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# 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://barcuvaseq.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

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

GTEx - https://www.gtexportal.org/home/

GTEx 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

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[1-4]. 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[5,6] 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[7]. 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[8]. 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[9]. 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[10]. 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[11]. 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/)[12,13]. DGN: Whole blood data from 922 samples from the Depression Genes and Networks (DGN) cohort[14] 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[15] 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[1]. 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)[16] 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)[17]. 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[18].

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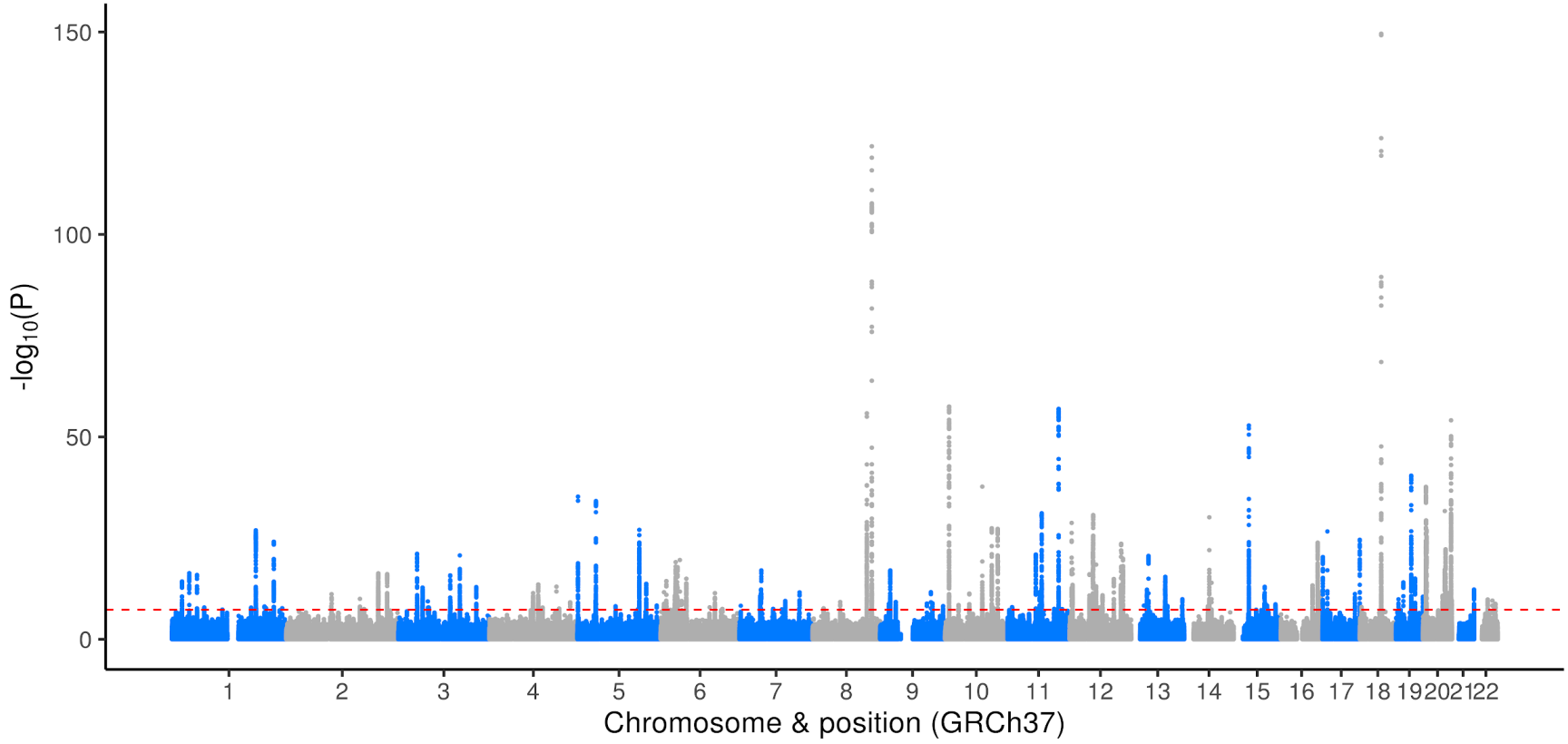
http://www.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Short%20List.pdf

**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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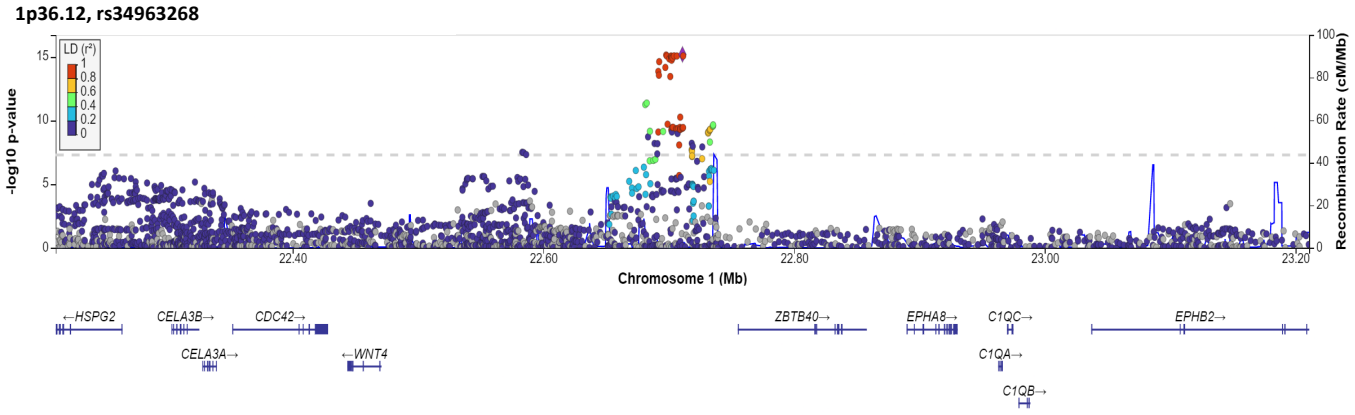


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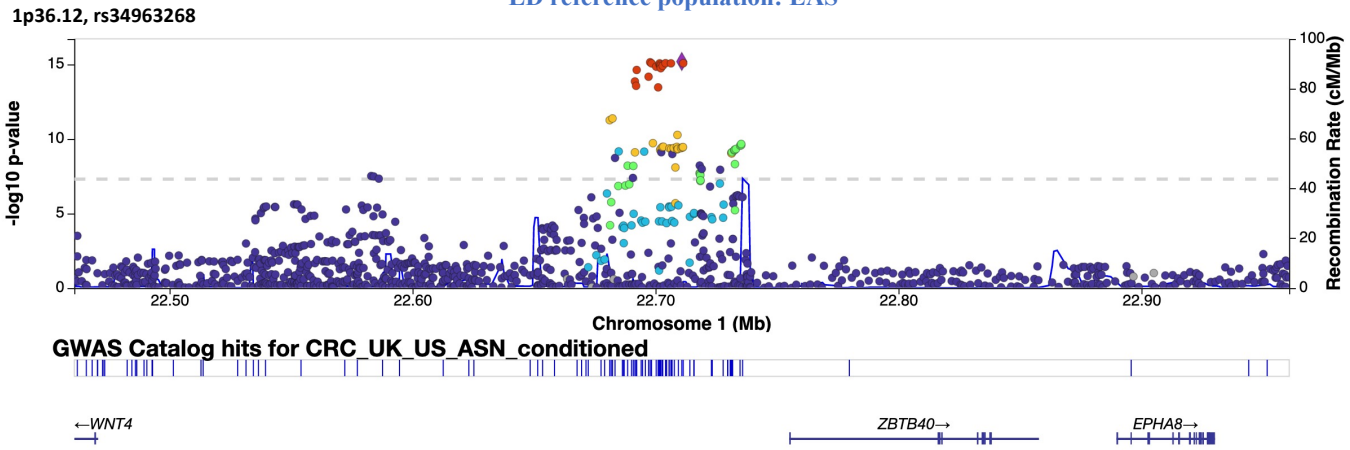

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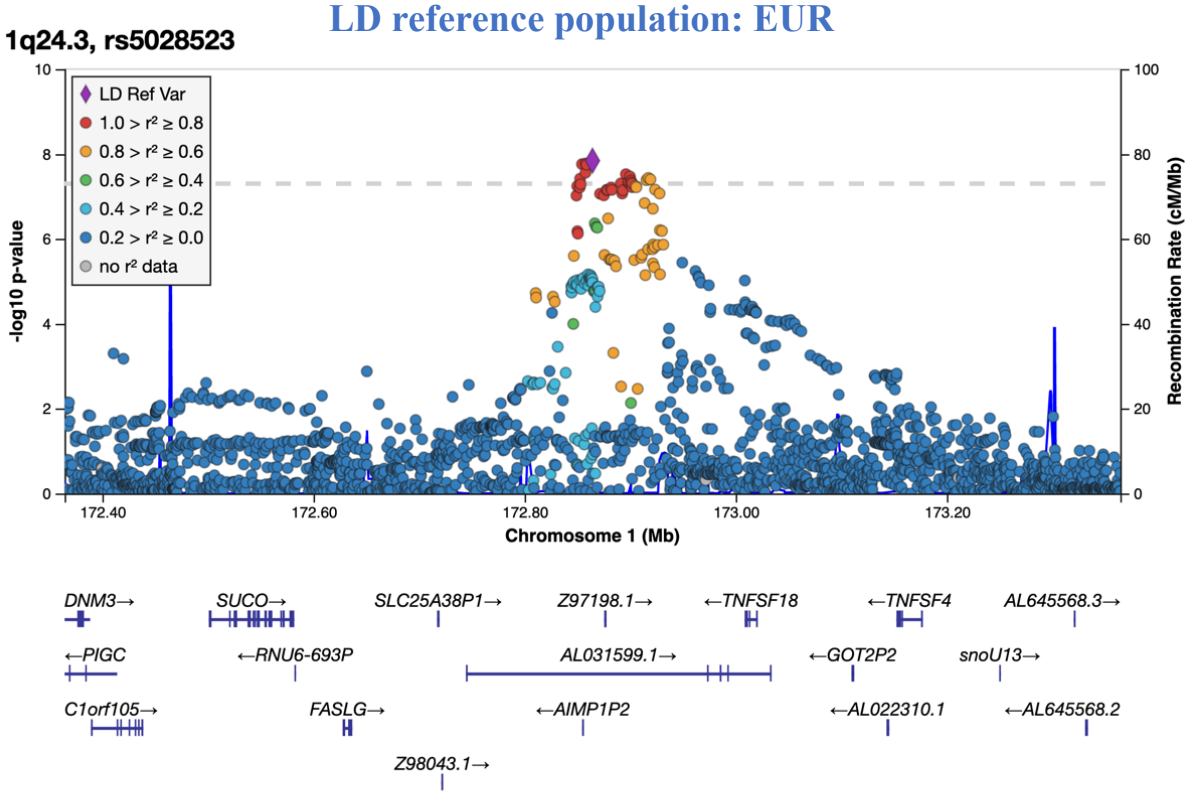


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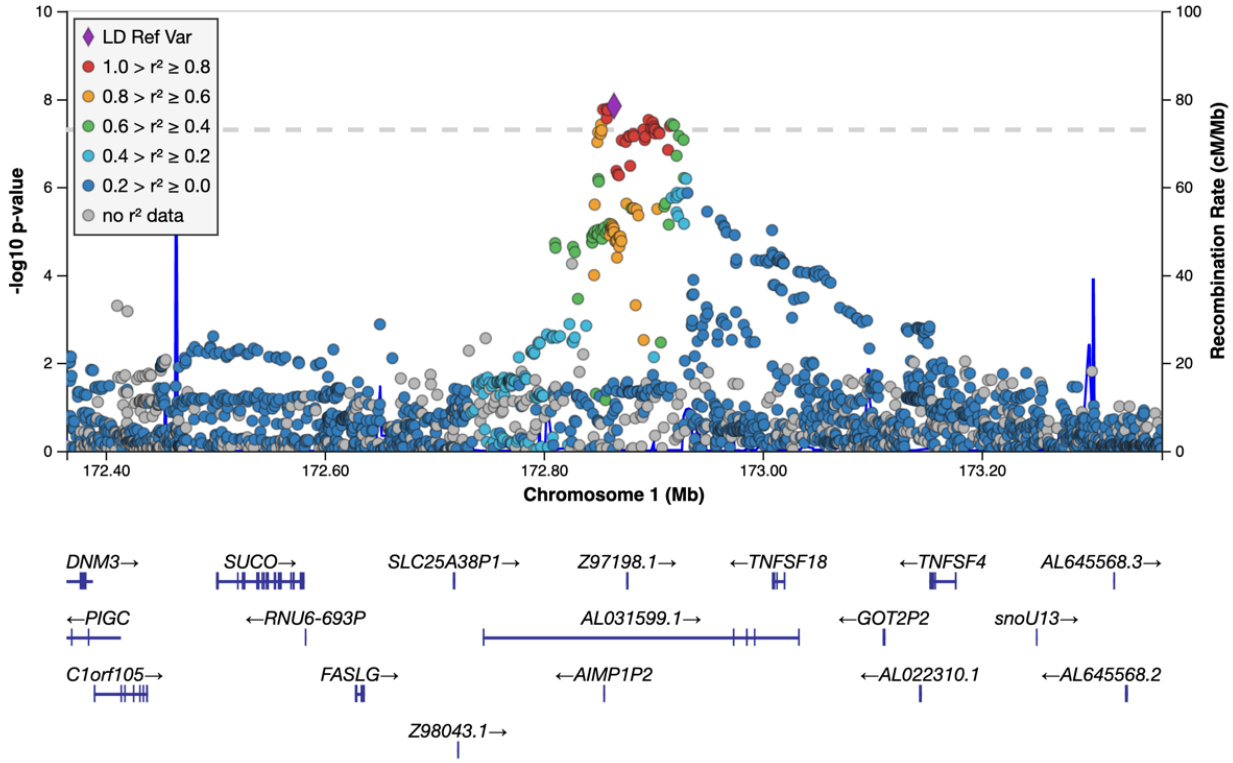

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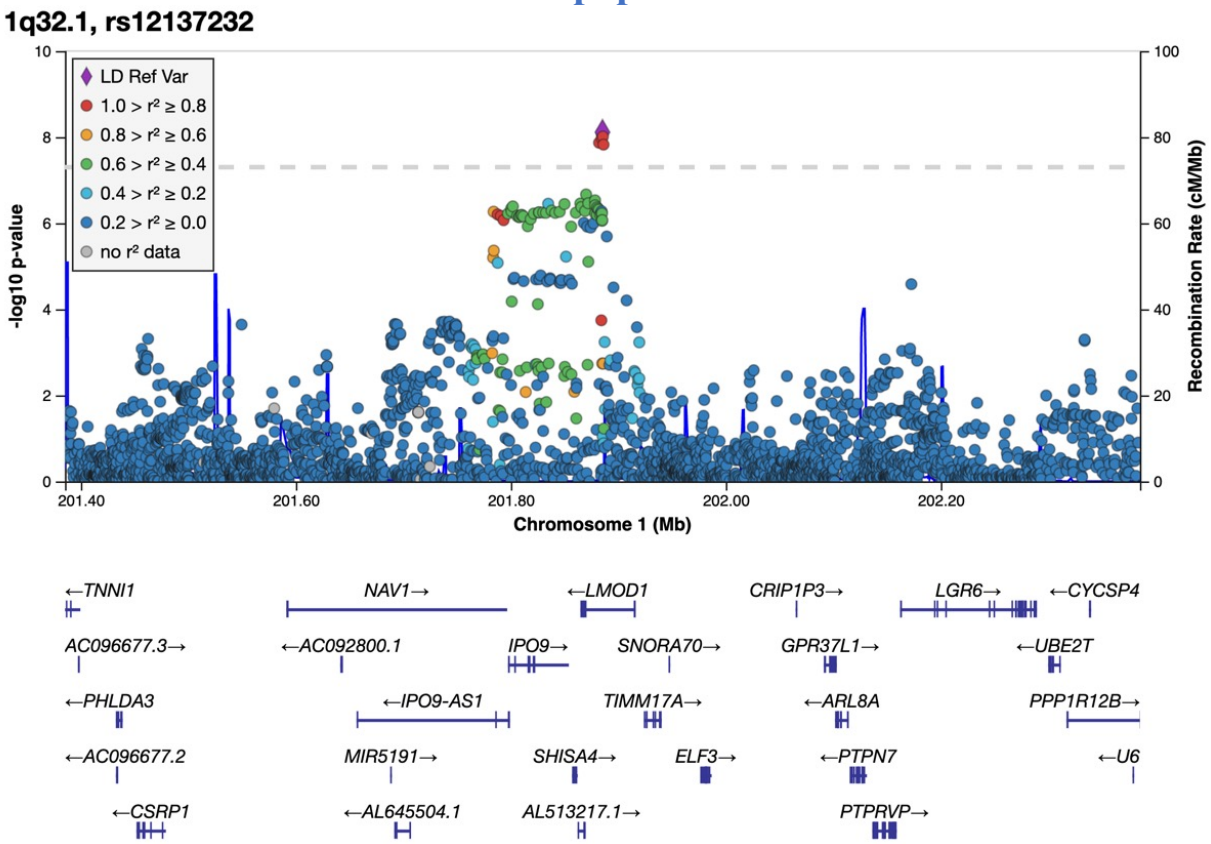


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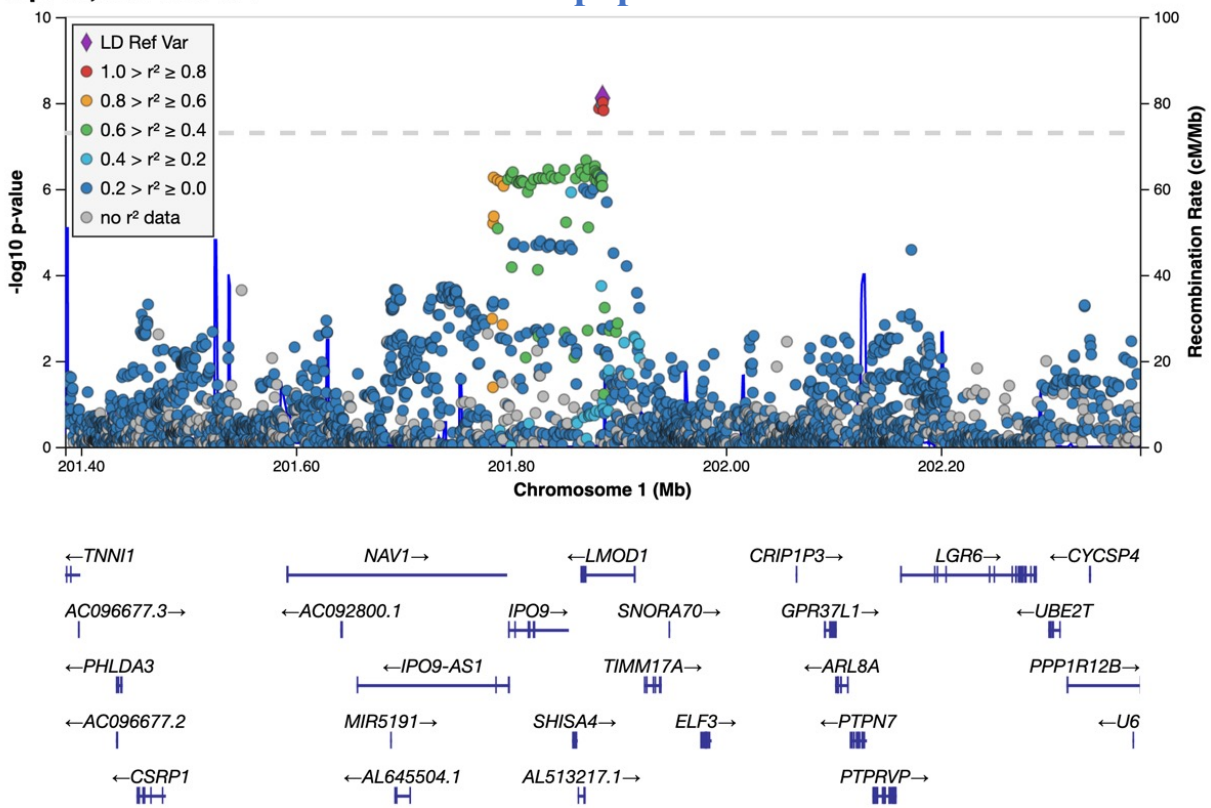

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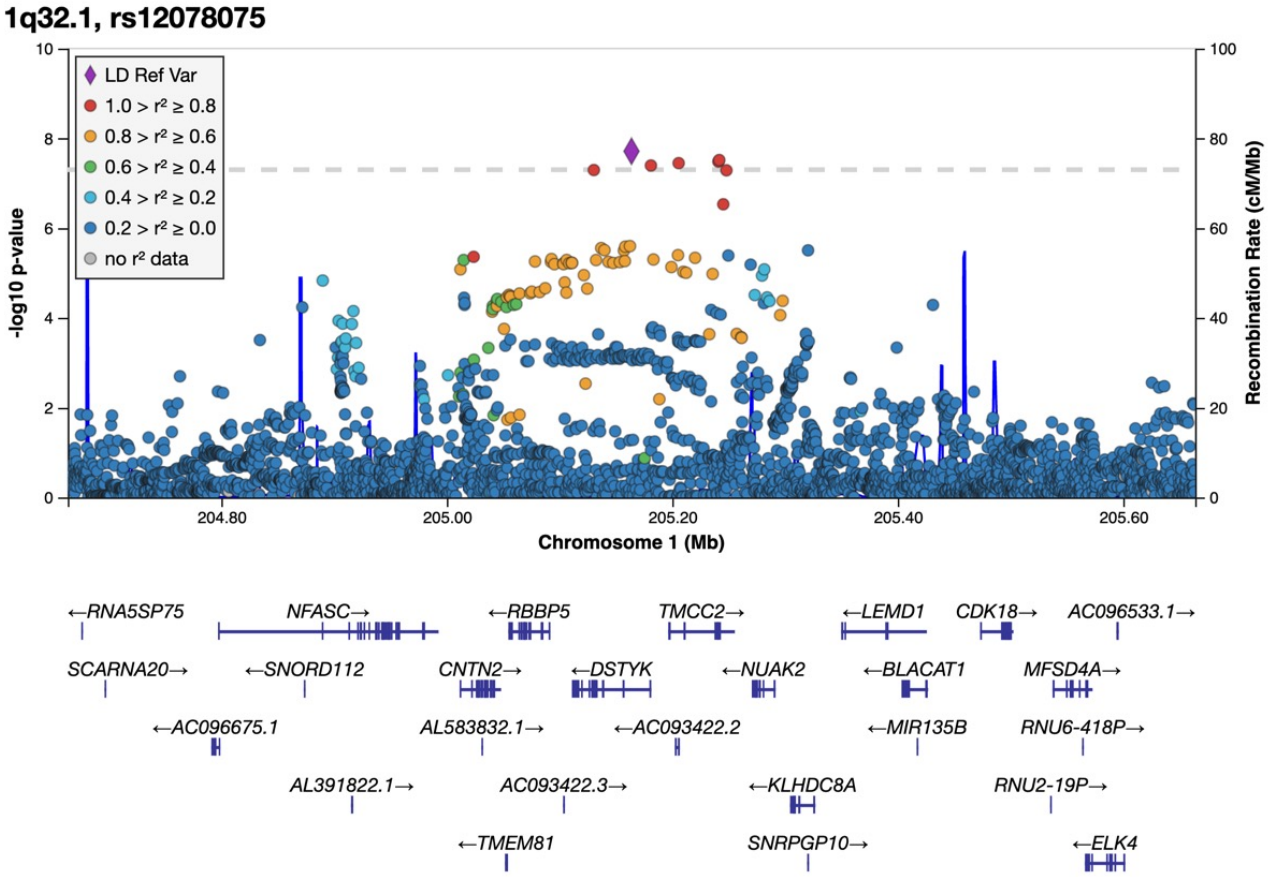


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rs12078075 is monoallelic in the EAS population

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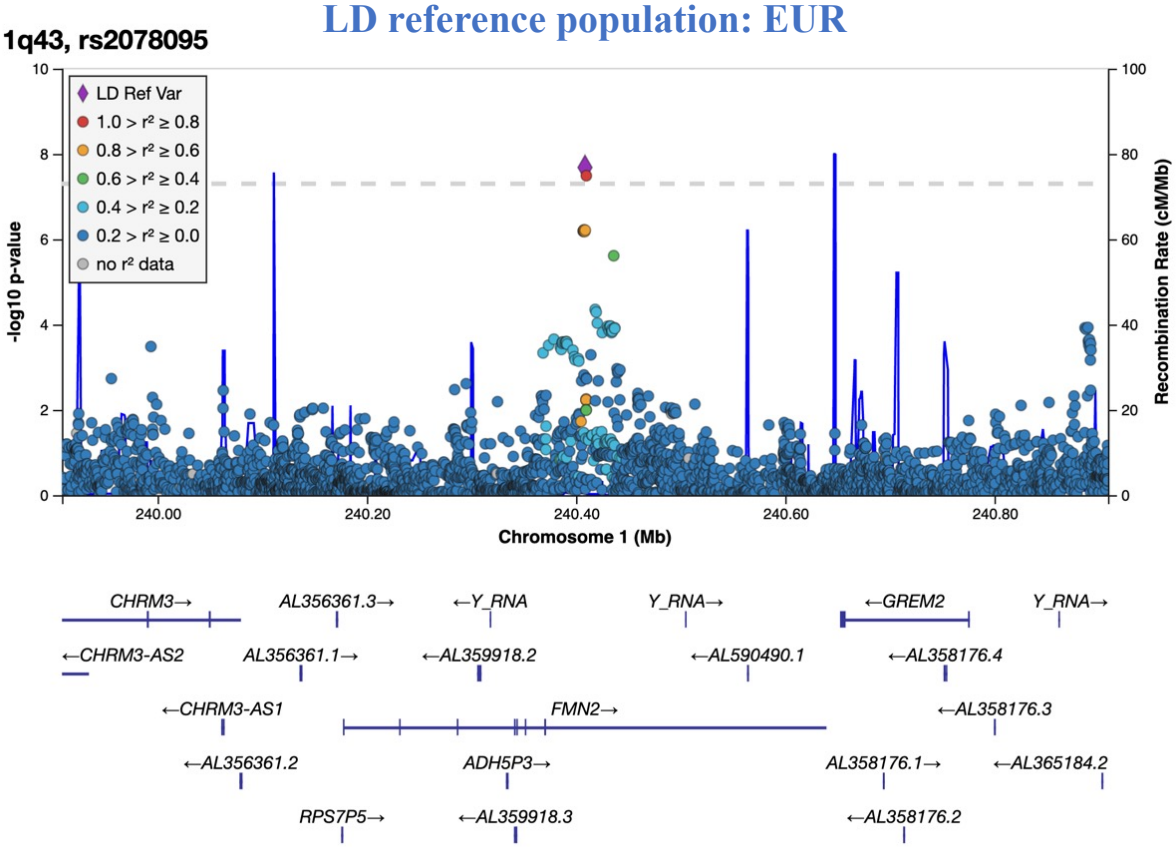


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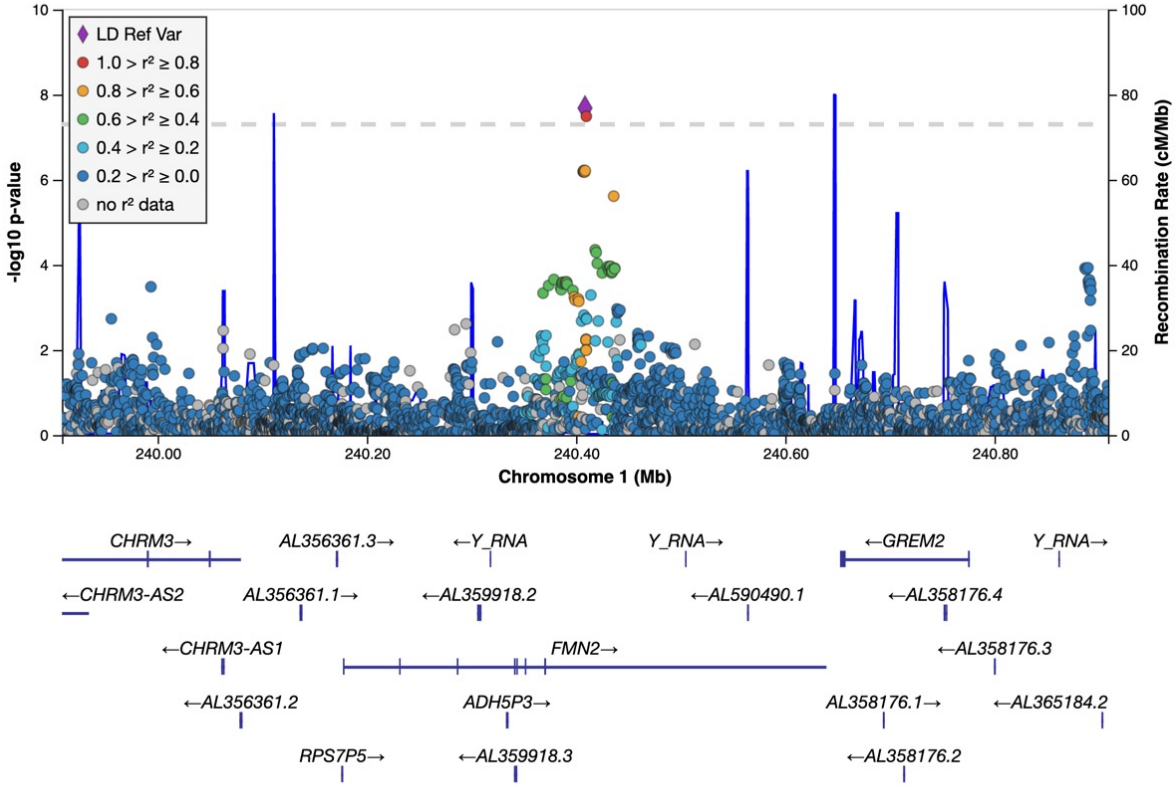

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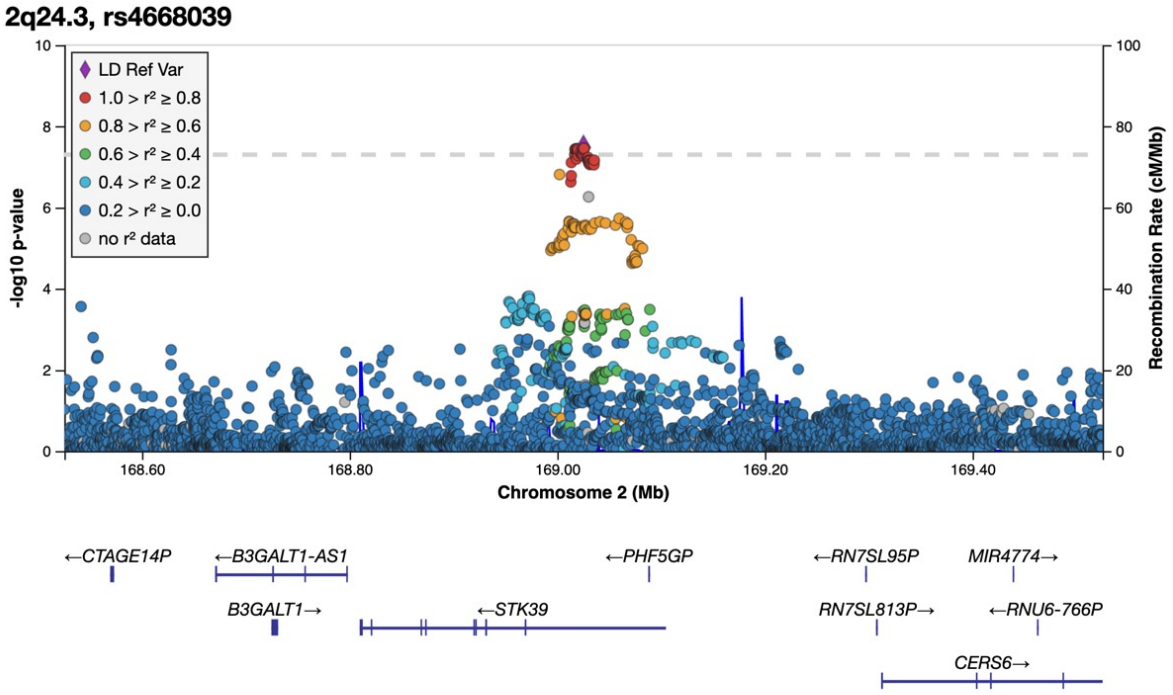


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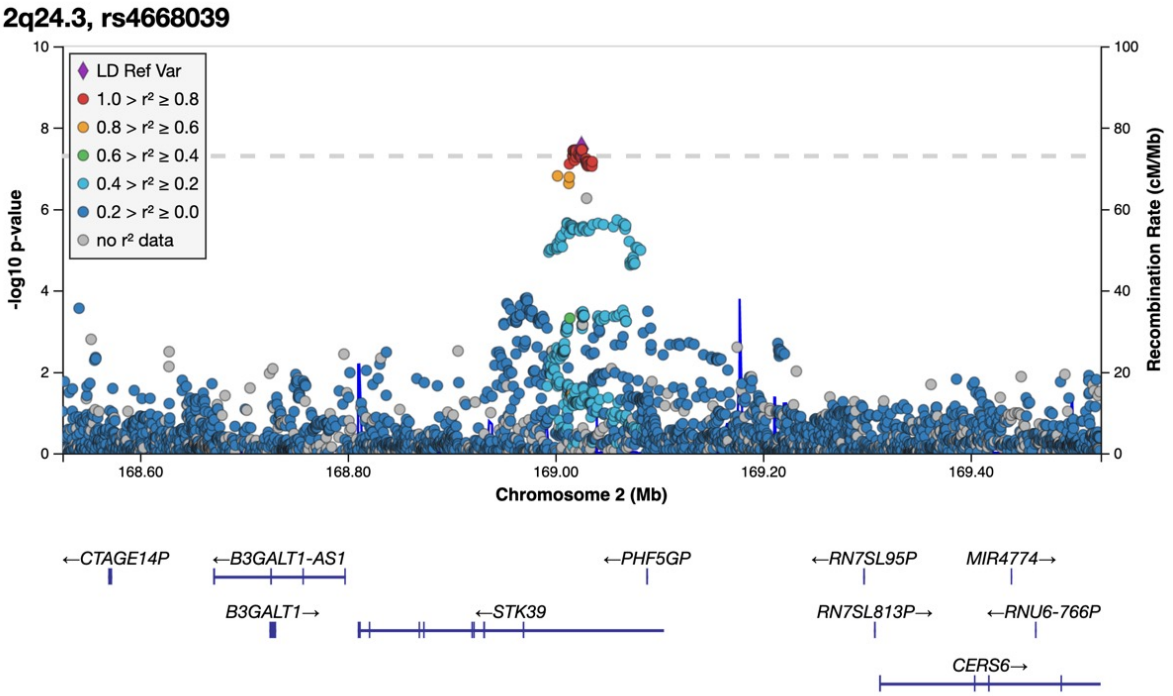

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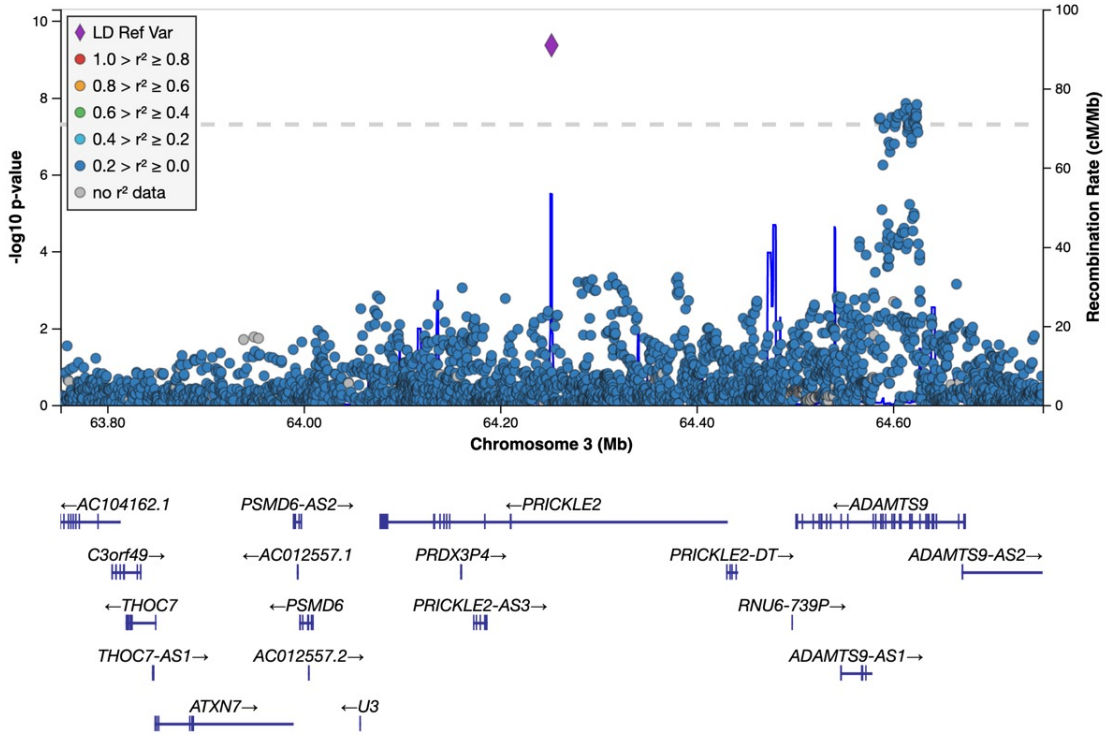


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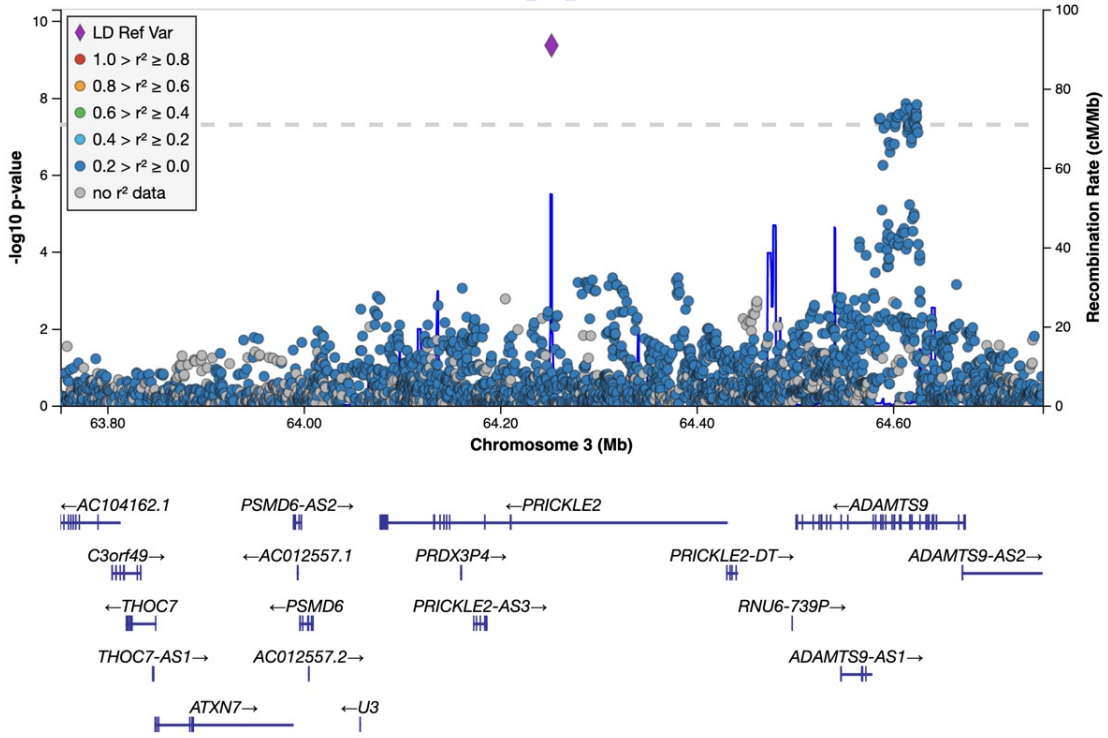
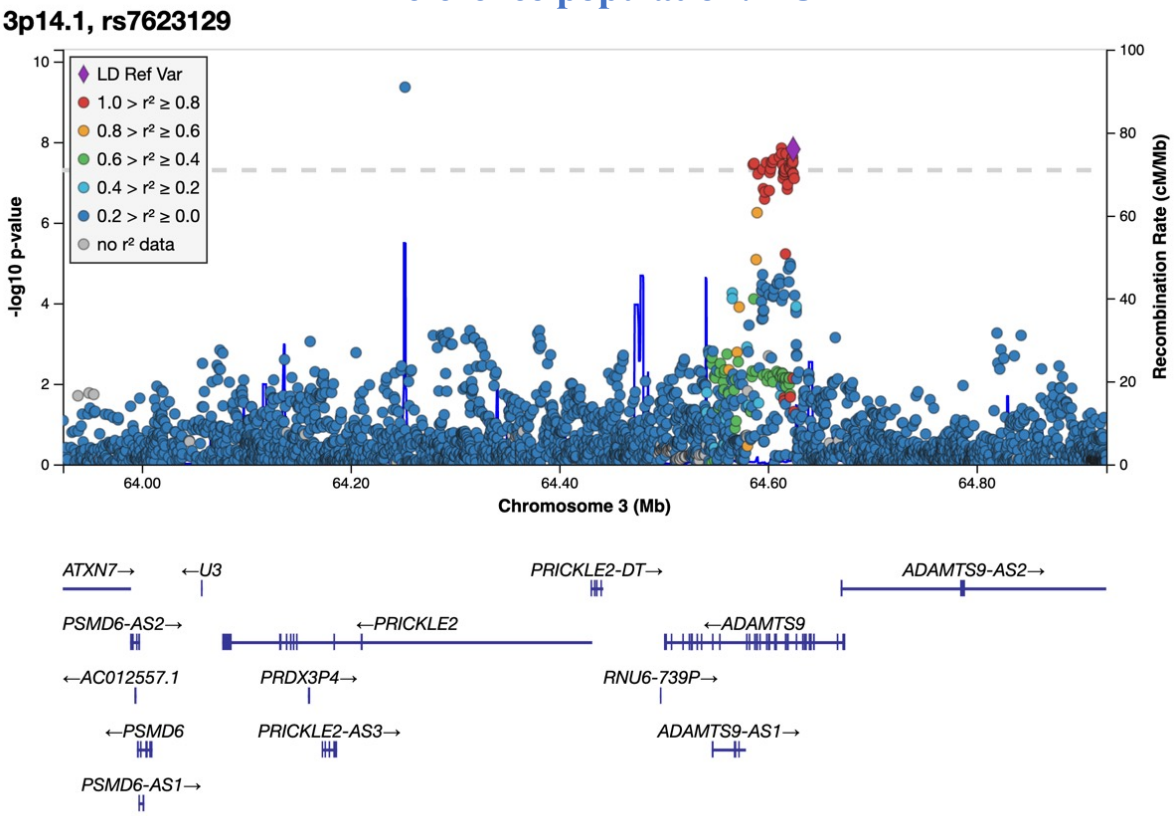
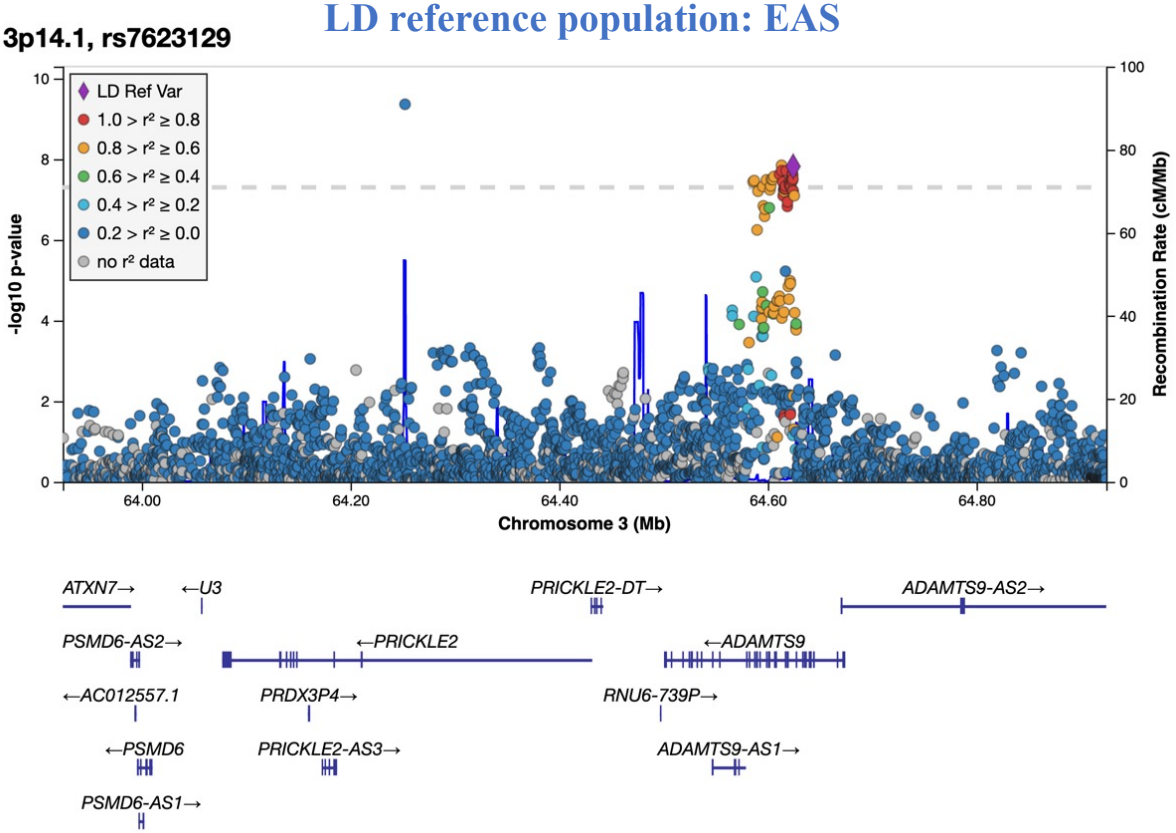


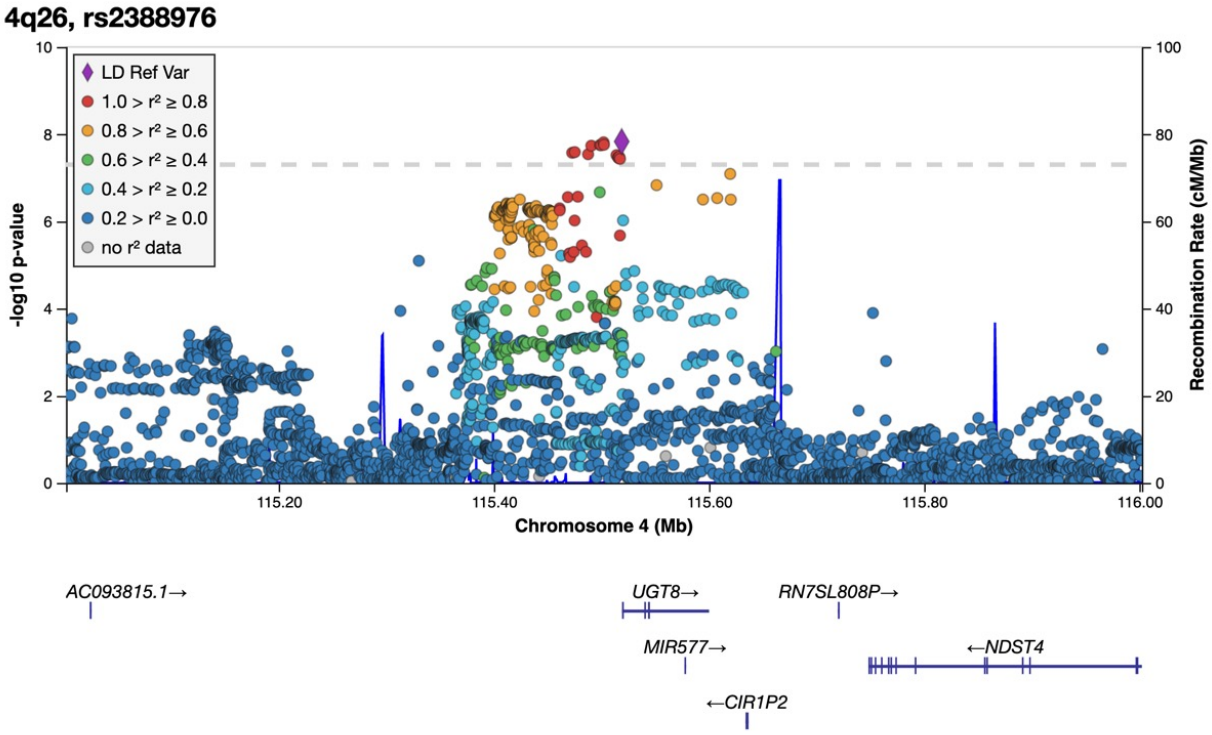
## LD reference population: EUR



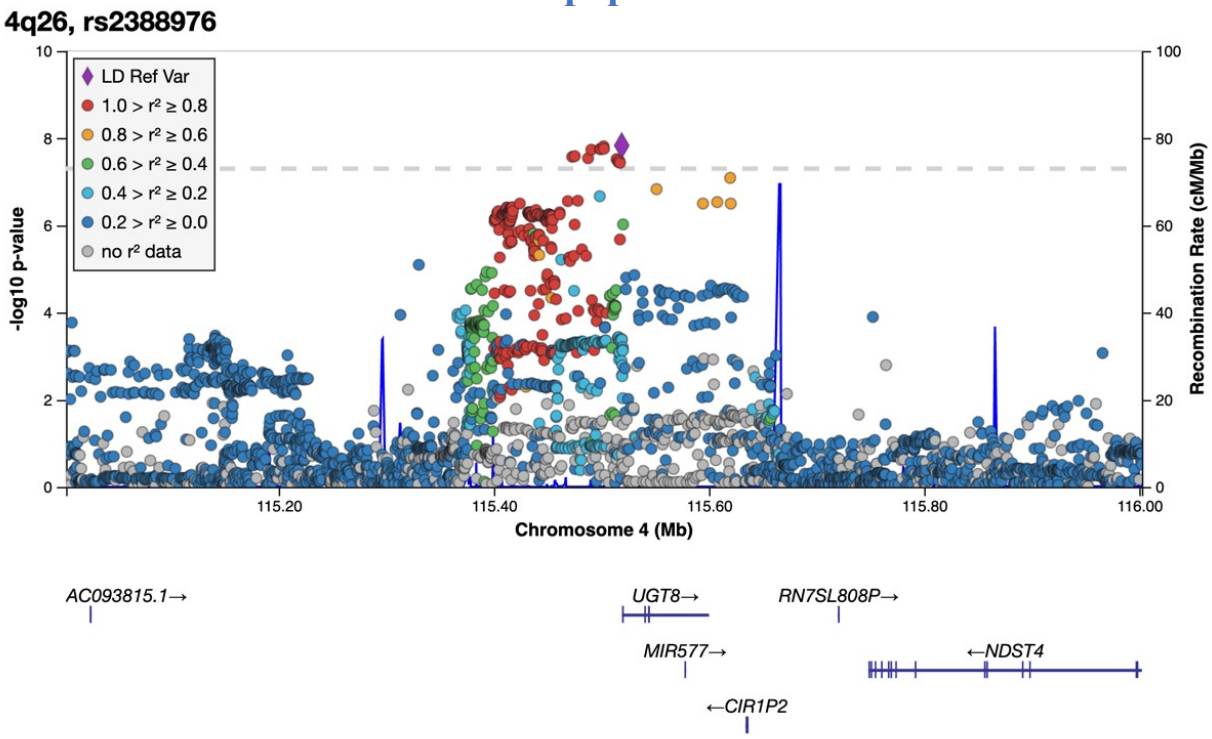

## LD reference population: EAS



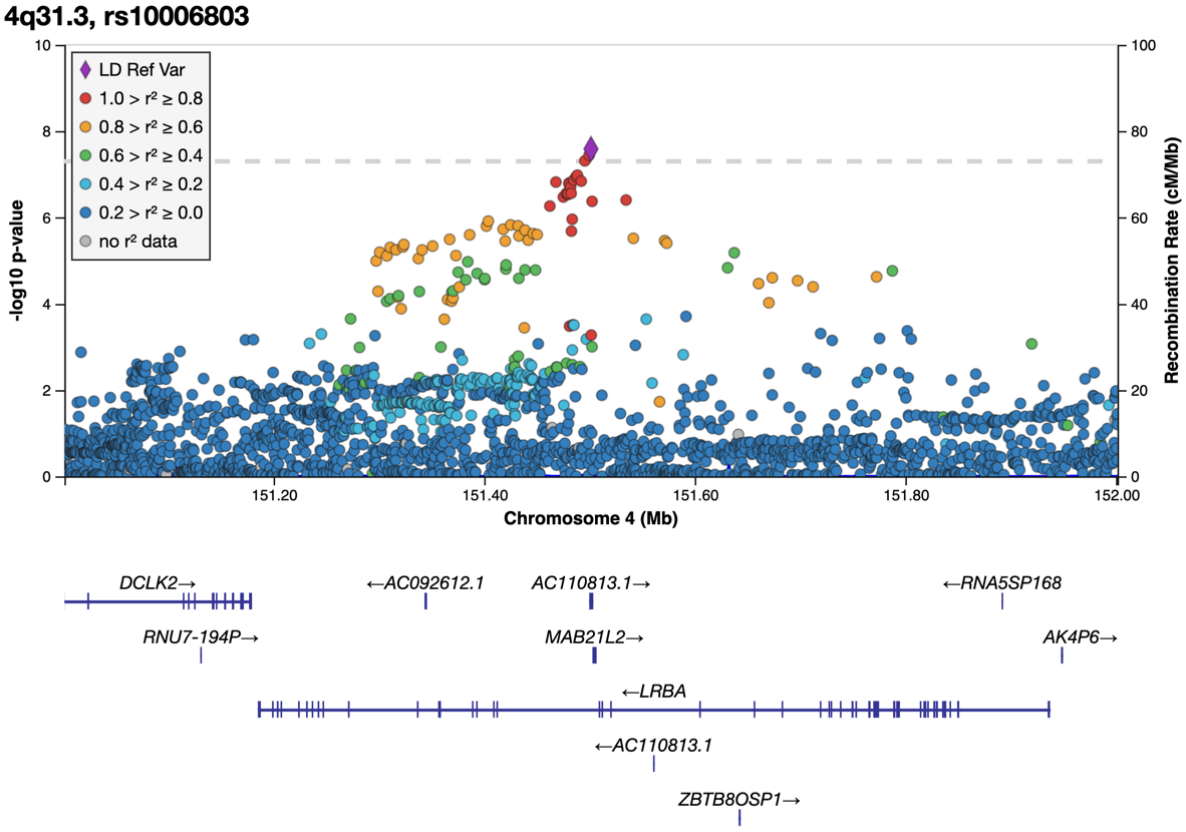
## LD reference population: EUR



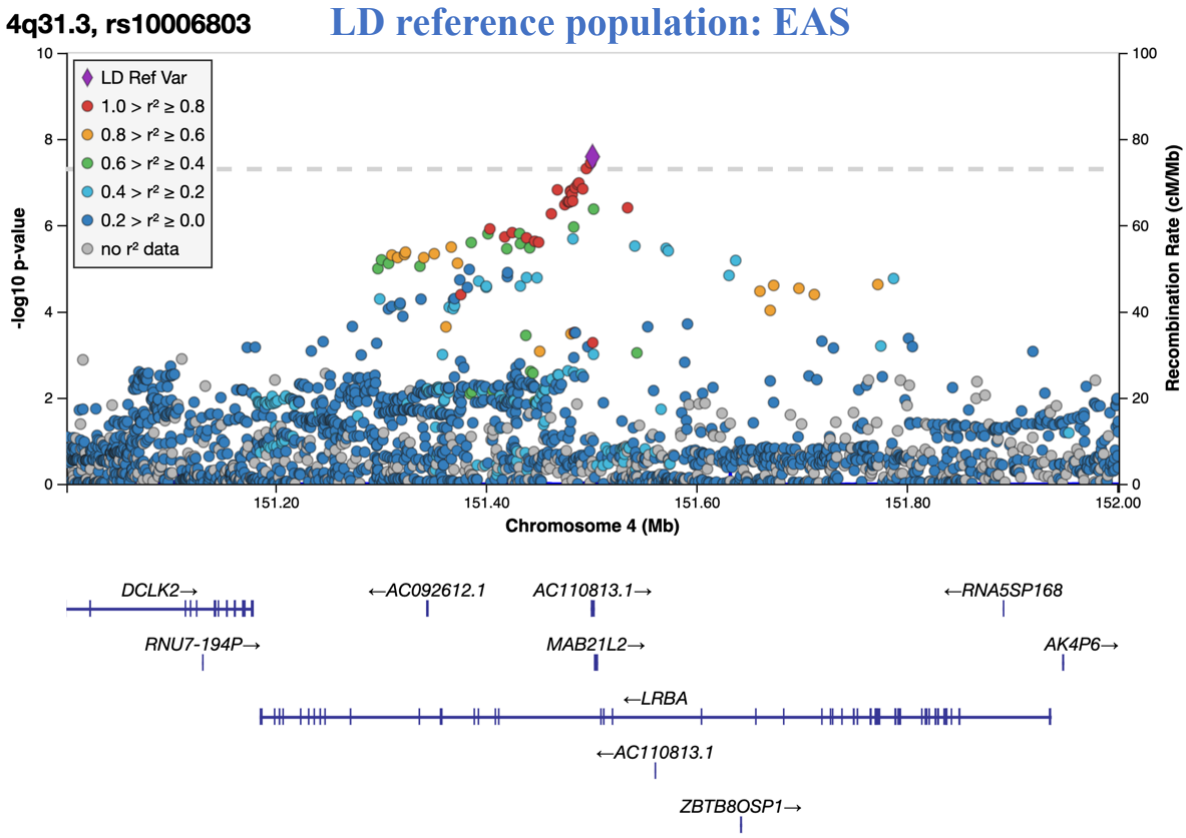

## LD reference population: EAS



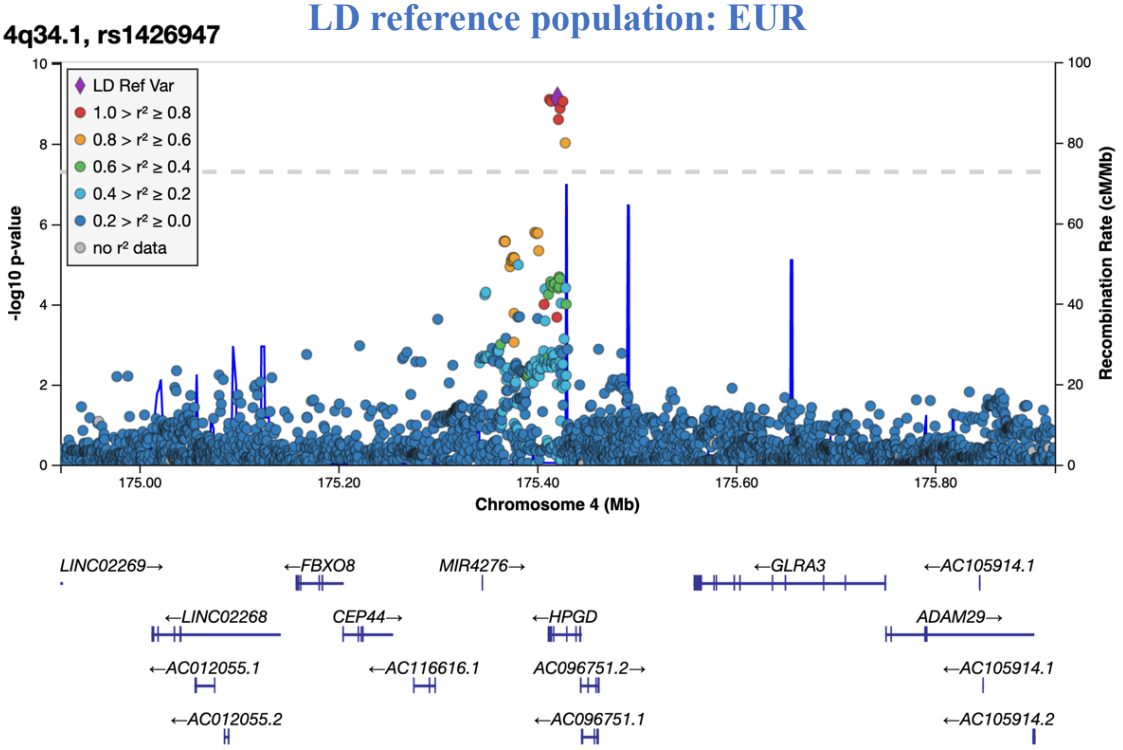
## LD reference population: EUR



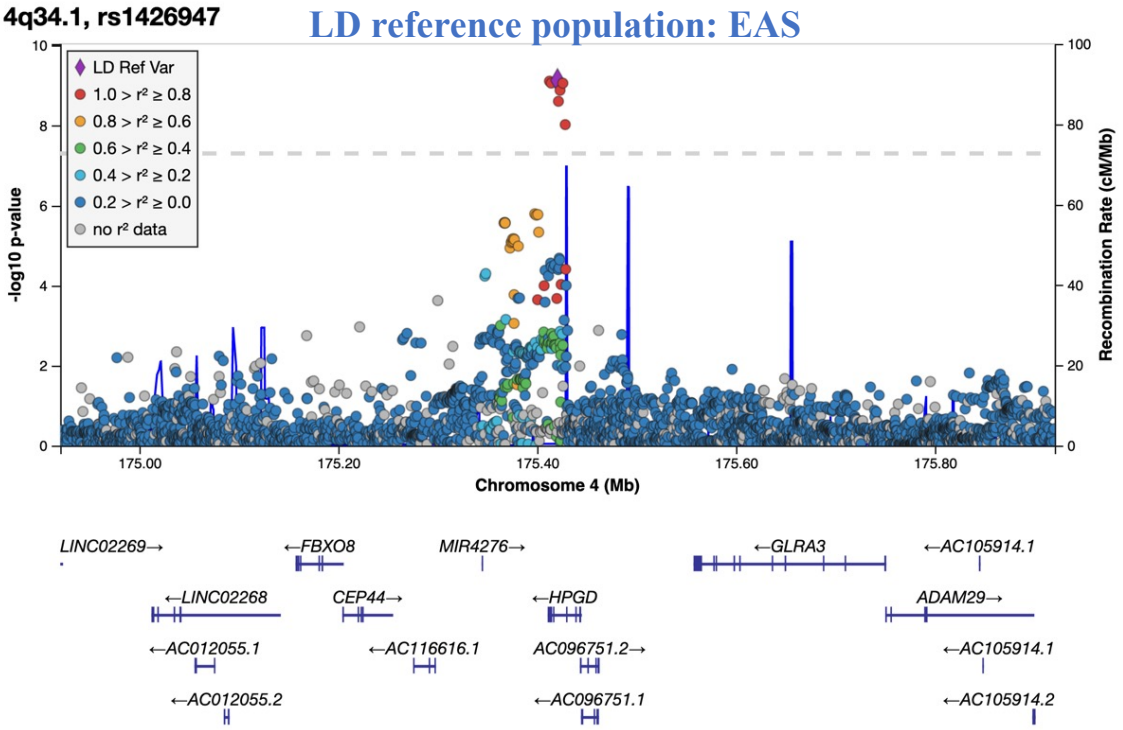

## LD reference population: EAS

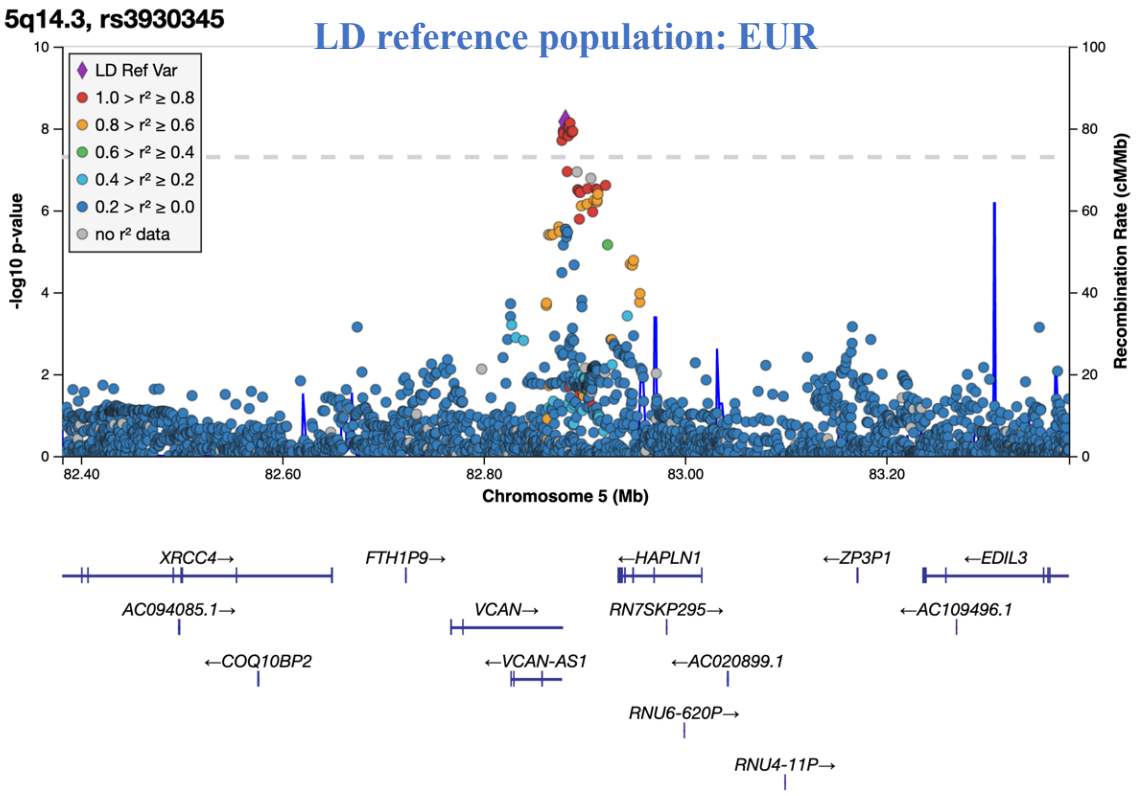


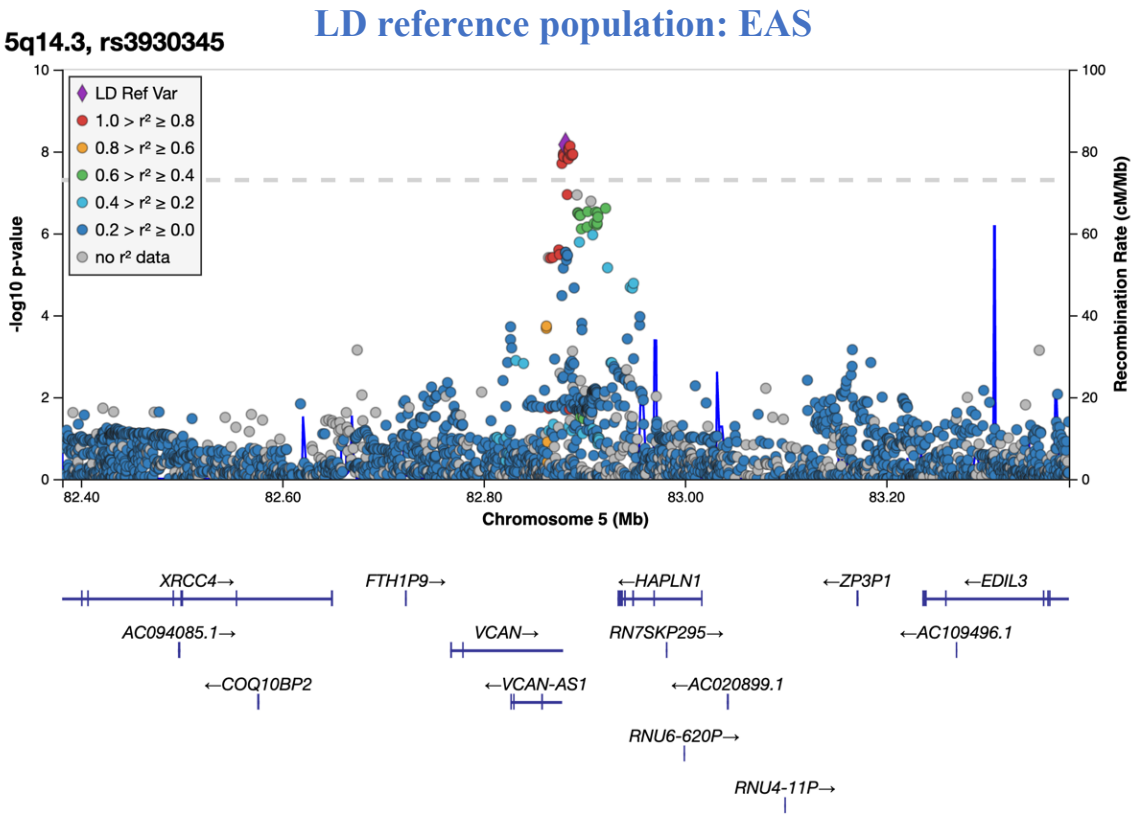
## LD reference population: EUR



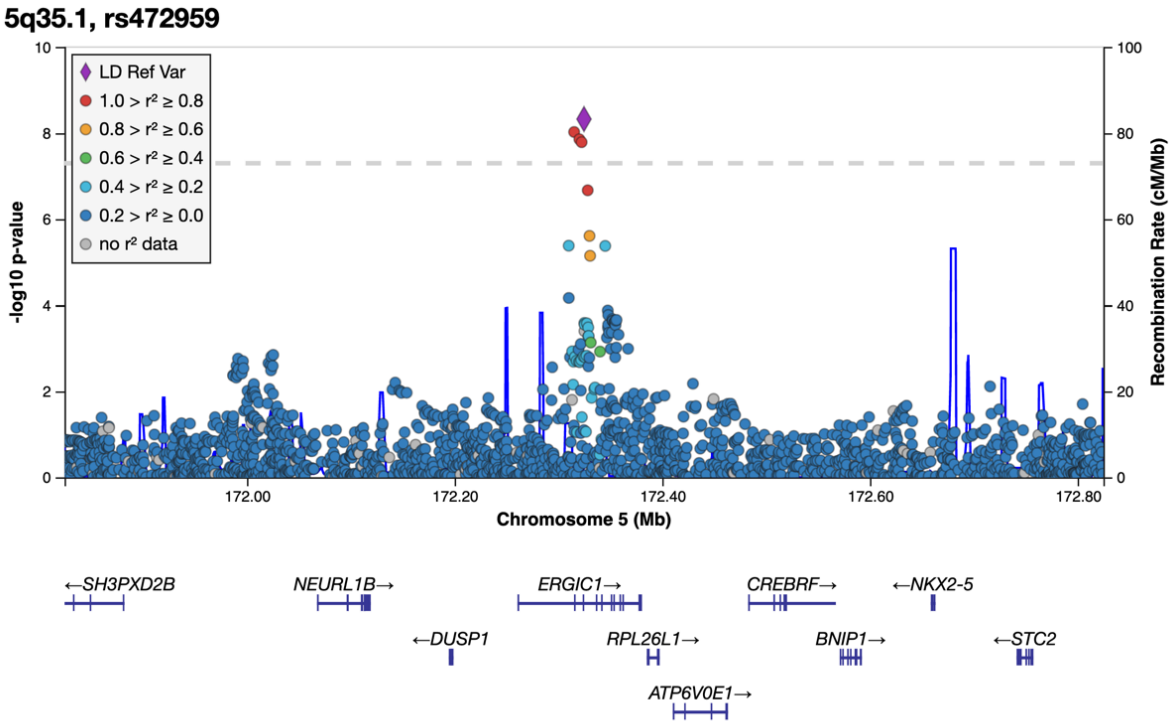

## LD reference population: EAS



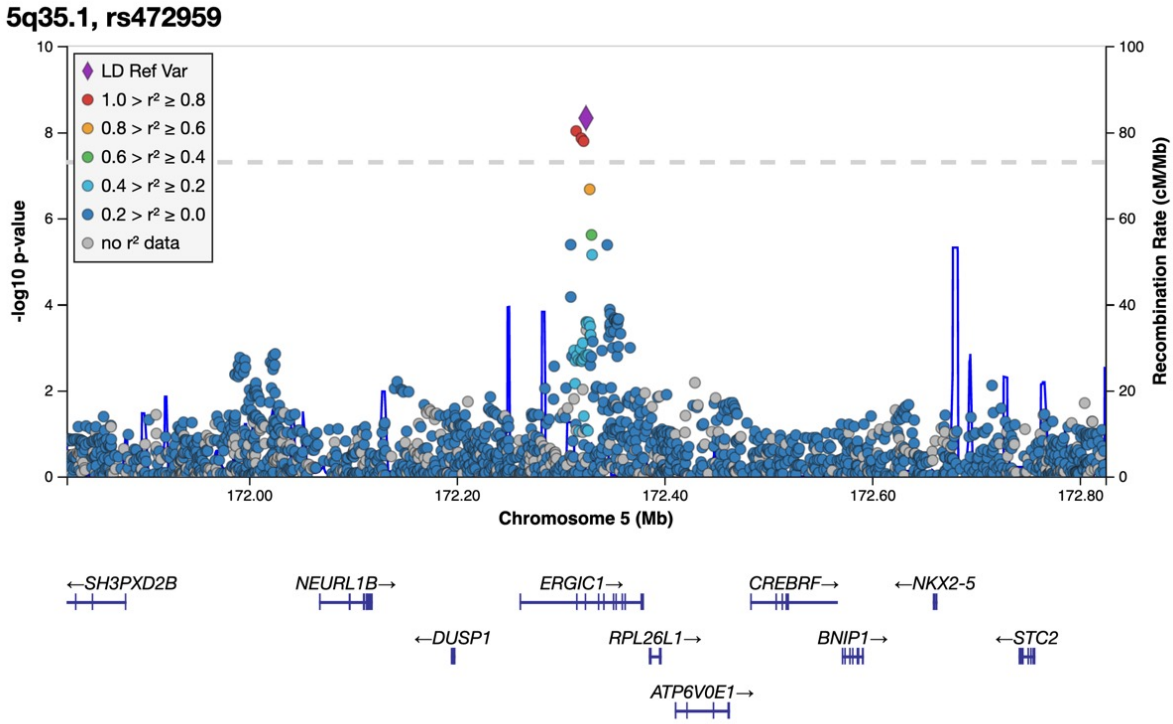

5q14.3, rs3930345
LD reference population: EUR
LD Ref Var
1.0 > r² ≥ 0.8
0.8 > r² ≥ 0.6
0.6 > r² ≥ 0.4
0.4 > r² ≥ 0.2
0.2 > r² ≥ 0.0
no r² data
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 5 (Mb)
82.40
82.60
82.80
83.00
83.20
XRCC4→
FTH1P9→
←HAPLN1
←ZP3P1
←EDIL3
AC094085.1→
VCAN→
RN7SKP295→
←AC109496.1
←COQ10BP2
←VCAN-AS1
←AC020899.1
RNU6-620P→
RNU4-11P→


5q14.3, rs3930345
LD reference population: EAS
LD Ref Var
1.0 > r² ≥ 0.8
0.8 > r² ≥ 0.6
0.6 > r² ≥ 0.4
0.4 > r² ≥ 0.2
0.2 > r² ≥ 0.0
no r² data
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 5 (Mb)
82.40
82.60
82.80
83.00
83.20
XRCC4→
FTH1P9→
←HAPLN1
←ZP3P1
←EDIL3
AC094085.1→
VCAN→
RN7SKP295→
←AC109496.1
←COQ10BP2
←VCAN-AS1
←AC020899.1
RNU6-620P→
RNU4-11P→

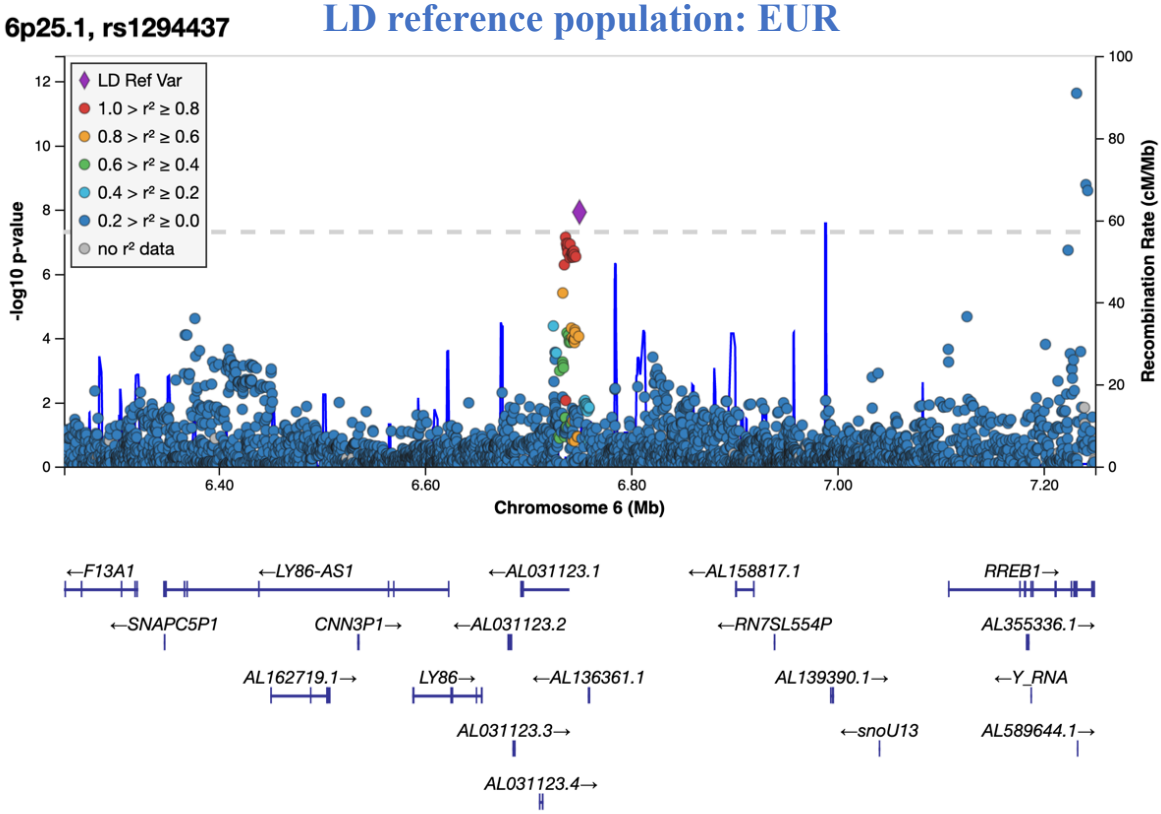
## LD reference population: EUR



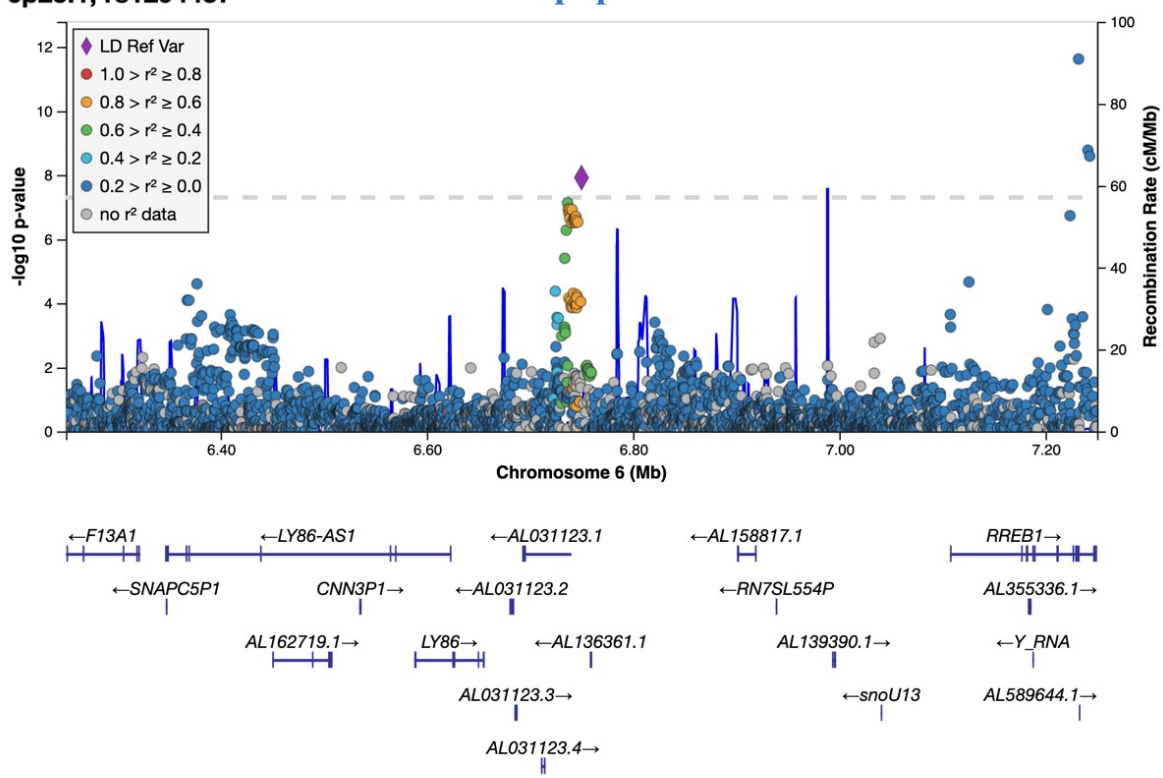

## LD reference population: EAS



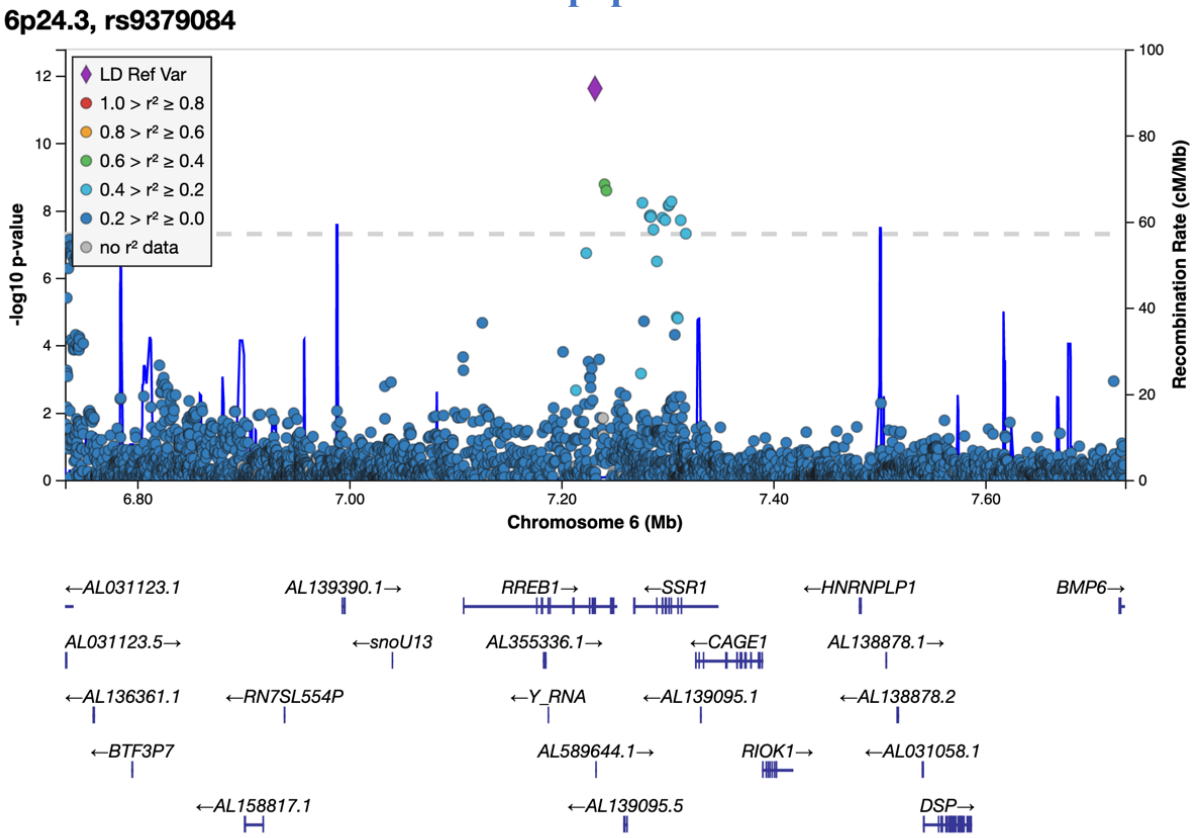
## LD reference population: EUR



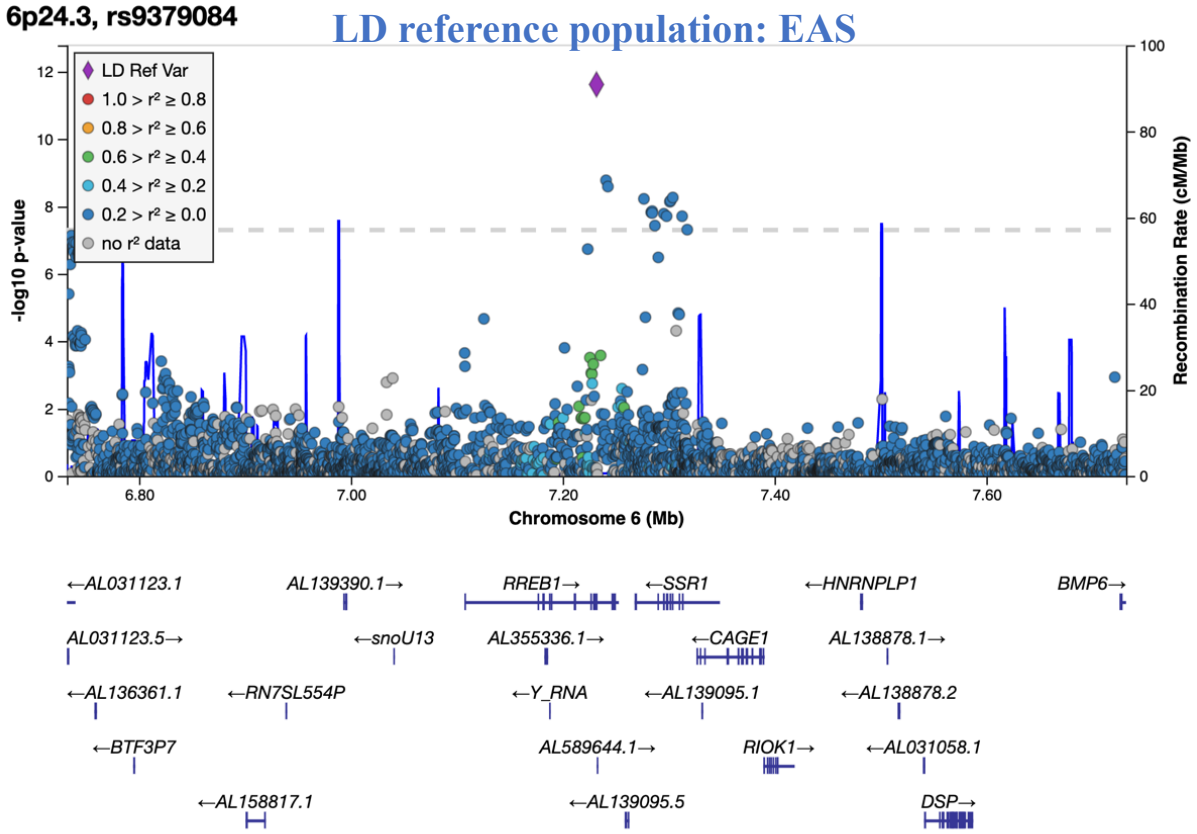

## LD reference population: EAS

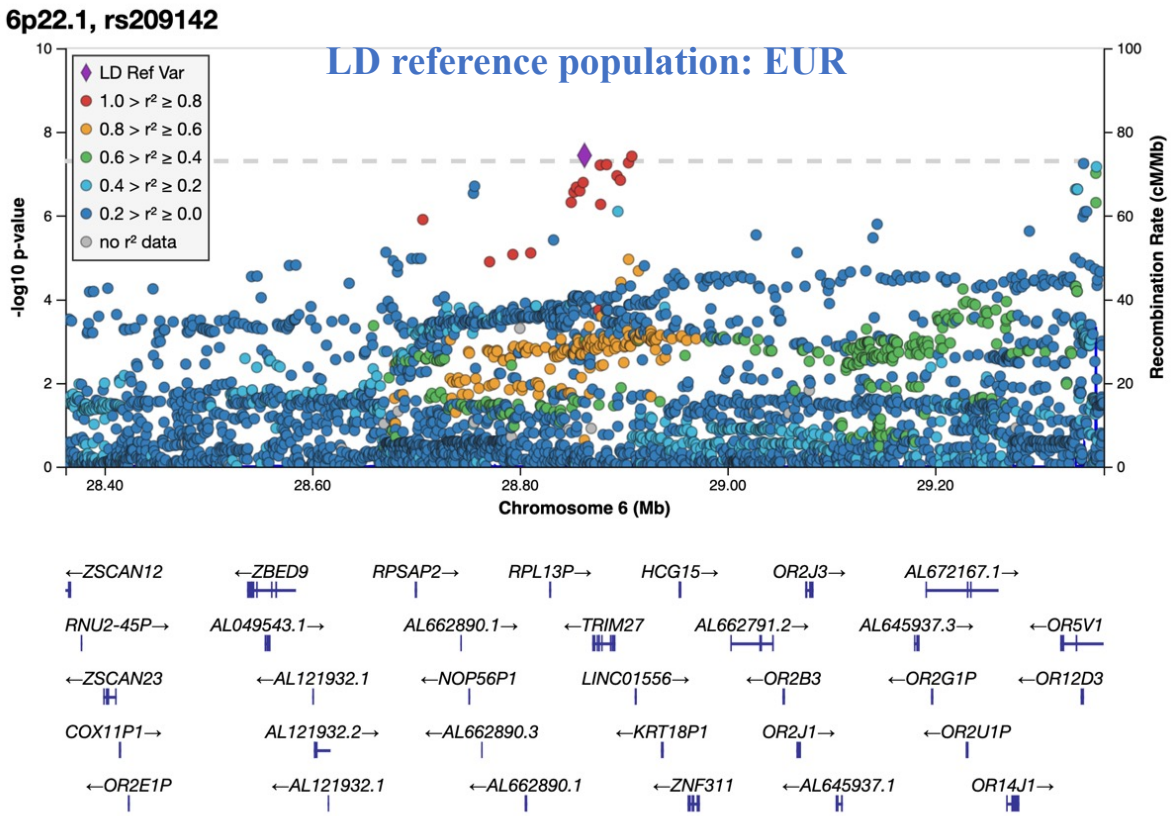


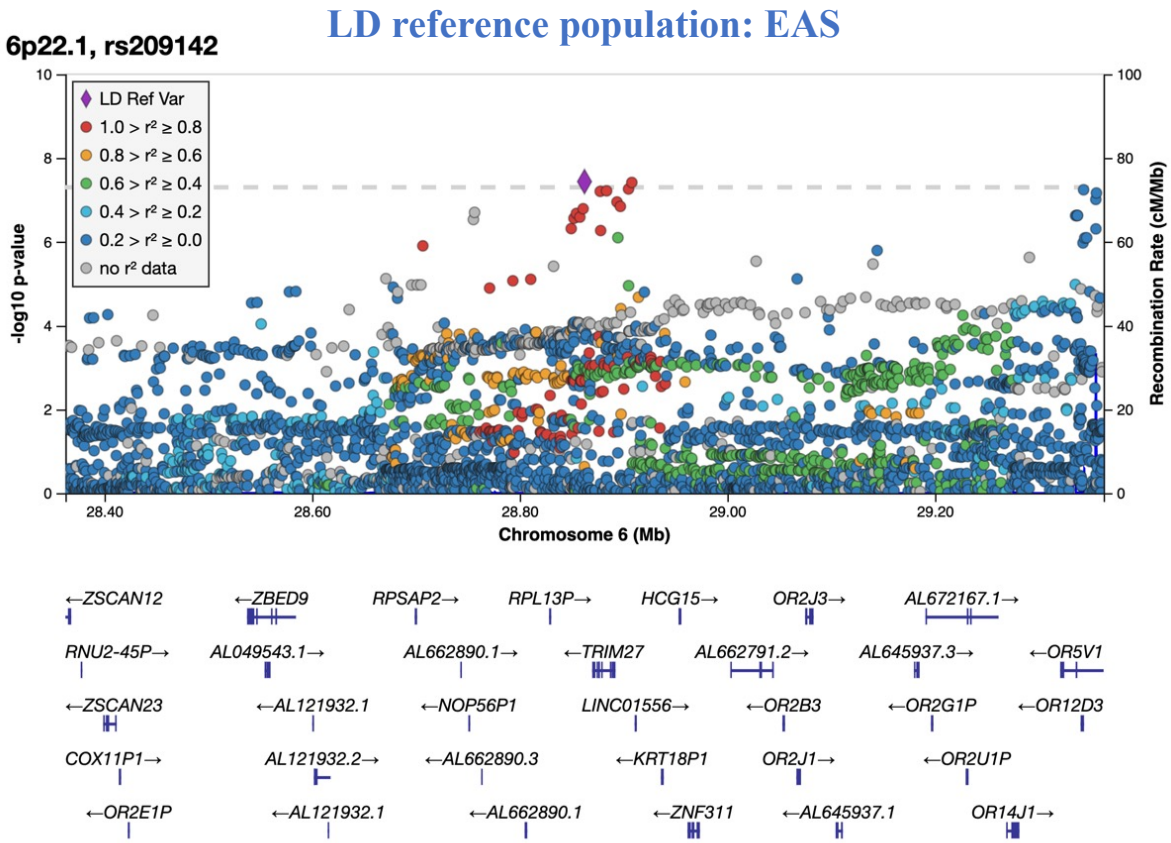
## LD reference population: EUR



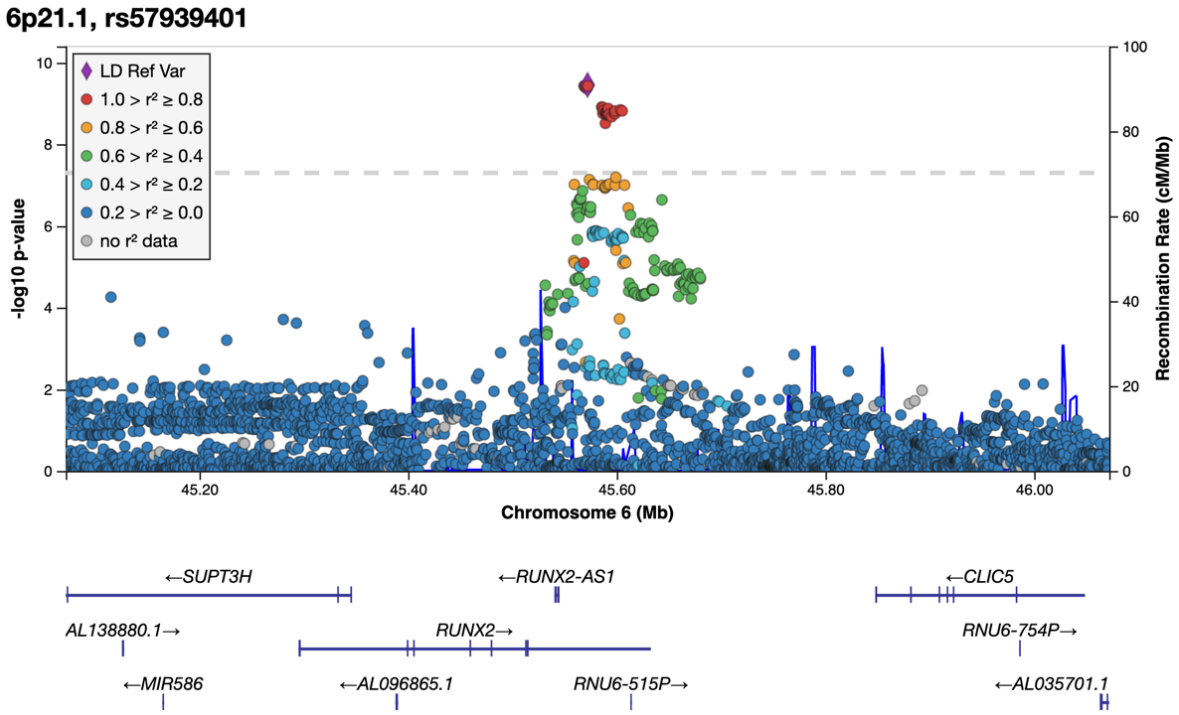

## LD reference population: EAS



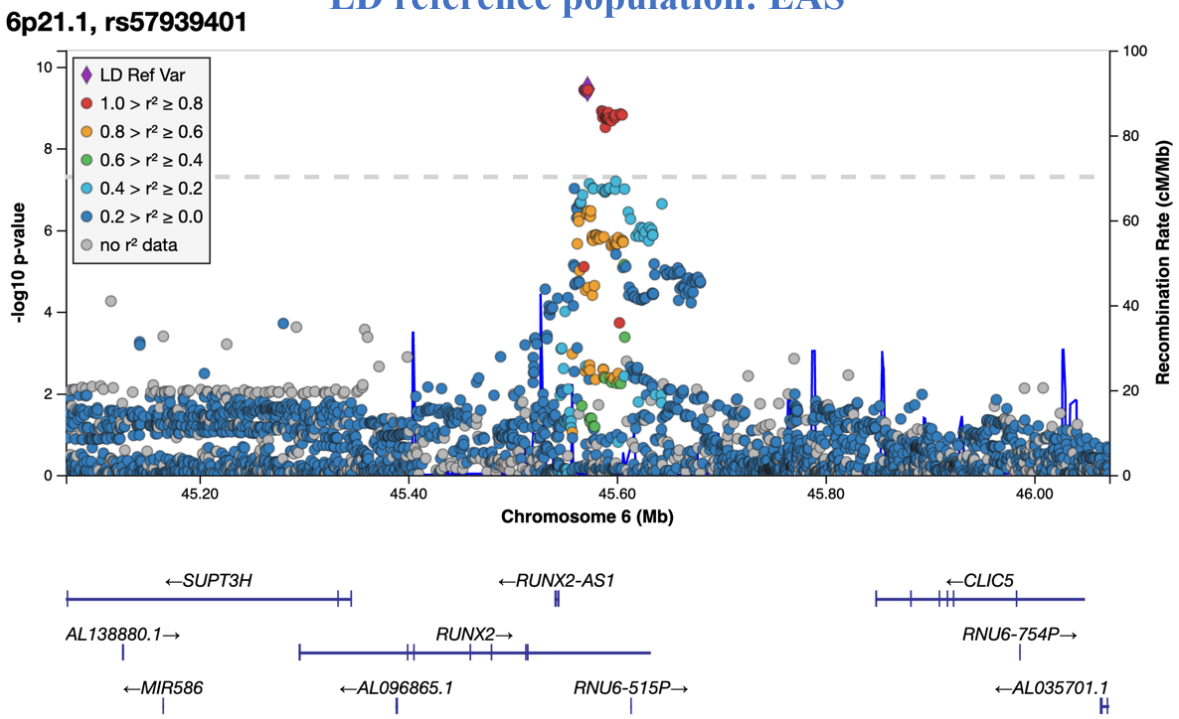

6p22.1, rs209142
LD reference population: EUR
LD Ref Var
1.0 > r² ≥ 0.8
0.8 > r² ≥ 0.6
0.6 > r² ≥ 0.4
0.4 > r² ≥ 0.2
0.2 > r² ≥ 0.0
no r² data
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 6 (Mb)
28.40
28.60
28.80
29.00
29.20
←ZSCAN12
←ZBED9
RPSAP2→
RPL13P→
HCG15→
OR2J3→
AL672167.1→
RNU2-45P→
AL049543.1→
AL662890.1→
←TRIM27
AL662791.2→
AL645937.3→
←OR5V1
←ZSCAN23
←AL121932.1
←NOP56P1
LINC01556→
←OR2B3
←OR2G1P
←OR12D3
COX11P1→
AL121932.2→
←AL662890.3
←KRT18P1
OR2J1→
←OR2U1P
←OR2E1P
←AL121932.1
←AL662890.1
←ZNF311
←AL645937.1
OR14J1→


LD reference population: EAS
6p22.1, rs209142
LD Ref Var
1.0 > r² ≥ 0.8
0.8 > r² ≥ 0.6
0.6 > r² ≥ 0.4
0.4 > r² ≥ 0.2
0.2 > r² ≥ 0.0
no r² data
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 6 (Mb)
28.40
28.60
28.80
29.00
29.20
←ZSCAN12
←ZBED9
RPSAP2→
RPL13P→
HCG15→
OR2J3→
AL672167.1→
RNU2-45P→
AL049543.1→
AL662890.1→
←TRIM27
AL662791.2→
AL645937.3→
←OR5V1
←ZSCAN23
←AL121932.1
←NOP56P1
LINC01556→
←OR2B3
←OR2G1P
←OR12D3
COX11P1→
AL121932.2→
←AL662890.3
←KRT18P1
OR2J1→
←OR2U1P
←OR2E1P
←AL121932.1
←AL662890.1
←ZNF311
←AL645937.1
OR14J1→

## LD reference population: EUR

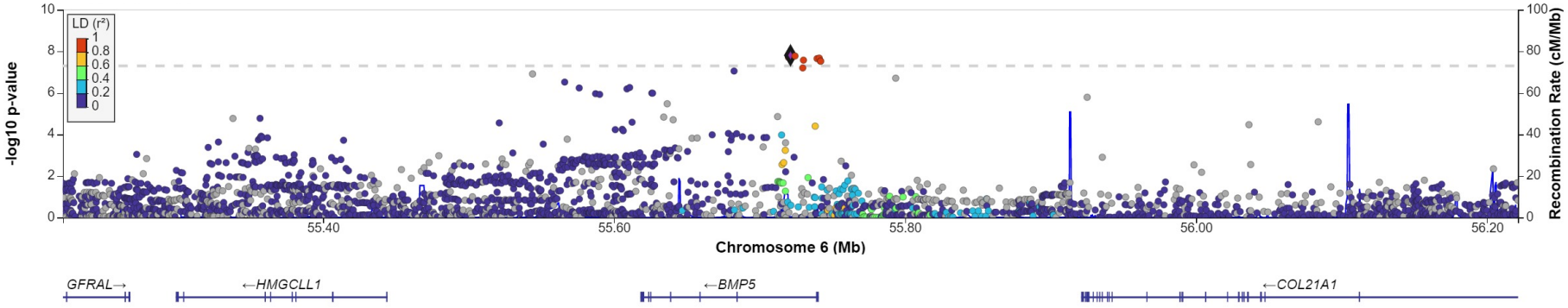



## LD reference population: EAS



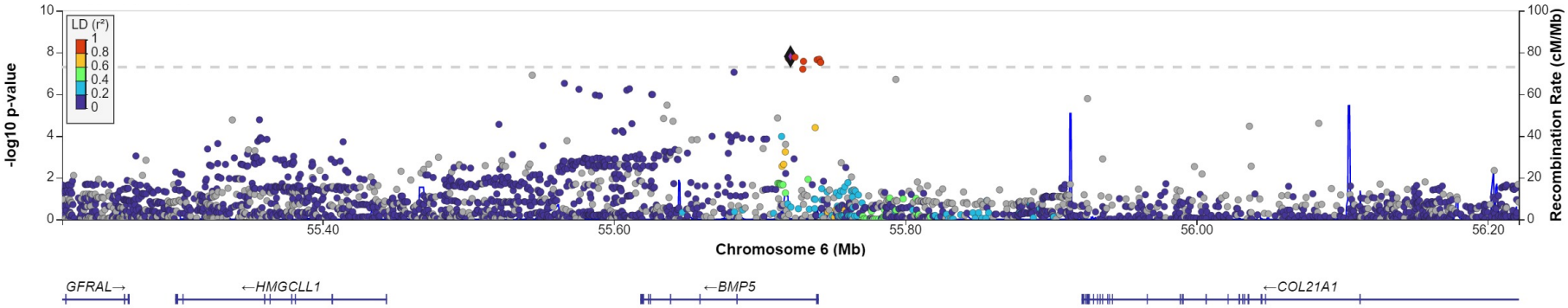
## LD reference population: EUR

**6p12.1, rs6912214**

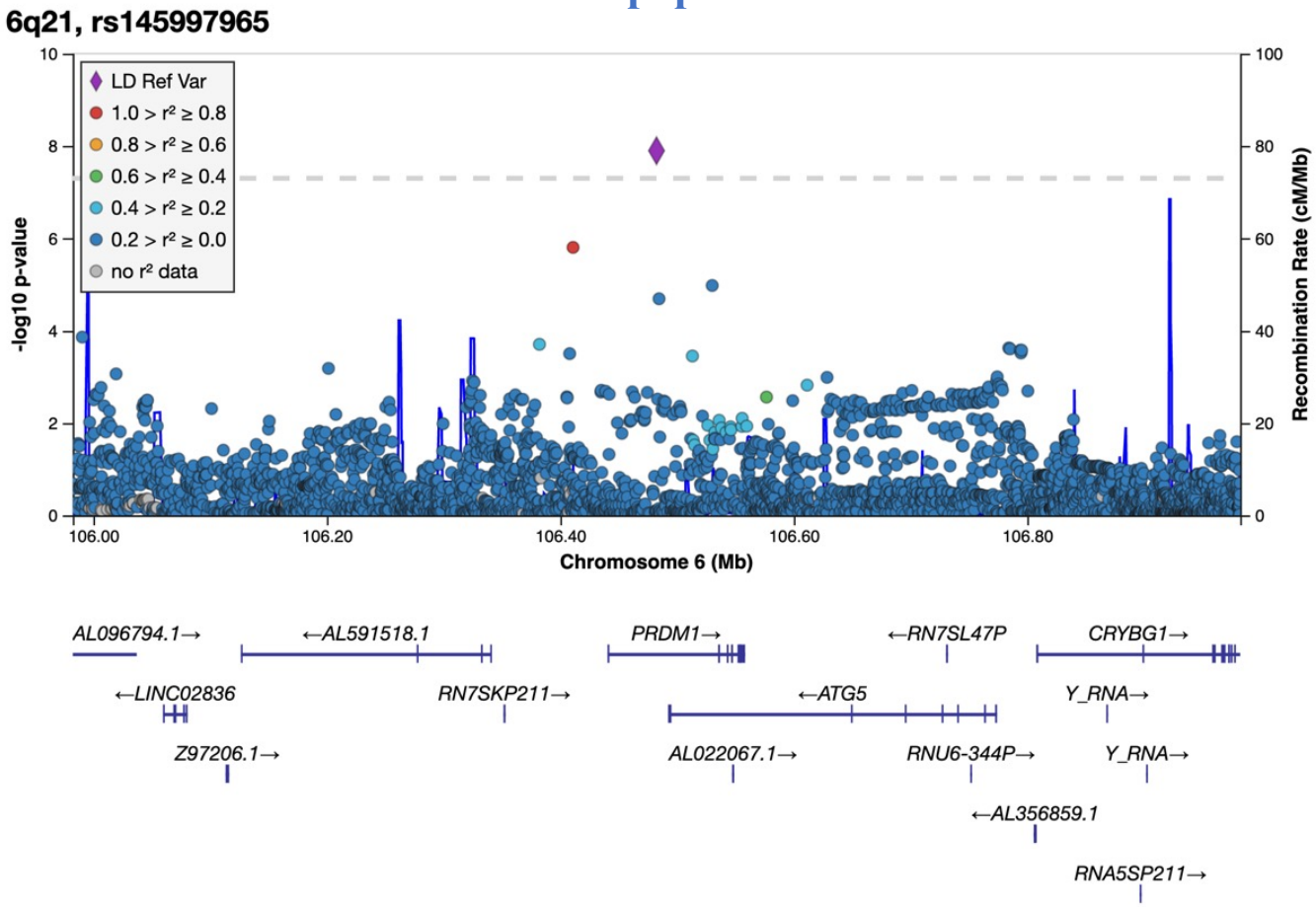



## LD reference population: EAS

**6p12.1, rs6912214**



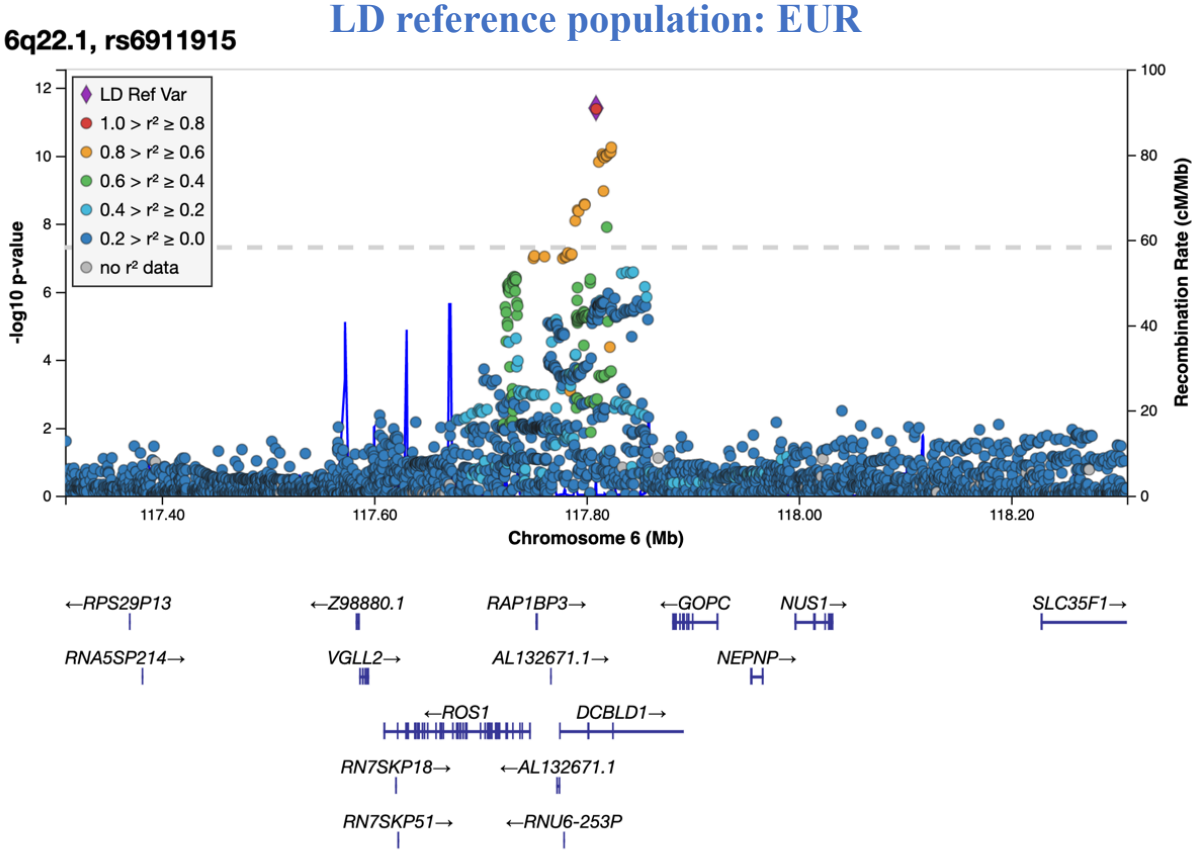
## LD reference population: EUR



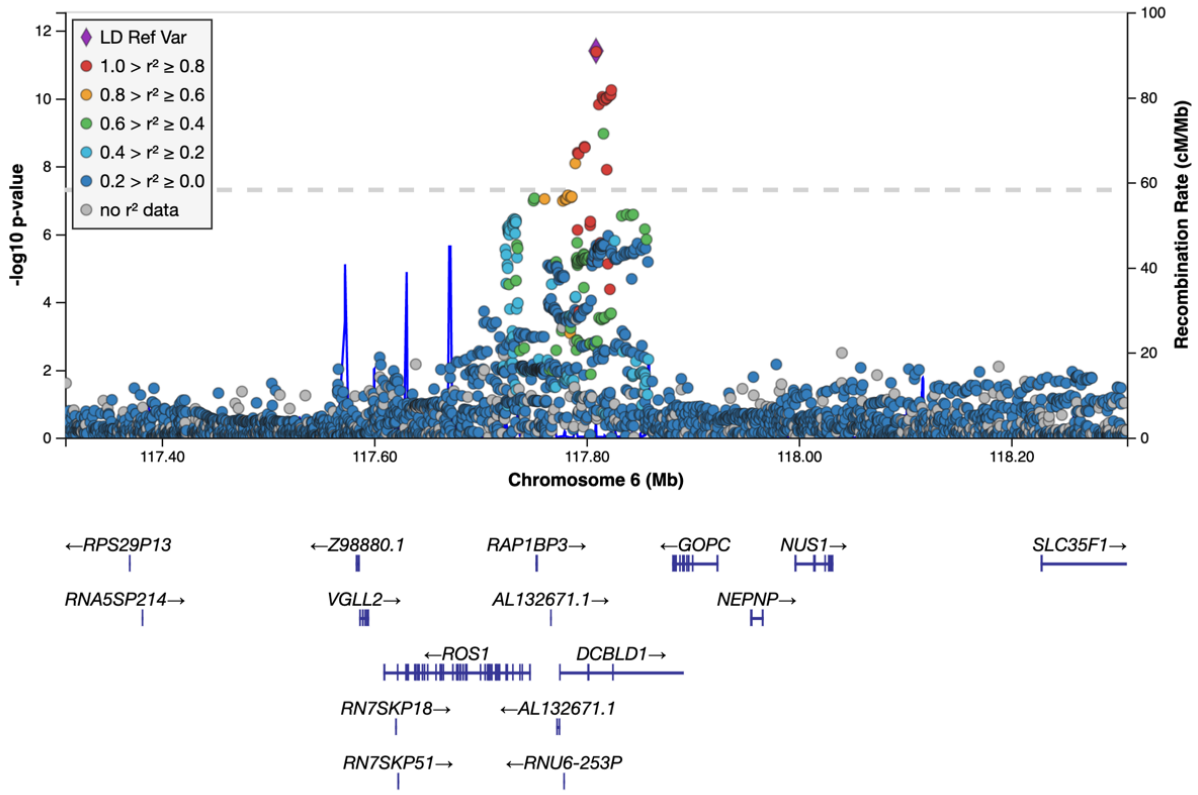

## LD reference population: EAS

rs145997965 is monoallelic in the EAS population

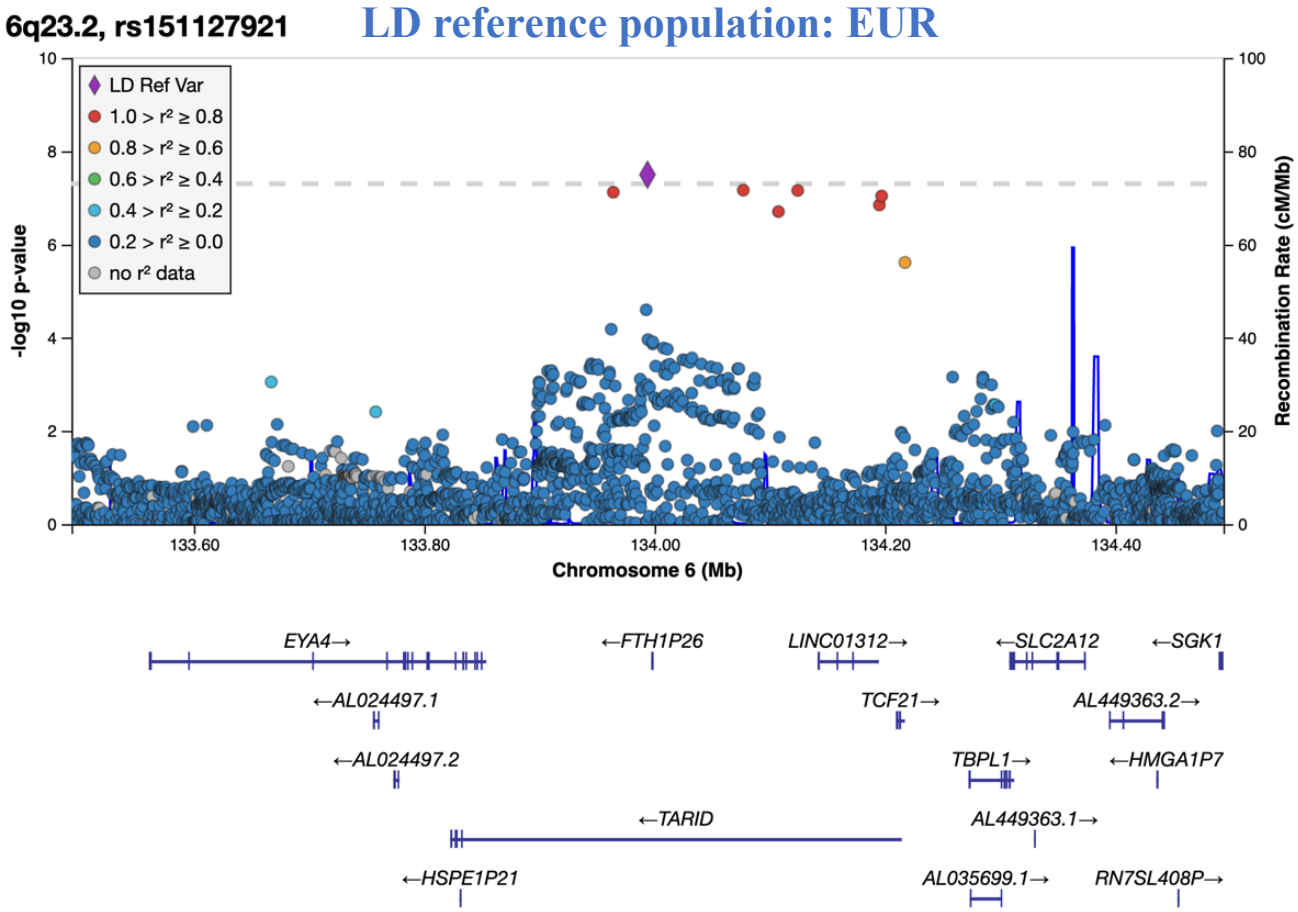
## LD reference population: EUR




## LD reference population: EAS



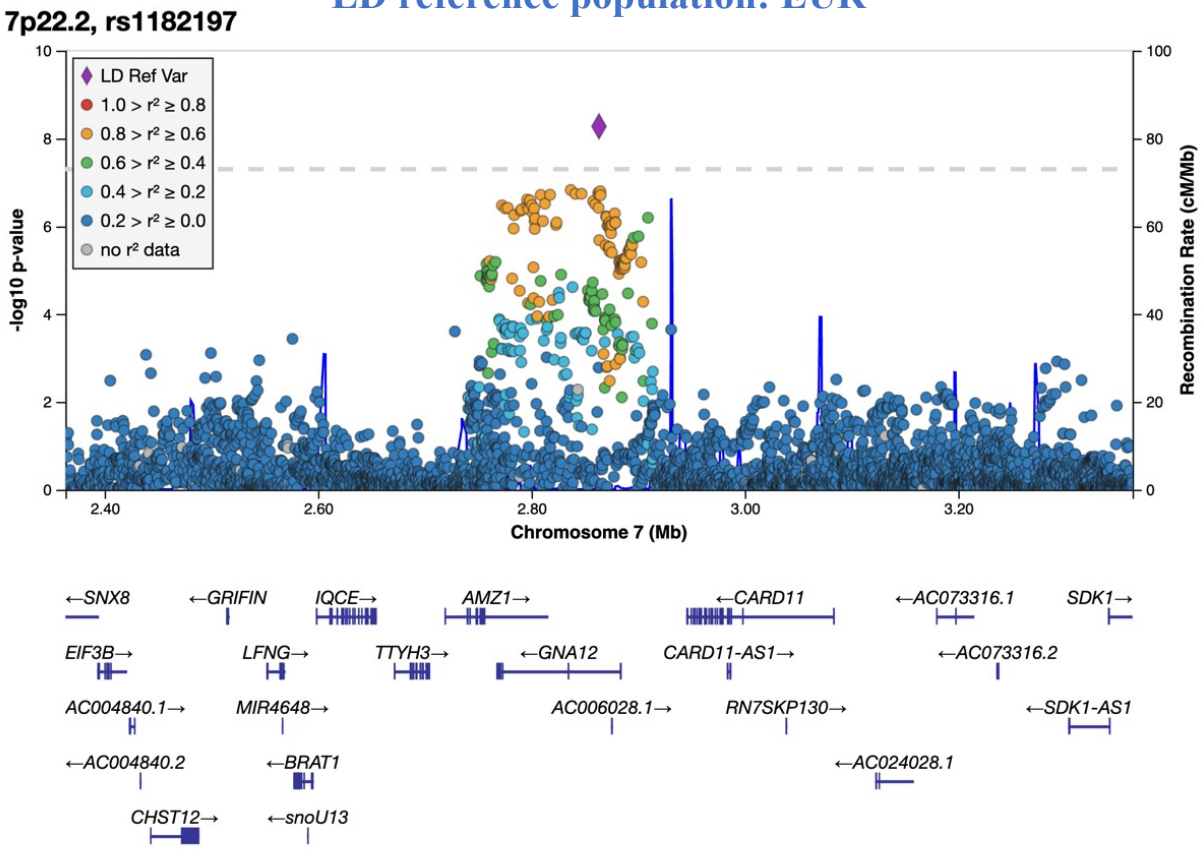
## LD reference population: EUR



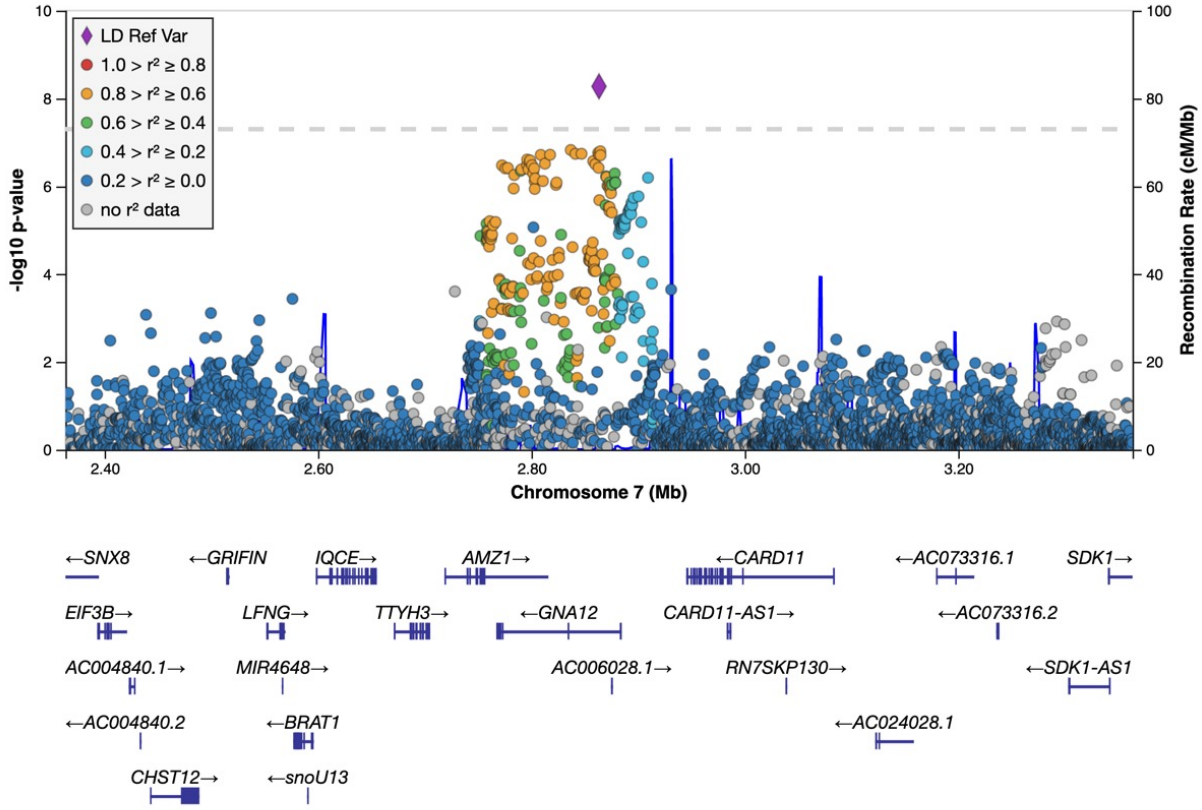

## LD reference population: EAS

rs151127921 is monoallelic in the EAS population

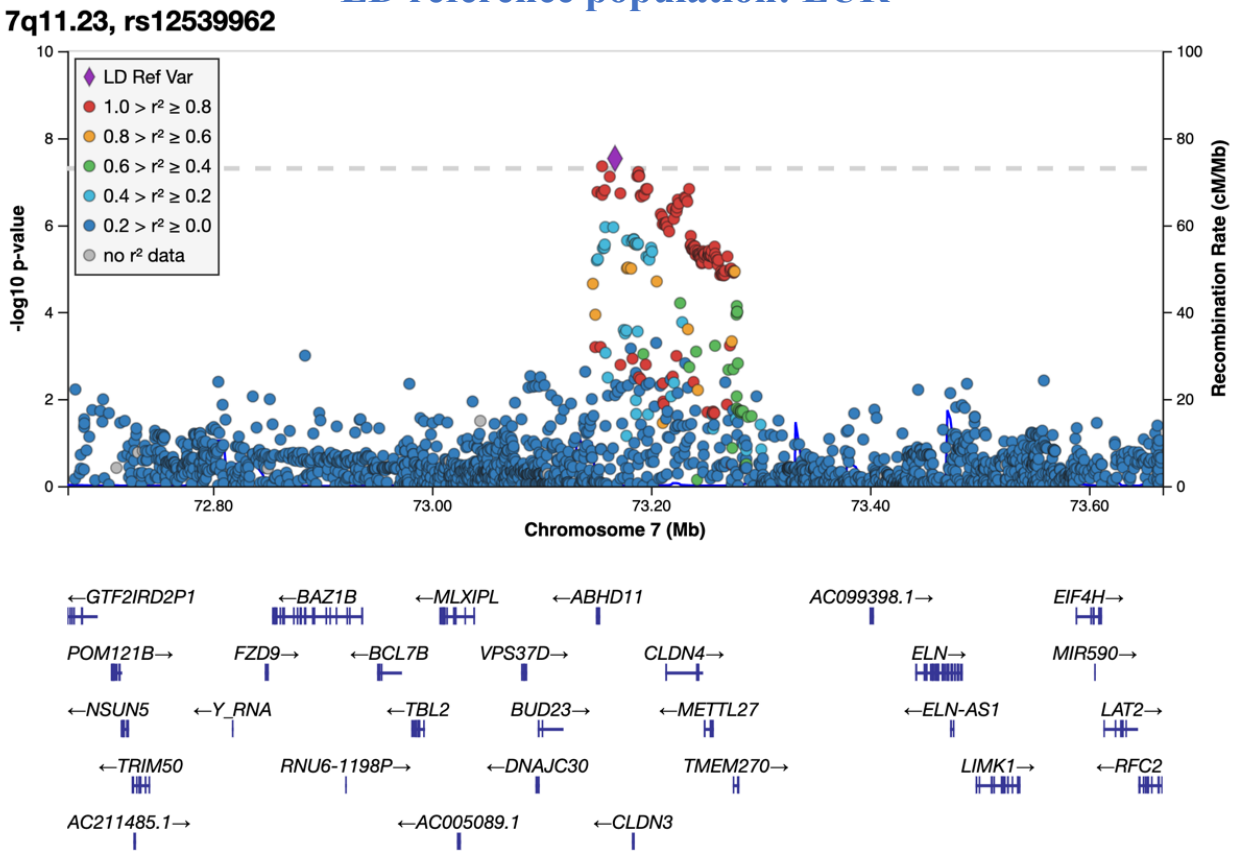
## LD reference population: EUR



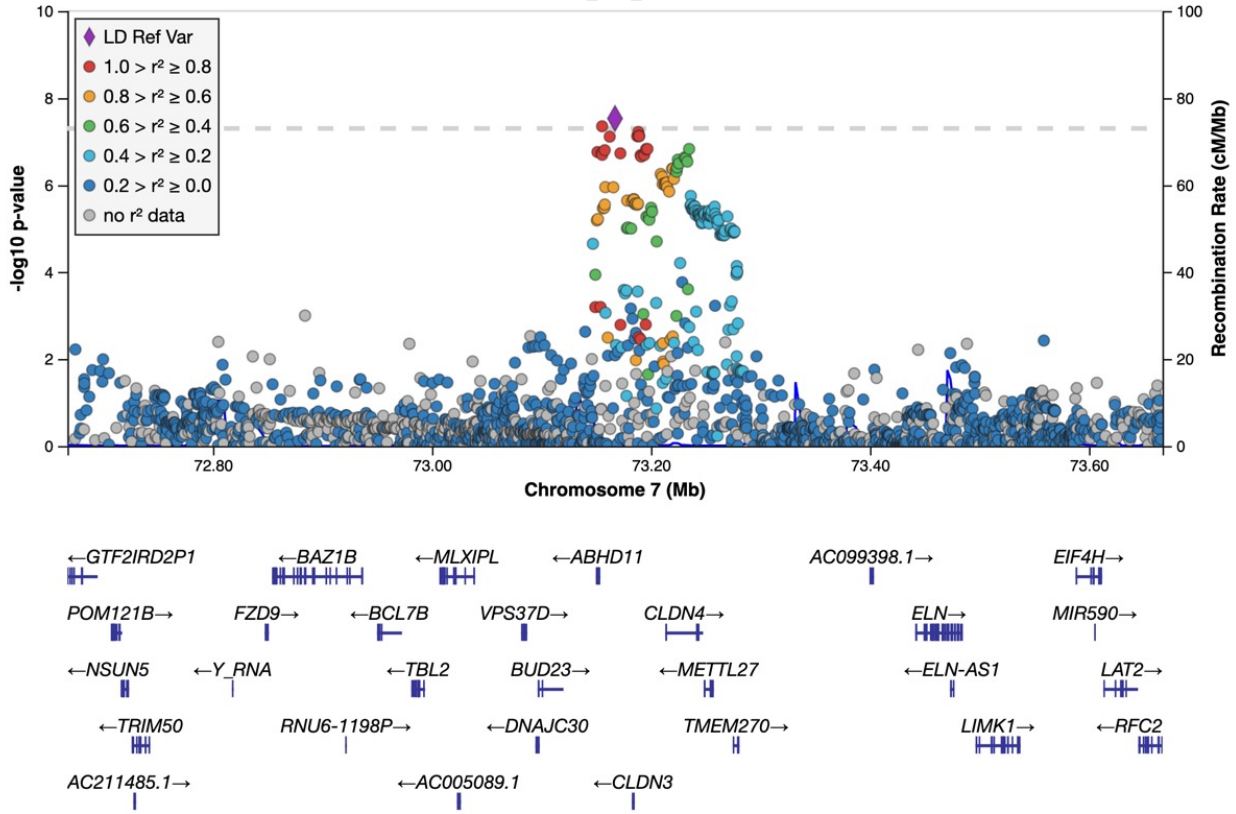

## LD reference population: EAS



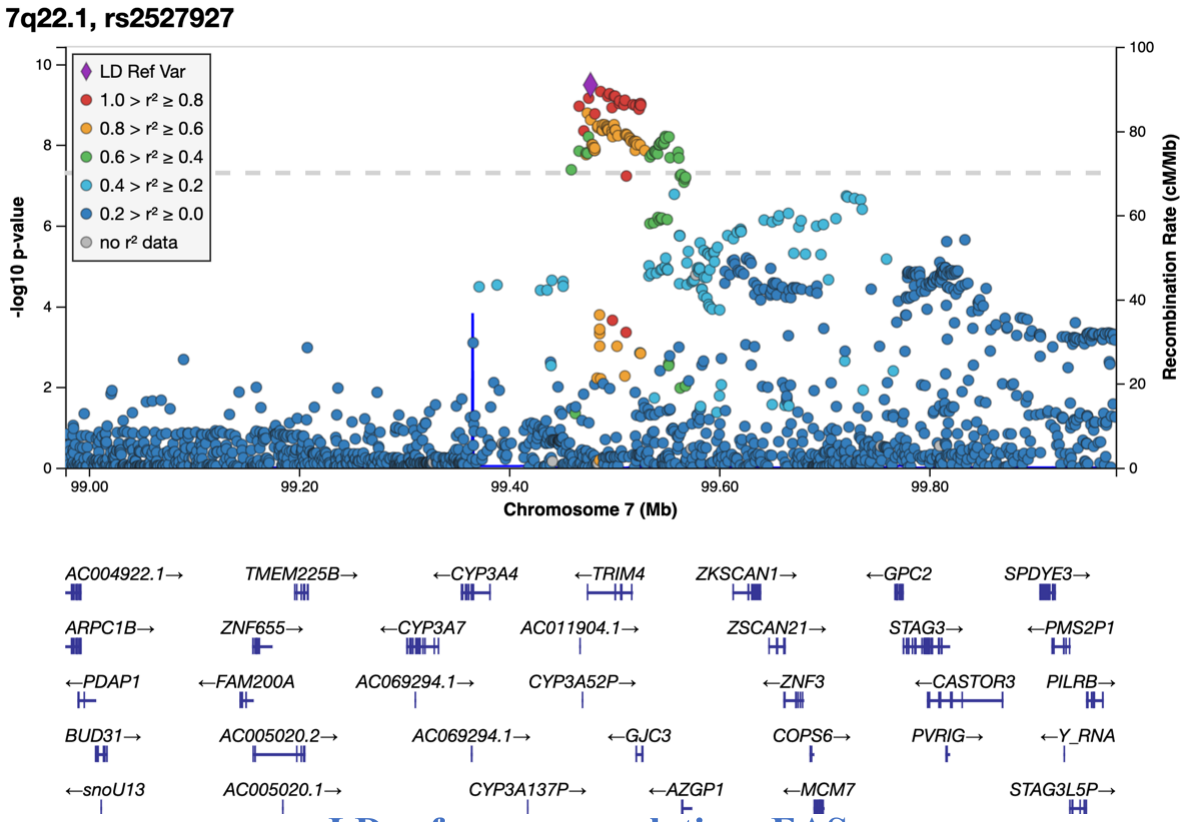
## LD reference population: EUR



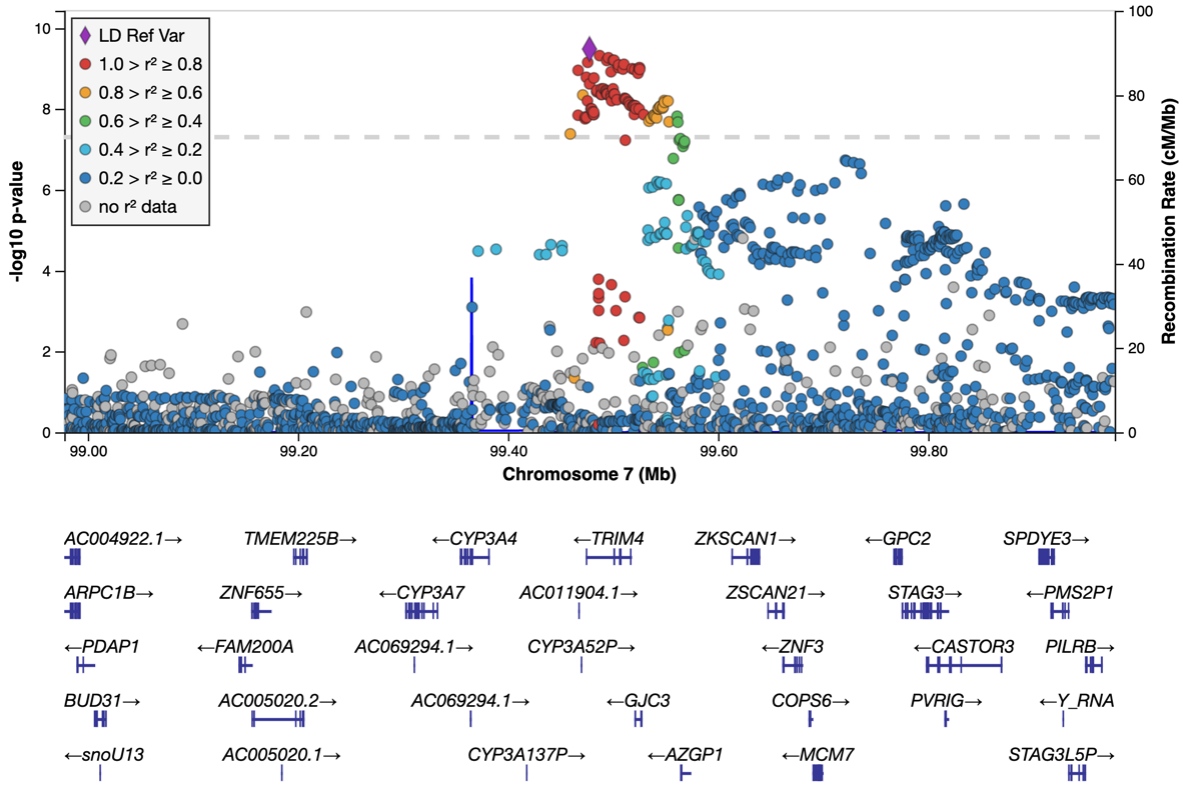

## LD reference population: EAS



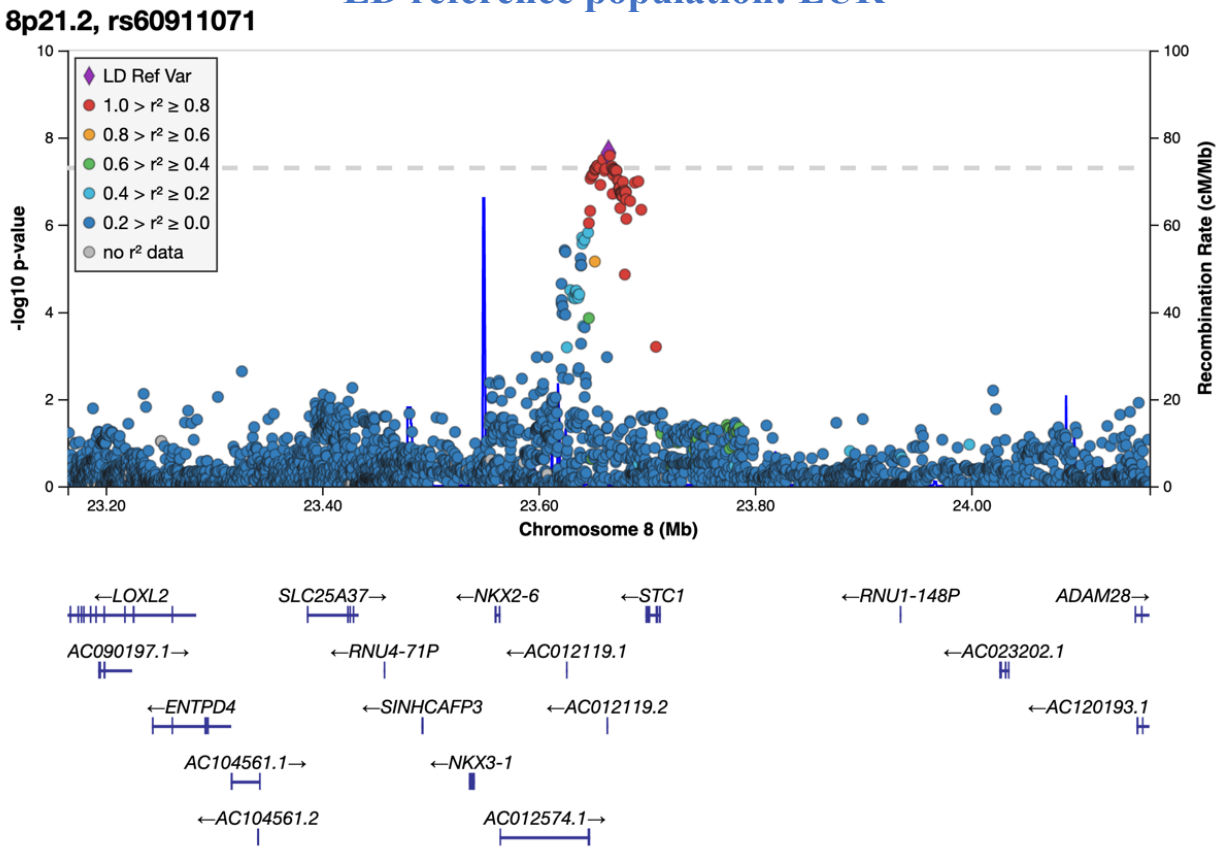
## LD reference population: EUR



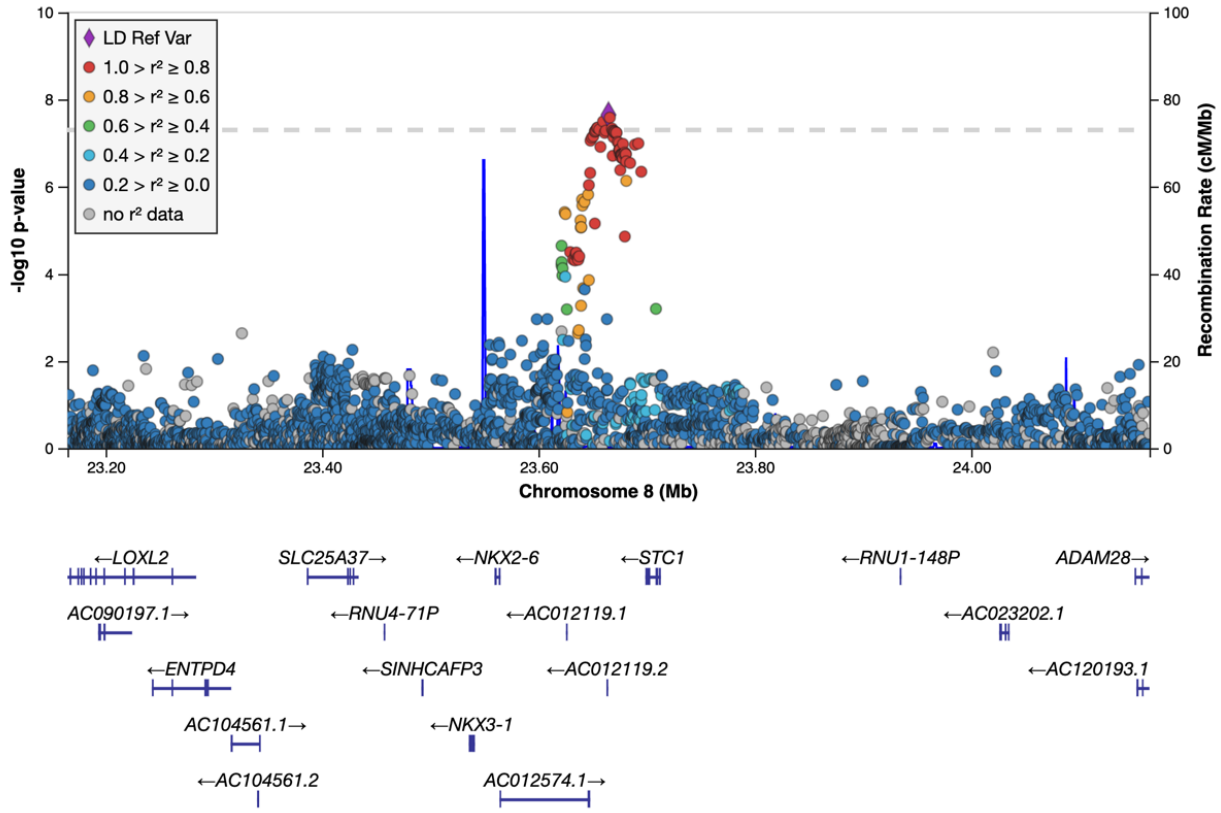

## LD reference population: EAS



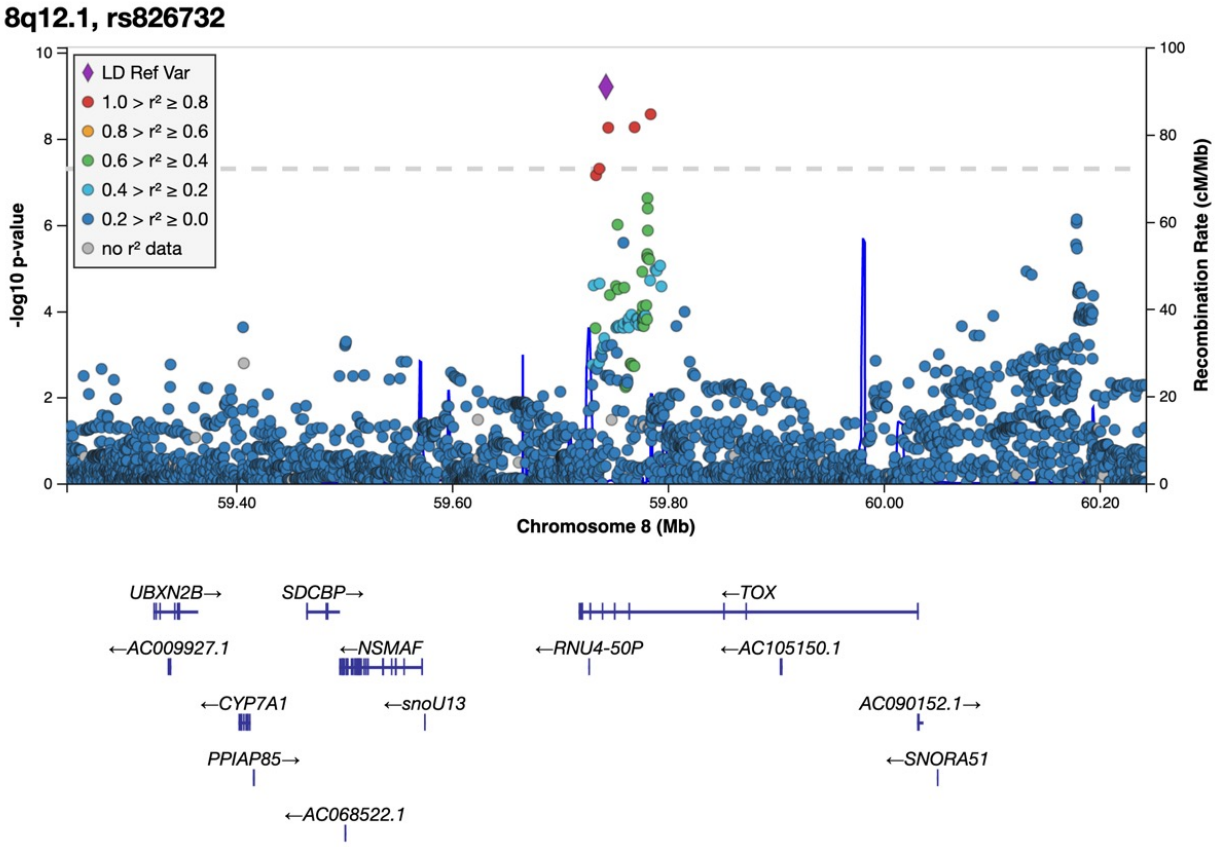
## LD reference population: EUR



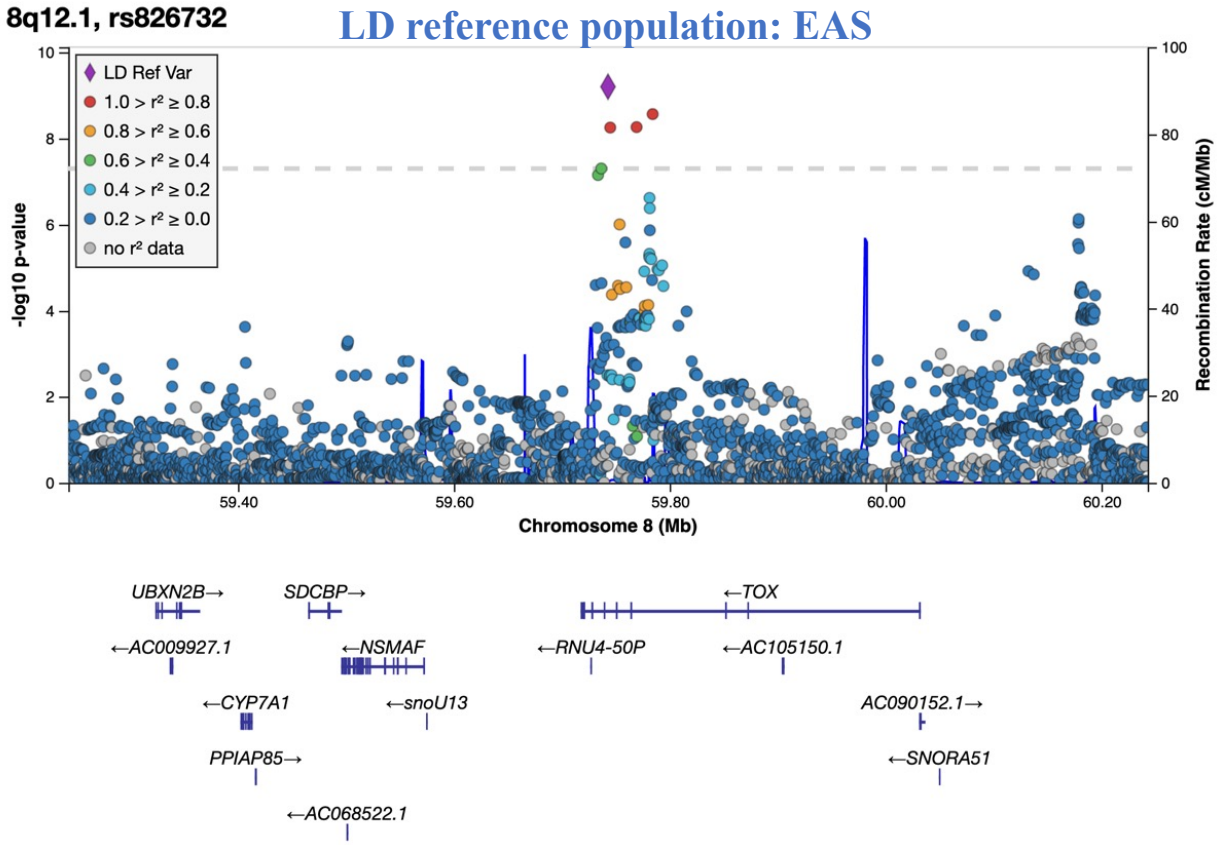

## LD reference population: EAS



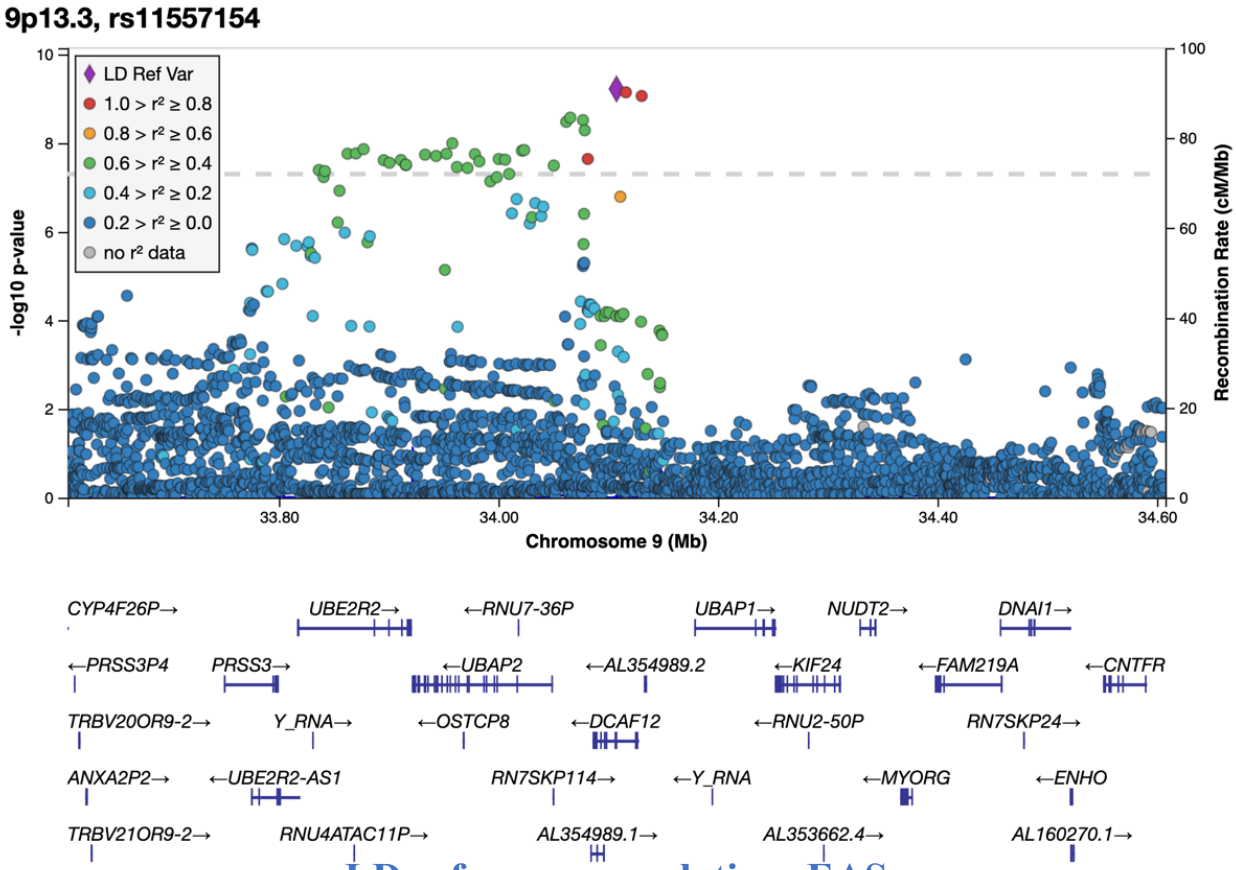
## LD reference population: EUR



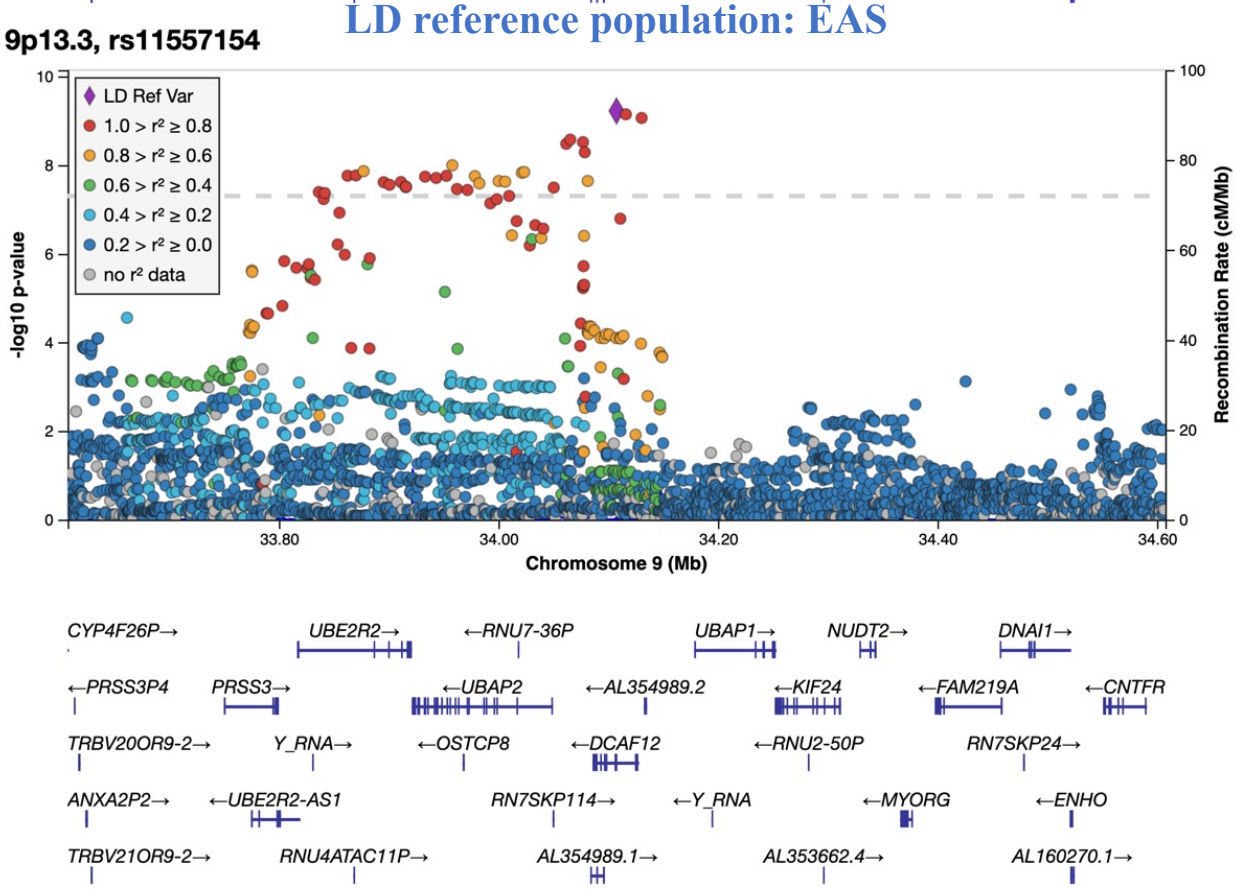

## LD reference population: EAS



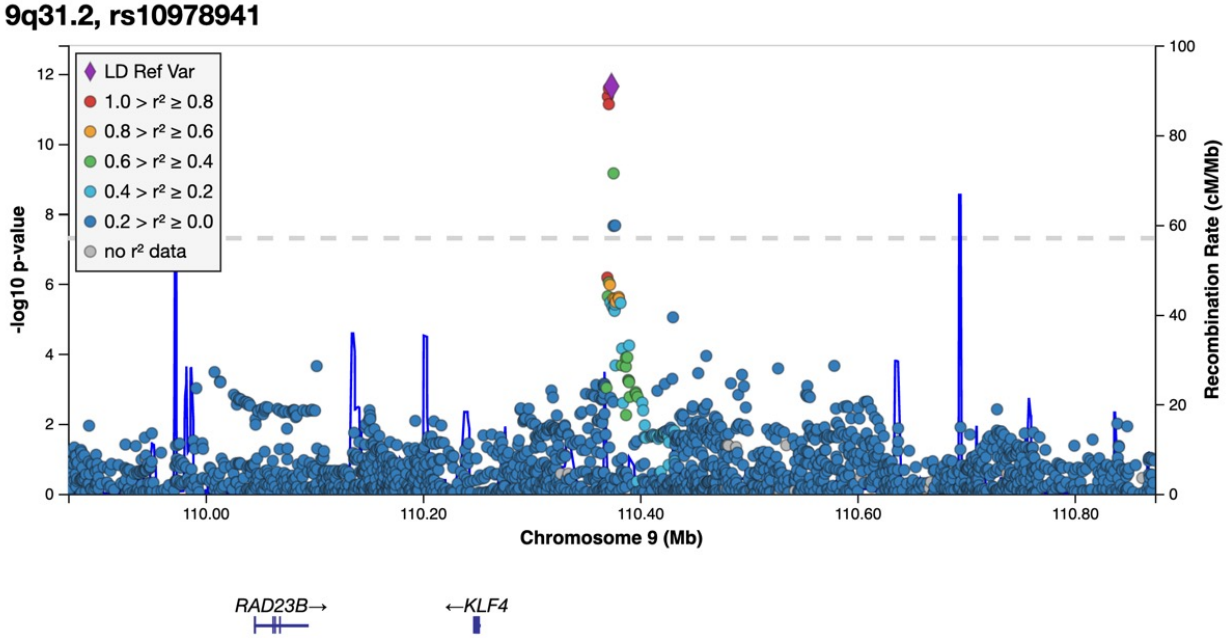
## LD reference population: EUR



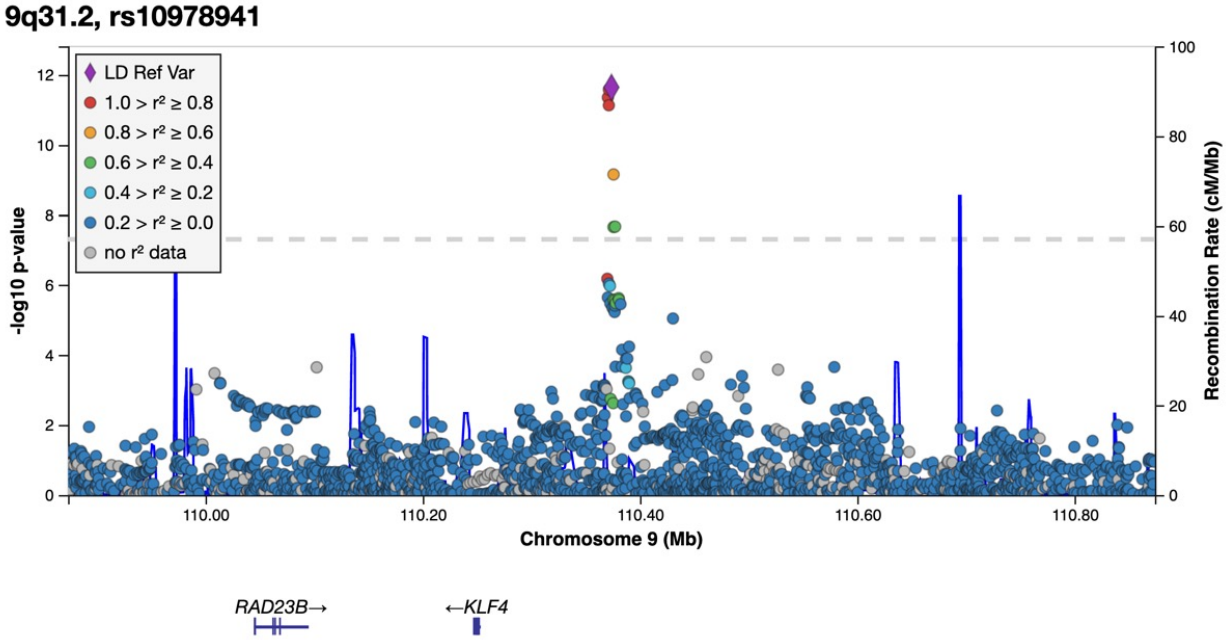

## LD reference population: EAS



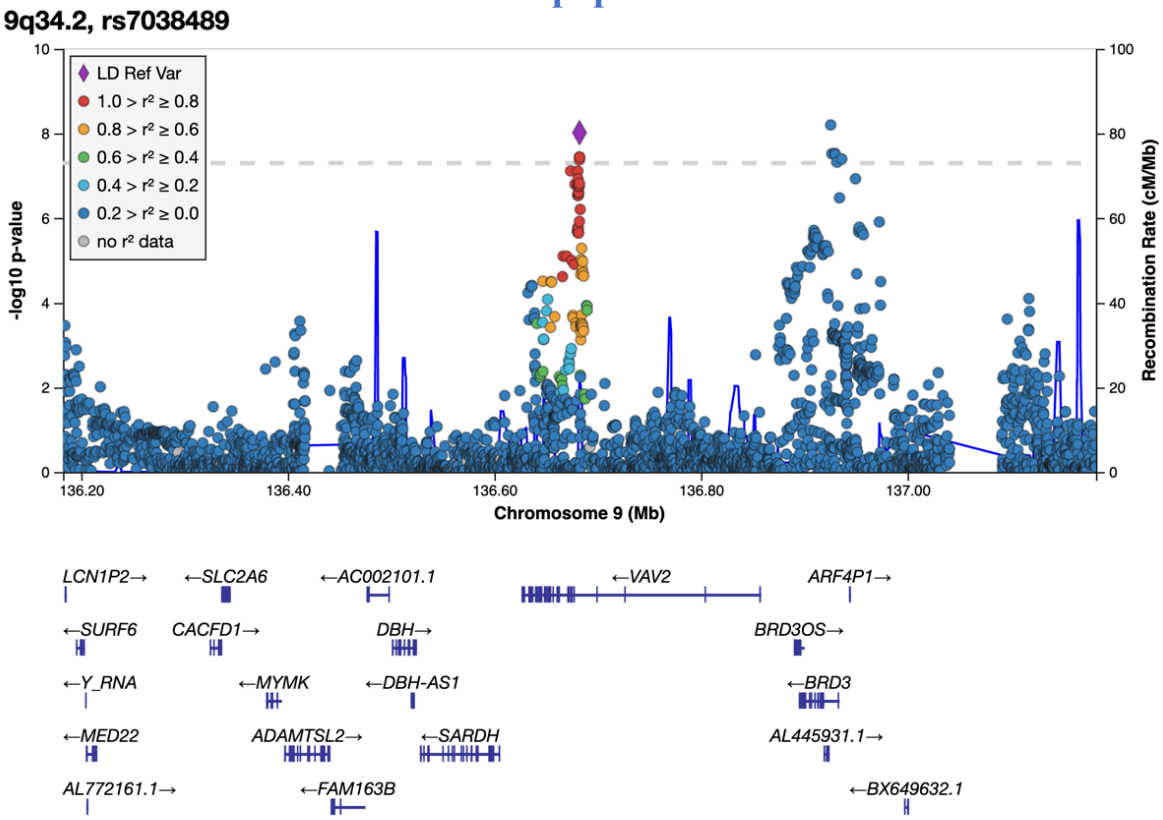
## LD reference population: EUR



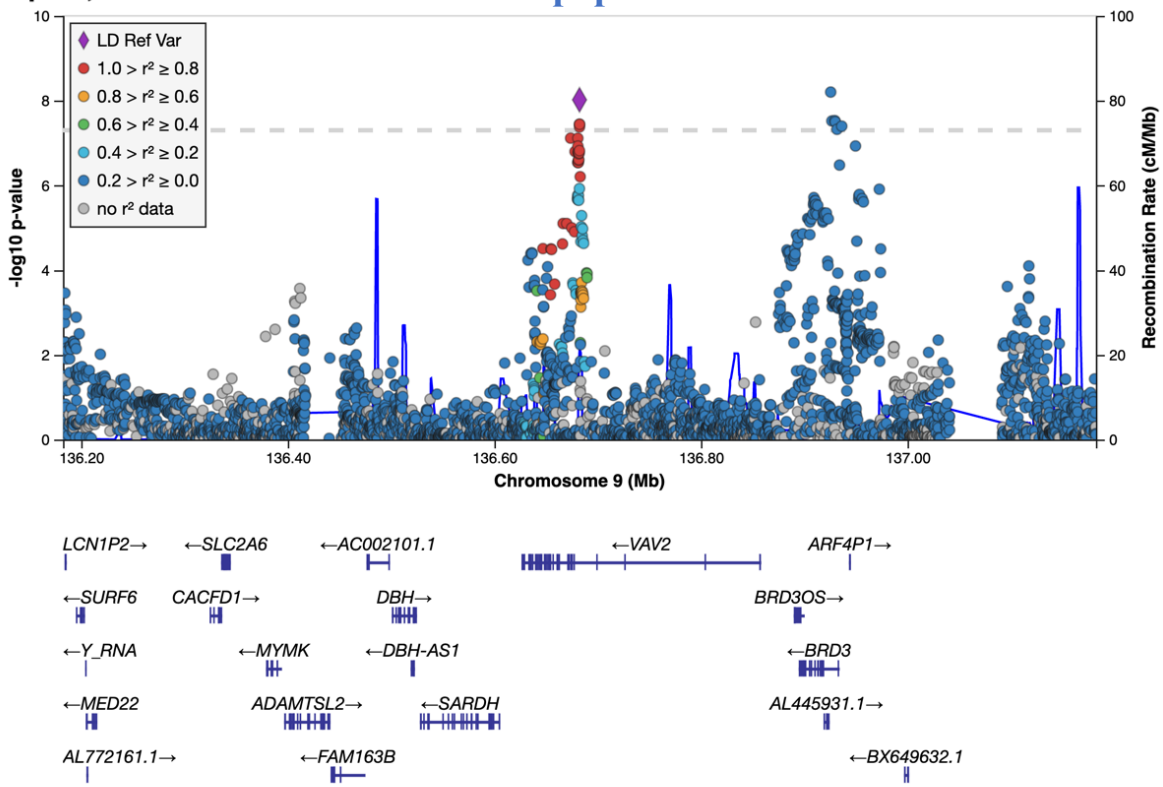

## LD reference population: EAS

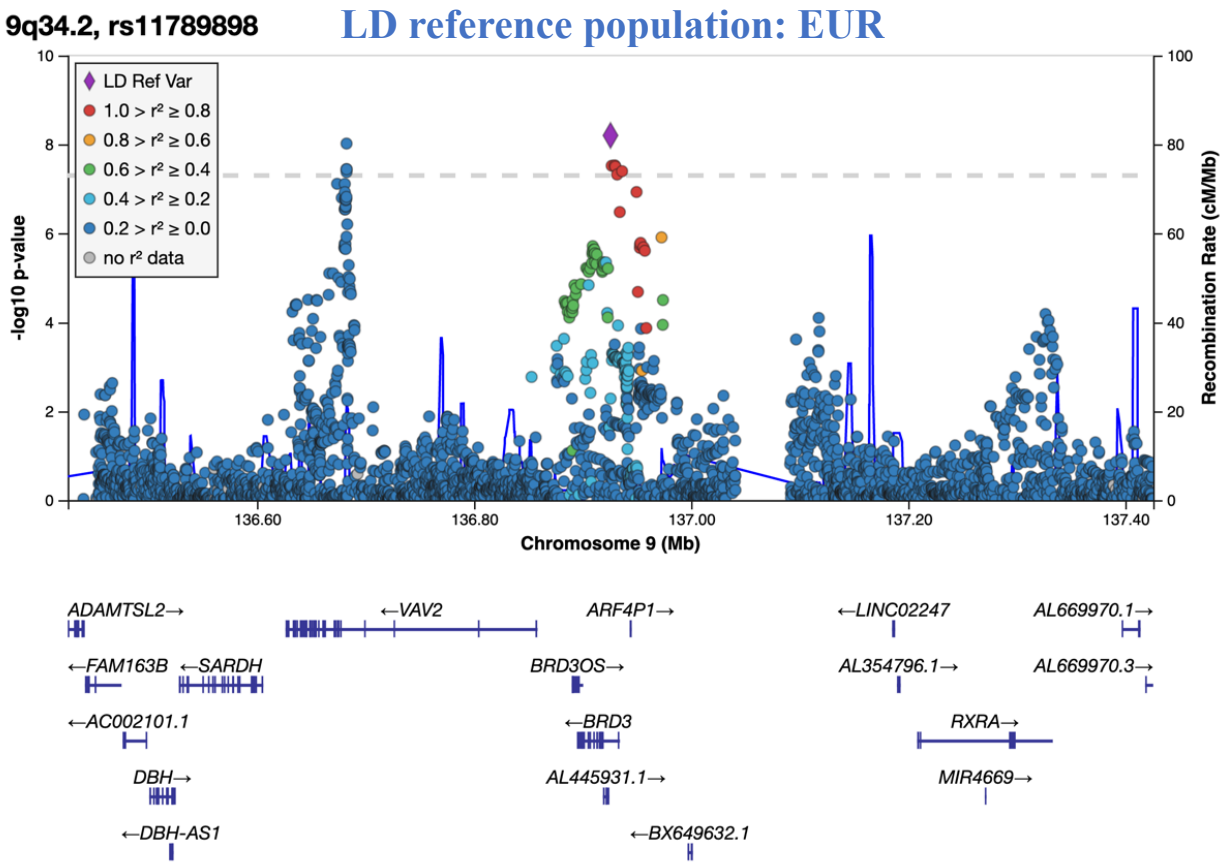


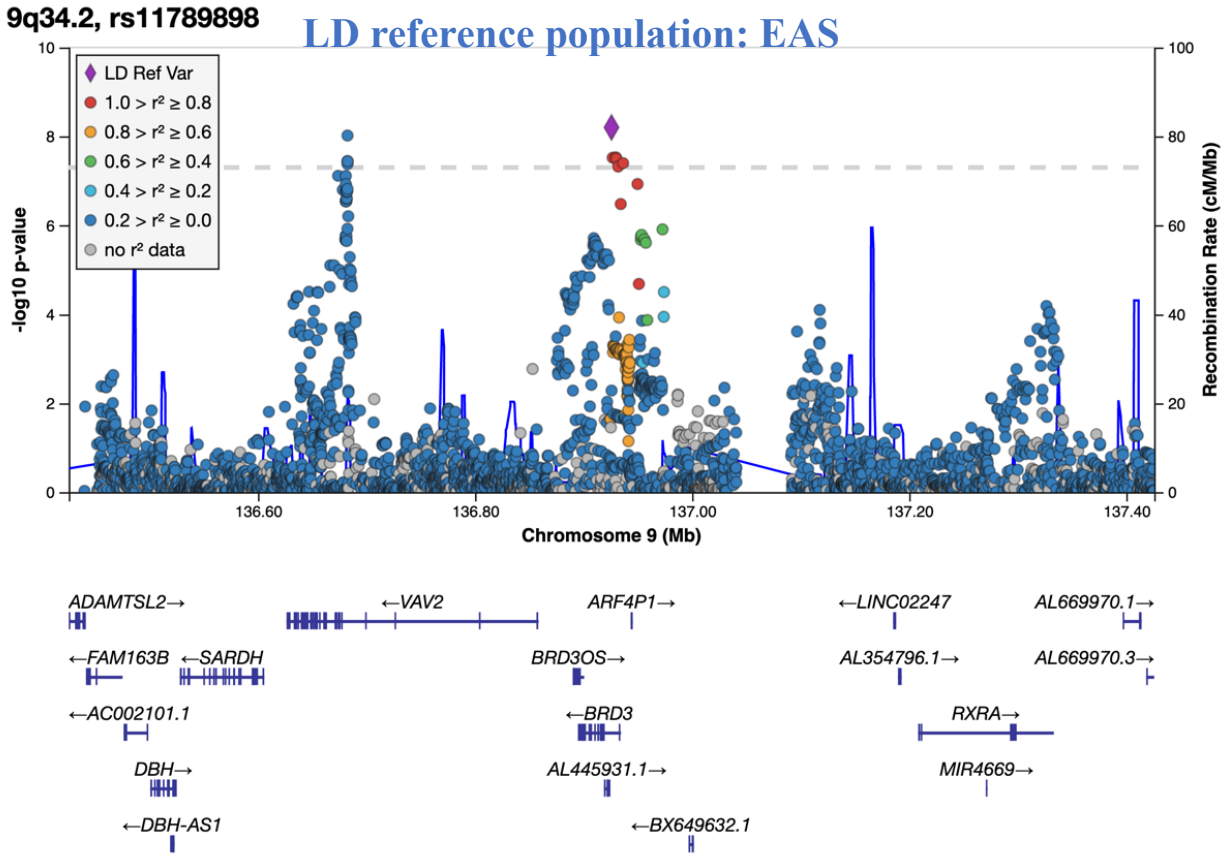
## LD reference population: EUR




## LD reference population: EAS

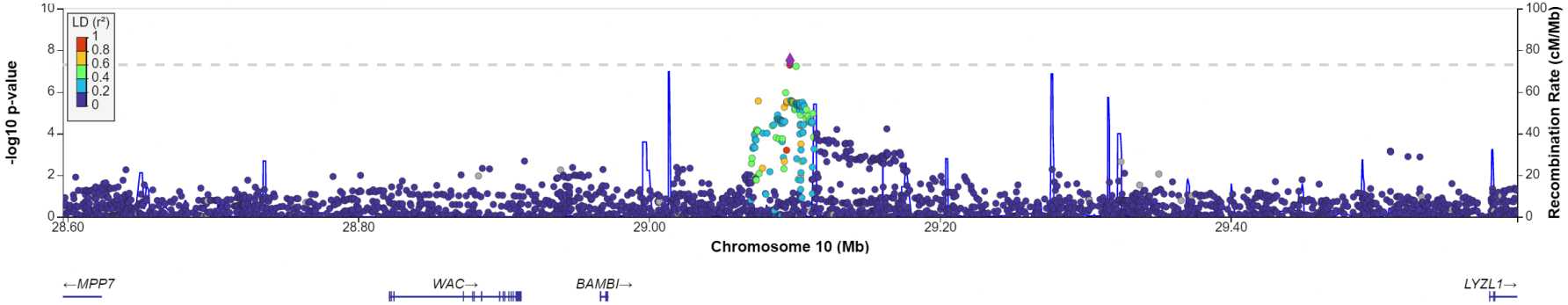



9q34.2, rs11789898
LD reference population: EUR
LD Ref Var
1.0 > r² ≥ 0.8
0.8 > r² ≥ 0.6
0.6 > r² ≥ 0.4
0.4 > r² ≥ 0.2
0.2 > r² ≥ 0.0
no r² data
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 9 (Mb)
136.60
136.80
137.00
137.20
137.40
ADAMTSL2→
←VAV2
ARF4P1→
←LINC02247
AL669970.1→
←FAM163B
←SARDH
BRD3OS→
AL354796.1→
AL669970.3→
←AC002101.1
←BRD3
RXRA→
DBH→
AL445931.1→
MIR4669→
←DBH-AS1
←BX649632.1


9q34.2, rs11789898
LD reference population: EAS
LD Ref Var
1.0 > r² ≥ 0.8
0.8 > r² ≥ 0.6
0.6 > r² ≥ 0.4
0.4 > r² ≥ 0.2
0.2 > r² ≥ 0.0
no r² data
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 9 (Mb)
136.60
136.80
137.00
137.20
137.40
ADAMTSL2→
←VAV2
ARF4P1→
←LINC02247
AL669970.1→
←FAM163B
←SARDH
BRD3OS→
AL354796.1→
AL669970.3→
←AC002101.1
←BRD3
RXRA→
DBH→
AL445931.1→
MIR4669→
←DBH-AS1
←BX649632.1

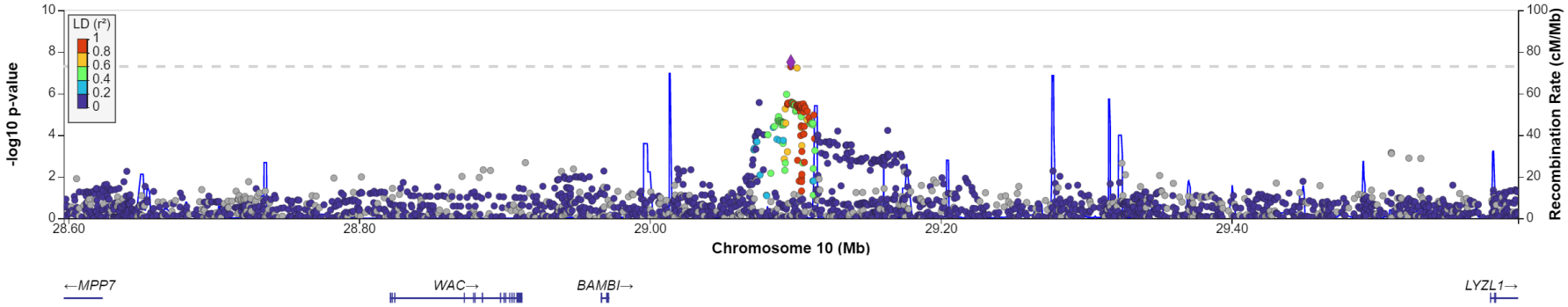
## LD reference population: EUR

**10p12.1, rs1775910**

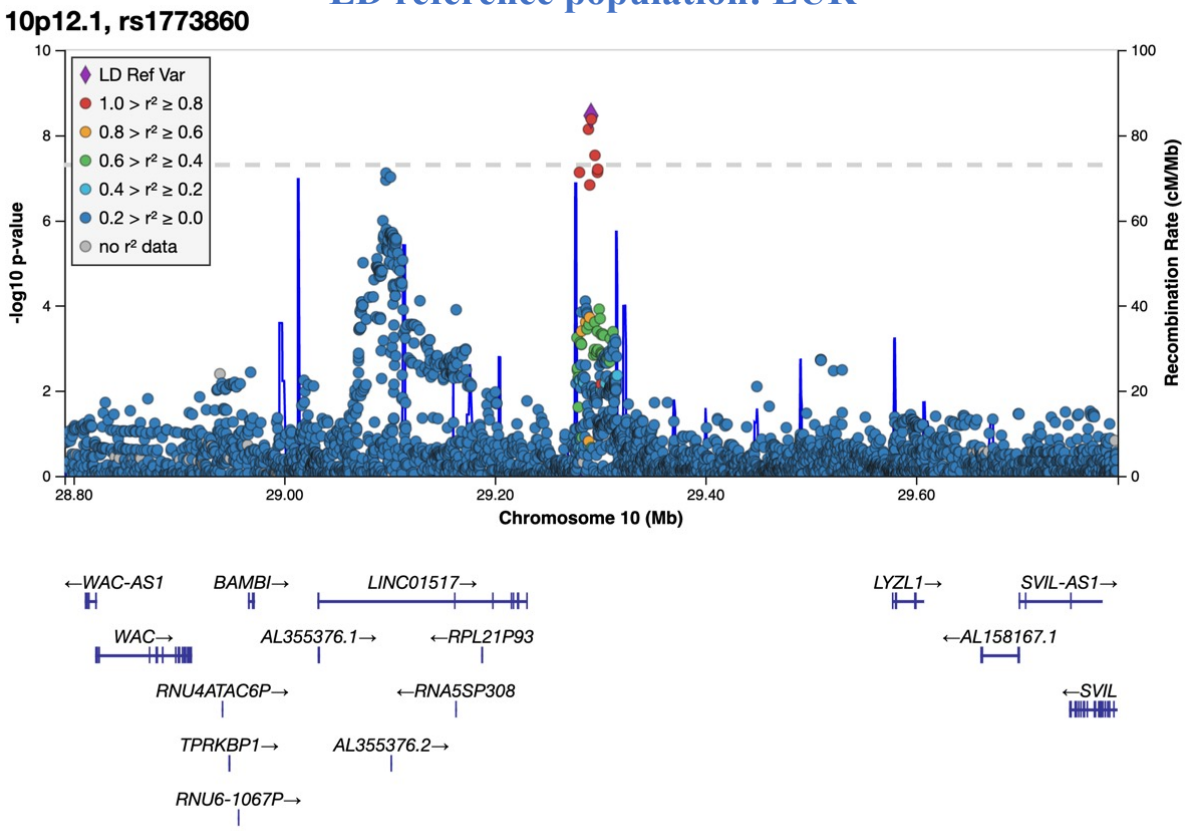



## LD reference population: EAS

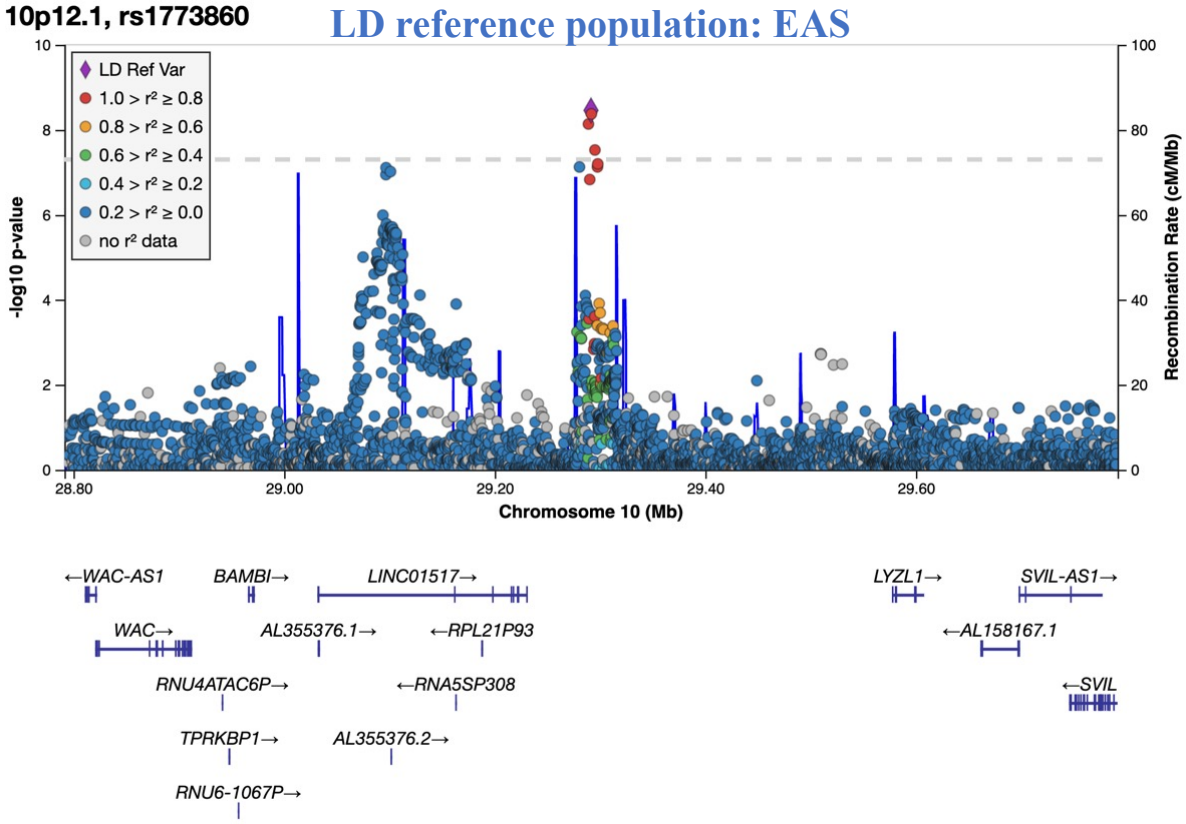
**10p12.1, rs1775910**



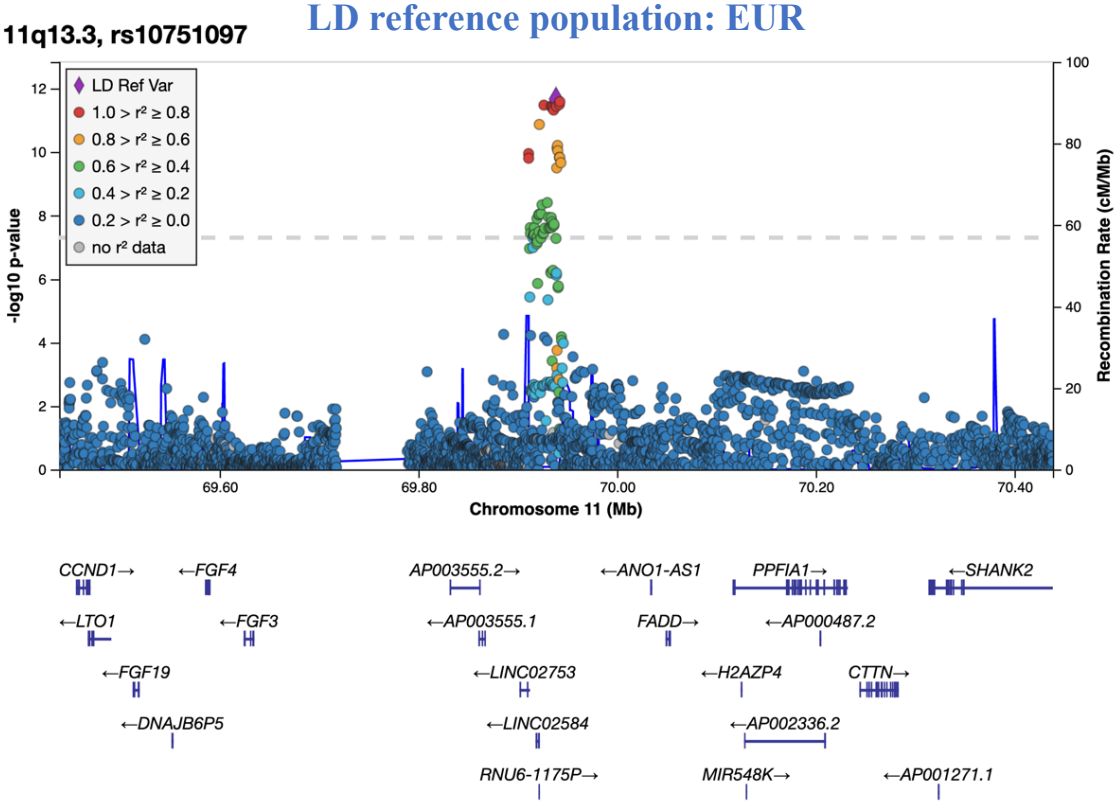
## LD reference population: EUR



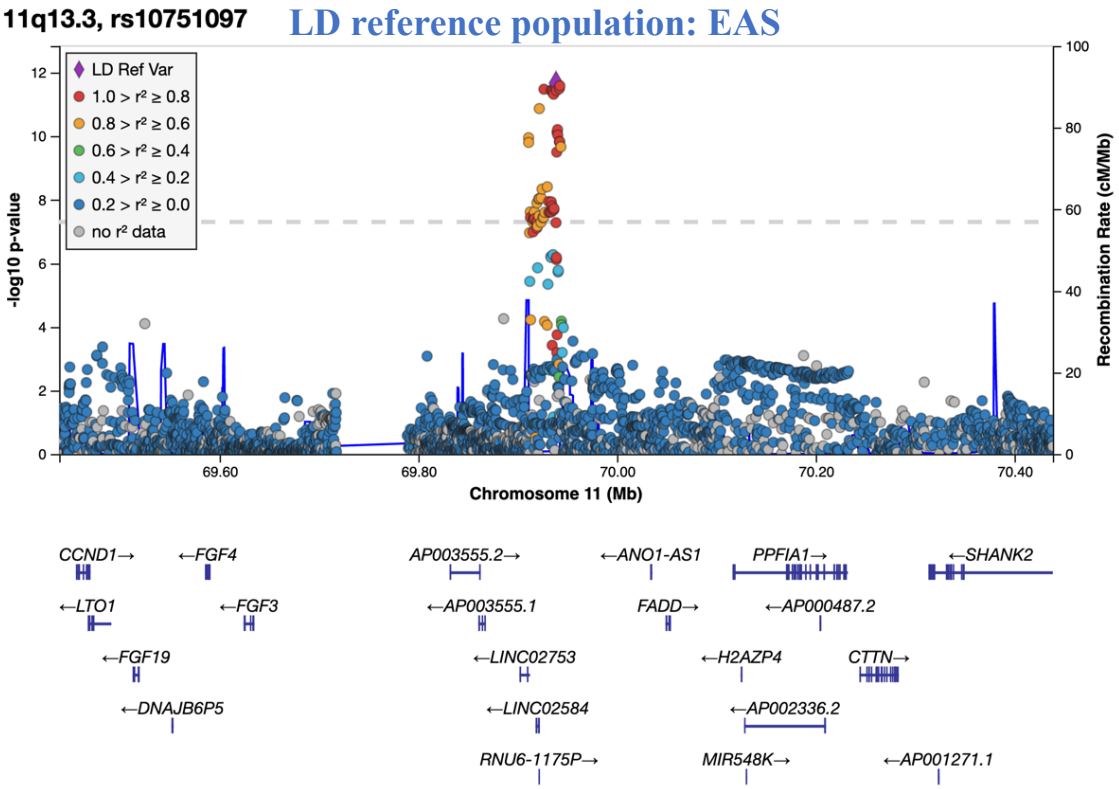

## LD reference population: EAS



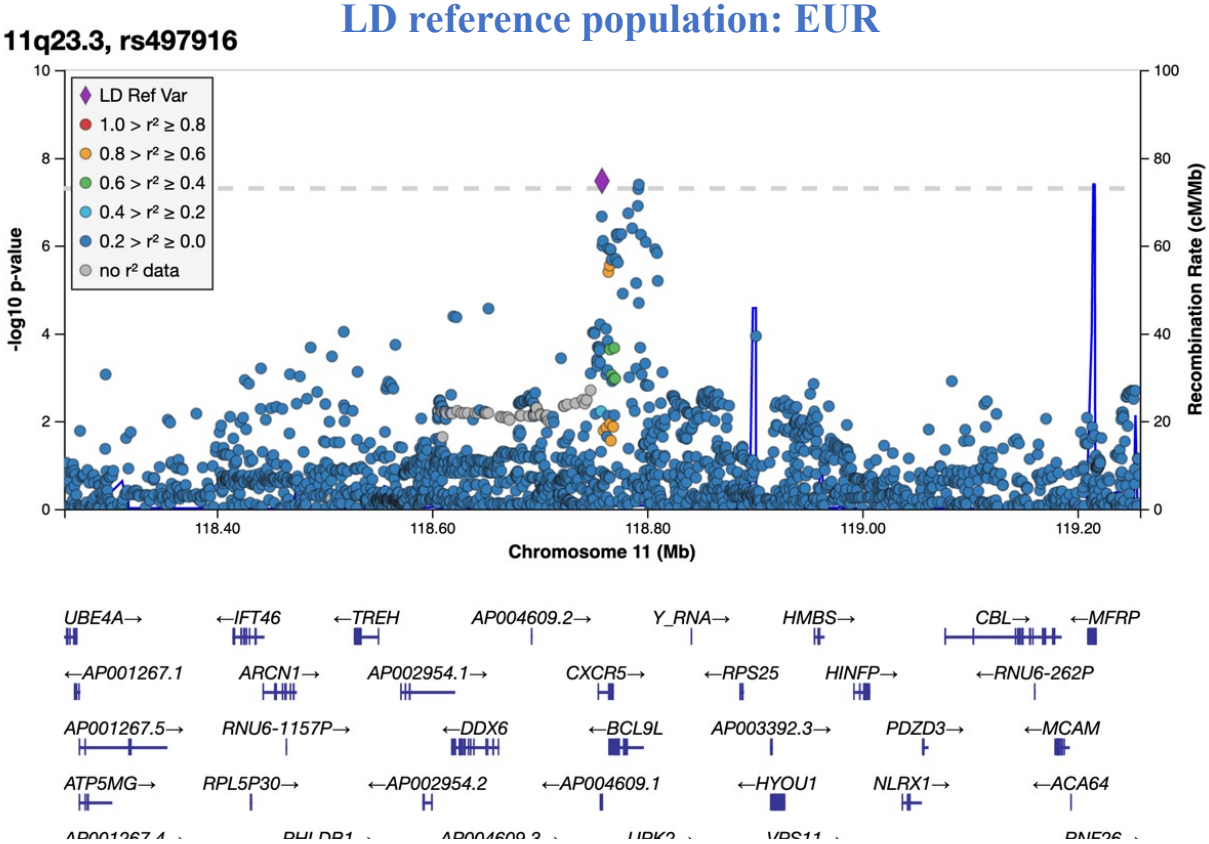
## LD reference population: EUR



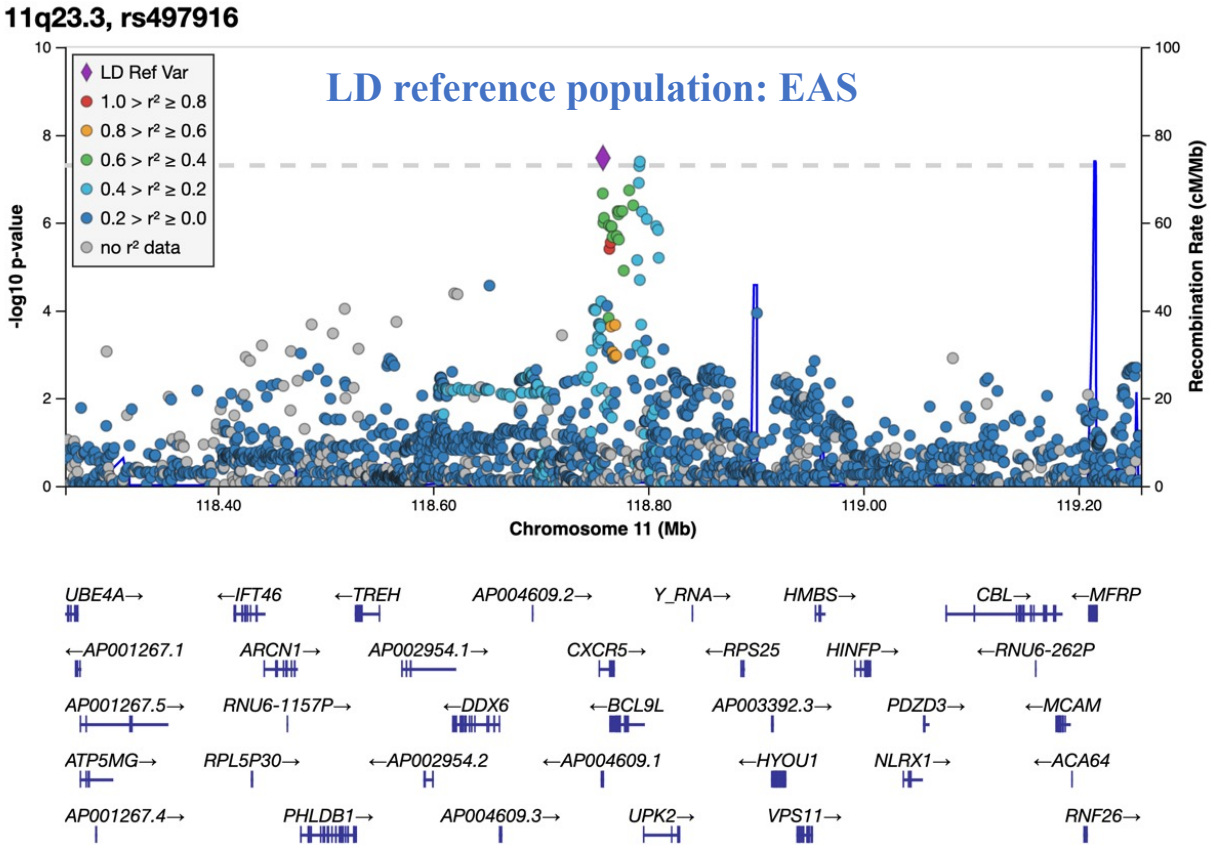

## LD reference population: EAS

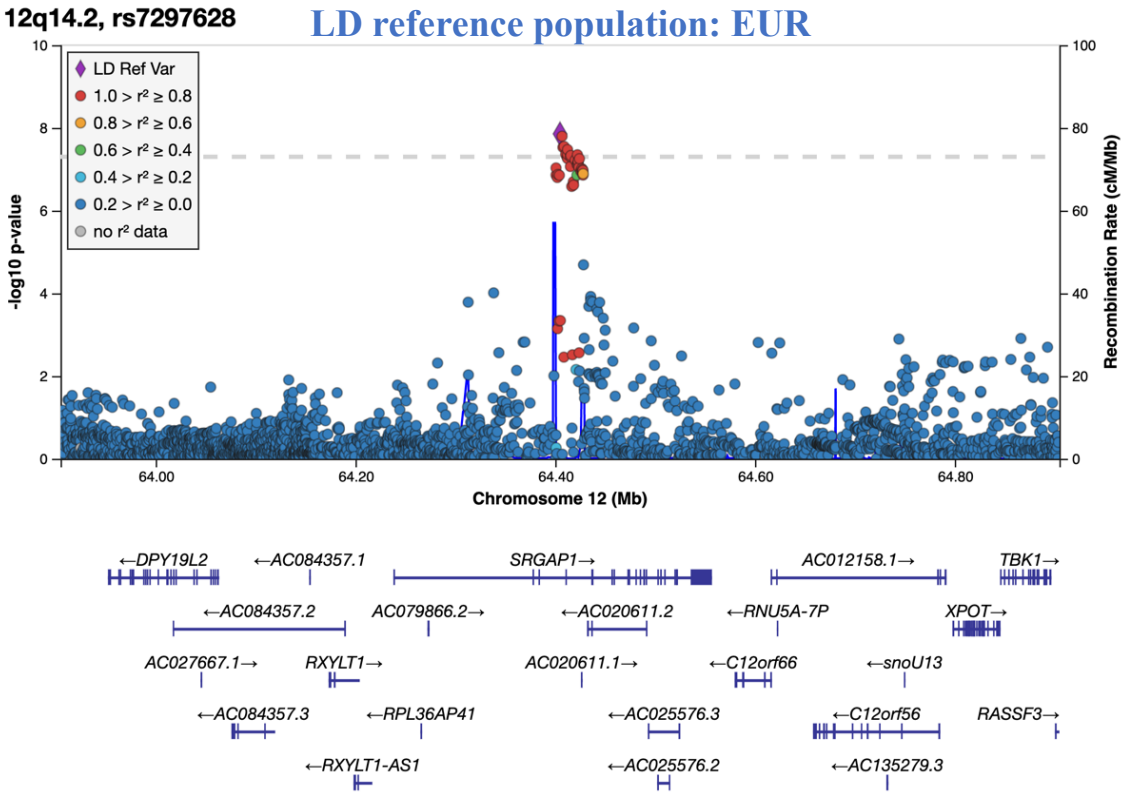


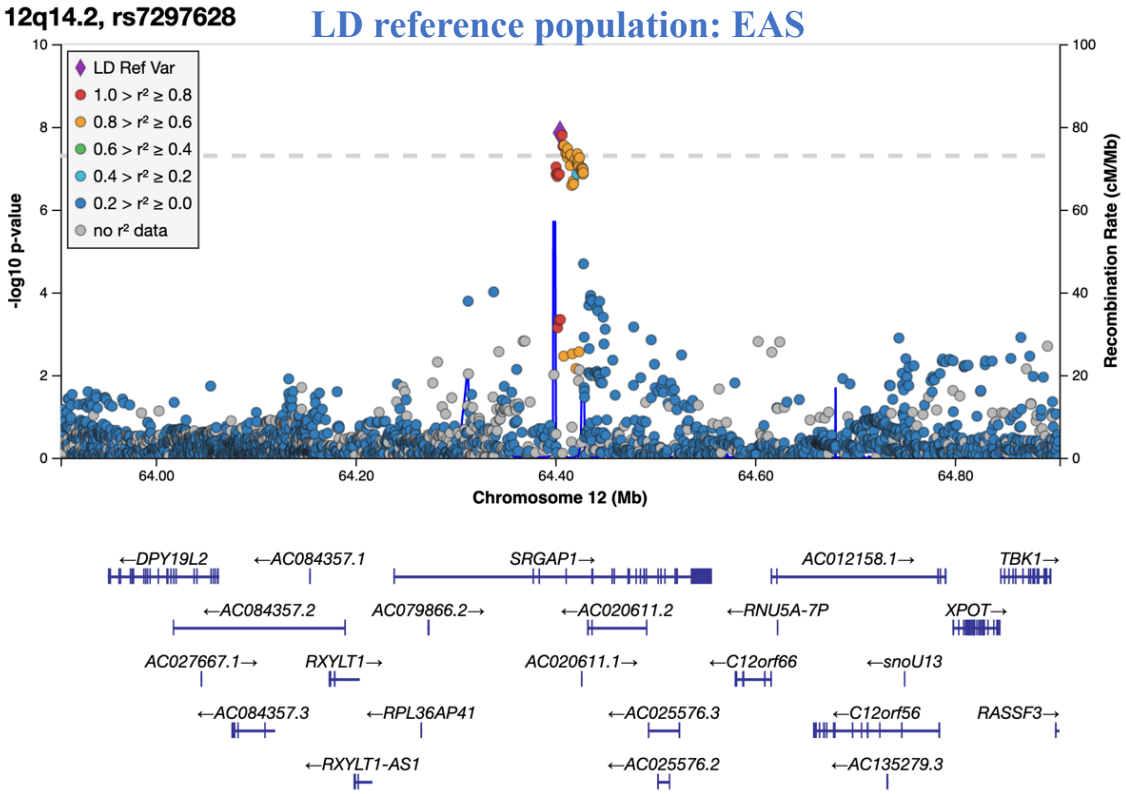
## LD reference population: EUR



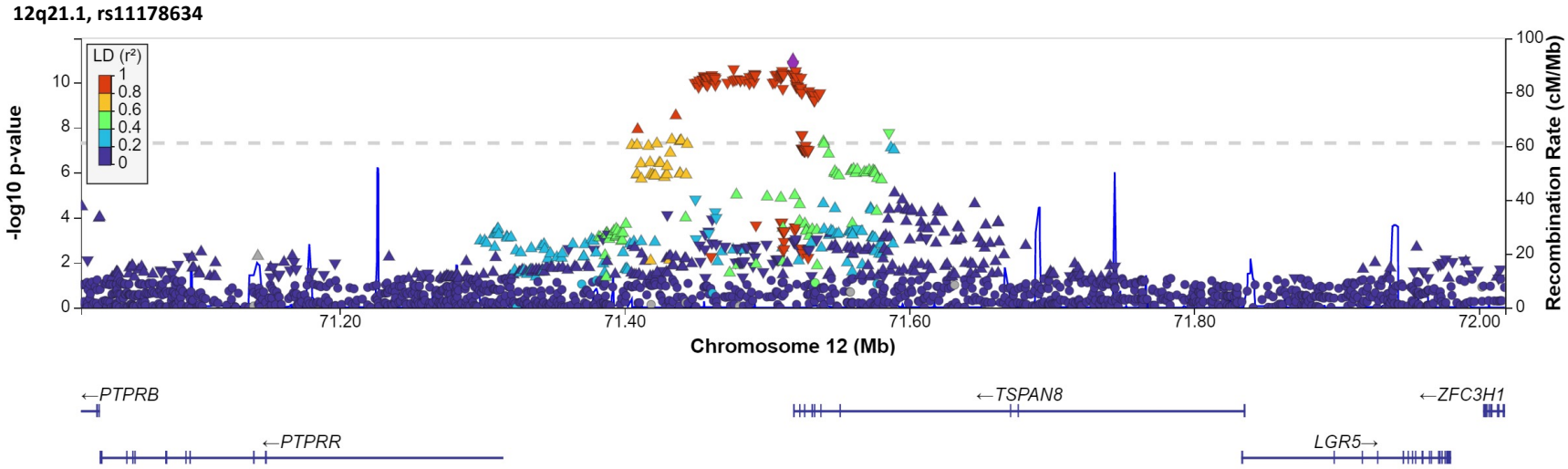

## LD reference population: EAS



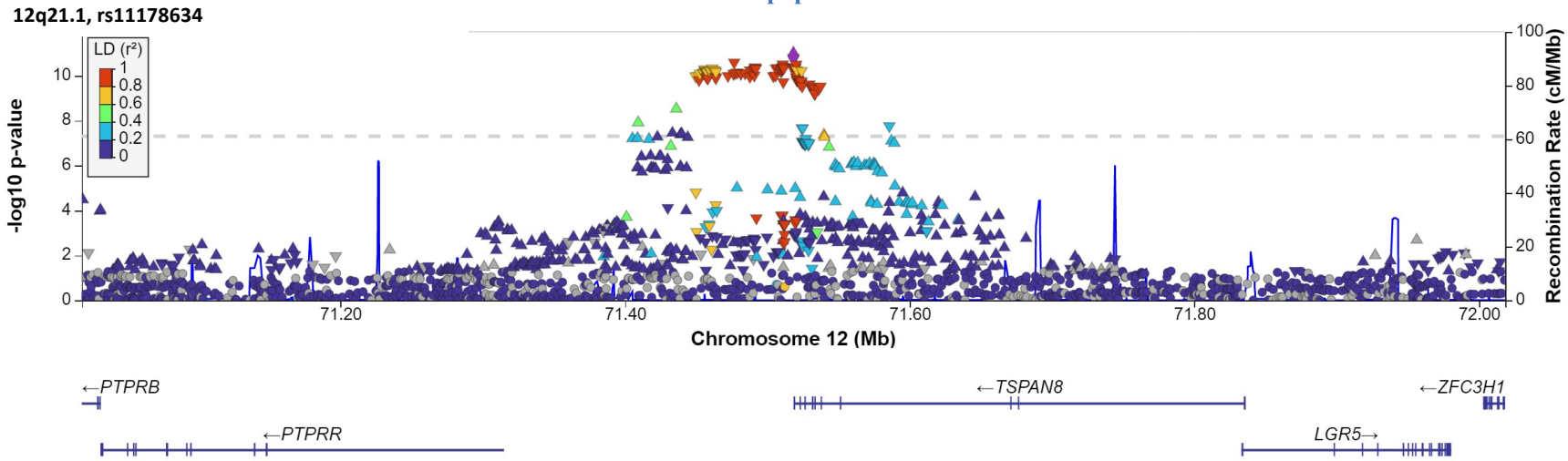

12q14.2, rs7297628
LD reference population: EUR
LD Ref Var
1.0 > r² ≥ 0.8
0.8 > r² ≥ 0.6
0.6 > r² ≥ 0.4
0.4 > r² ≥ 0.2
0.2 > r² ≥ 0.0
no r² data
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 12 (Mb)
64.00
64.20
64.40
64.60
64.80
←DPY19L2
←AC084357.1
SRGAP1→
AC012158.1→
TBK1→
←AC084357.2
AC079866.2→
←AC020611.2
←RNU5A-7P
XPOT→
AC027667.1→
RXYLT1→
AC020611.1→
←C12orf66
←snoU13
←AC084357.3
←RPL36AP41
←AC025576.3
←C12orf56
RASSF3→
←RXYLT1-AS1
←AC025576.2
←AC135279.3


12q14.2, rs7297628
LD reference population: EAS
LD Ref Var
1.0 > r² ≥ 0.8
0.8 > r² ≥ 0.6
0.6 > r² ≥ 0.4
0.4 > r² ≥ 0.2
0.2 > r² ≥ 0.0
no r² data
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 12 (Mb)
64.00
64.20
64.40
64.60
64.80
←DPY19L2
←AC084357.1
SRGAP1→
AC012158.1→
TBK1→
←AC084357.2
AC079866.2→
←AC020611.2
←RNU5A-7P
XPOT→
AC027667.1→
RXYLT1→
AC020611.1→
←C12orf66
←snoU13
←AC084357.3
←RPL36AP41
←AC025576.3
←C12orf56
RASSF3→
←RXYLT1-AS1
←AC025576.2
←AC135279.3

## LD reference population: EUR

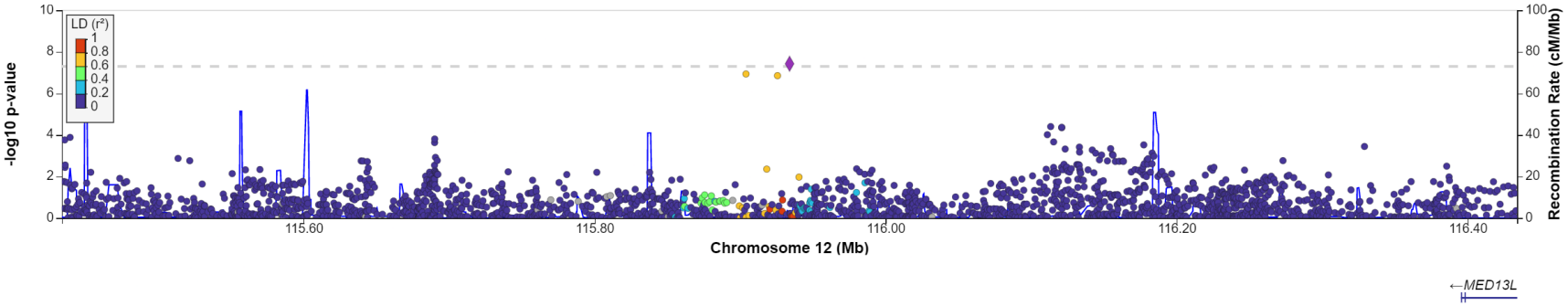



## LD reference population: EAS



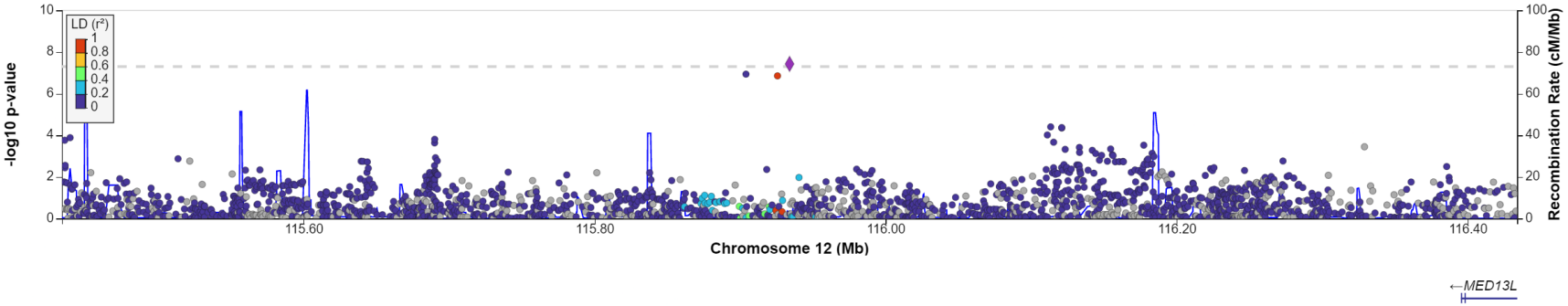
## LD reference population: EUR

**12q24.1, rs7299936**

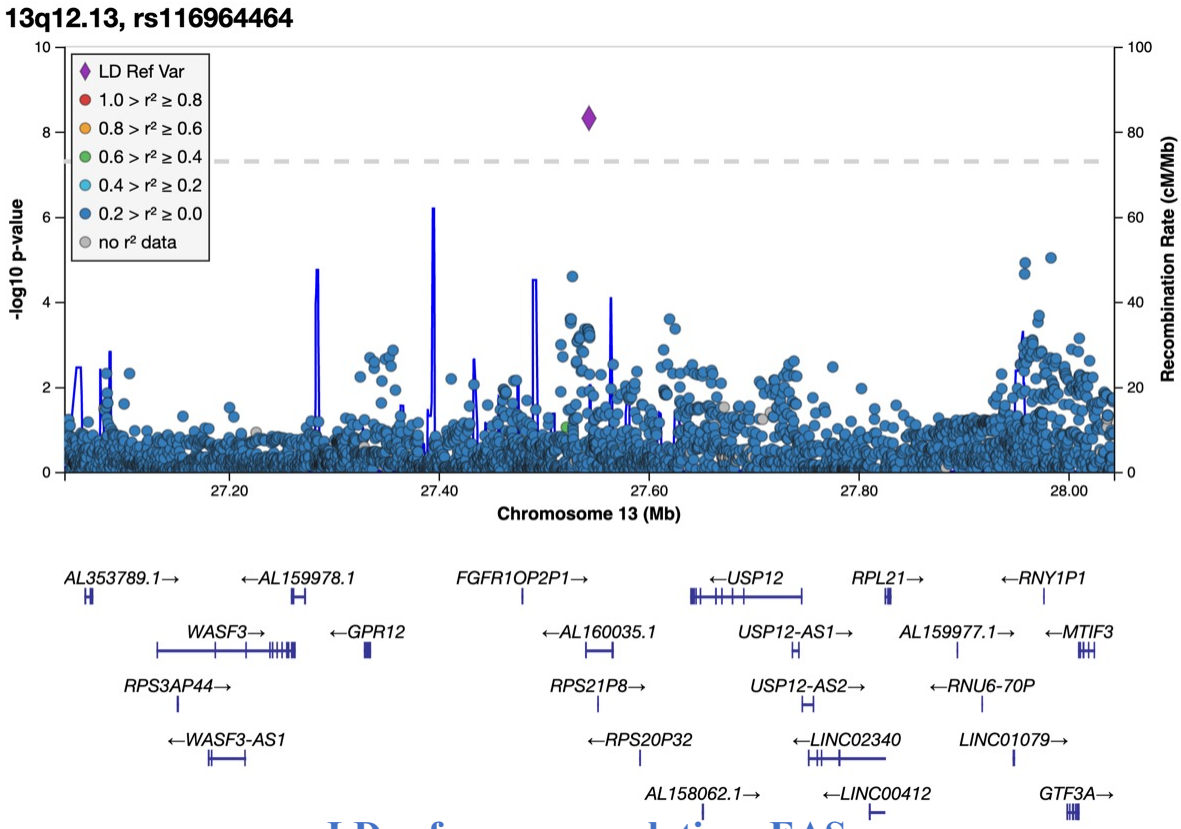



## LD reference population: EAS

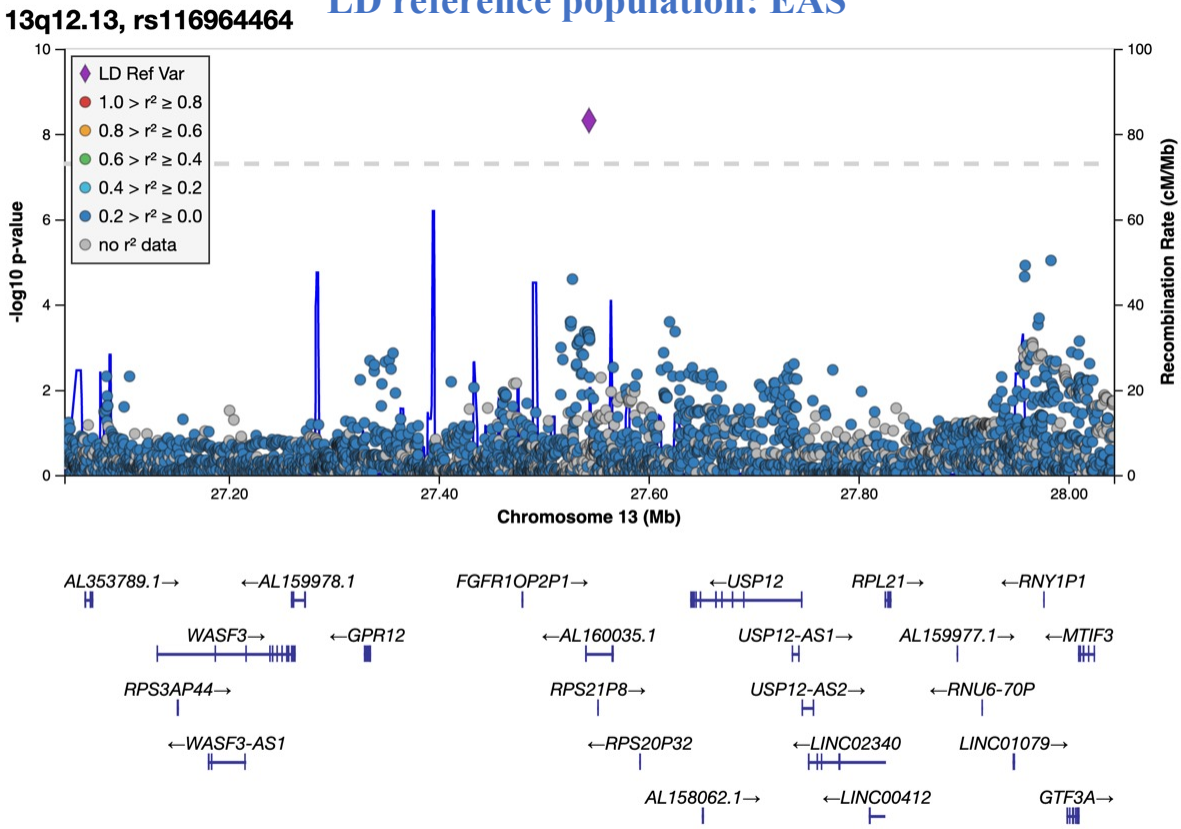
**12q24.1, rs7299936**

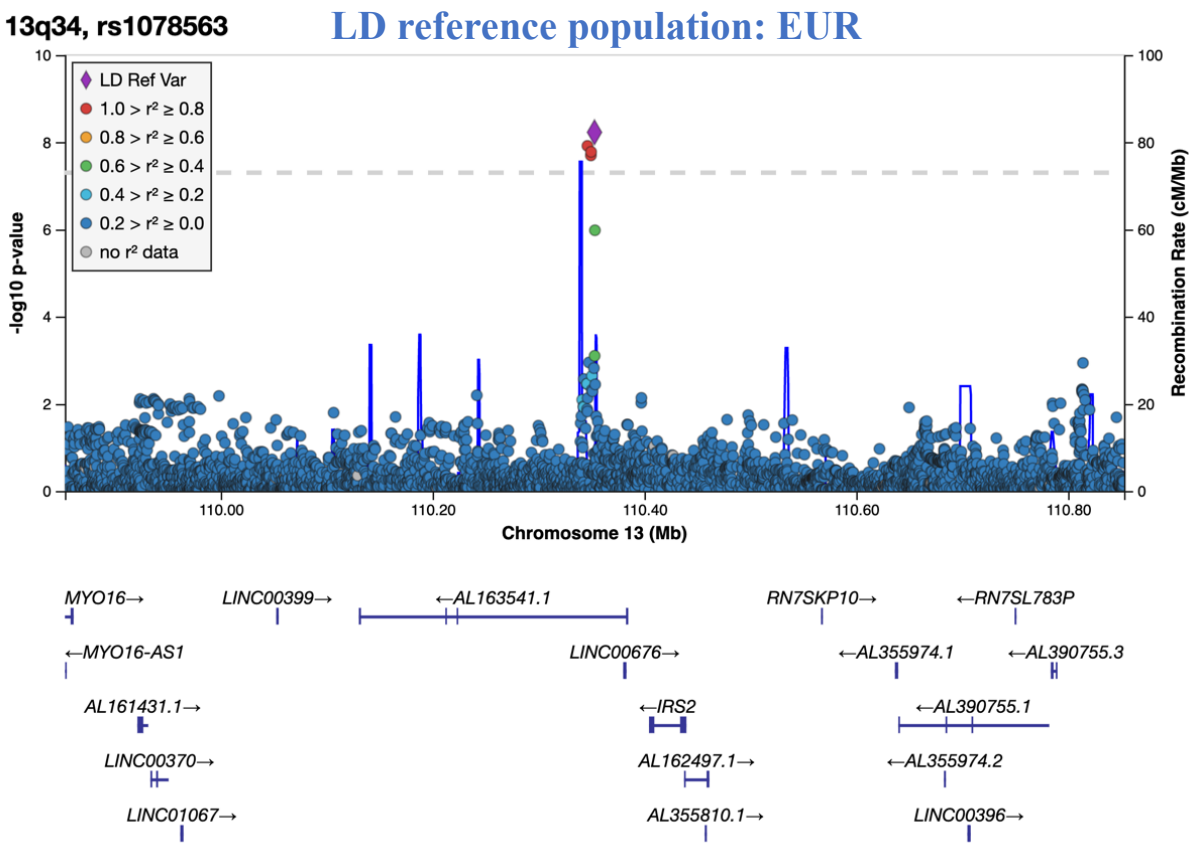


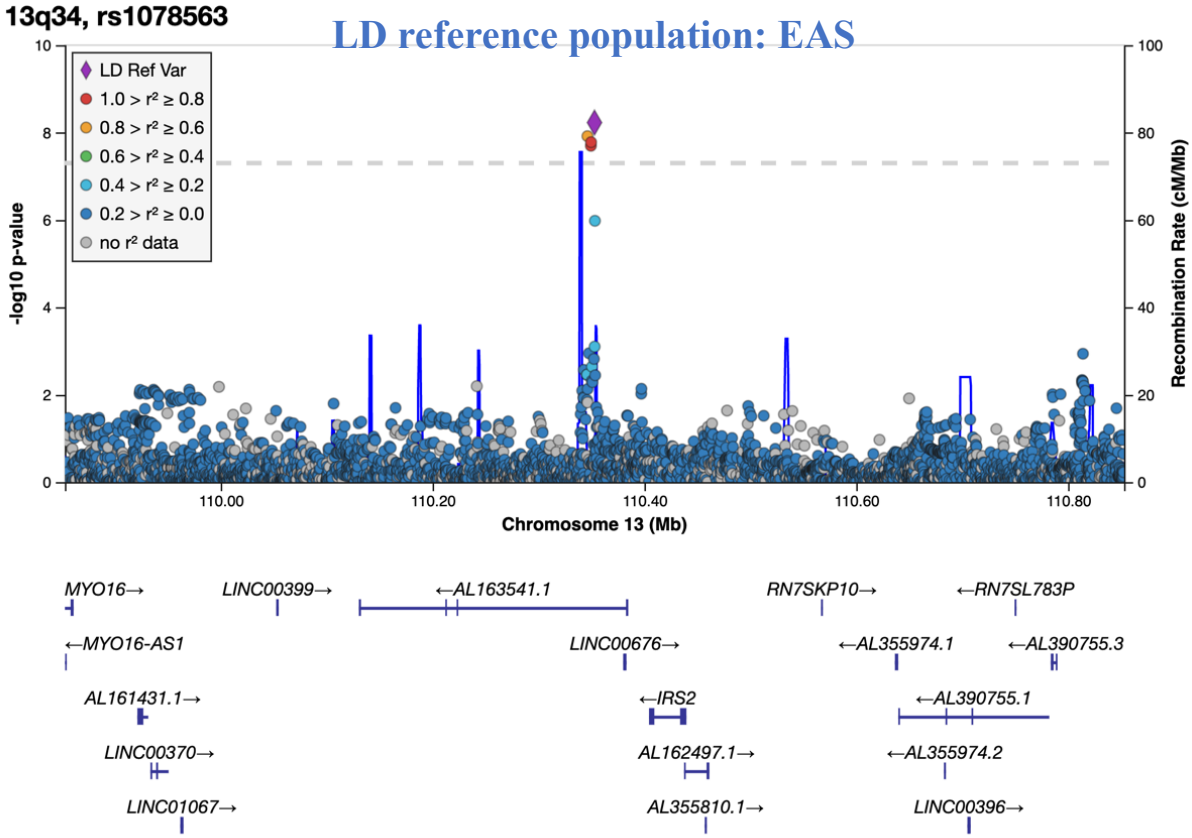
## LD reference population: EUR



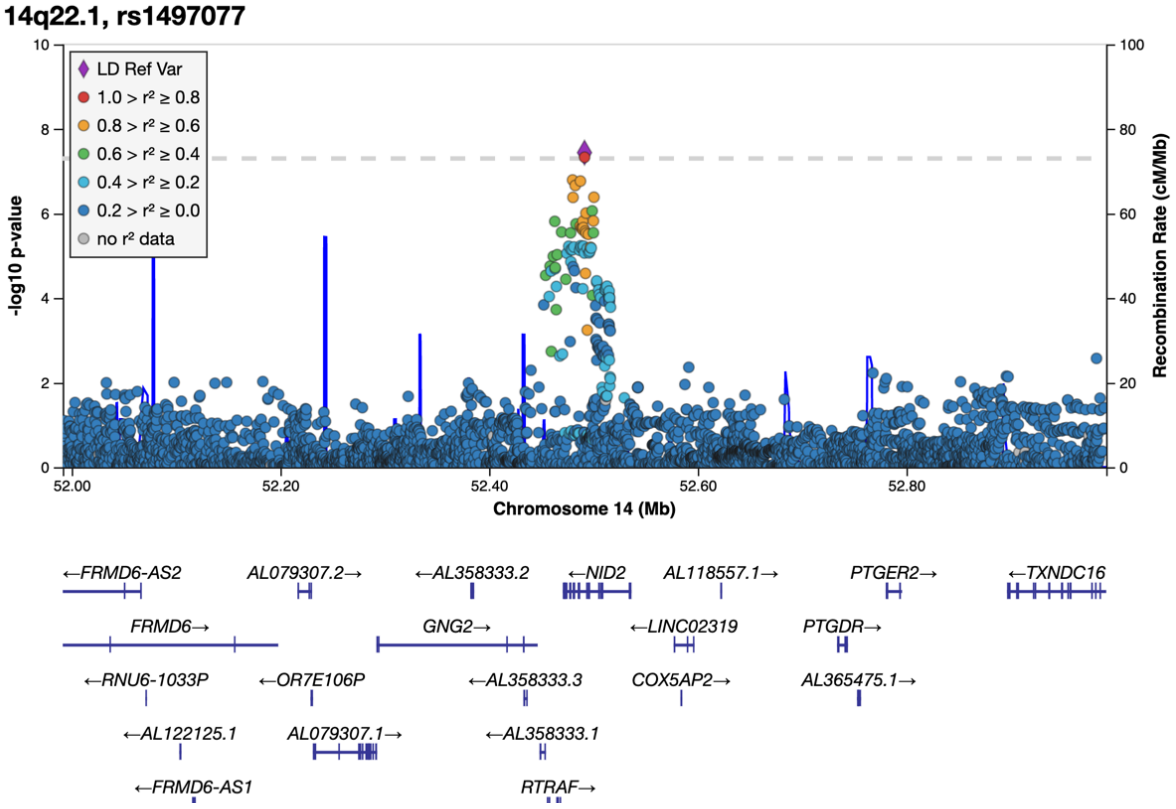

## LD reference population: EAS



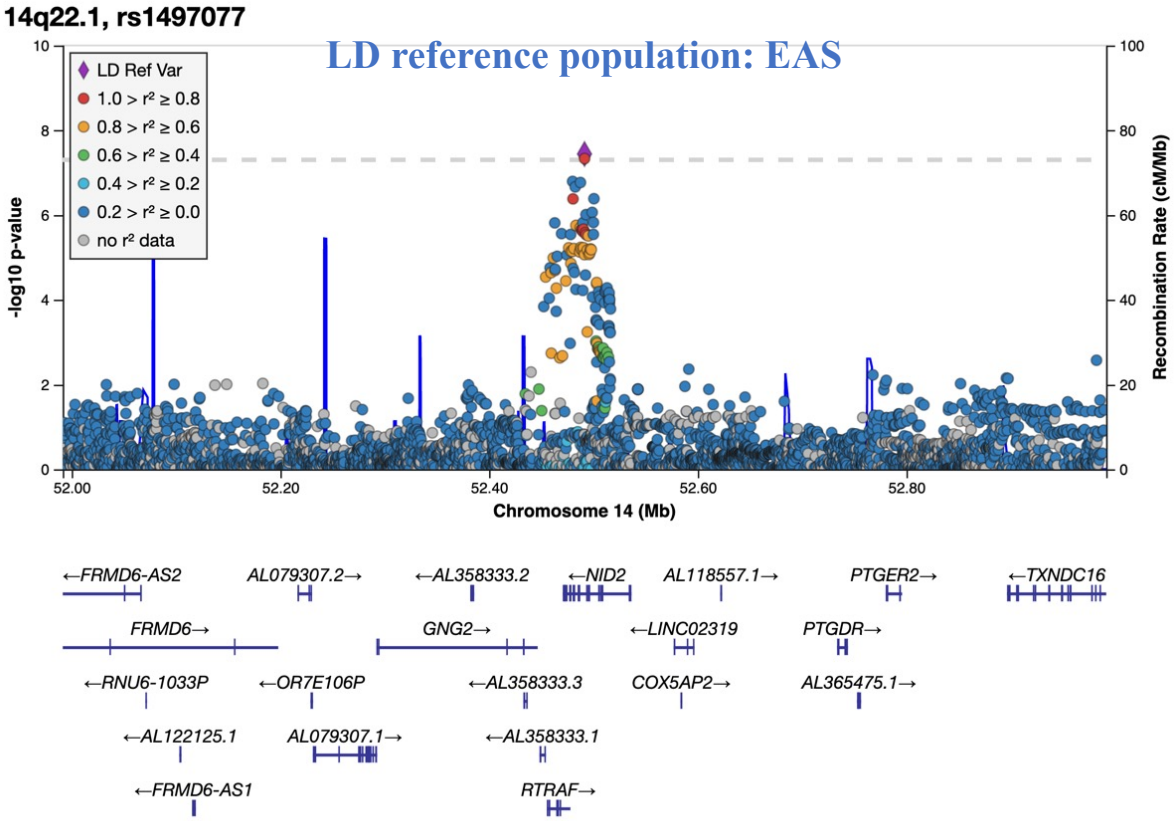

13q34, rs1078563
LD reference population: EUR
LD Ref Var
1.0 > r² ≥ 0.8
0.8 > r² ≥ 0.6
0.6 > r² ≥ 0.4
0.4 > r² ≥ 0.2
0.2 > r² ≥ 0.0
no r² data
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 13 (Mb)
110.00
110.20
110.40
110.60
110.80
MYO16→
LINC00399→
←AL163541.1
RN7SKP10→
←RN7SL783P
←MYO16-AS1
LINC00676→
←AL355974.1
←AL390755.3
AL161431.1→
←IRS2
←AL390755.1
LINC00370→
AL162497.1→
←AL355974.2
LINC01067→
AL355810.1→
LINC00396→


13q34, rs1078563
LD reference population: EAS
LD Ref Var
1.0 > r² ≥ 0.8
0.8 > r² ≥ 0.6
0.6 > r² ≥ 0.4
0.4 > r² ≥ 0.2
0.2 > r² ≥ 0.0
no r² data
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 13 (Mb)
110.00
110.20
110.40
110.60
110.80
MYO16→
LINC00399→
←AL163541.1
RN7SKP10→
←RN7SL783P
←MYO16-AS1
LINC00676→
←AL355974.1
←AL390755.3
AL161431.1→
←IRS2
←AL390755.1
LINC00370→
AL162497.1→
←AL355974.2
LINC01067→
AL355810.1→
LINC00396→

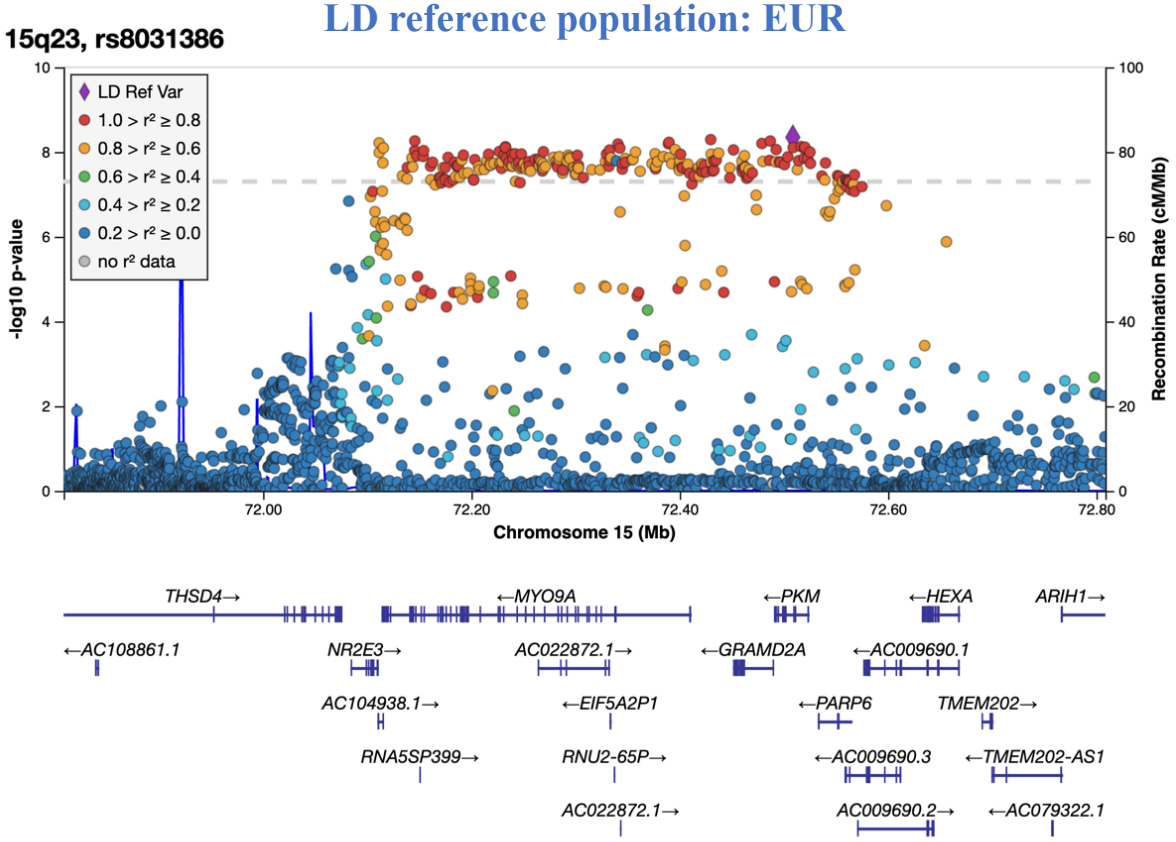
## LD reference population: EUR



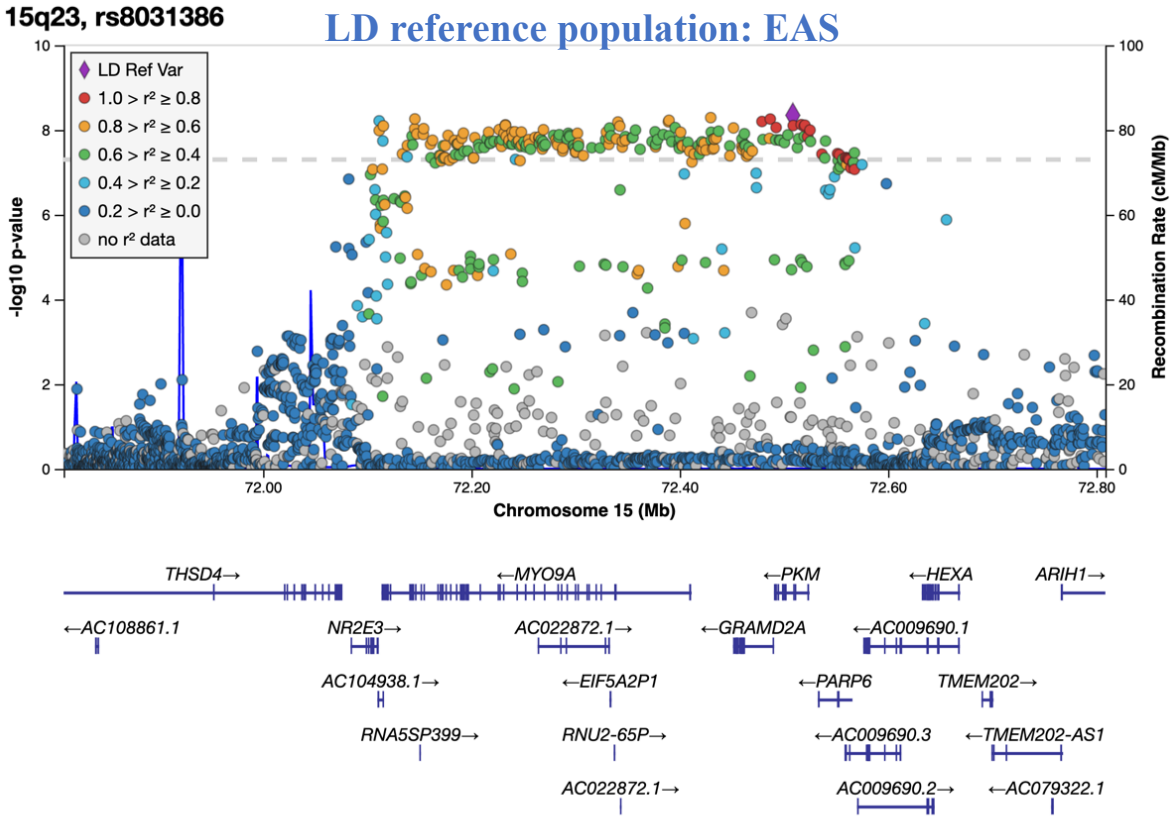

## LD reference population: EAS



## LD reference population: EUR

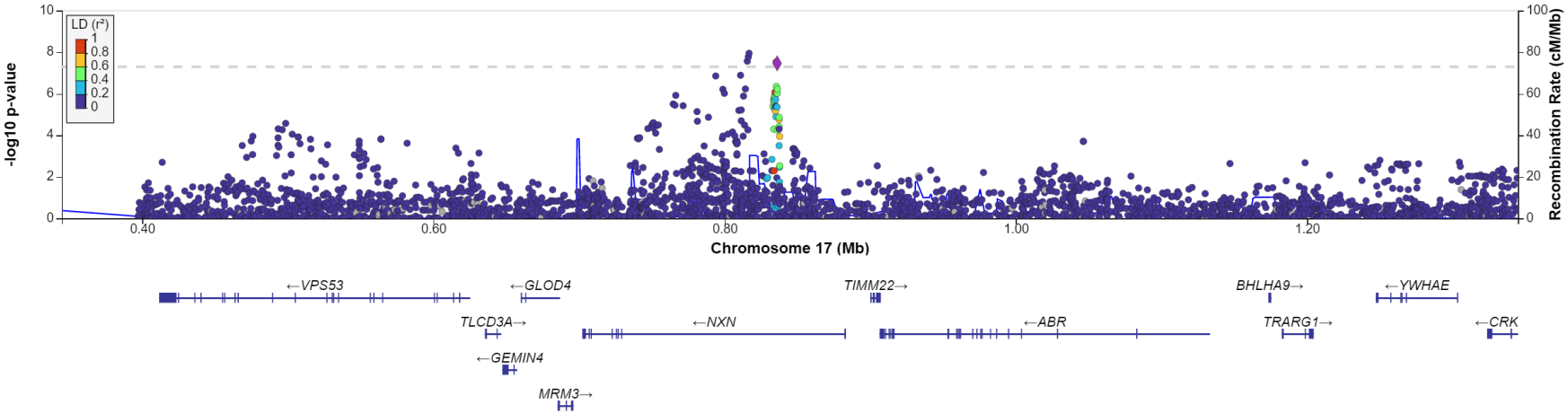



## LD reference population: EAS



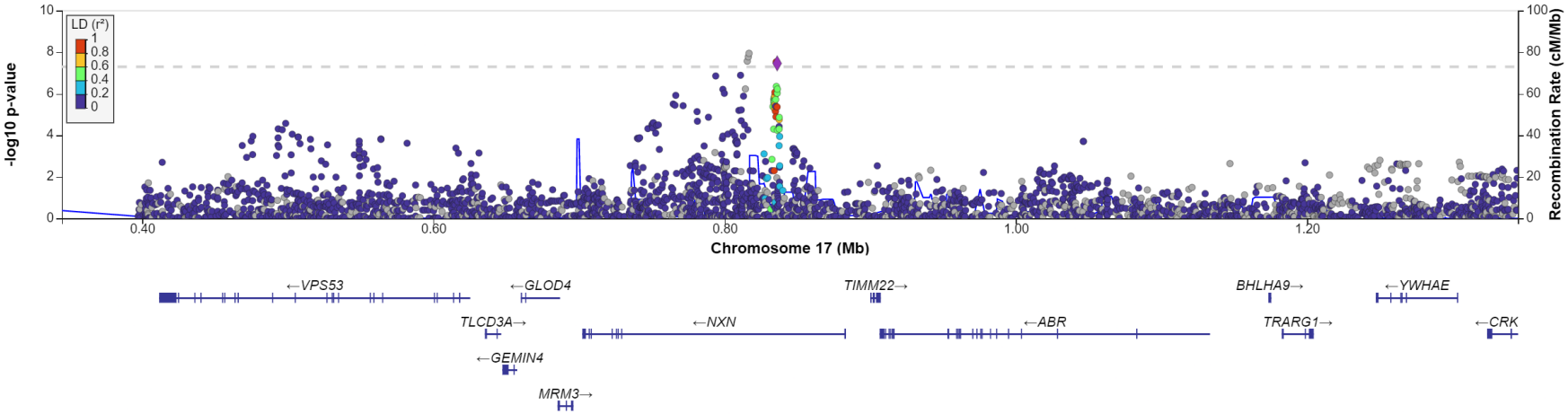
## LD reference population: EUR

**17p13.3, rs11247566**

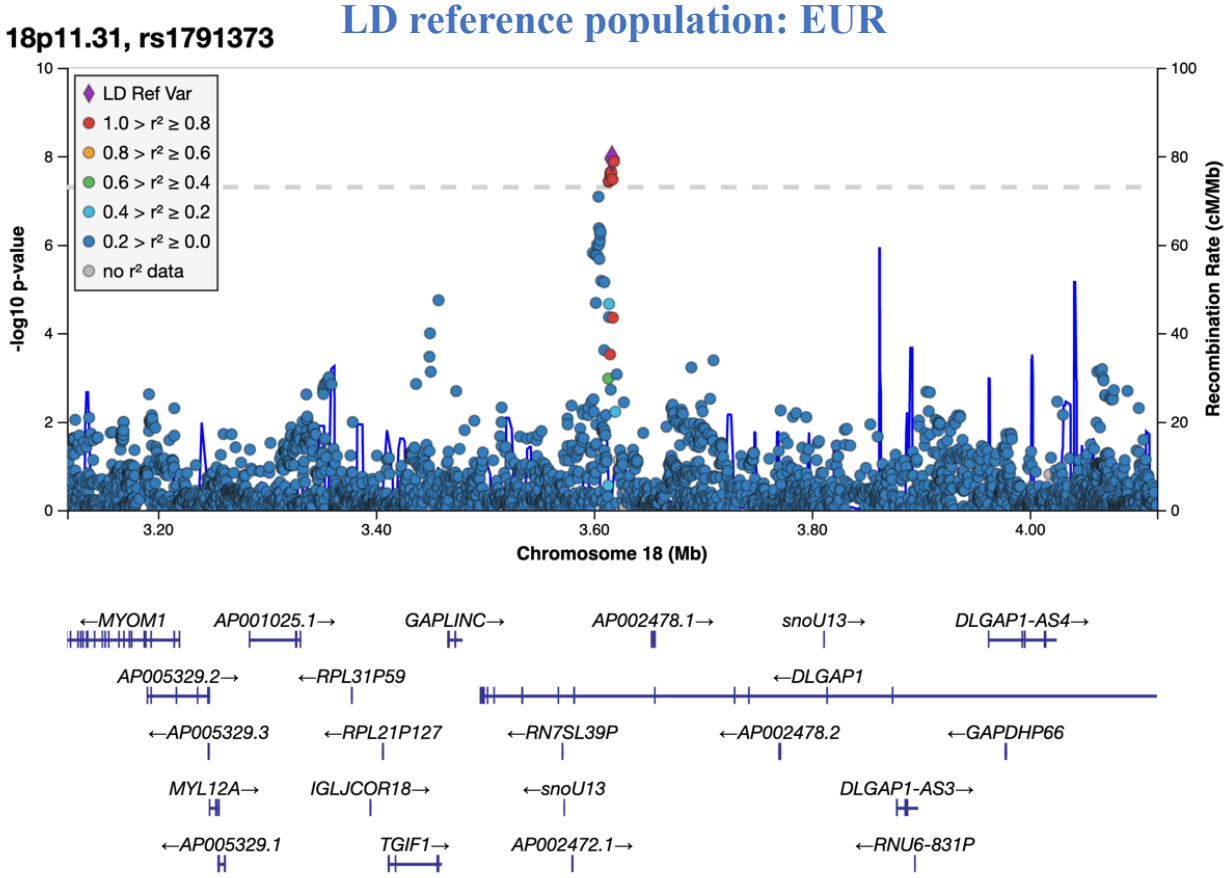



## LD reference population: EAS

**17p13.3, rs11247566**



## LD reference population: EUR

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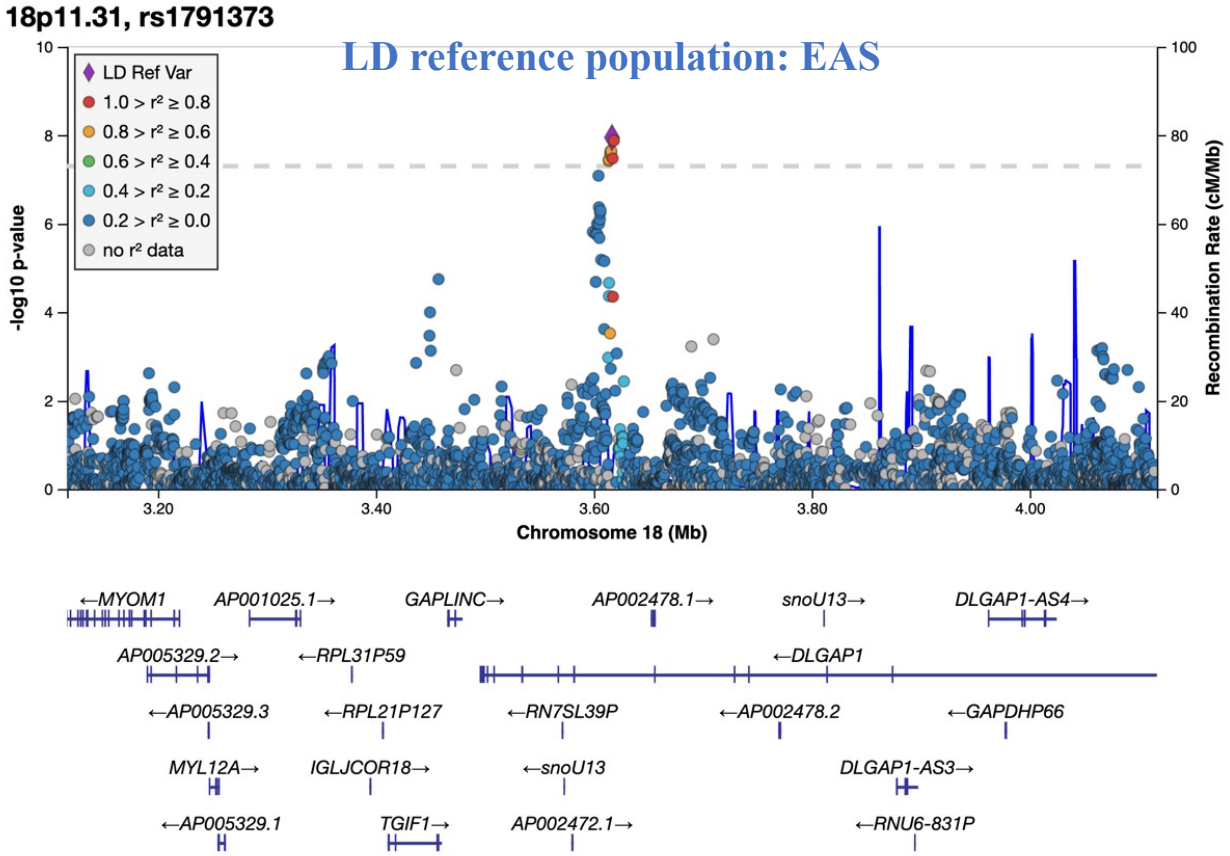

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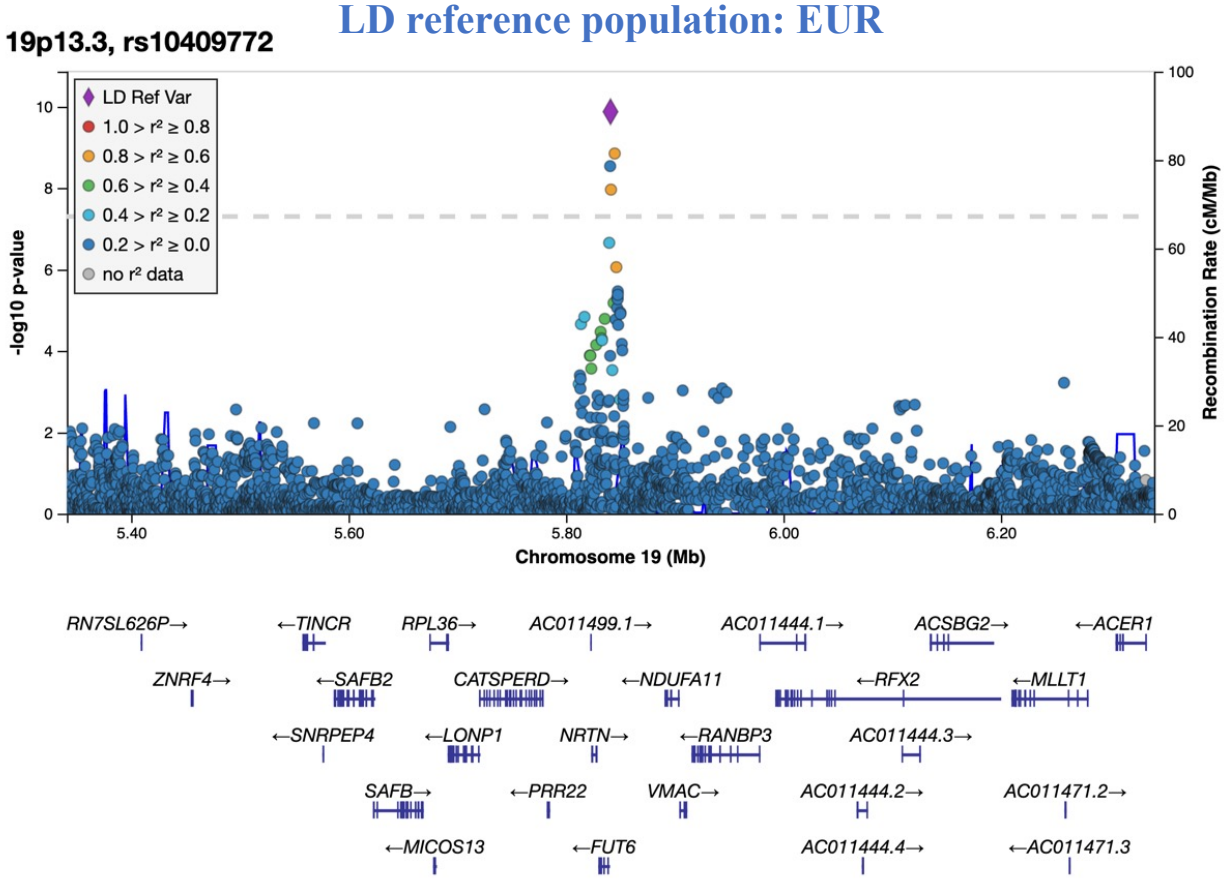


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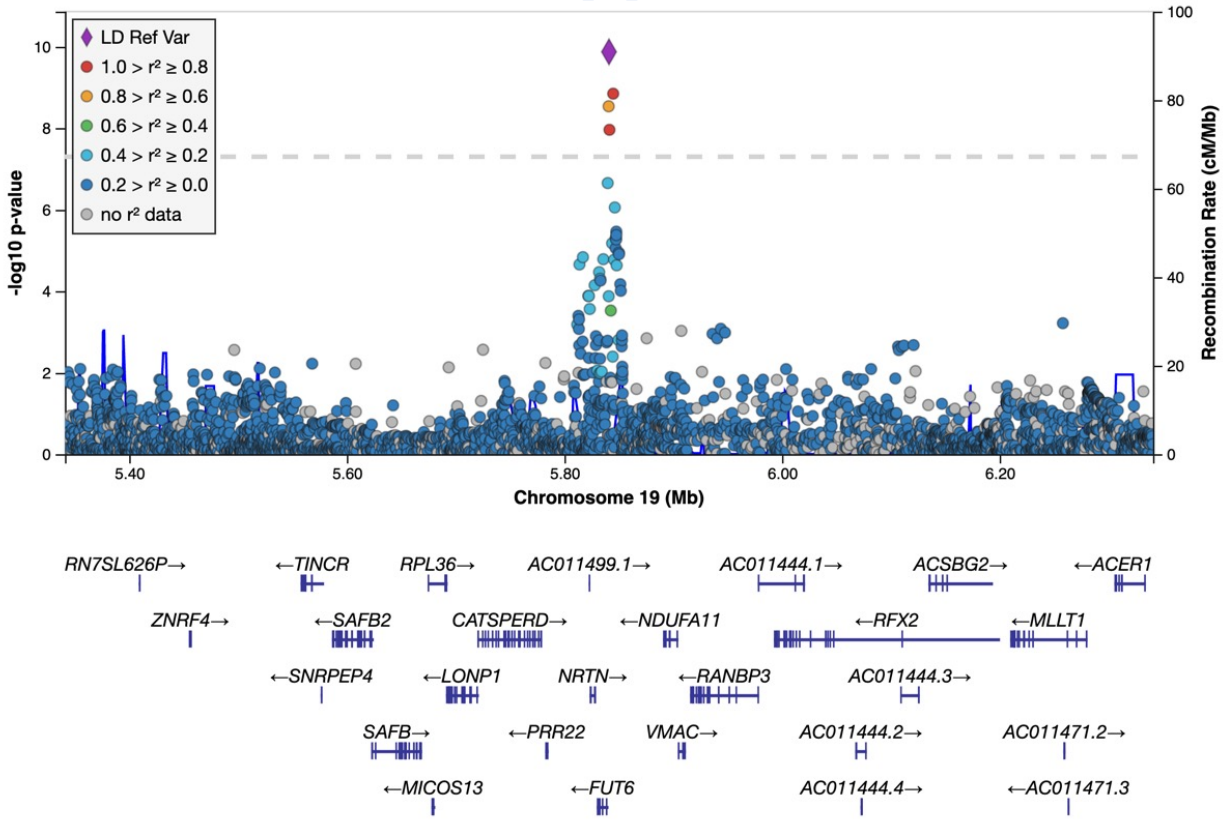
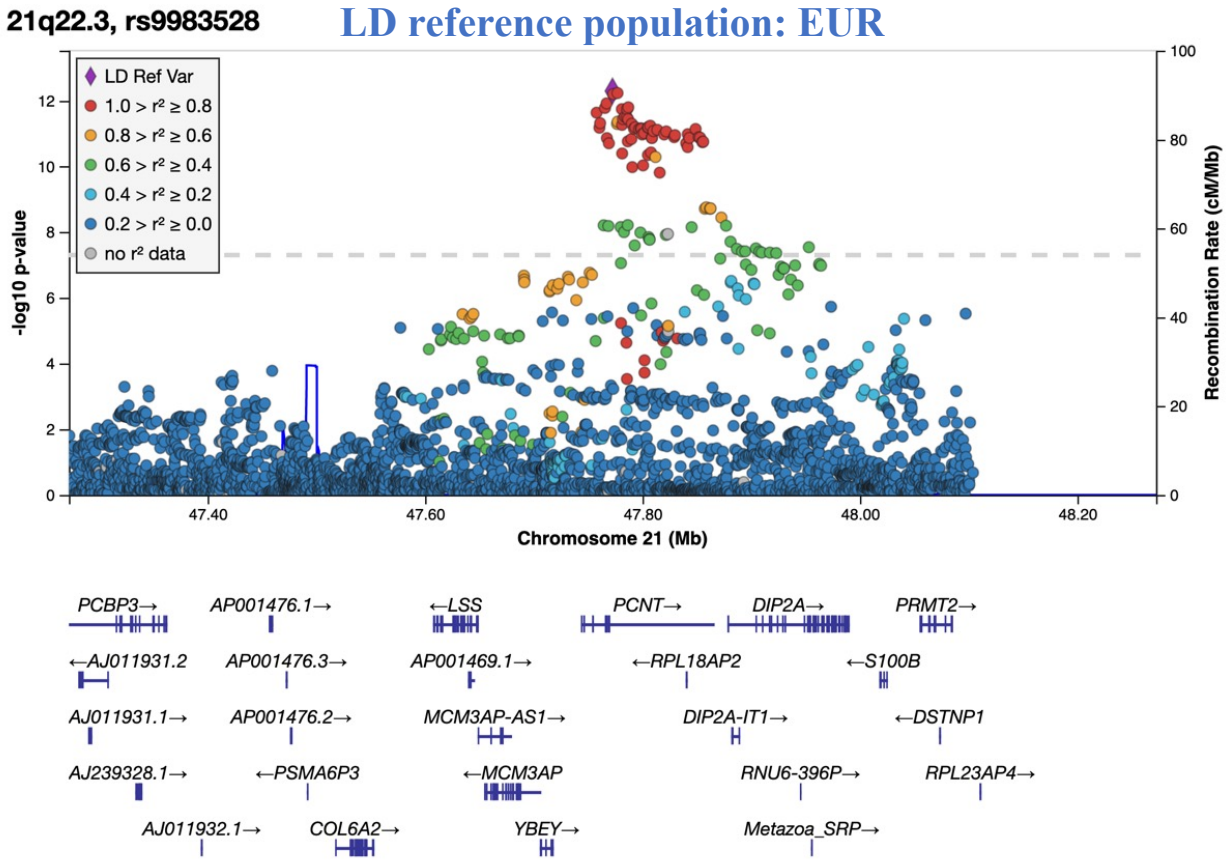
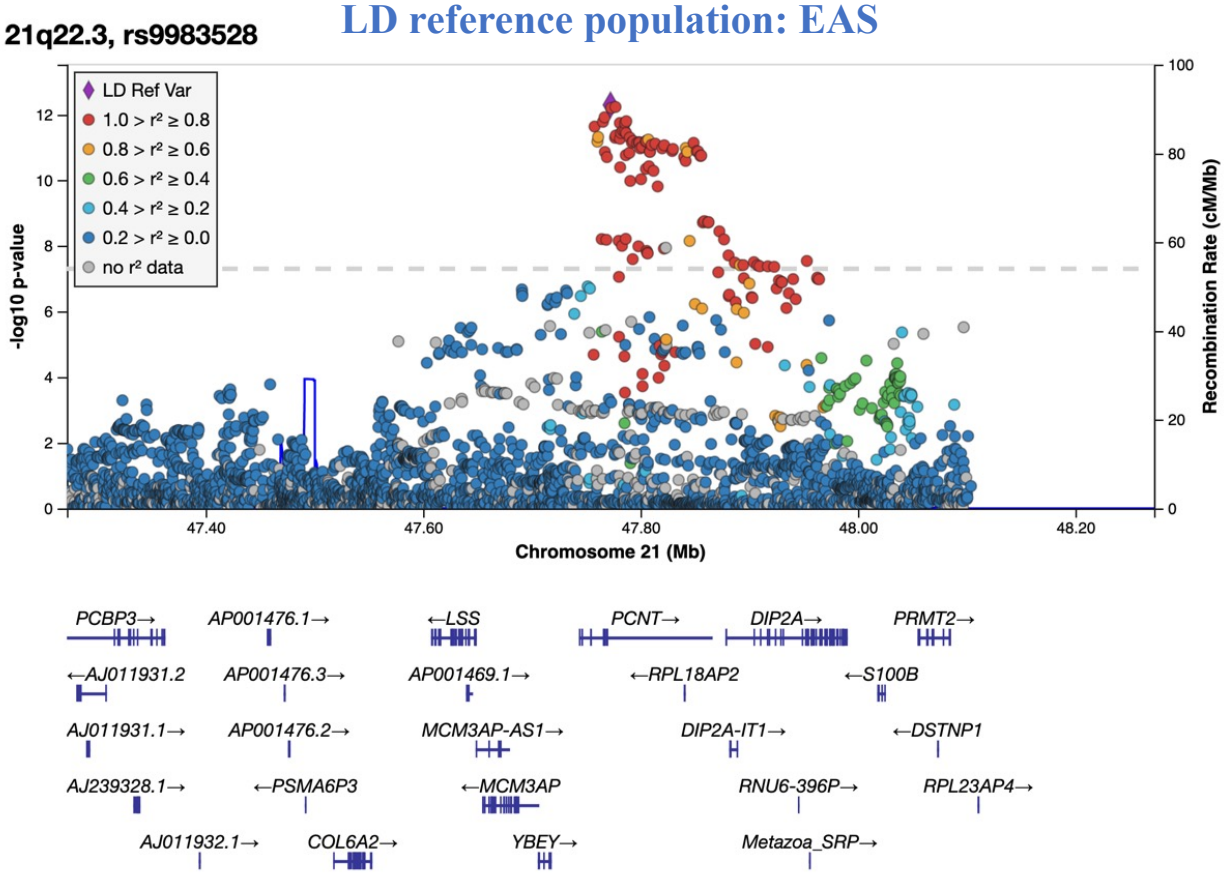


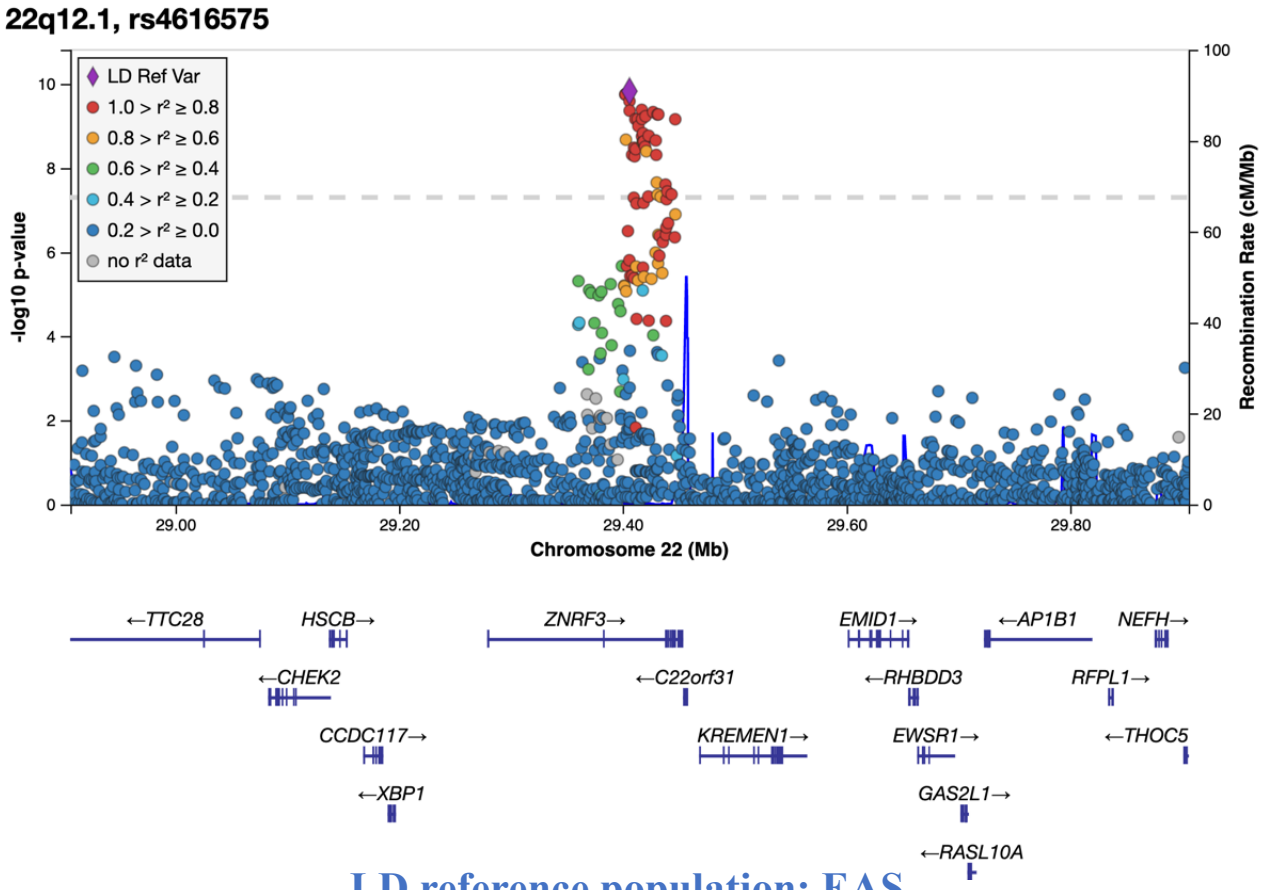
## LD reference population: EUR



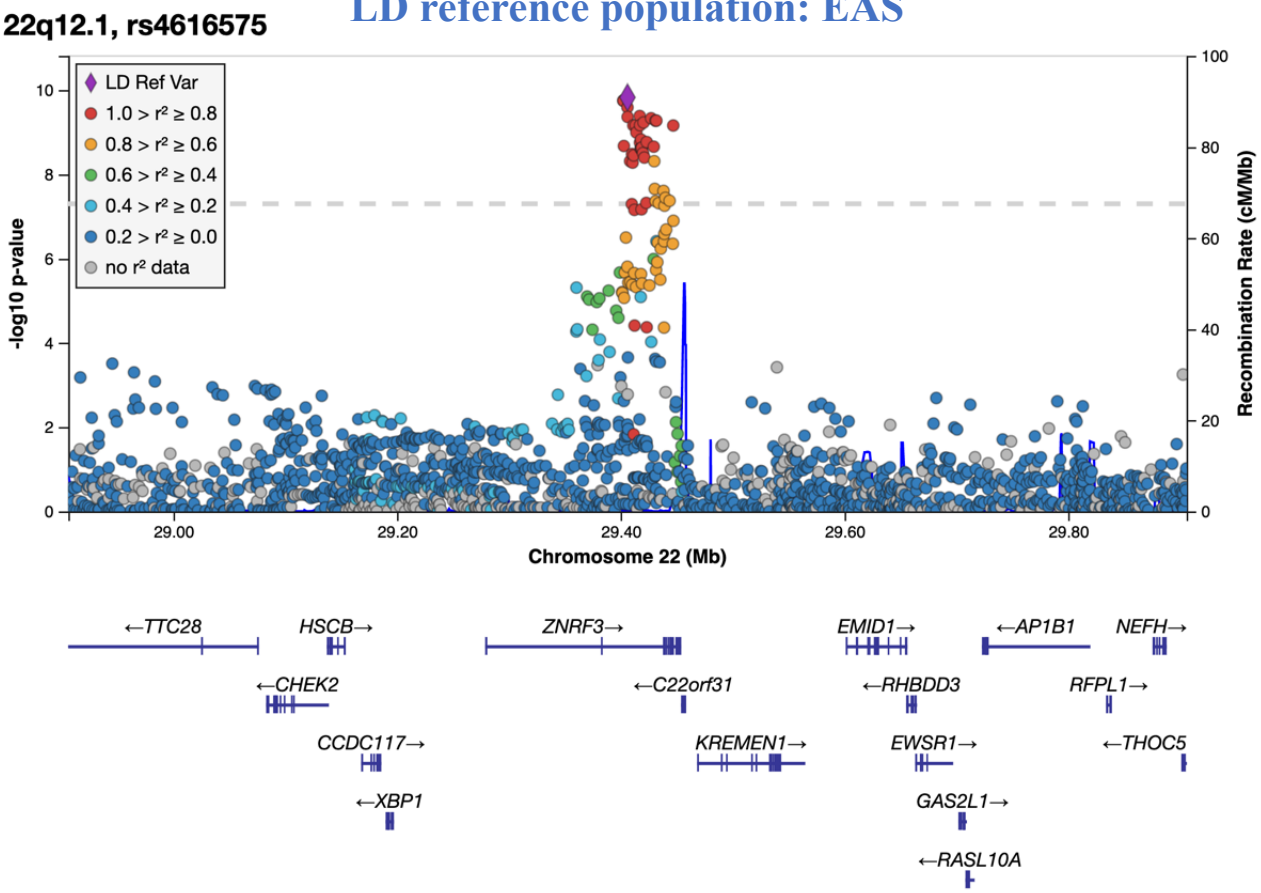

## LD reference population: EAS



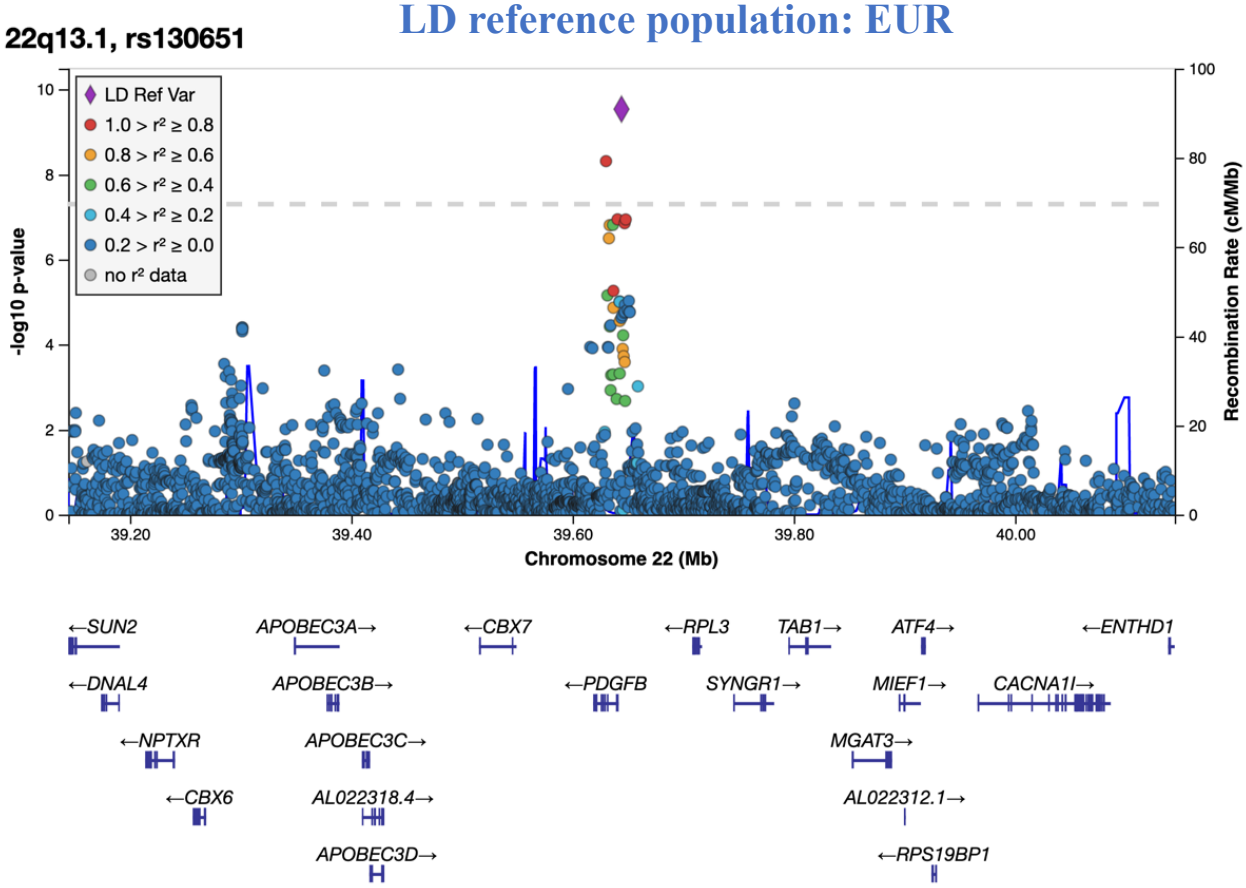
## LD reference population: EUR



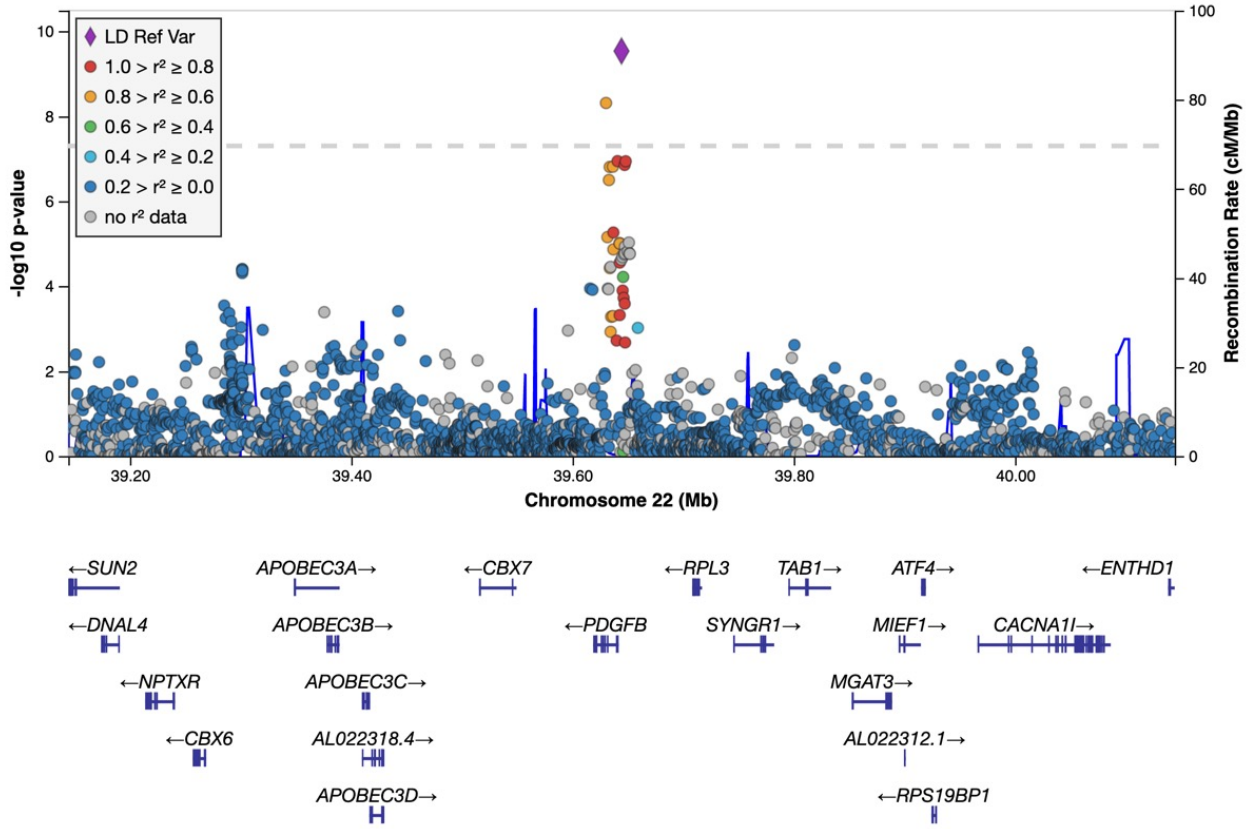

## LD reference population: EAS



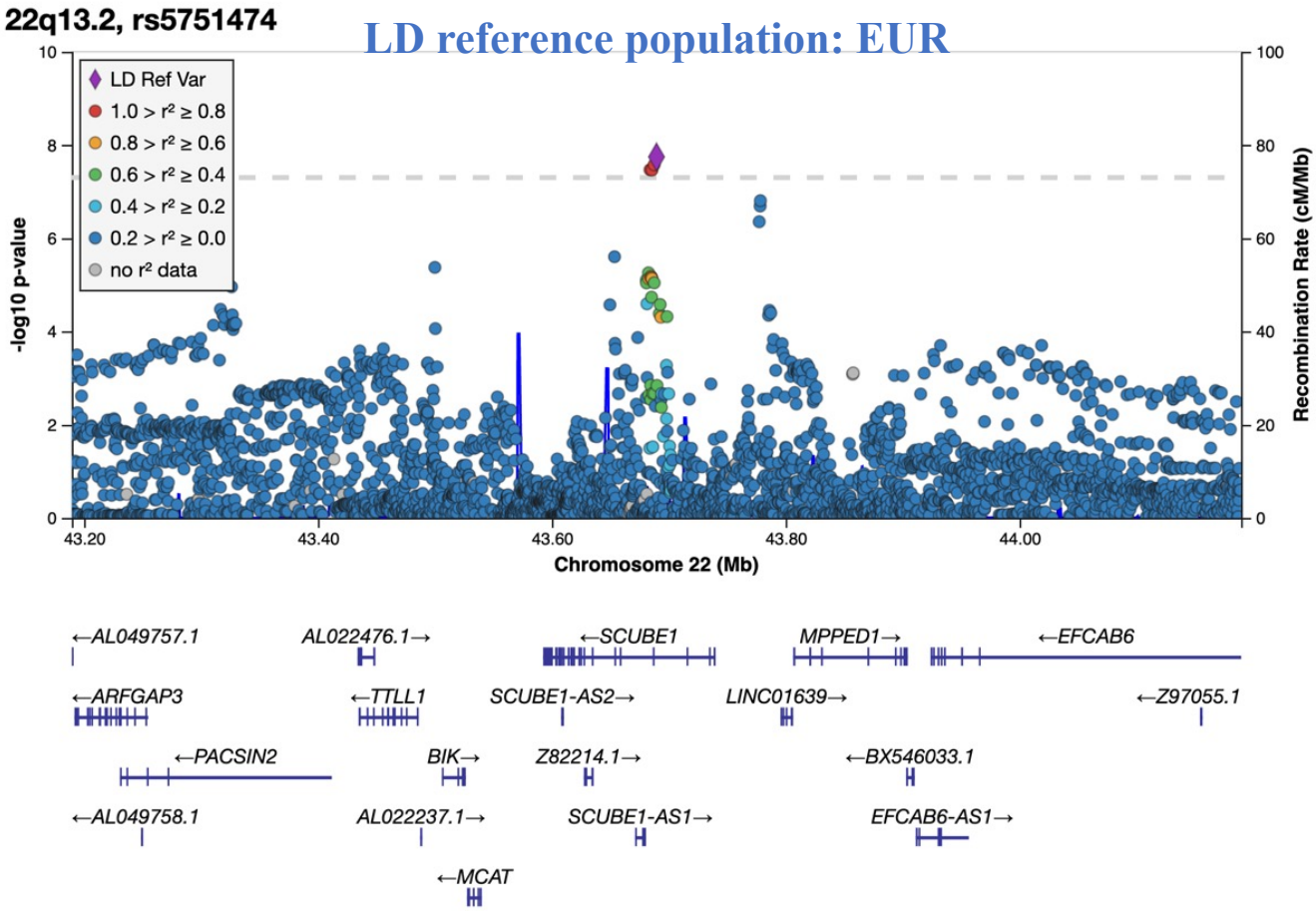
## LD reference population: EUR




## LD reference population: EAS



## LD reference population: EUR

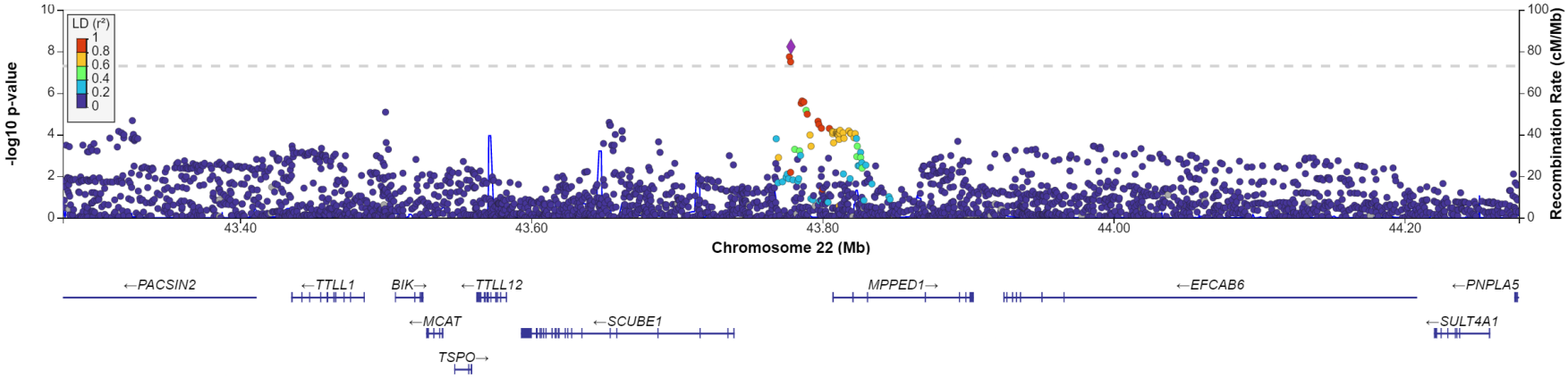



## LD reference population: EAS

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

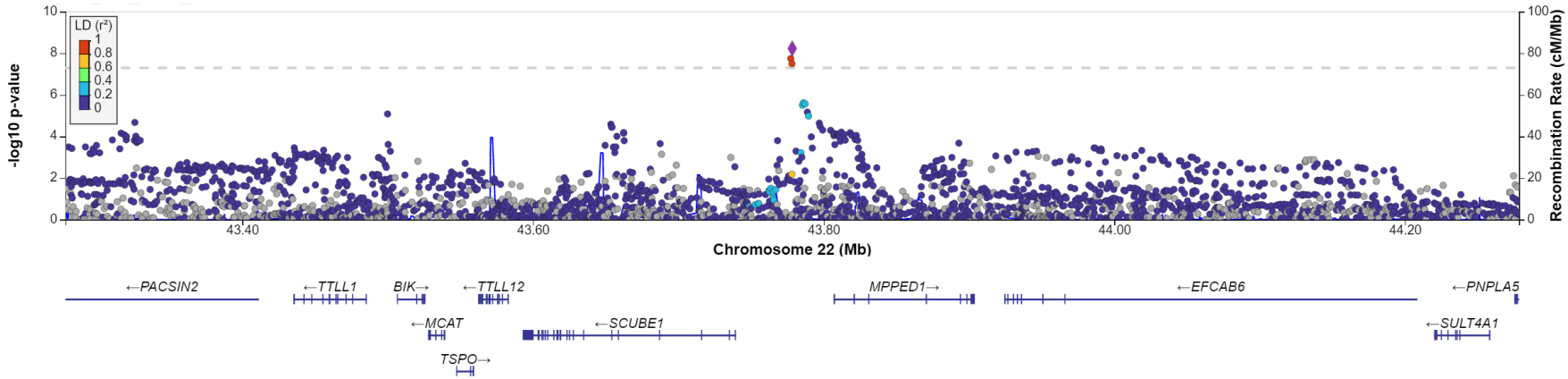
## LD reference population: EUR

**22q13.2, rs34256596**

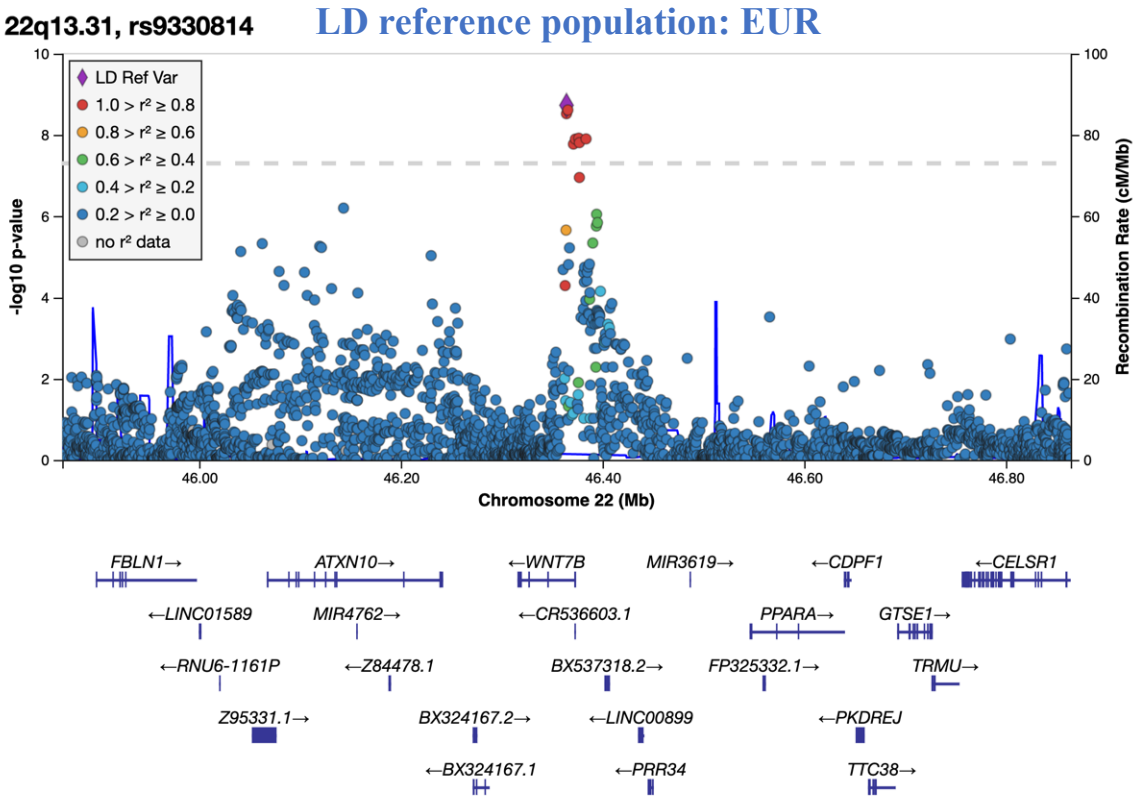



## LD reference population: EAS

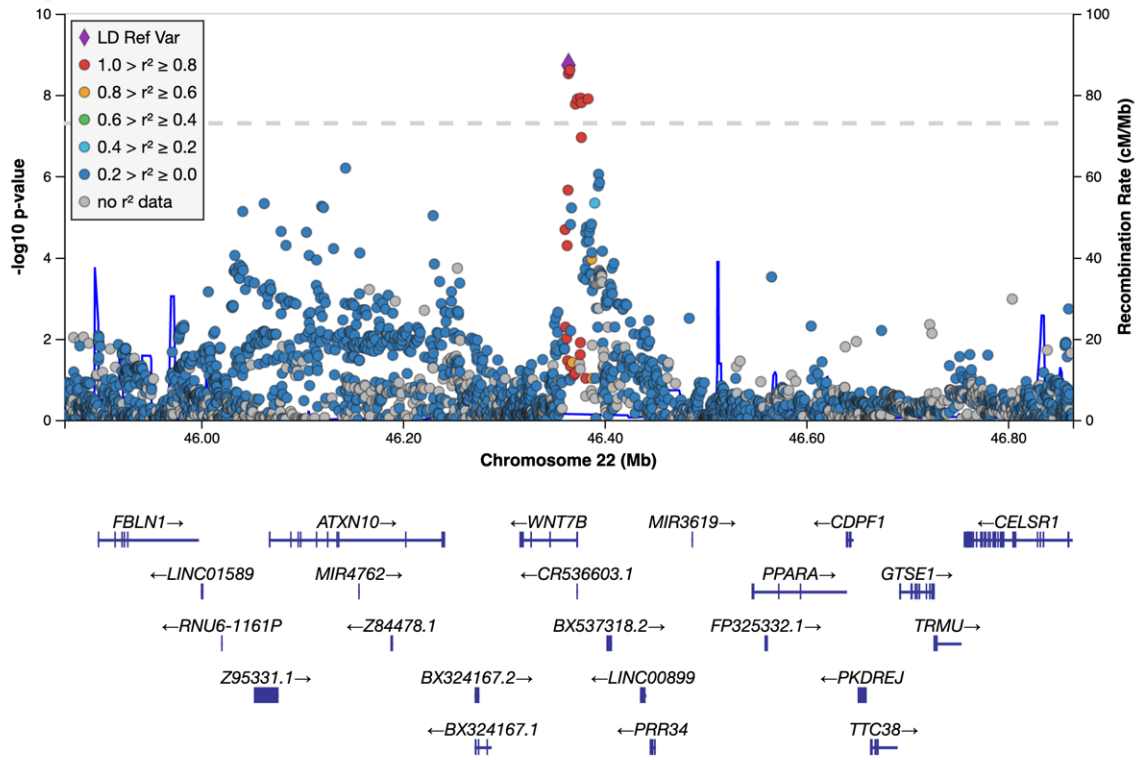
**22q13.2, rs34256596**



## LD reference population: EUR

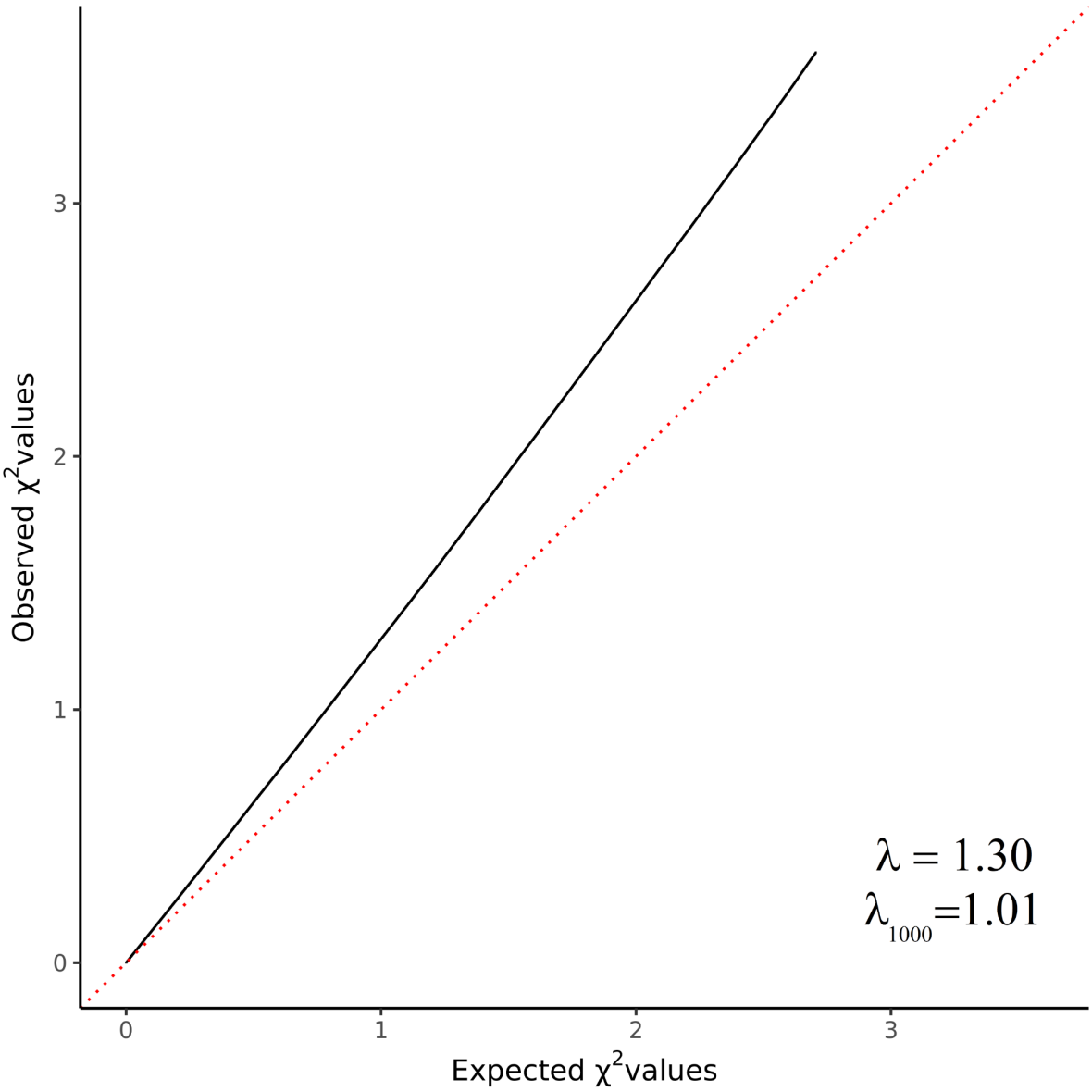



## LD reference population: EAS



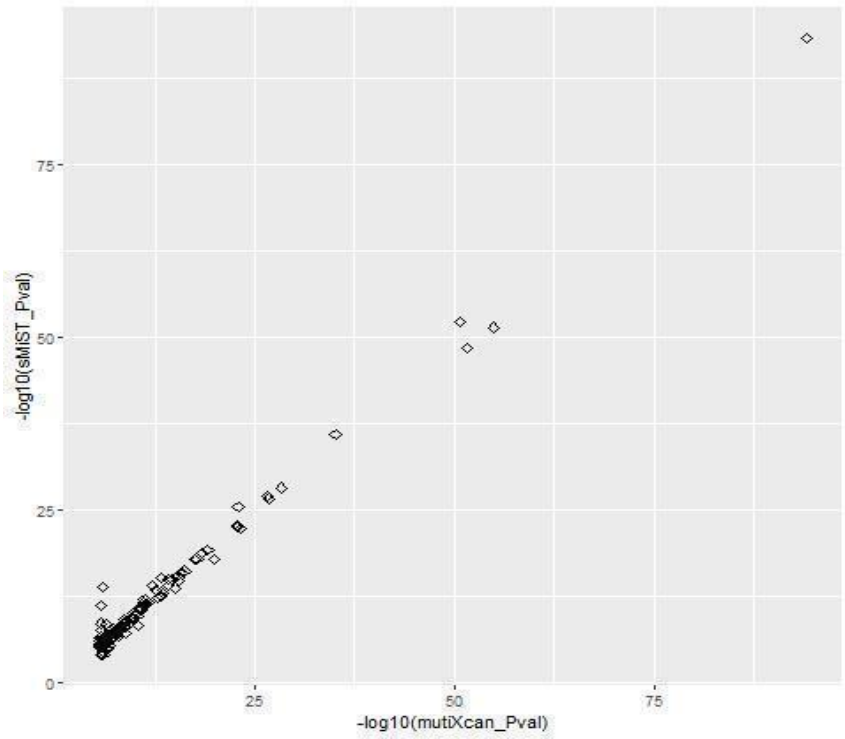

2

**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.

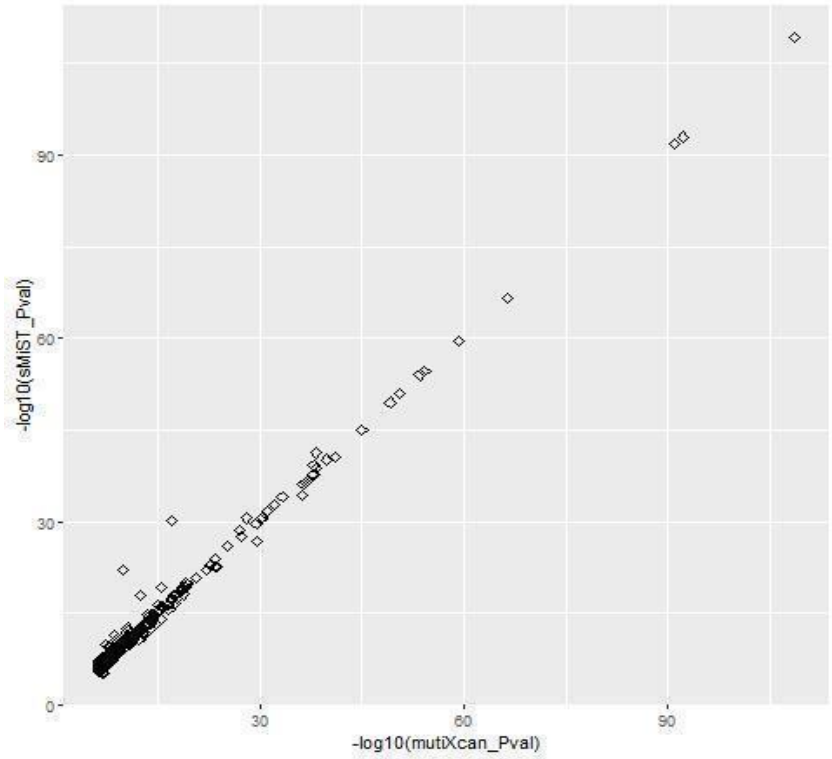


**Supplementary Figure 4. P-values from sMultiXcan and unconditional sMiST analysis of the sPrediXcan models for the 12,017 TWAS genes (A) and 88,888 MWAS CpGs (B).** All p-values are two-sided.

(A)



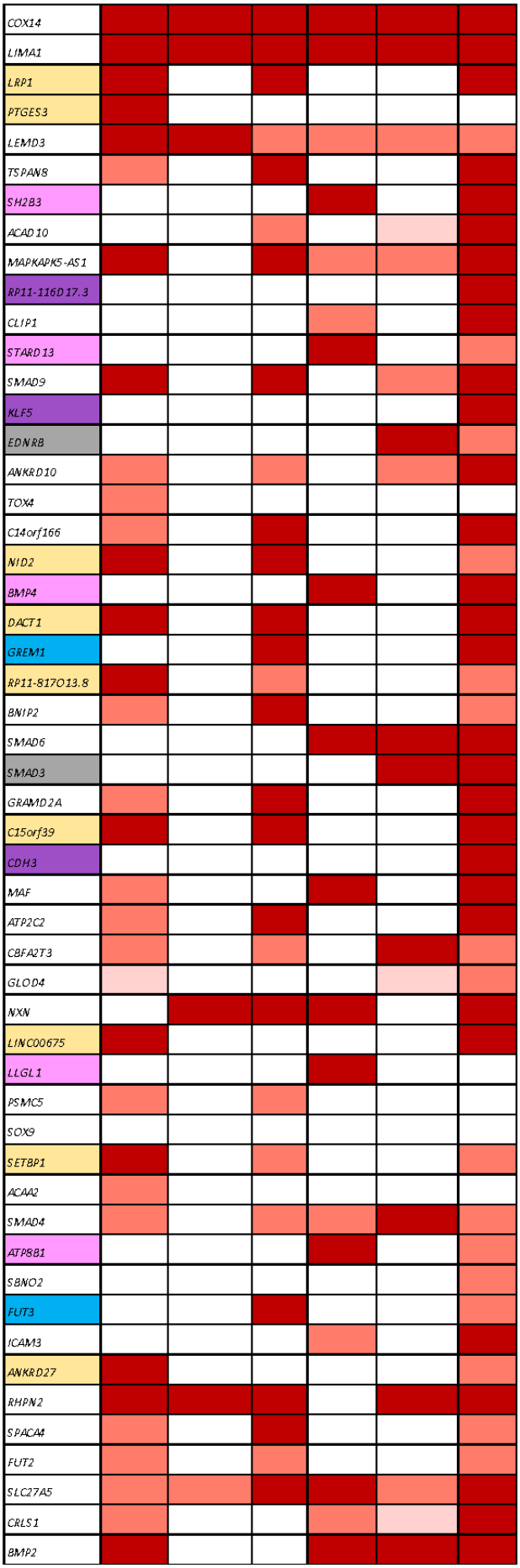

(B)

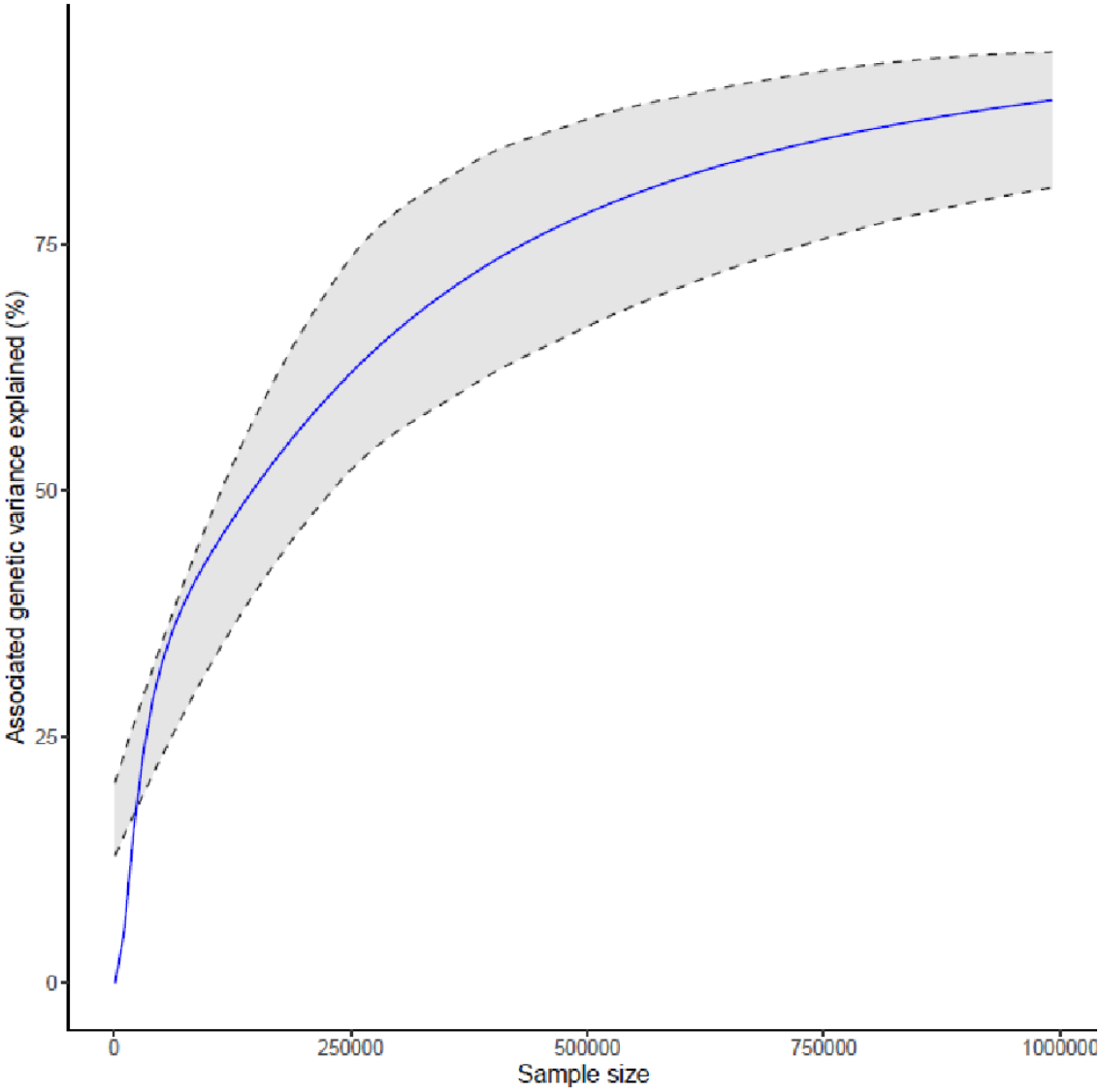


**Supplementary Figure 5. Association between effector genes and CRC risk from TWAS across tissue types.** Shading represents strength of association in each tissue in TWAS (colorectal mucosa (yellow), sigmoid colon (orange), pan-gastrointestinal "GI" (blue), immune cells (pink), mesenchyme (gray) and 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 | | | | | | |
| ARHGEF19 | | | | | | |
| WNT4 | | | | | | |
| C1QB | | | | | | |
| FHL3 | | | | | | |
| TTC22 | | | | | | |
| RPL5 | | | | | | |
| ACP6 | | | | | | |
| LINGO4 | | | | | | |
| LAMC1 | | | | | | |
| ARPC5 | | | | | | |
| LMOD1 | | | | | | |
| DSTYK | | | | | | |
| DUSP10 | | | | | | |
| FAM98A | | | | | | |
| ACTR1B | | | | | | |
| FBLN7 | | | | | | |
| ARHGEF4 | | | | | | |
| TANC1 | | | | | | |
| STK39 | | | | | | |
| SATB2 | | | | | | |
| CSRNP1 | | | | | | |
| SFMBT1 | | | | | | |
| RFT1 | | | | | | |
| ATXN7 | | | | | | |
| LRIG1 | | | | | | |
| GBE1 | | | | | | |
| BOC | | | | | | |
| WDR52 | | | | | | |
| DIRC2 | | | | | | |
| RYK | | | | | | |
| ACTRT3 | | | | | | |
| SMARCAD1 | | | | | | |
| TET2 | | | | | | |
| UGT8 | | | | | | |
| GAB1 | | | | | | |
| SMAD1 | | | | | | |
| MAB21L2 | | | | | | |
| TERT | | | | | | |
| TTC33 | | | | | | |
| CDKN2AIPNL | | | | | | |
| TXNDC15 | | | | | | |
| ERGIC1 | | | | | | |
| FBXO38 | | | | | | |
| CDX1 | | | | | | |
| RREB1 | | | | | | |
| HIVEP1 | | | | | | |
| CDKAL1 | | | | | | |
| ZKSCAN4 | | | | | | |
| TRIM27 | | | | | | |
| TULP1 | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| CDKN1A | | | | | | |
| TFEB | | | | | | |
| RP1-166H4.2 | | | | | | |
| BMP5 | | | | | | |
| DCBLD1 | | | | | | |
| EPB41L2 | | | | | | |
| TCF21 | | | | | | |
| GNA12 | | | | | | |
| TBRG4 | | | | | | |
| TNS3 | | | | | | |
| RP11-114G11.5 | | | | | | |
| WBSCR27 | | | | | | |
| CDK6 | | | | | | |
| TRIM4 | | | | | | |
| LINC00513 | | | | | | |
| TOX | | | | | | |
| UTP23 | | | | | | |
| POU5F18 | | | | | | |
| RP11-384P7.7 | | | | | | |
| DCAF12 | | | | | | |
| LPAR1 | | | | | | |
| BRD3 | | | | | | |
| ABCA2 | | | | | | |
| ITIH5 | | | | | | |
| BAMBI | | | | | | |
| GPRIN2 | | | | | | |
| A1CF | | | | | | |
| SFTPA2 | | | | | | |
| LINC01475 | | | | | | |
| CUTC | | | | | | |
| CNNM2 | | | | | | |
| TCF7L2 | | | | | | |
| IFITM1 | | | | | | |
| RHOG | | | | | | |
| F2 | | | | | | |
| KBTBD4 | | | | | | |
| FADS3 | | | | | | |
| MYRF | | | | | | |
| AP000439.5 | | | | | | |
| POLD3 | | | | | | |
| CHRDL2 | | | | | | |
| ME3 | | | | | | |
| TRPC6 | | | | | | |
| COLCA1 | | | | | | |
| COLCA2 | | | | | | |
| TAGLN | | | | | | |
| BCL9L | | | | | | |
| ADAMTS15 | | | | | | |
| CCND2 | | | | | | |
| PLEKHG6 | | | | | | |
| RP1-102E24.8 | | | | | | |
| LMBR1L | | | | | | |


COX14
LIMA1
LRP1
PTGES3
LEMD3
TSPAN8
SH2B3
ACAD10
MAPKAPK5-AS1
RP11-116D17.3
CLIP1
STARD13
SMAD9
KLF5
EDNRB
ANKRD10
TOX4
C14orf166
NID2
BMP4
DACT1
GREM1
RP11-817O13.8
BNIP2
SMAD6
SMAD3
GRAMD2A
C15orf39
CDH3
MAF
ATP2C2
CBFA2T3
GLOD4
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.