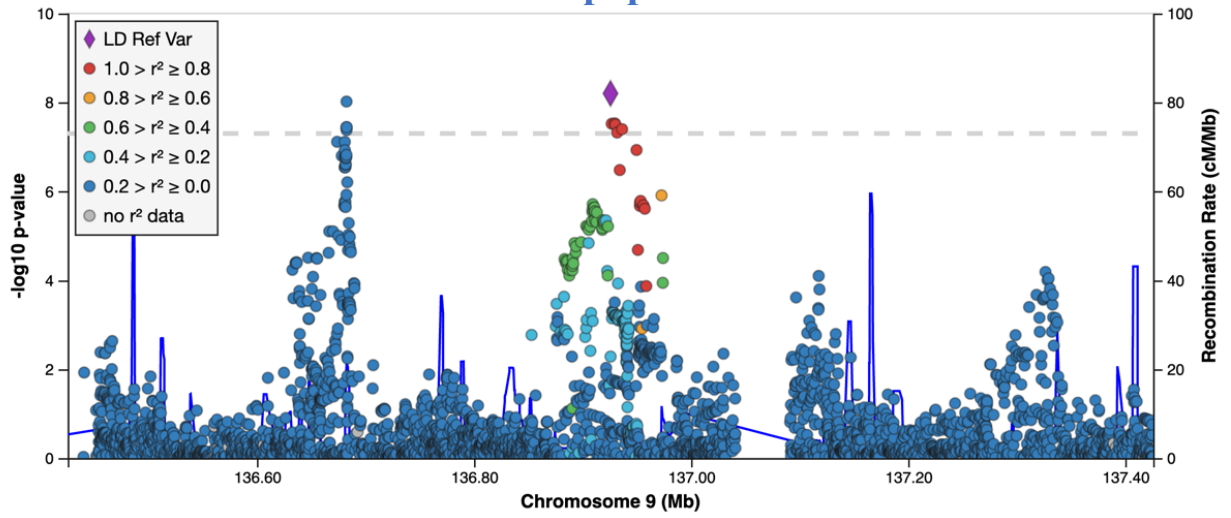
## LD reference population: EAS

9q34.2, rs7038489



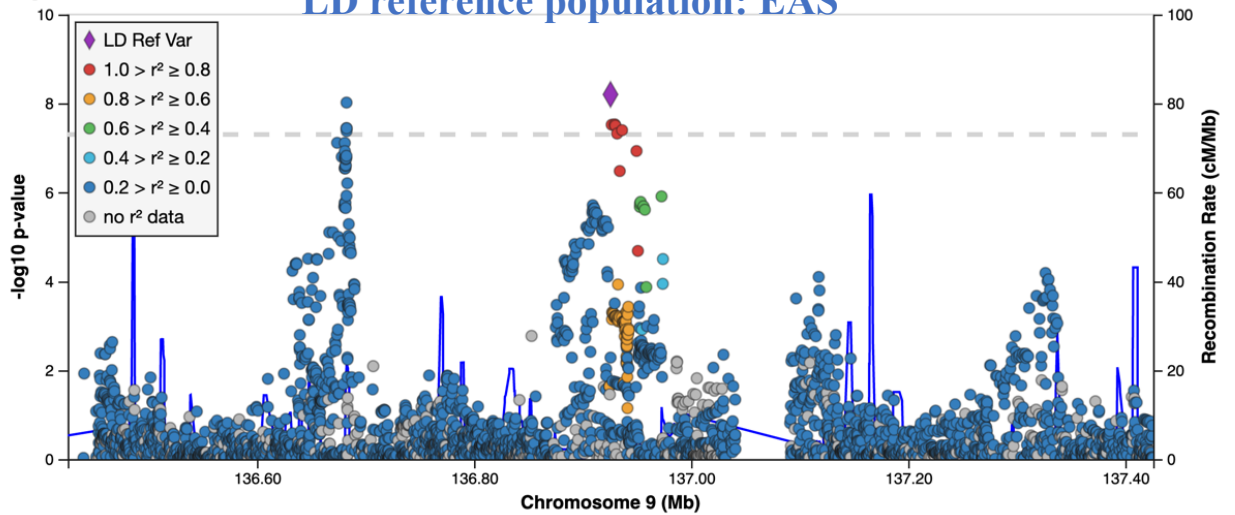
9q34.2, rs11789898

### LD reference population: EUR



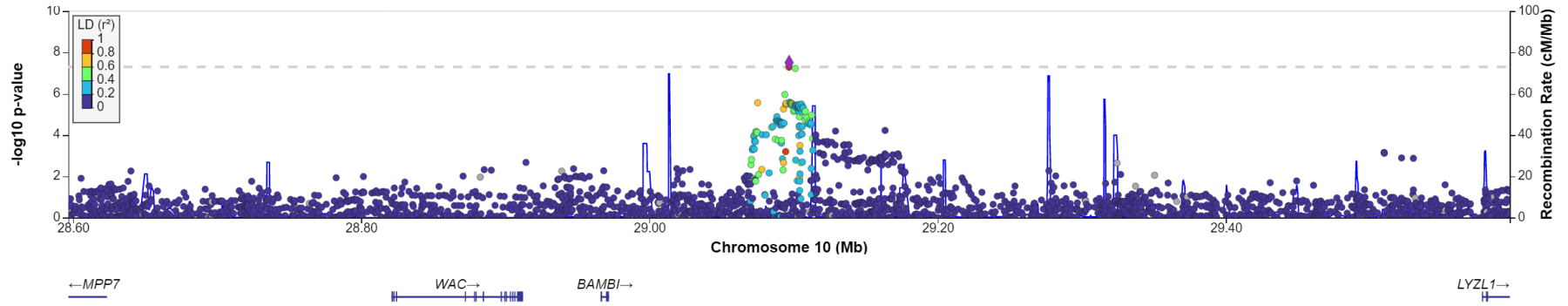
9q34.2, rs11789898

### LD reference population: EAS



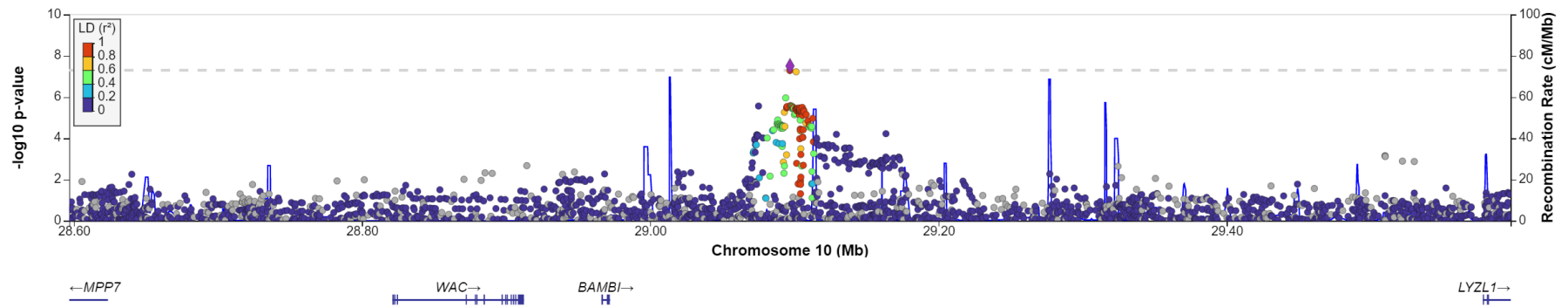
### LD reference population: EUR

10p12.1, rs1775910



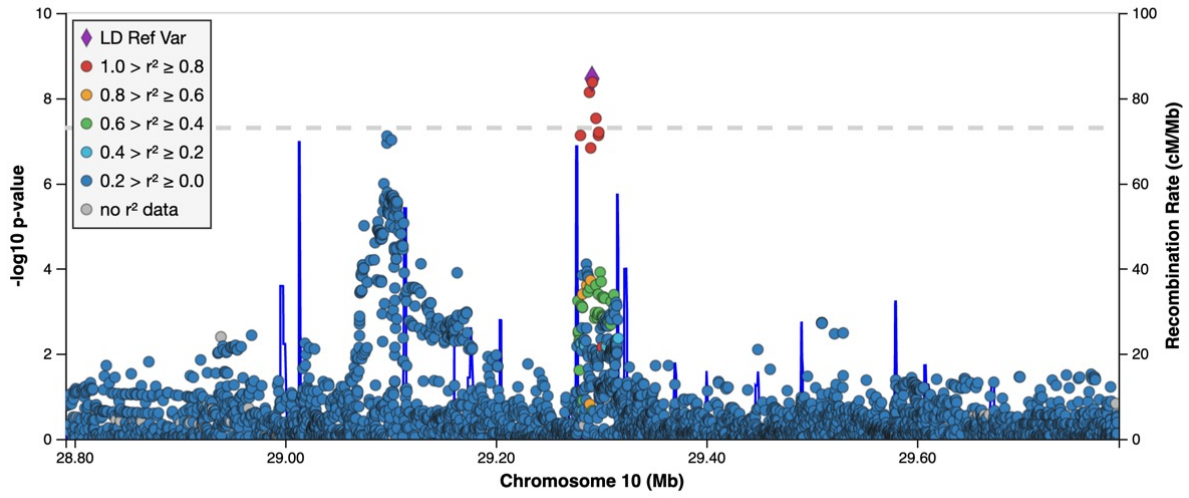
### LD reference population: EAS

10p12.1, rs1775910



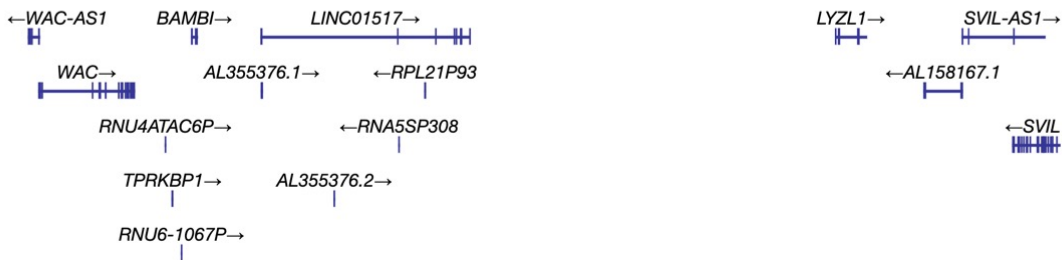
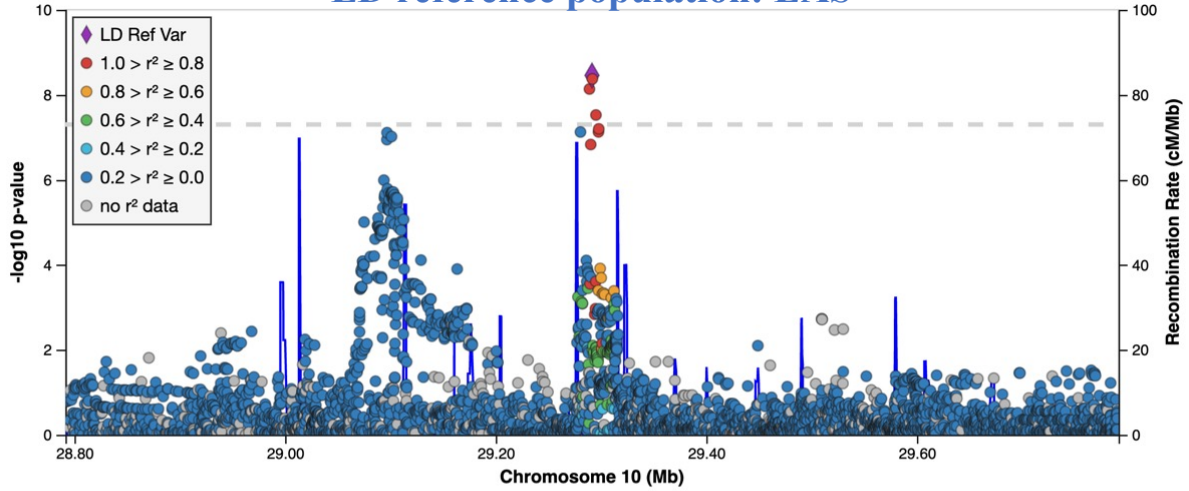
## LD reference population: EUR

10p12.1, rs1773860



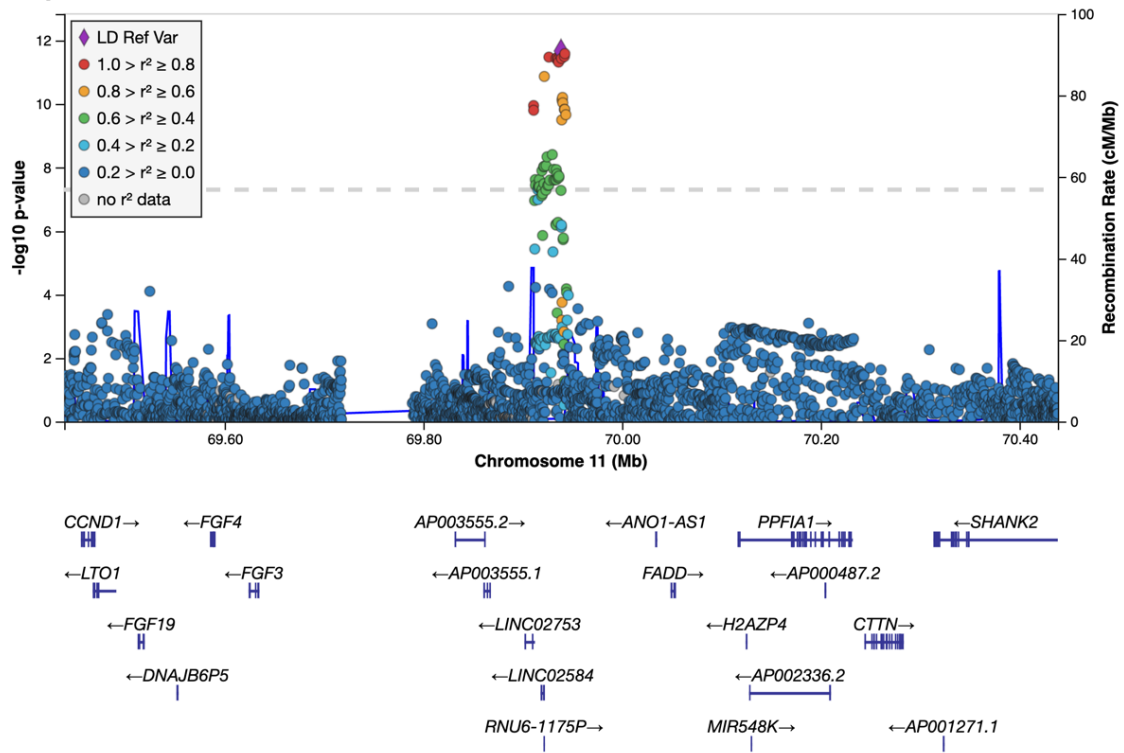
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## LD reference population: EAS



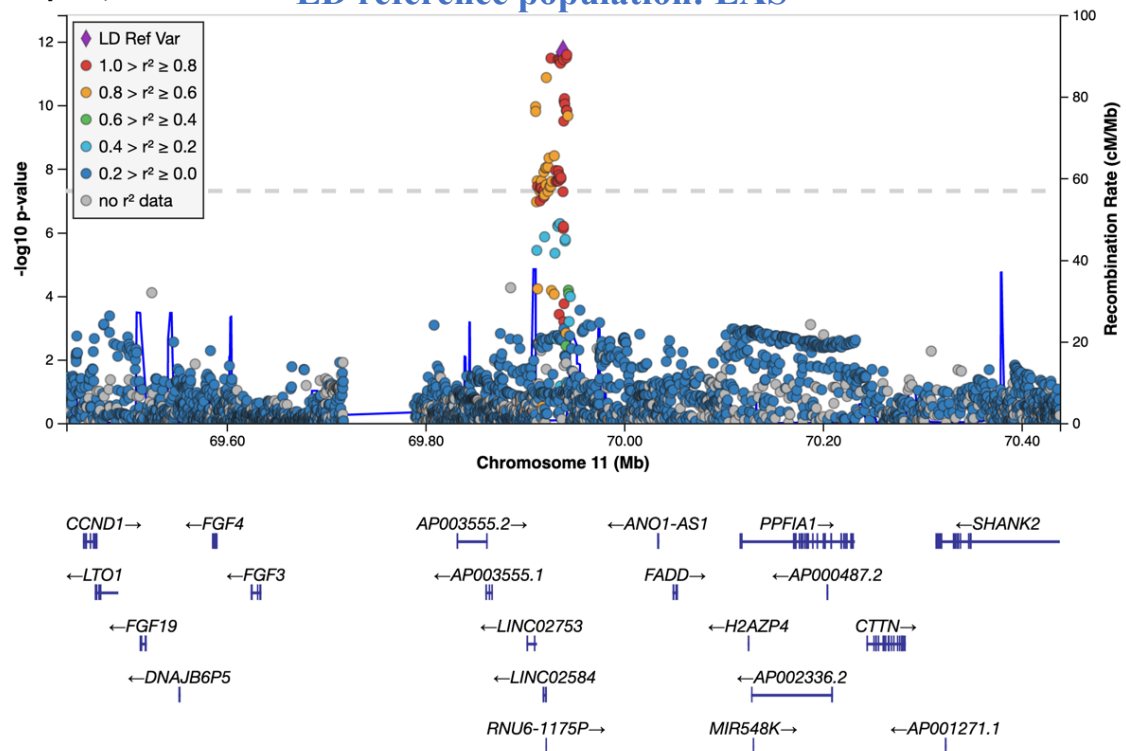
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### LD reference population: EUR



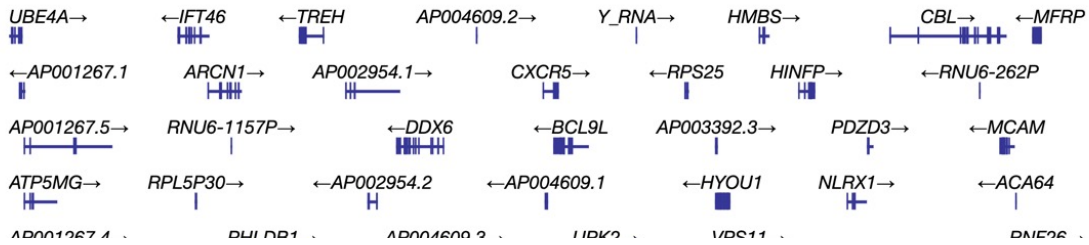
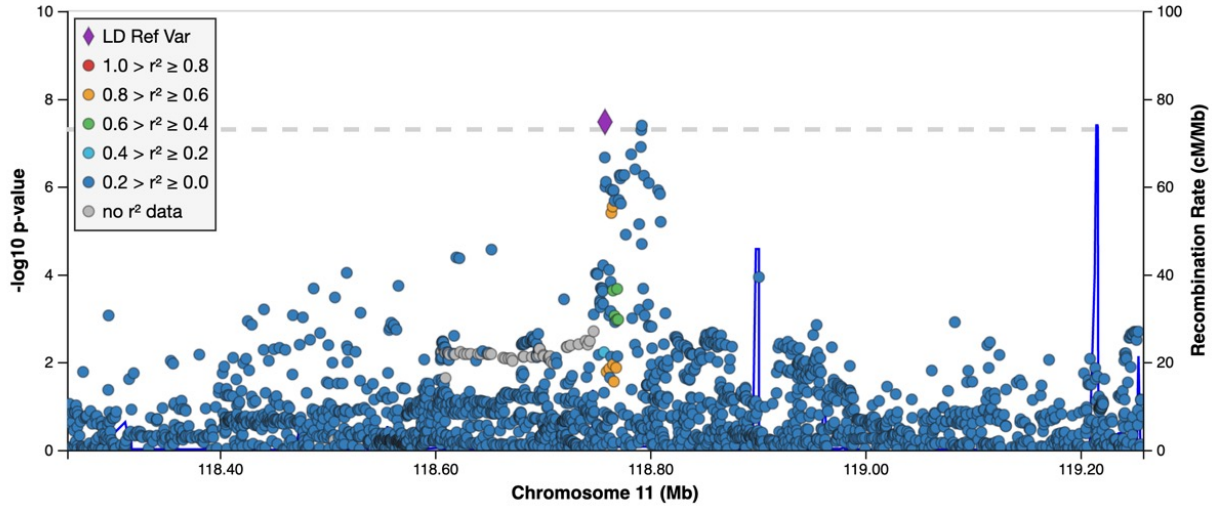
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### LD reference population: EAS



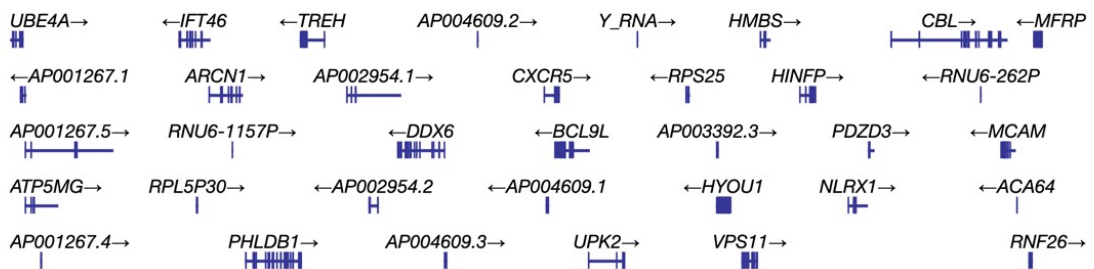
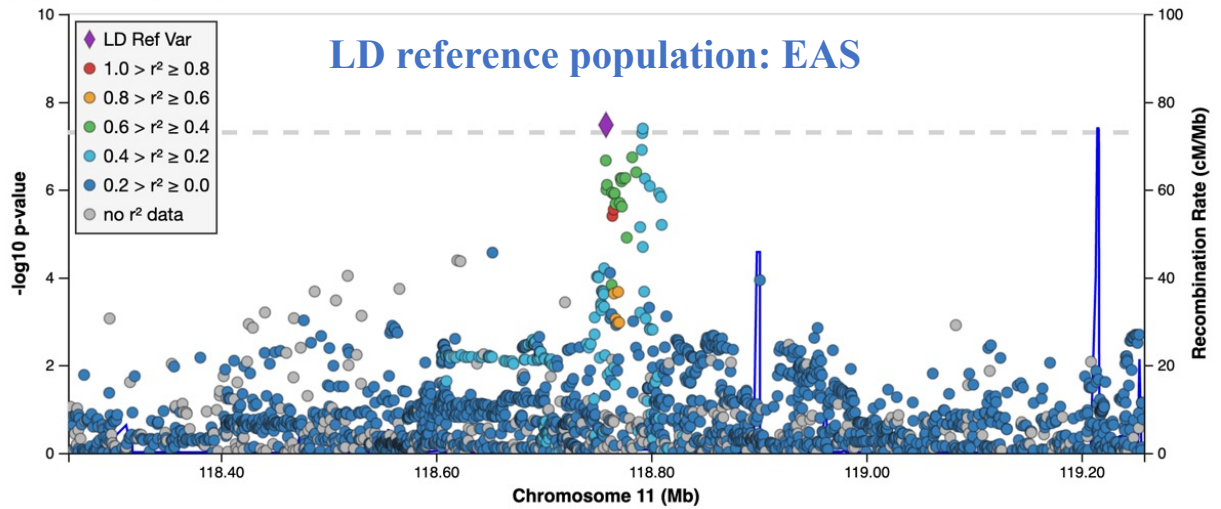
## LD reference population: EUR

11q23.3, rs497916



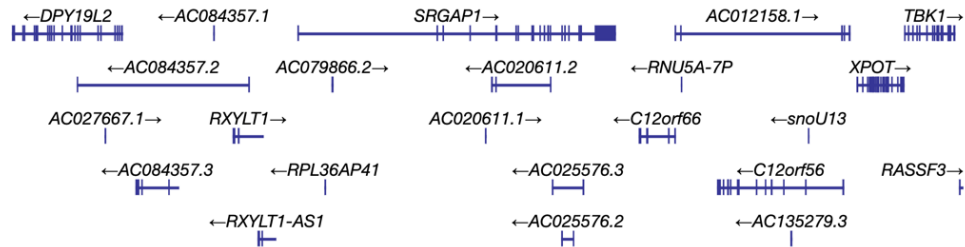
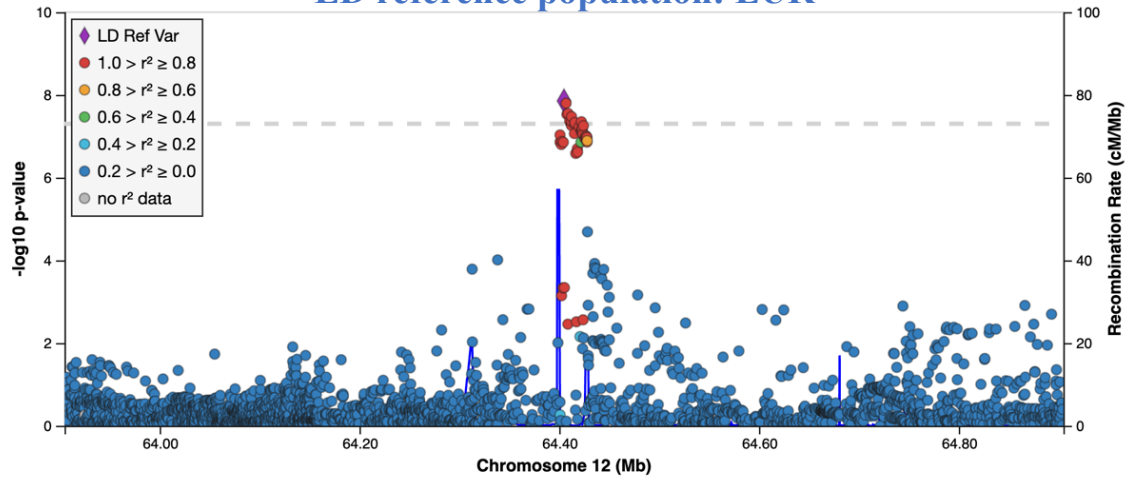
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## LD reference population: EAS



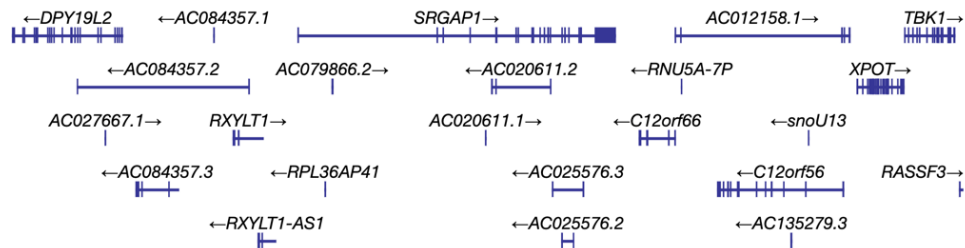
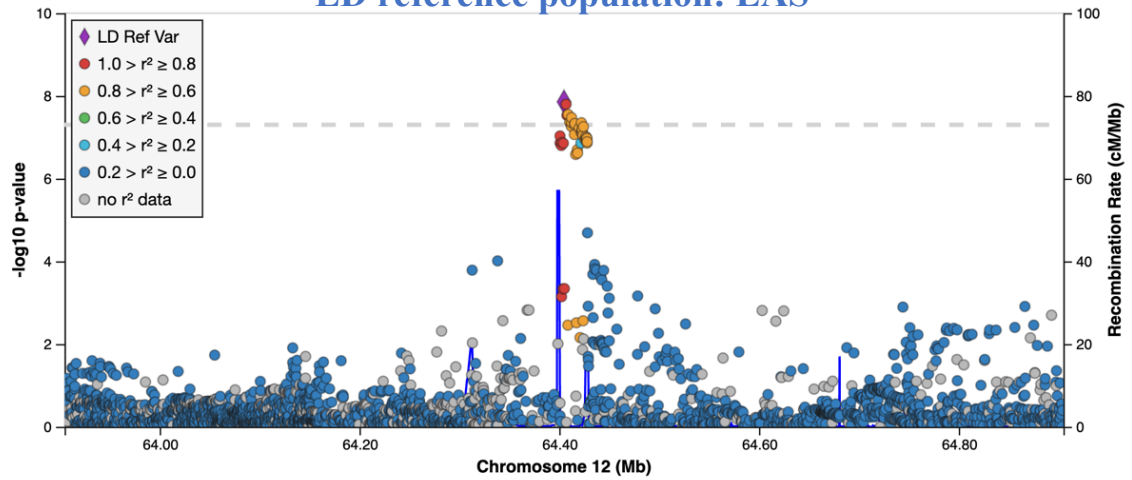
12q14.2, rs7297628

LD reference population: EUR



12q14.2, rs7297628

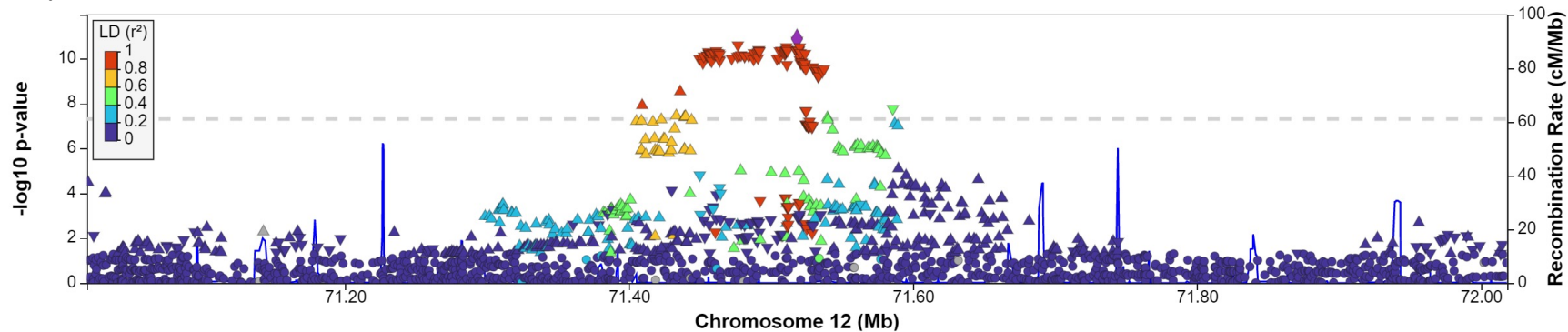
LD reference population: EAS





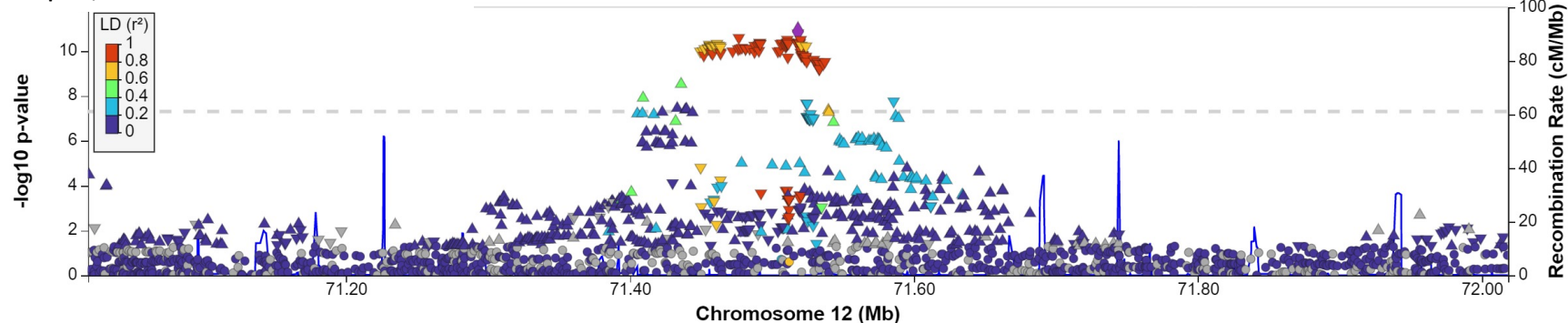
LD reference population: EUR

12q21.1, rs11178634



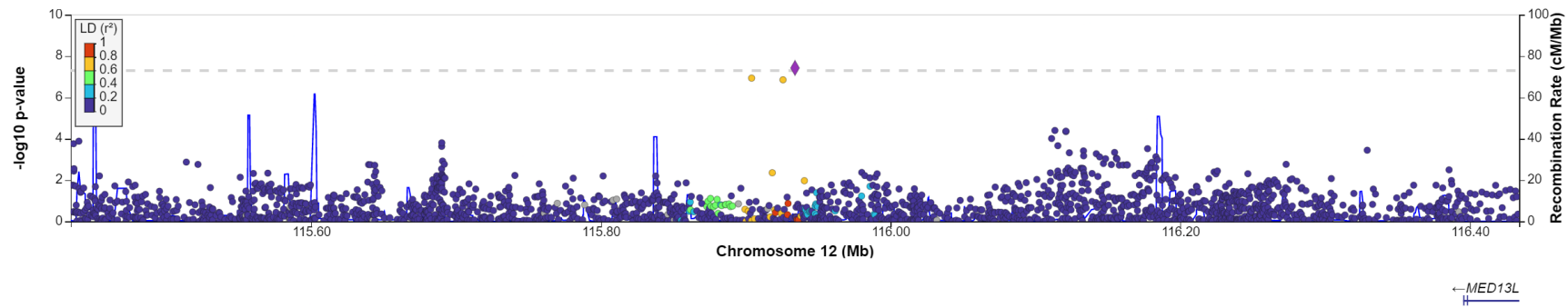
LD reference population: EAS

12q21.1, rs11178634



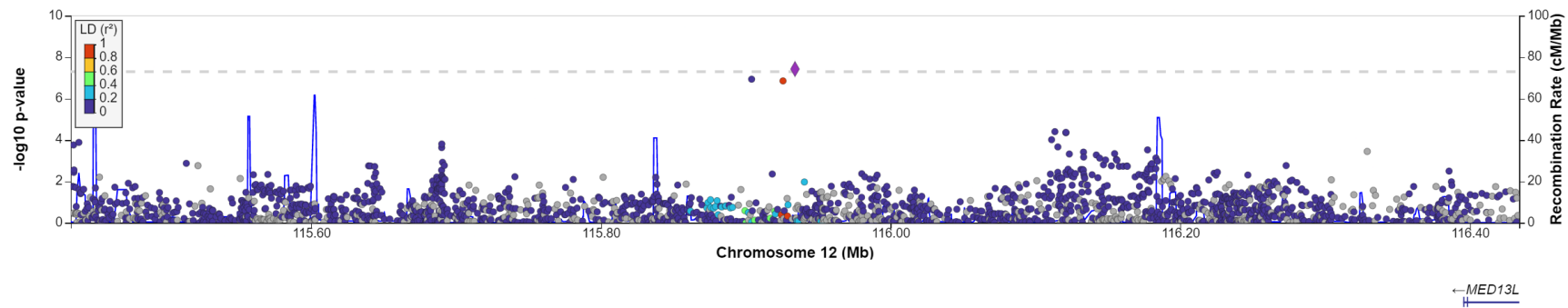
### LD reference population: EUR

12q24.1, rs7299936



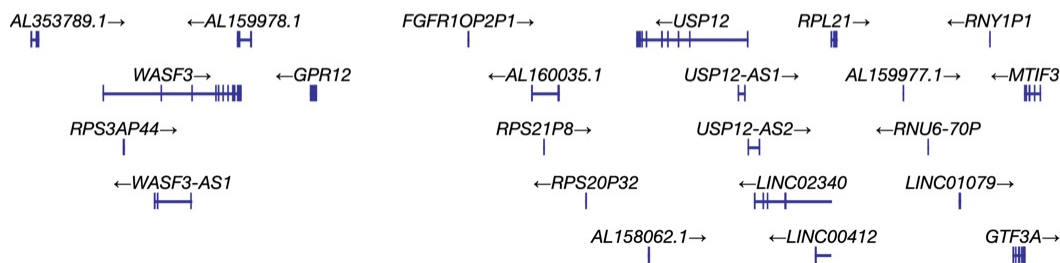
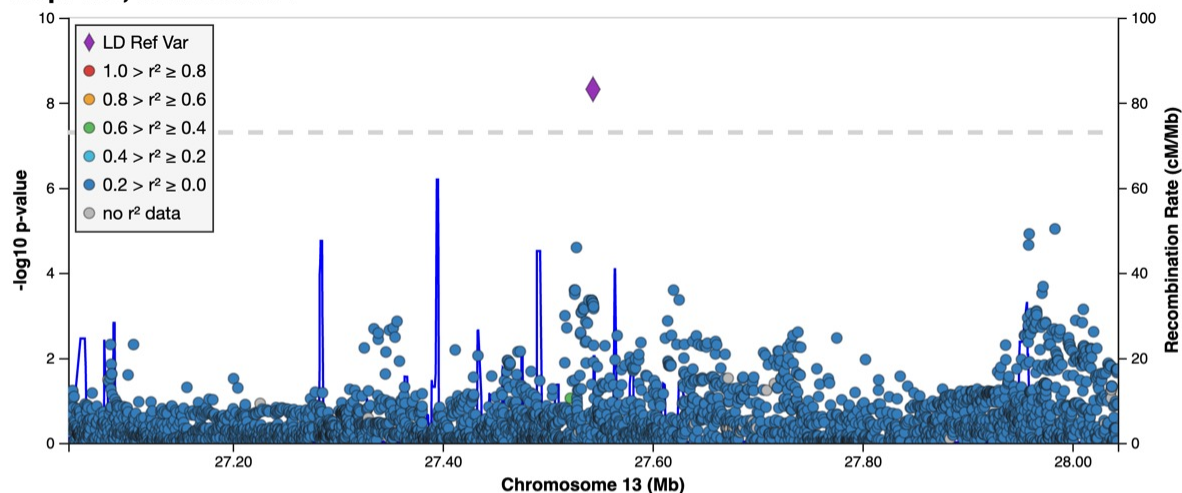
### LD reference population: EAS

12q24.1, rs7299936



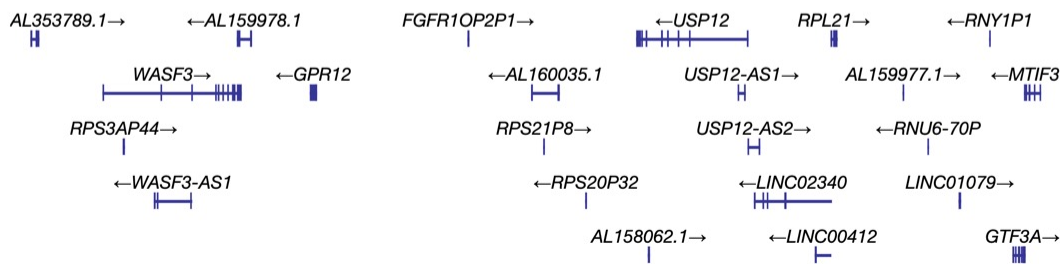
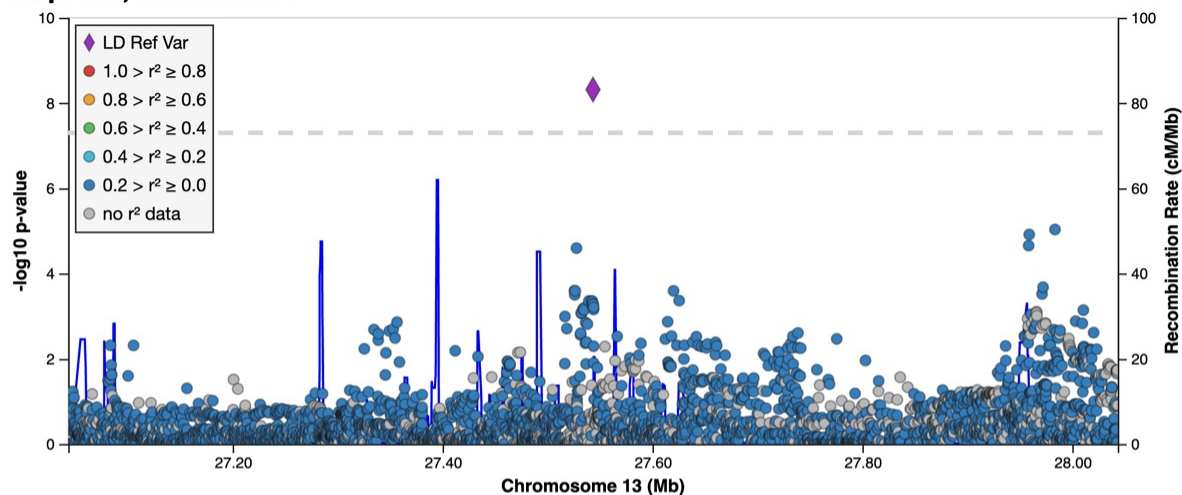
## LD reference population: EUR

13q12.13, rs116964464



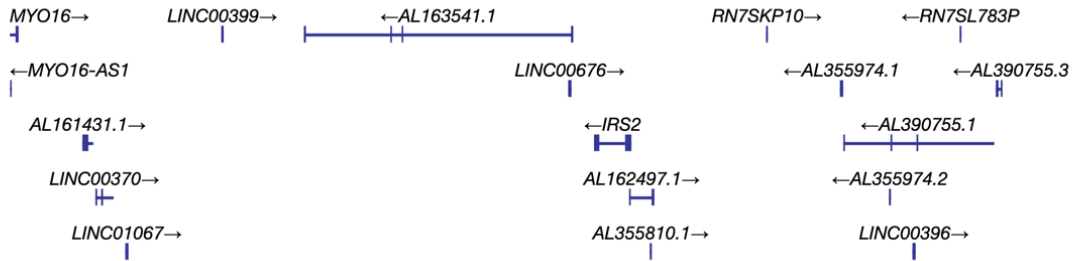
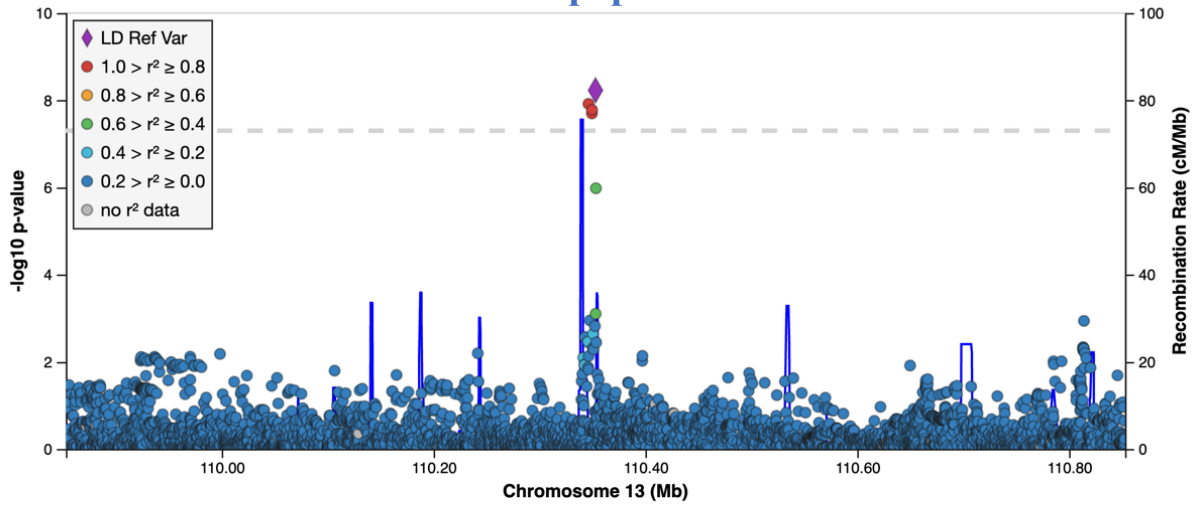
## LD reference population: EAS

13q12.13, rs116964464



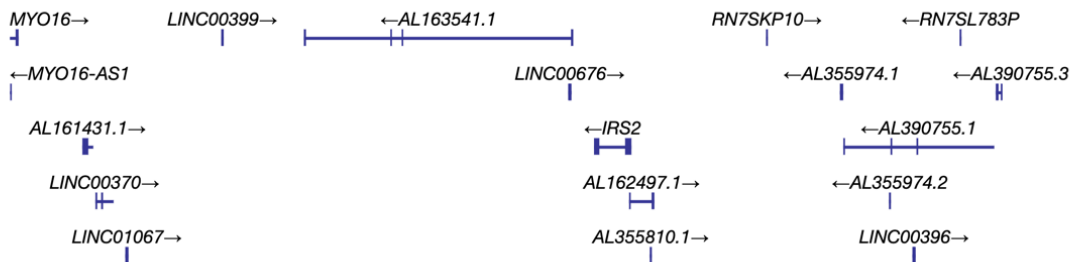
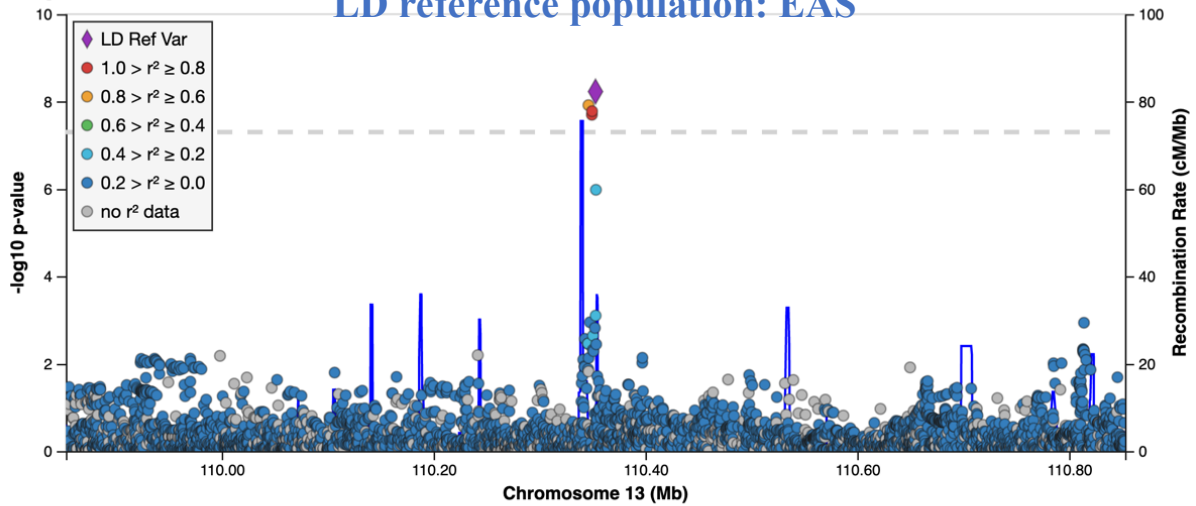
13q34, rs1078563

### LD reference population: EUR



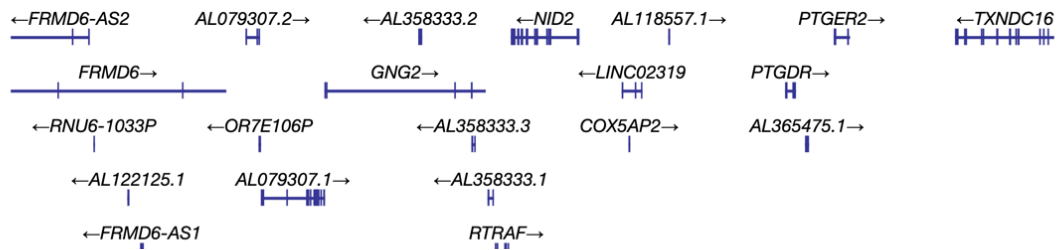
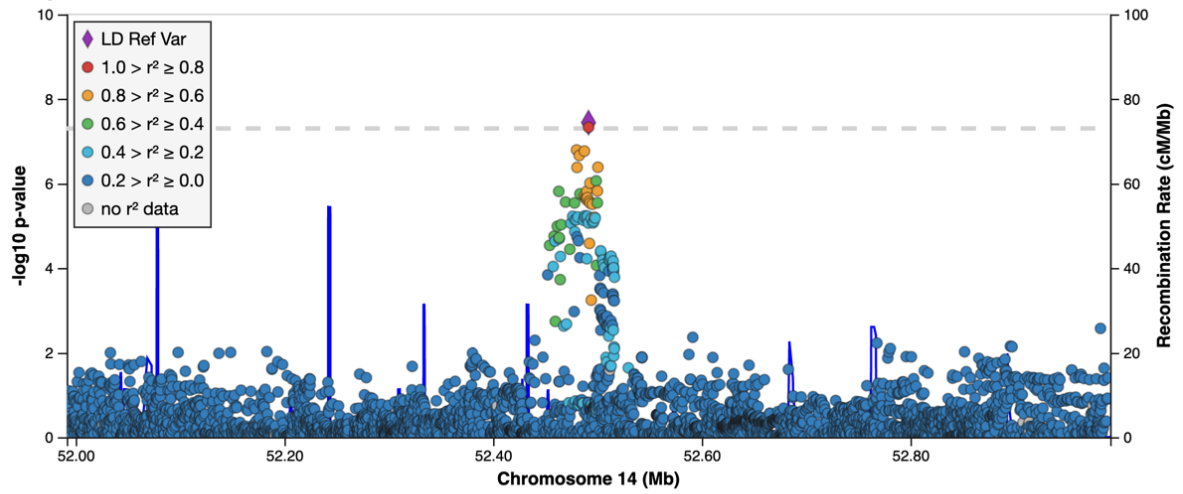
13q34, rs1078563

### LD reference population: EAS



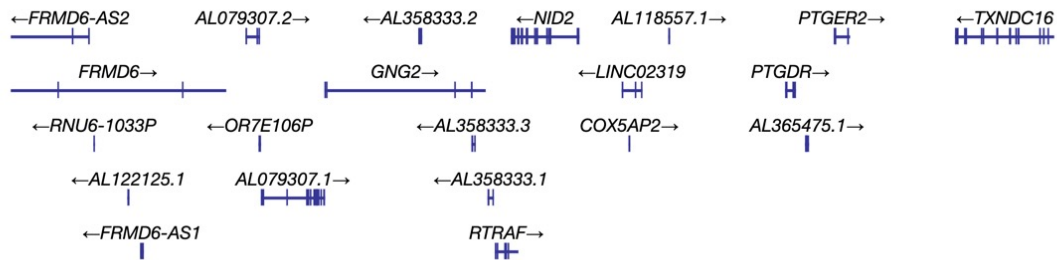
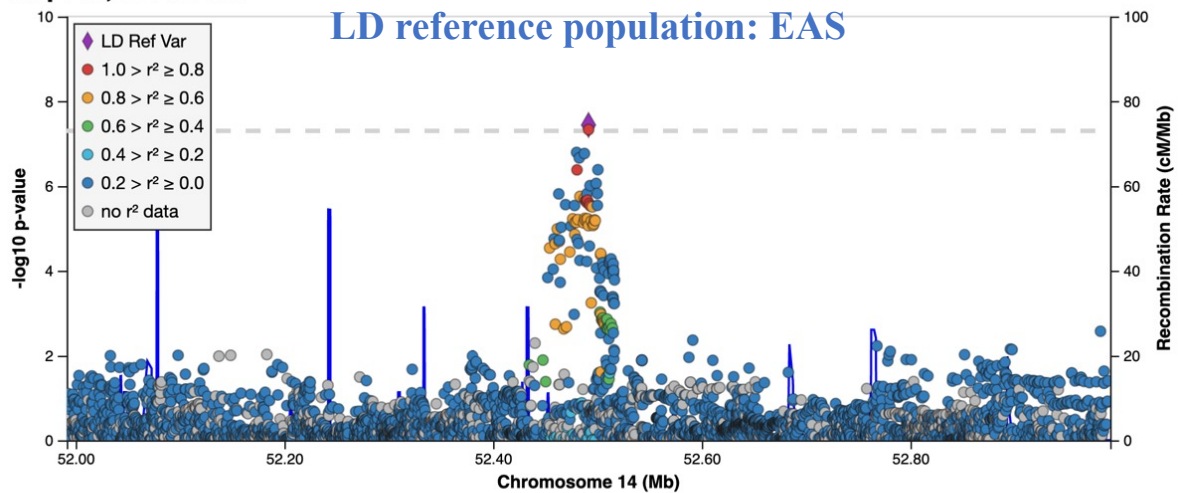
## LD reference population: EUR

14q22.1, rs1497077



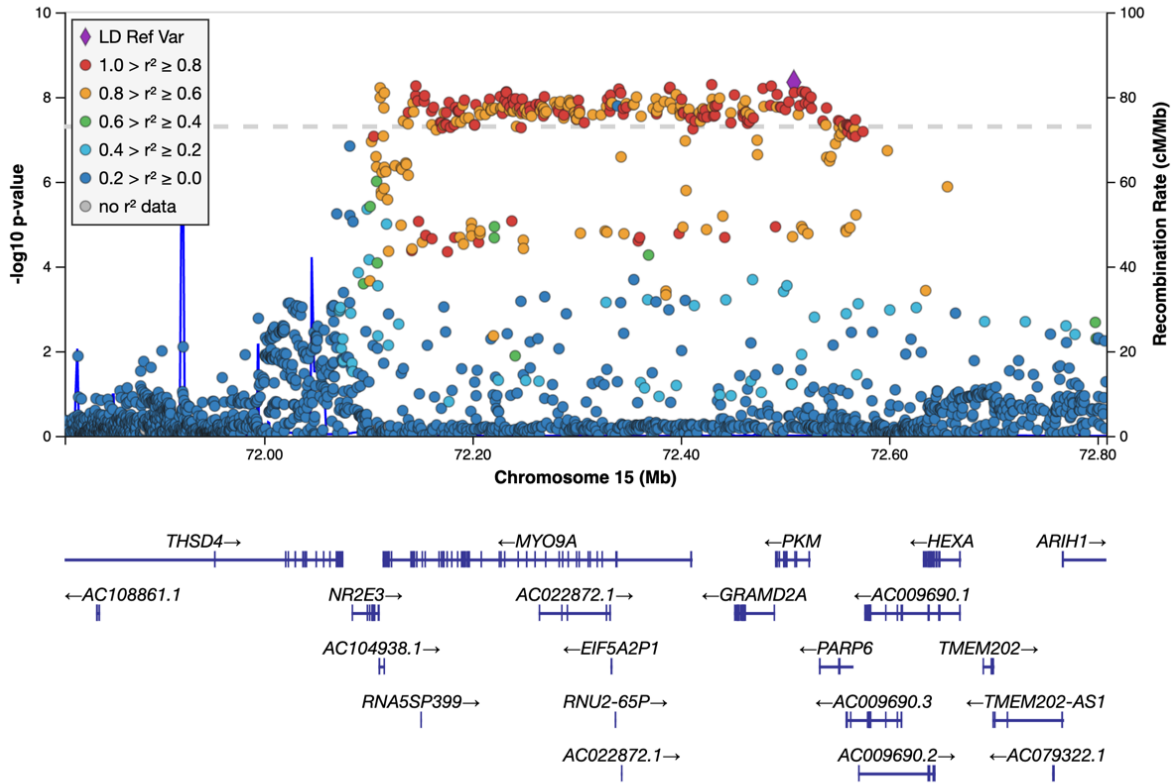
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## LD reference population: EAS



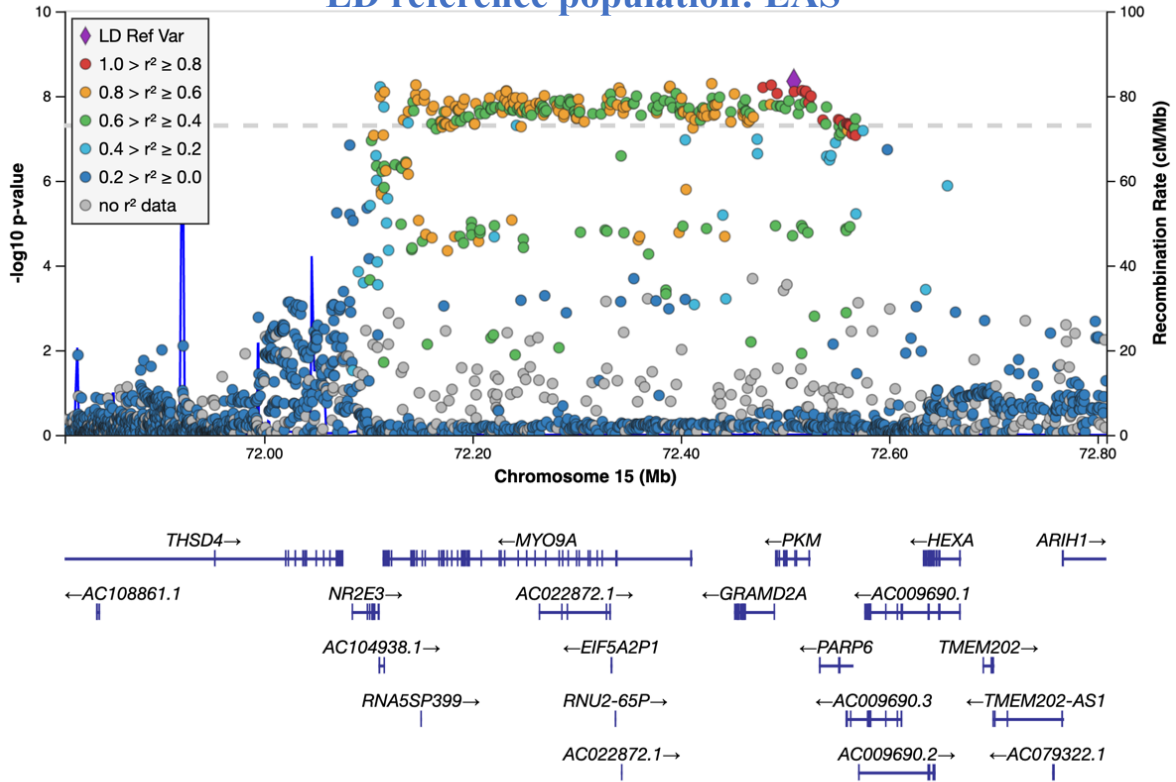
15q23, rs8031386

### LD reference population: EUR



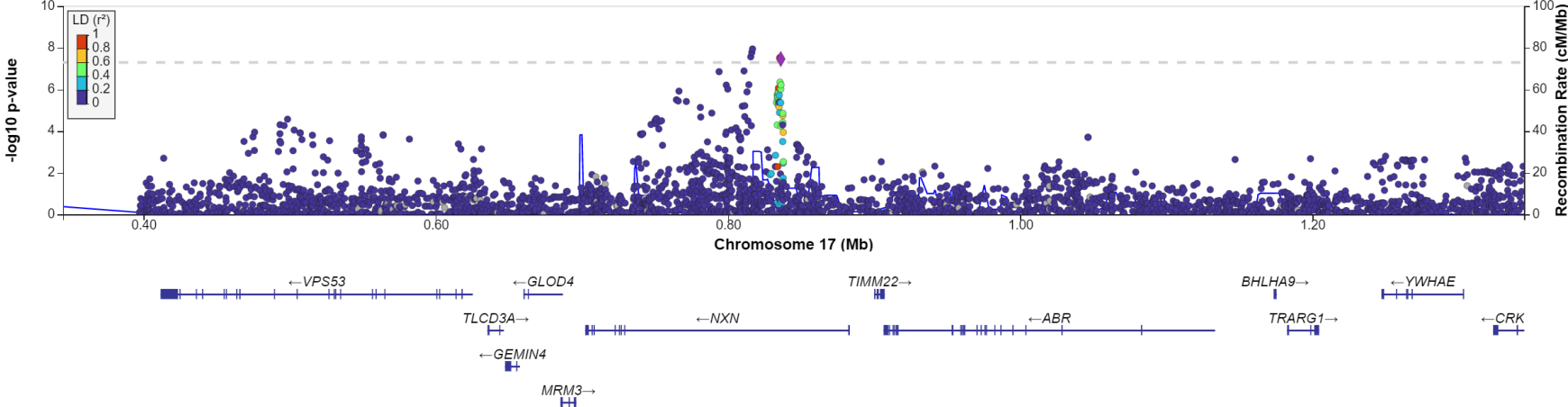
15q23, rs8031386

### LD reference population: EAS



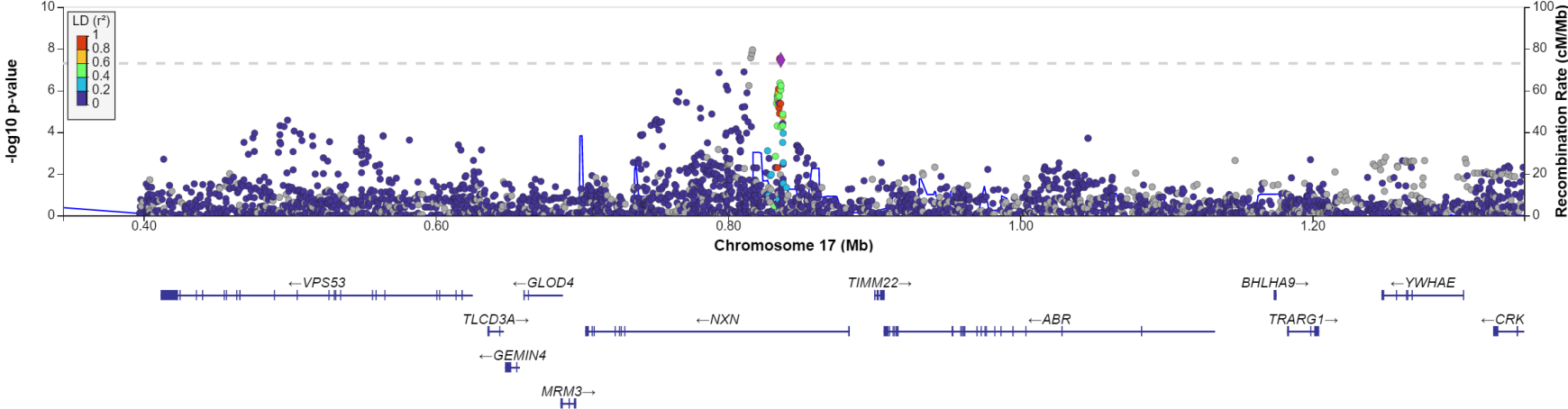
LD reference population: EUR

17p13.3, rs11247566



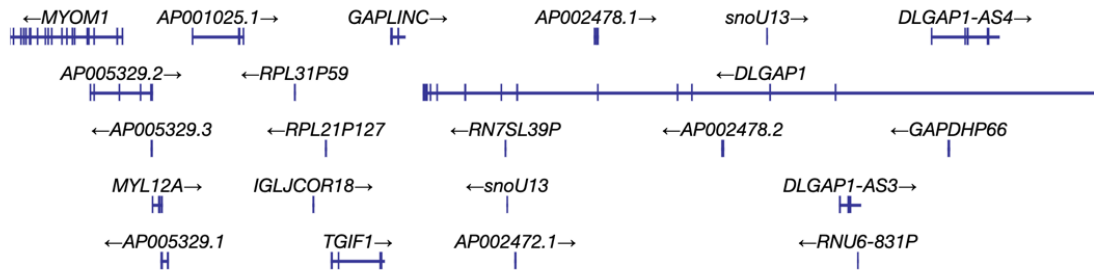
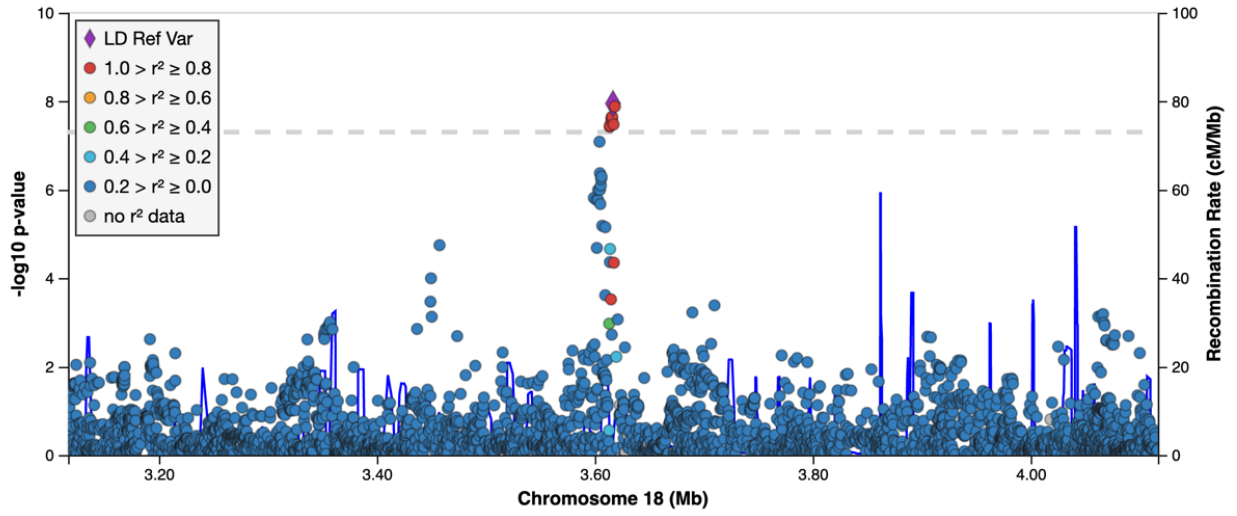
LD reference population: EAS

17p13.3, rs11247566



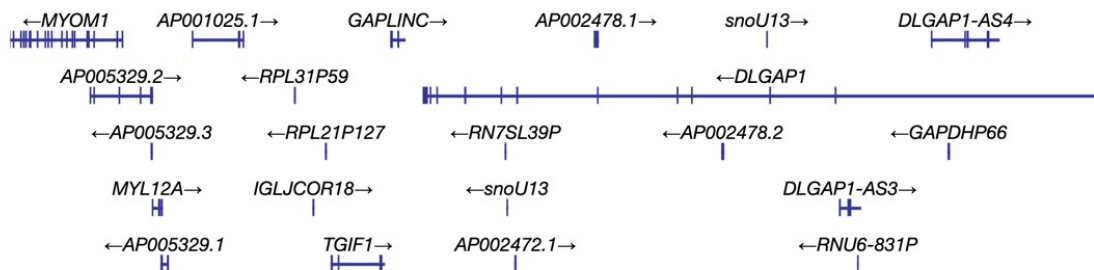
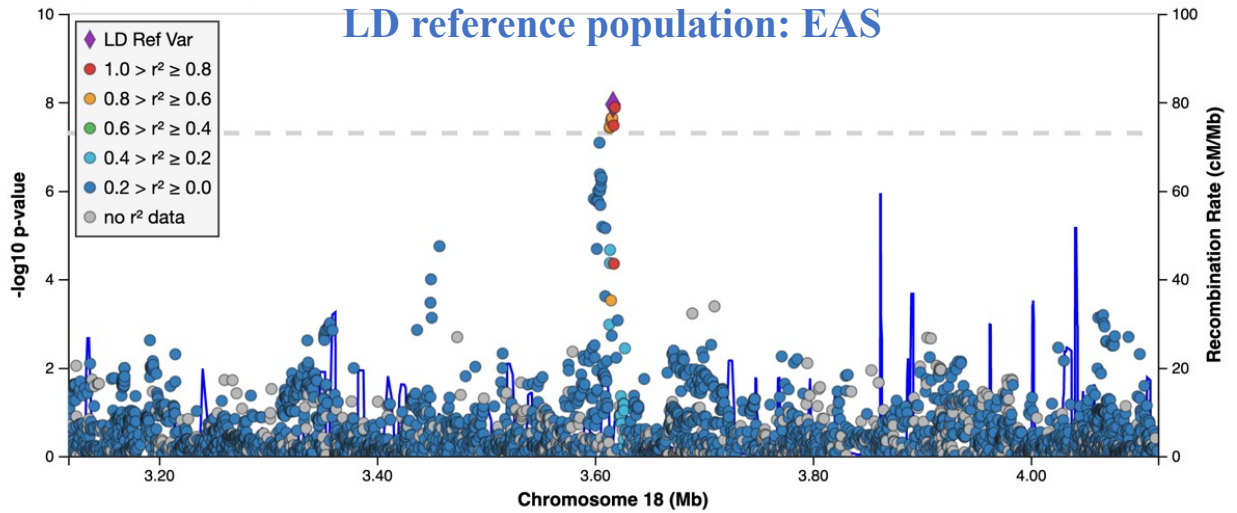
18p11.31, rs1791373

### LD reference population: EUR



18p11.31, rs1791373

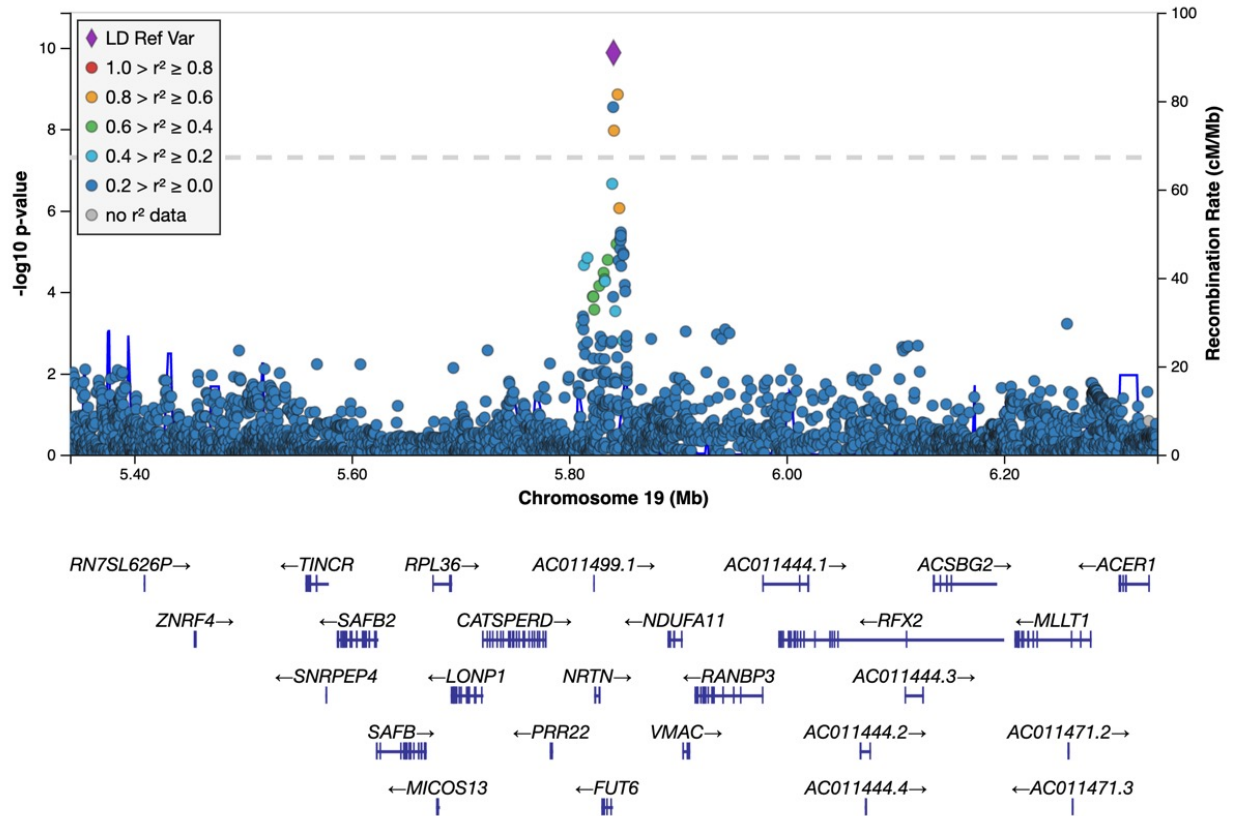
### LD reference population: EAS





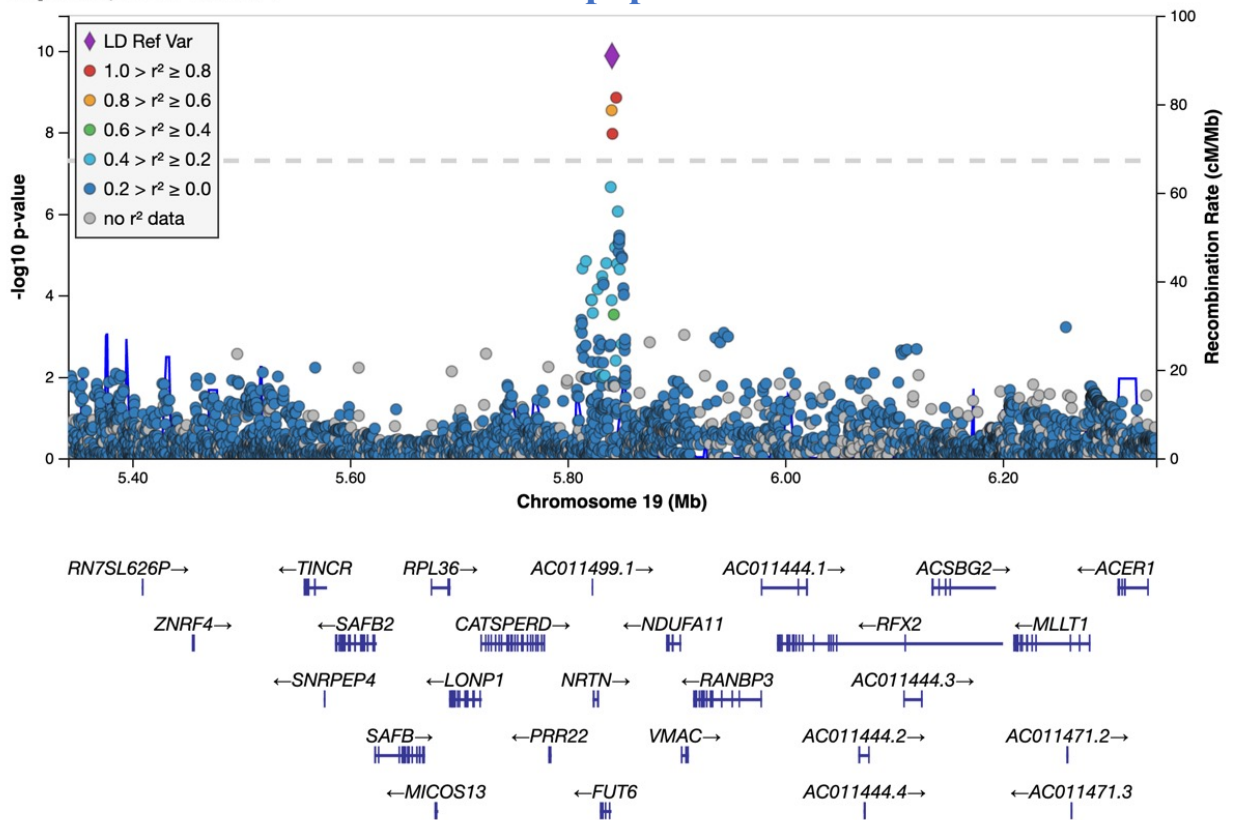
## LD reference population: EUR

19p13.3, rs10409772



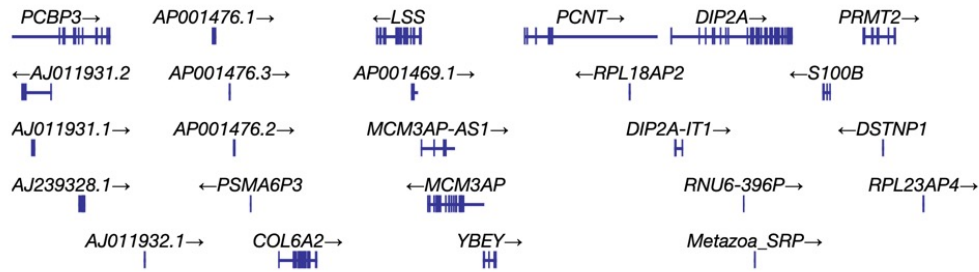
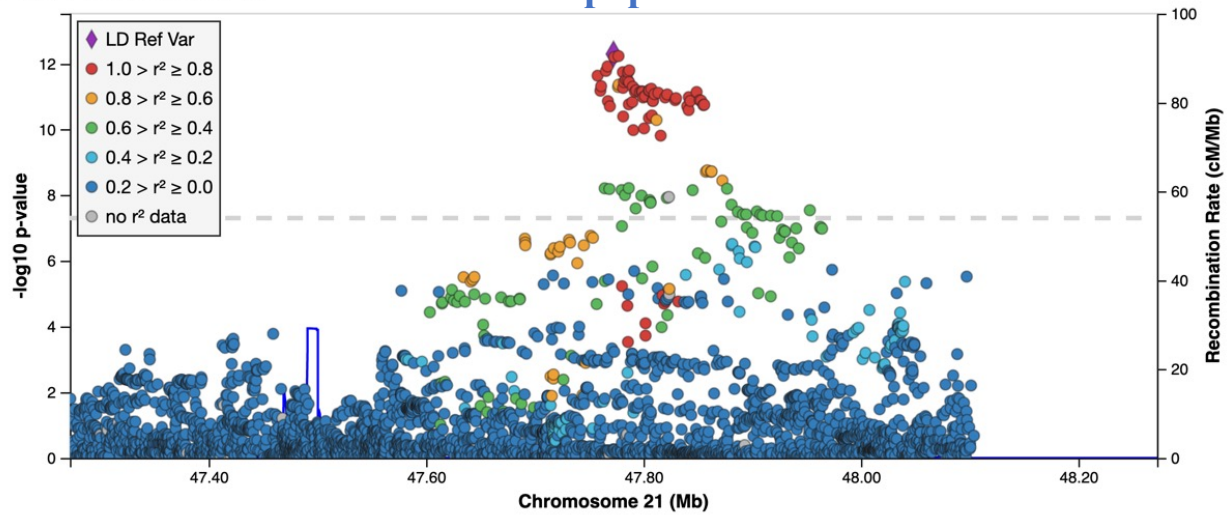
19p13.3, rs10409772

## LD reference population: EAS



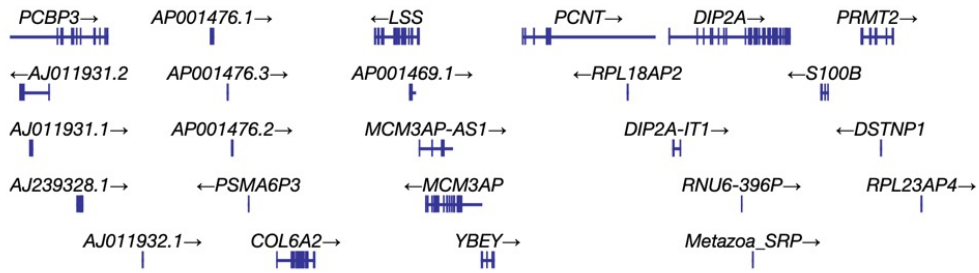
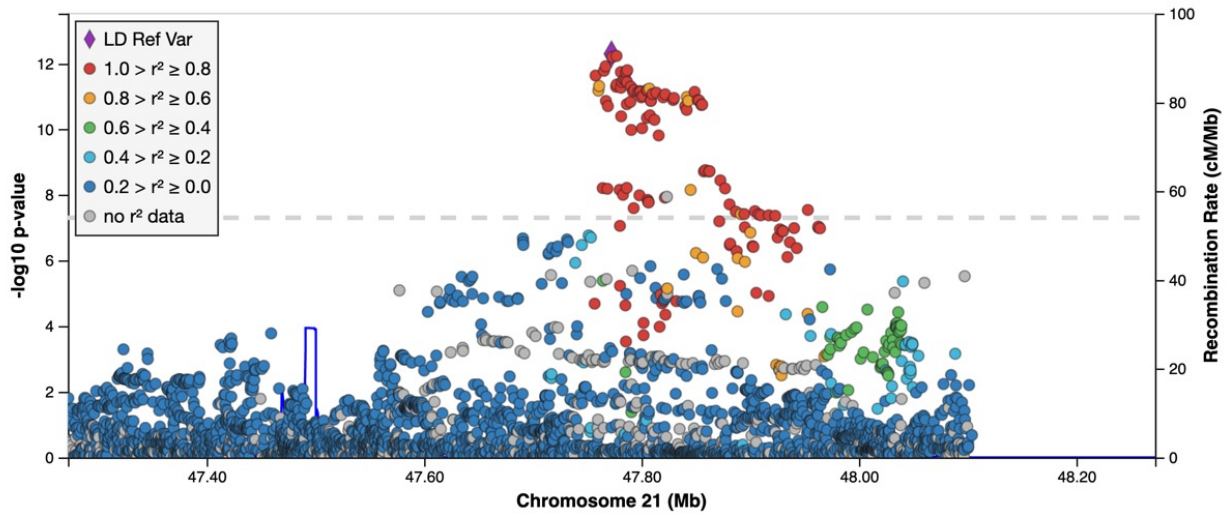
21q22.3, rs9983528

LD reference population: EUR



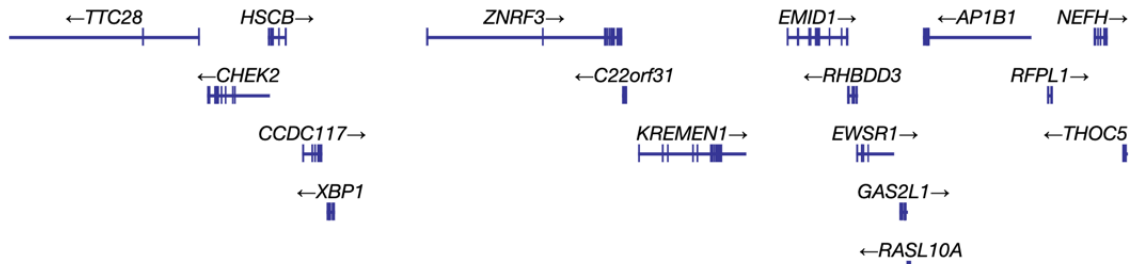
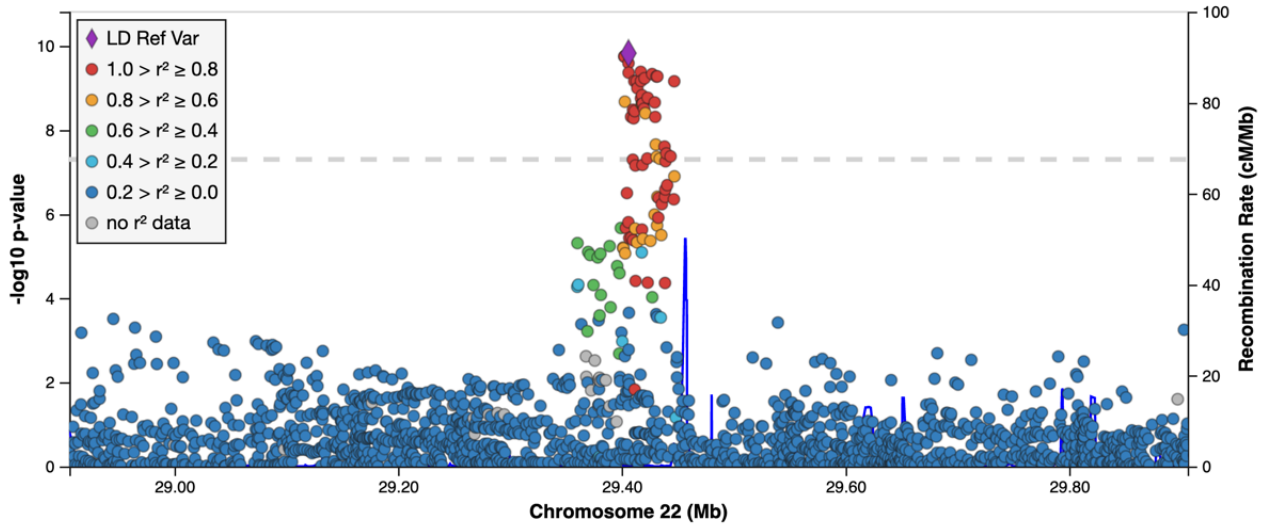
21q22.3, rs9983528

LD reference population: EAS



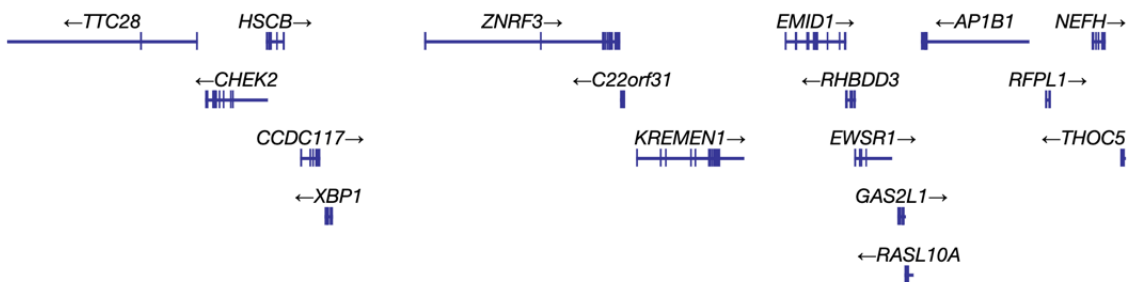
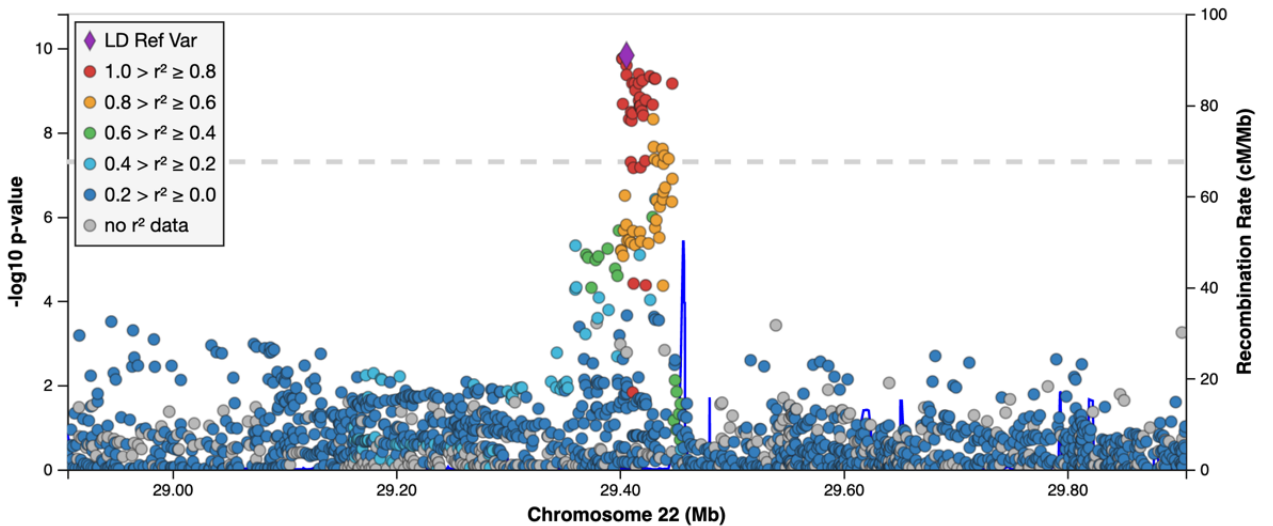
## LD reference population: EUR

22q12.1, rs4616575



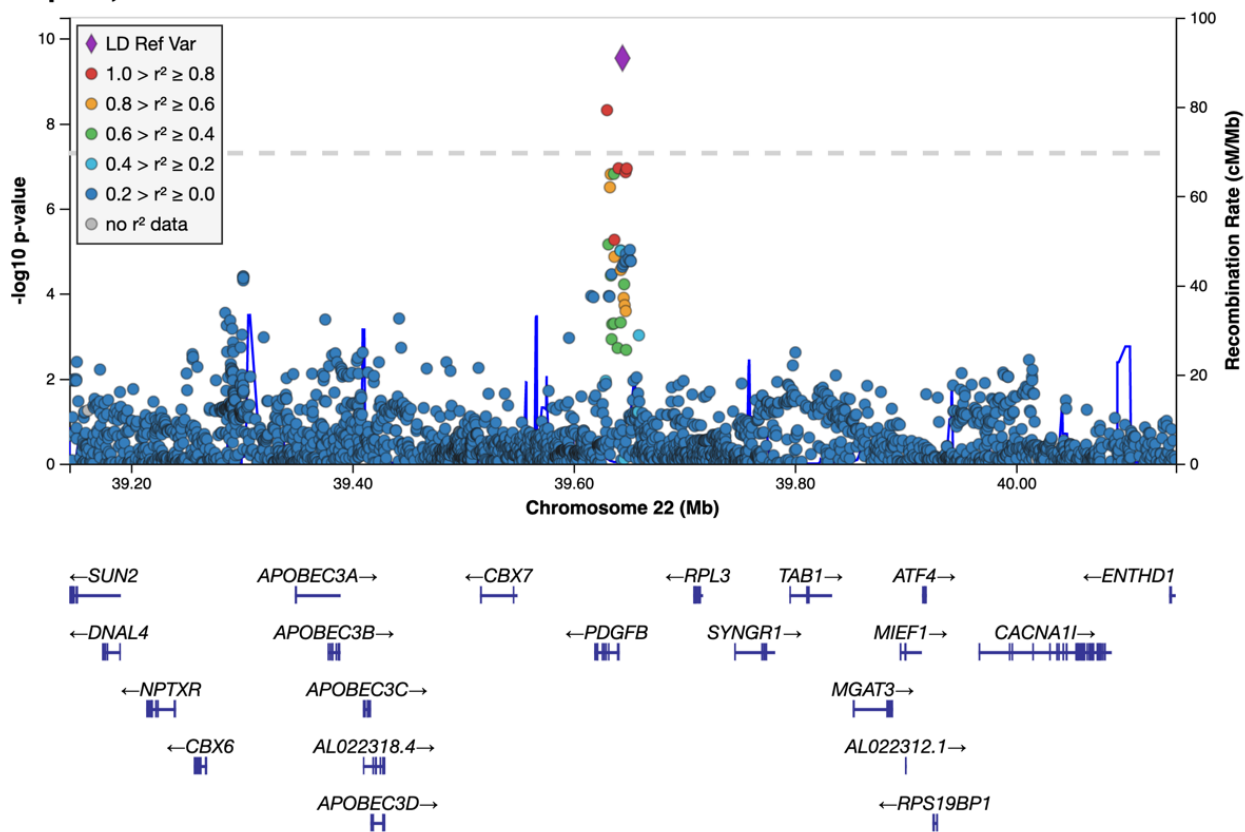
## LD reference population: EAS

22q12.1, rs4616575



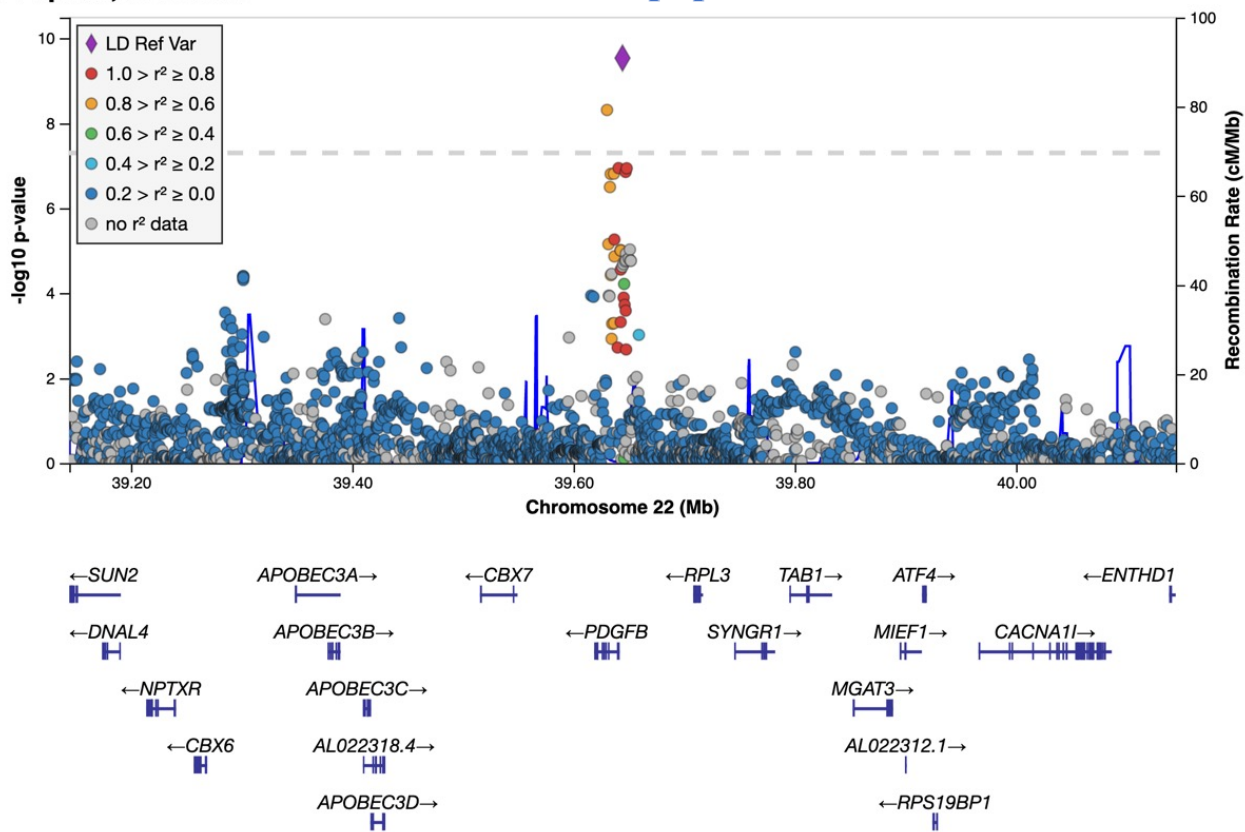
## LD reference population: EUR

22q13.1, rs130651



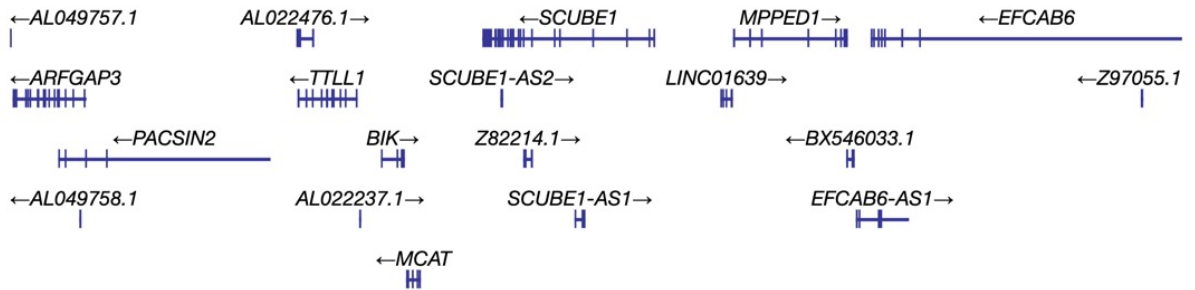
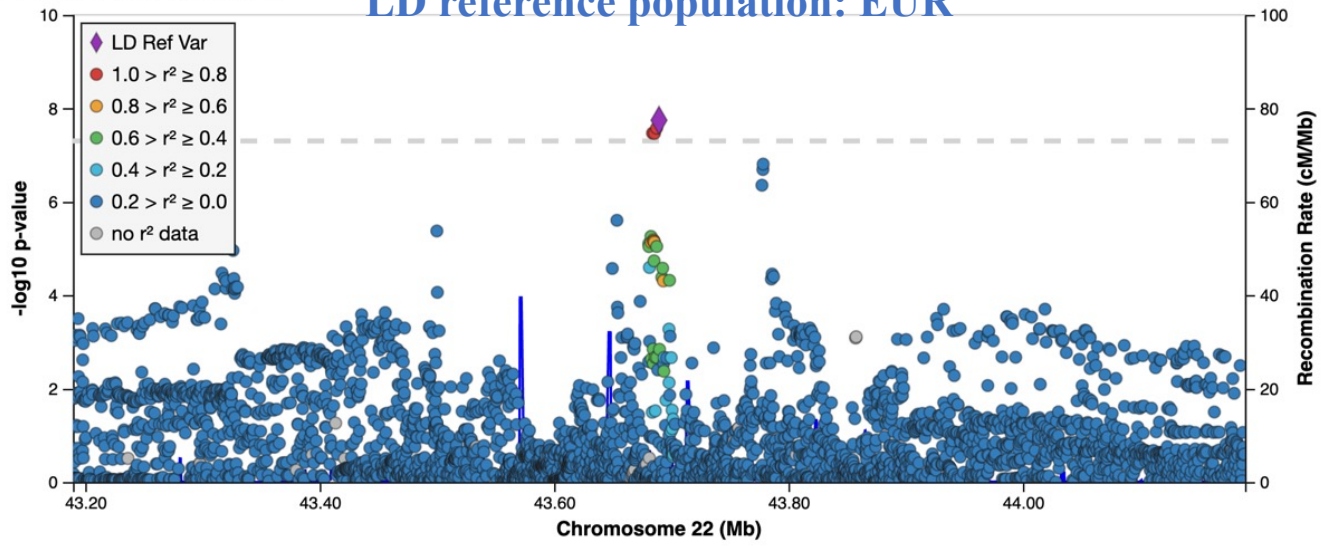
## LD reference population: EAS

22q13.1, rs130651



22q13.2, rs5751474

## LD reference population: EUR

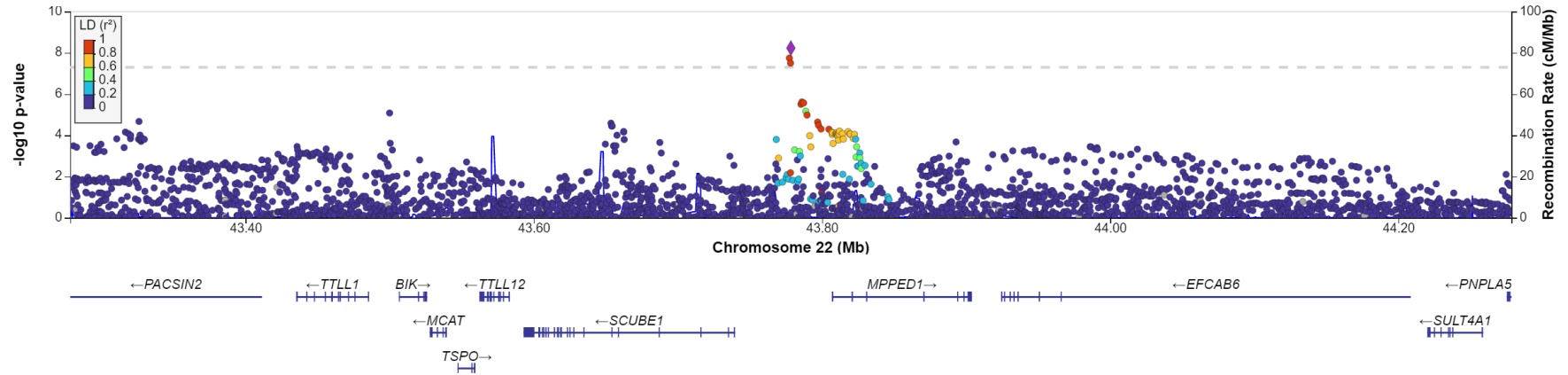


## LD reference population: EAS

rs5751474 is rare in the EAS population (MAF=0.006)

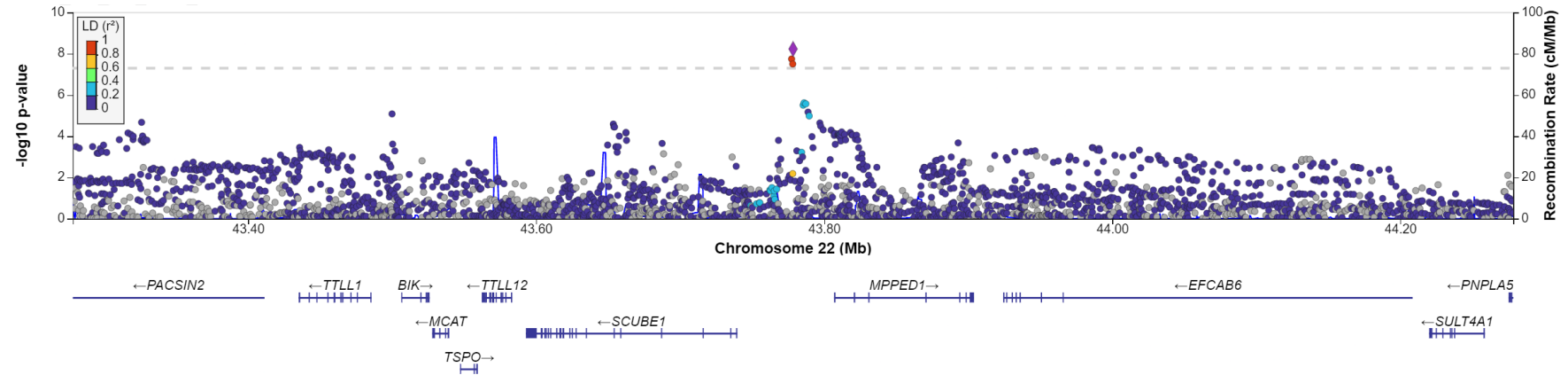
### LD reference population: EUR

22q13.2, rs34256596



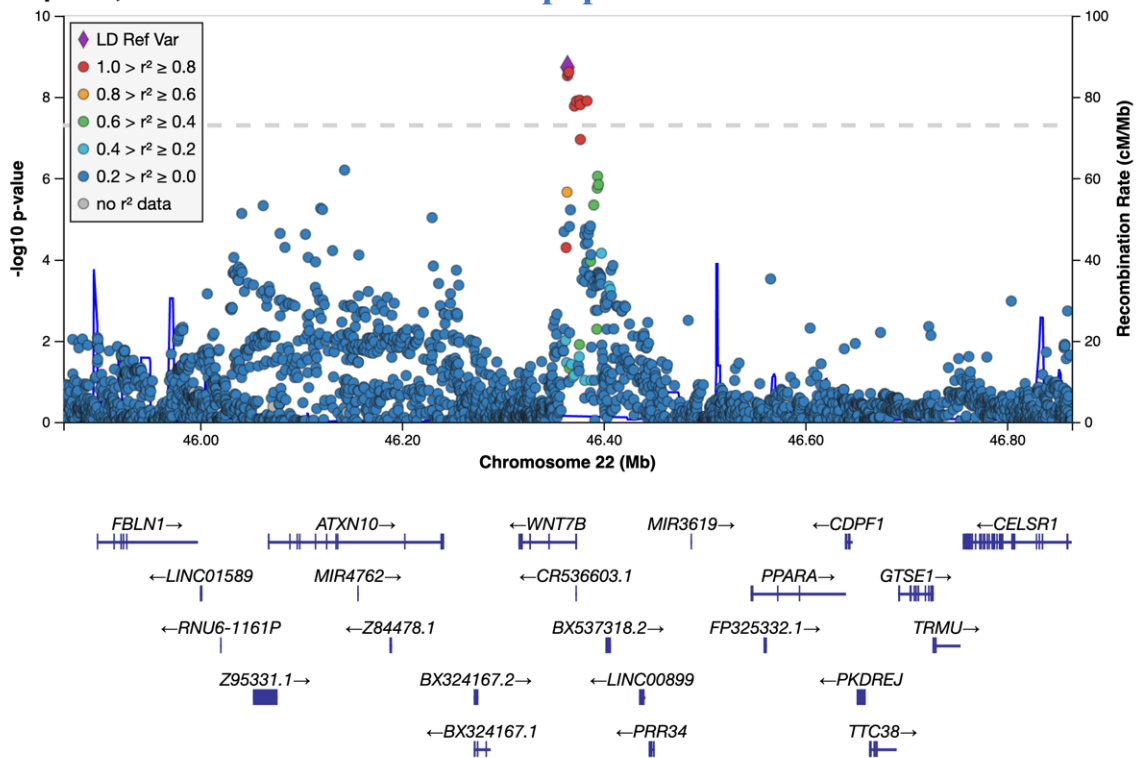
### LD reference population: EAS

22q13.2, rs34256596



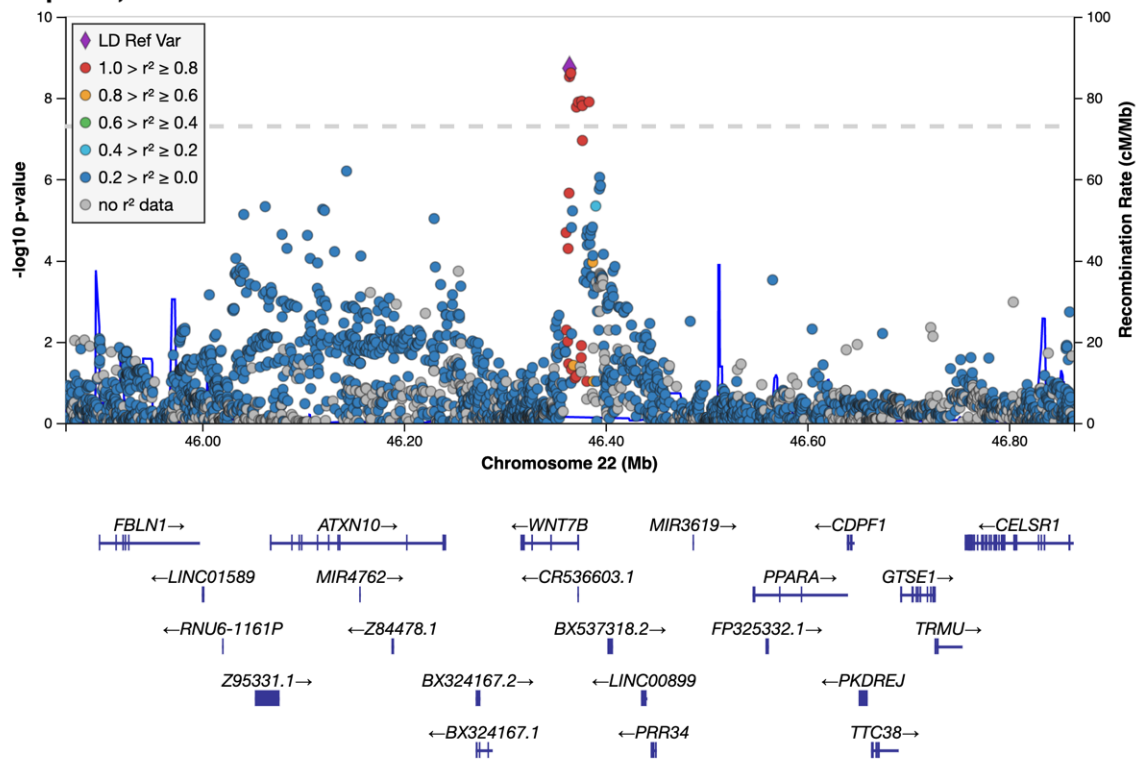
22q13.31, rs9330814

### LD reference population: EUR

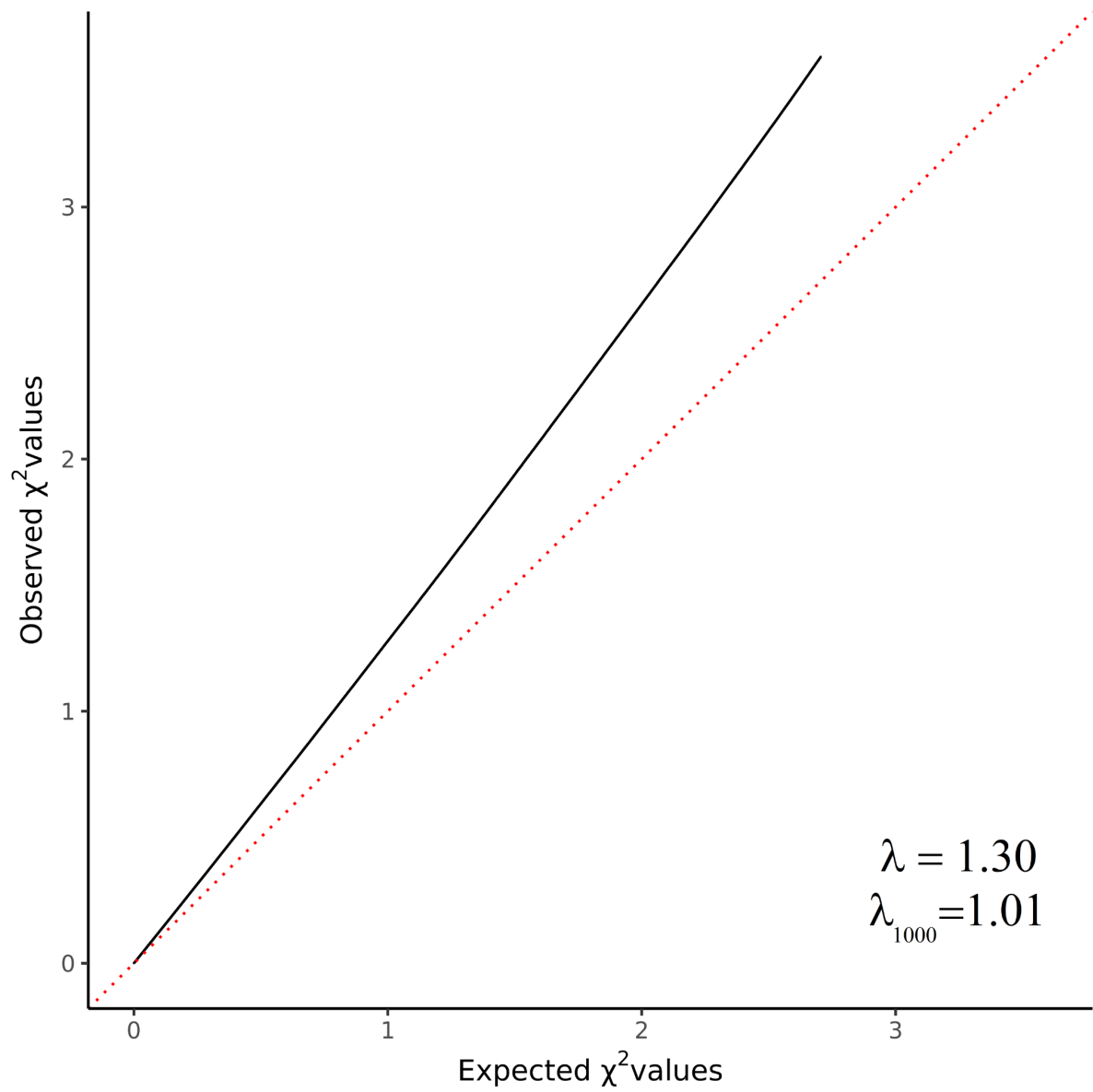


22q13.31, rs9330814

### LD reference population: EAS

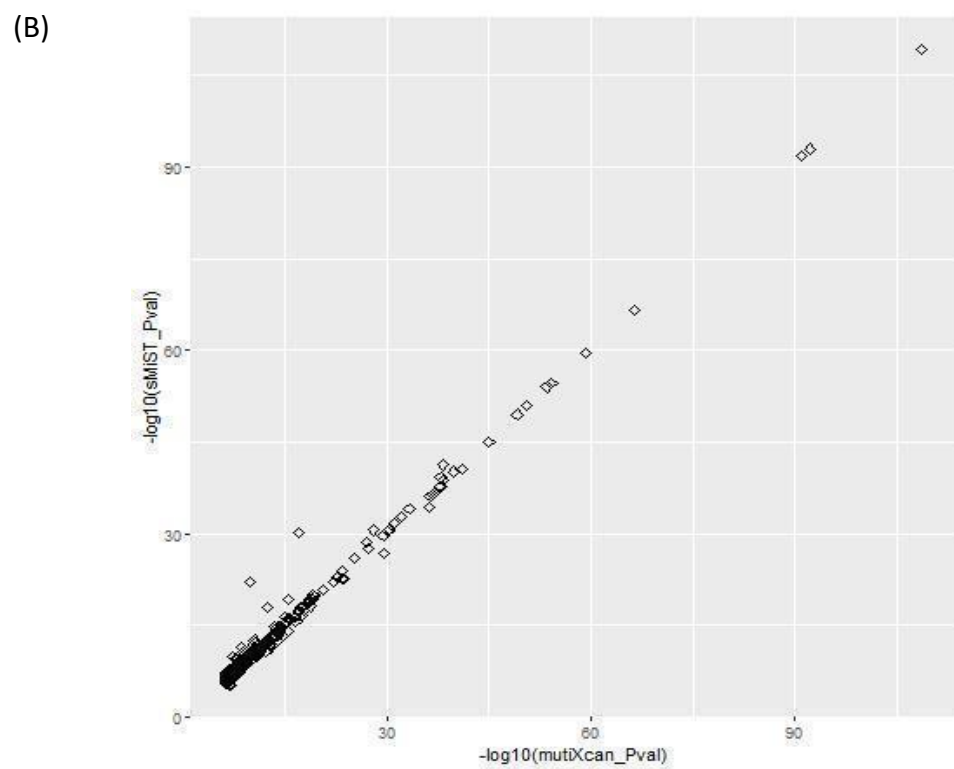
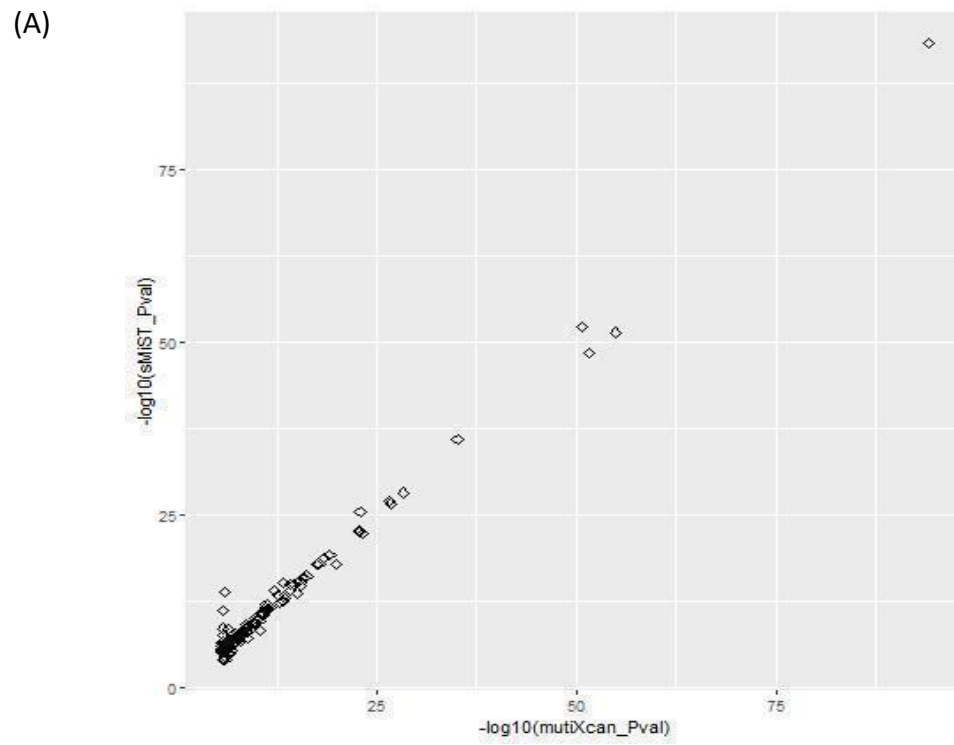


**Supplementary Figure 3: Quantile-Quantile (QQ) plot of observed and expected  $\chi^2$  values of association between SNP genotype and colorectal cancer. Meta  $\lambda_{GC} = 1.30$ ,  $\lambda_{1000} = 1.01$ . The red line represents the null hypothesis of no true association.**





**Supplementary Figure 4. P-values from sMultiXcan and unconditional sMiST analysis of the sPrediXcan models for the 12,017 TWAS genes (A) and 88,888 MWAS CpGs (B). All p-values are two-sided.**



**Supplementary Figure 5. Association between effector genes and CRC risk from TWAS across tissue types.** Shading represents strength of association in each tissue in TWAS (colorectal mucosa (yellow), sigmoid colon (orange), pan-gastrointestinal “GI” (blue), immune cells (pink), mesenchyme (gray) and pan-tissue/“All” (purple). Red=Bonferroni; pink=FDR; none=no significant gene expression model or TWAs association found. The MHC region is excluded from this list, with likely disproportional effects on immune genes. We identified likely tissue-specific effects on CRC risk based on Bonferroni-significant associations in one tissue (colorectal mucosa, sigmoid colon, immune cells or mesenchyme), with no association at FDR in any of the other tissue types (including “GI” but excluding the combined “All” analysis). Gene *RREB1* was removed from the cross-tissue analysis, since it harbors a coding variant and no significant TWAS models were available for any of the tissues. Genes in yellow are associated with mucosal tissue and those in pink are associated with immune tissues.

Single gene list	CR mucosa	Colon sigmoid	GI	Immune	Mesenchyme	All
SPSB1	Red	White	Red	White	White	Red
ARHGGEF19	Red	Light Red	Red	Light Red	Light Red	Red
WNT4	Red	White	Red	Light Red	White	Red
C1QB	White	White	White	White	White	Light Red
FHL3	Red	Light Red	Red	Red	Red	Red
TTC22	Light Red	Light Red	White	Light Red	White	Red
RPL5	White	White	White	Light Red	White	Red
ACP6	White	White	White	White	White	White
LINGO4	White	White	Light Red	White	White	Red
LAMC1	Red	Red	Red	Red	White	Red
ARPC5	Red	Light Red	Red	Red	Red	Red
LMOD1	Red	Red	Light Red	White	Light Red	Light Red
DSTYK	White	White	White	Light Red	Light Red	Light Red
DUSP10	Red	White	Red	White	White	Red
FAM98A	White	White	White	Red	White	Light Red
ACTR1B	Red	Red	Red	Red	Red	Red
FBLN7	Light Red	White	Light Red	White	White	Red
ARHGGEF4	White	White	White	White	White	Red
TANC1	White	White	White	Light Red	White	Red
STK39	Light Red	White	Light Red	Light Red	White	Light Red
SATB2	White	White	White	White	White	Red
CSRP1	Light Red	White	Red	White	White	Red
SFM8T1	Red	White	Red	Red	Red	Red
RFT1	Red	White	Red	White	White	Light Red
ATXN7	White	Red	Red	White	White	Light Red
LRI1G1	White	Light Red	White	Light Red	White	Light Red
GBE1	White	White	White	Light Red	White	Red
BOC	White	White	Red	Red	Red	Red
VDAR52	Light Red	White	Light Red	Light Red	White	Red
DIRC2	Light Red	White	Light Red	White	White	Red
RYK	White	White	White	White	Light Red	Red
ACTR3	White	White	White	White	White	Red
SMARCA4	White	White	White	White	White	Light Red
TET2	Red	White	Red	White	White	Red
UGT8	Light Red	White	Red	Light Red	Light Red	Red
GAB1	Light Red	White	Light Red	White	White	Red
SMAD1	White	White	White	Light Red	Red	Red
MAB21L2	Light Red	White	Red	White	White	Red
TERT	White	White	White	White	White	Red
TTC33	White	White	Light Red	White	Light Red	Red
CDKN2A/INK4	Red	White	Red	White	White	Red
TXND C15	Red	White	White	White	White	Red
ERGIC1	White	White	White	White	White	Light Red
FBXO38	White	White	Light Red	White	Red	Light Red
CDX1	White	White	White	White	White	Red
RREB1	White	White	White	White	White	White
HIVEP1	Light Red	White	Light Red	White	White	Light Red
CDKAL1	Light Red	Red	Light Red	Light Red	White	Red
ZKSCAN4	White	White	White	Light Red	Light Red	Red
TRIM27	White	White	White	White	Red	Light Red
TULP1	White	Light Red	White	White	Light Red	Red

CDKN1A						
TFEB						
RP1-166H4.2						
BMP5						
DCBLD1						
EPB41L2						
TCF21						
GNAI2						
TBRG4						
TWS3						
RP11-114G11.5						
WBSCR27						
CDK6						
TRIMM						
LINC00513						
TOX						
UTP23						
POU5F18						
RP11-384P7.7						
DCAF12						
LPAR1						
BRD3						
ABCA2						
ITIH5						
BAMBI						
GPRIN2						
AICF						
SFTPA2						
LINC01475						
CUTC						
CNNM2						
TCF7L2						
IFITM1						
RHOG						
F2						
KBTBD4						
FADS3						
MYRF						
AP000439.5						
POLD3						
CHRD12						
ME3						
TRPC6						
COLCA1						
COLCA2						
TAGLN						
BCL9L						
ADAMTS15						
CCND2						
PLEKHG6						
RP1-102E24.8						
LMBR1L						

COX14						
LIMA1						
LRP1						
PTGES3						
LEMD3						
TS PAN8						
SH2B3						
ACAD10						
MAPKAPK5-AS1						
RP11-116D17.3						
CLIP1						
STAR13						
SMAD9						
KLF5						
EDNRB						
ANKRD10						
TOX4						
C14orf166						
NID2						
BMP4						
DACT1						
GREM1						
RP11-817O13.8						
BNIP2						
SMAD6						
SMAD3						
GRAMD2A						
C15orf39						
CDH3						
MAF						
ATP2C2						
CBFA2T3						
GLO4						
NXN						
LINC00675						
LLGL1						
PSMC5						
SOX9						
SETBP1						
ACAA2						
SMAD4						
ATP8B1						
SBNO2						
FUT3						
ICAM3						
ANKRD27						
RHPN2						
SPACA4						
FUT2						
SLC27A5						
CRLS1						
BMP2						

TMX4						
MMP24						
JPH2						
PREX1						
RP11-112L6.3						
PARD6B						
GNAS						
CABLES2						
RBBP8NL						
YBEY						
PCNT						
ZNRF3						
LIF						
PDGFB						
RIBC2						

**Supplementary Figure 6: Projected percentage of GWAS heritability explained for a given sample size.** Results were obtained using a three-component model to estimate distribution of effect sizes. Grey shaded area represents the 95% confidence interval of the heritability estimate. The sample size indicates the total number of cases and controls, assuming a 1:1 ratio.

