Genome-wide association meta-analyses and fine-mapping elucidate pathways influencing albuminuria

Teumer *et al.*

SUPPLEMENTARY INFORMATION

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Supplementary Note 1: Extended acknowledgements

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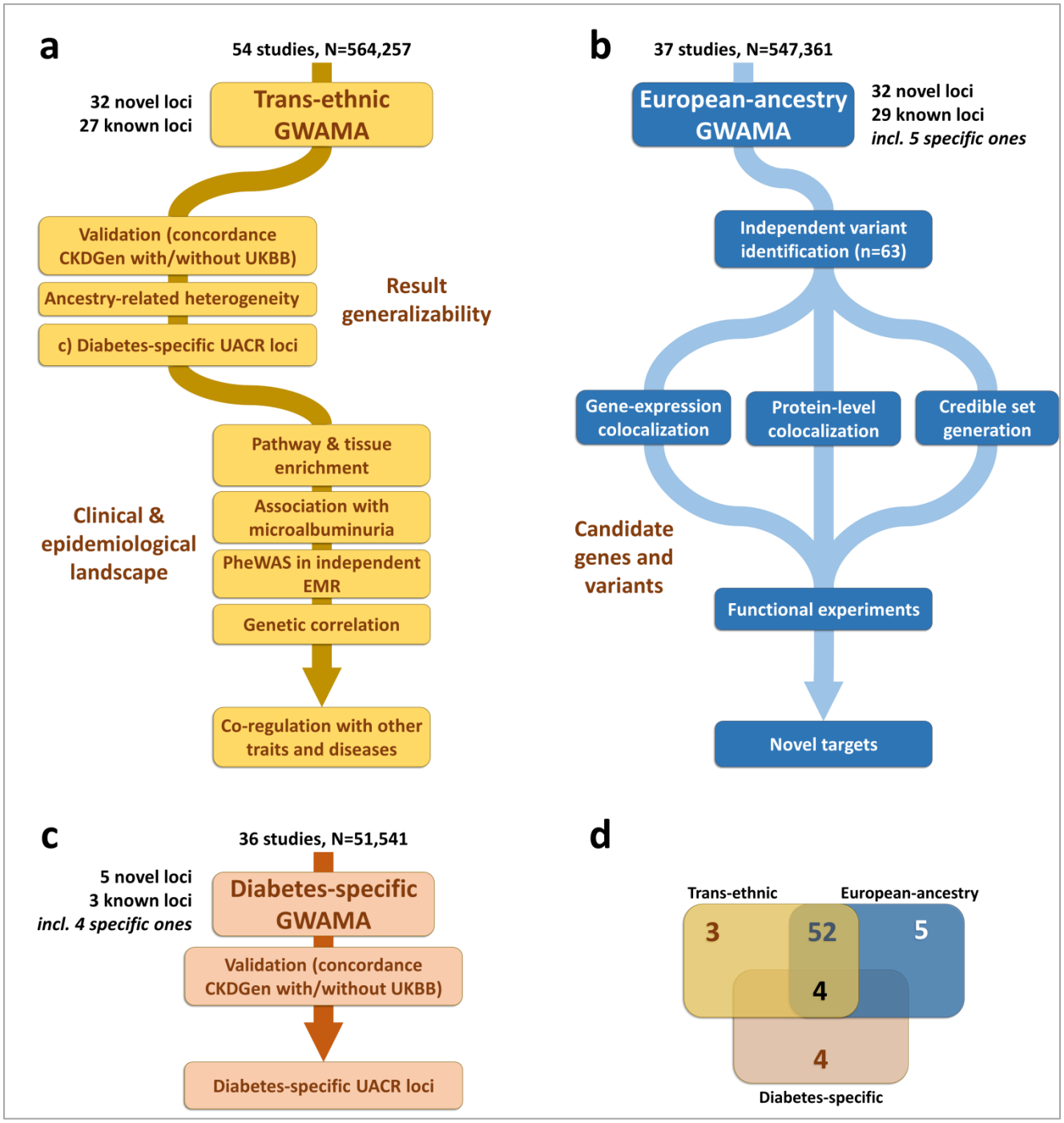
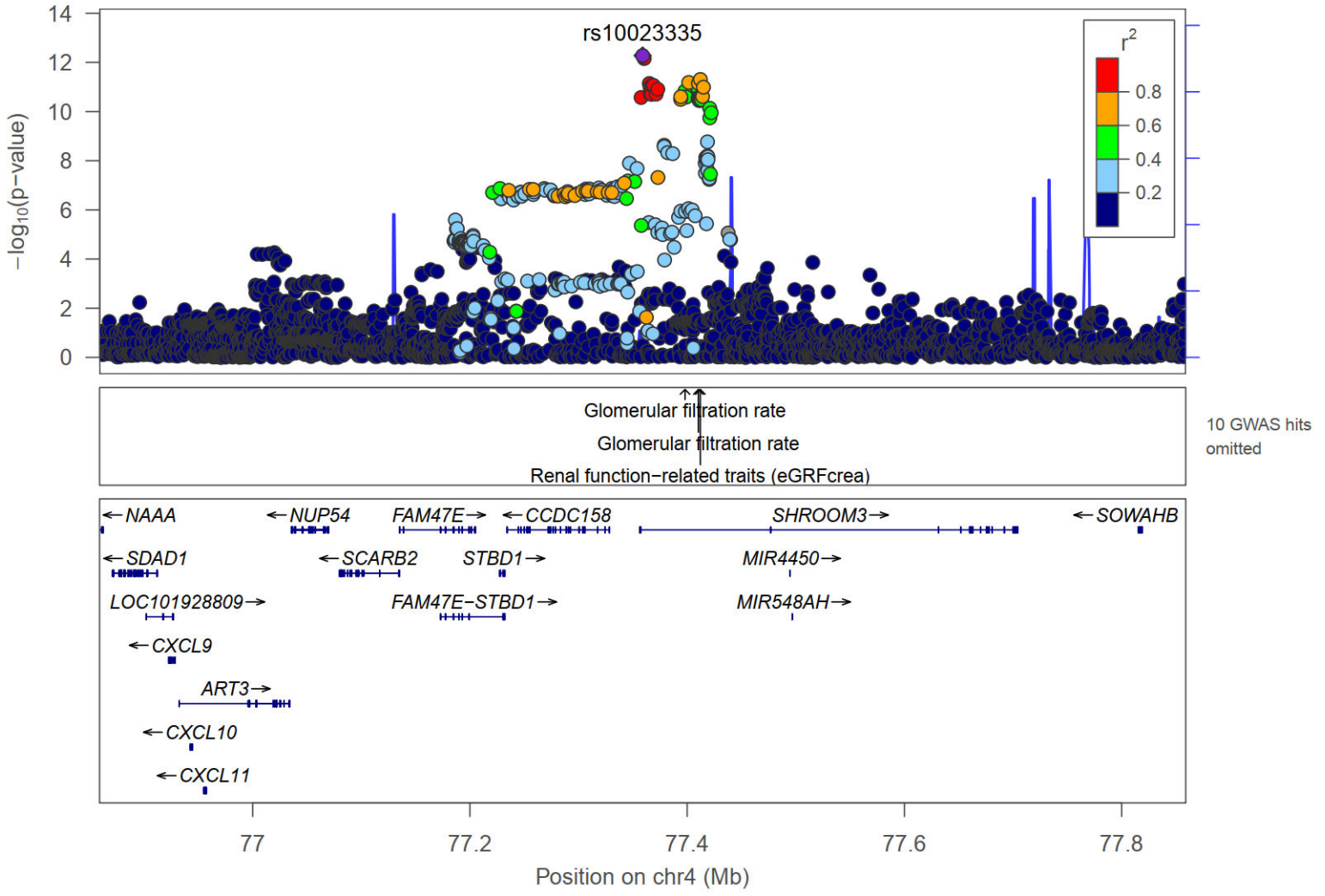
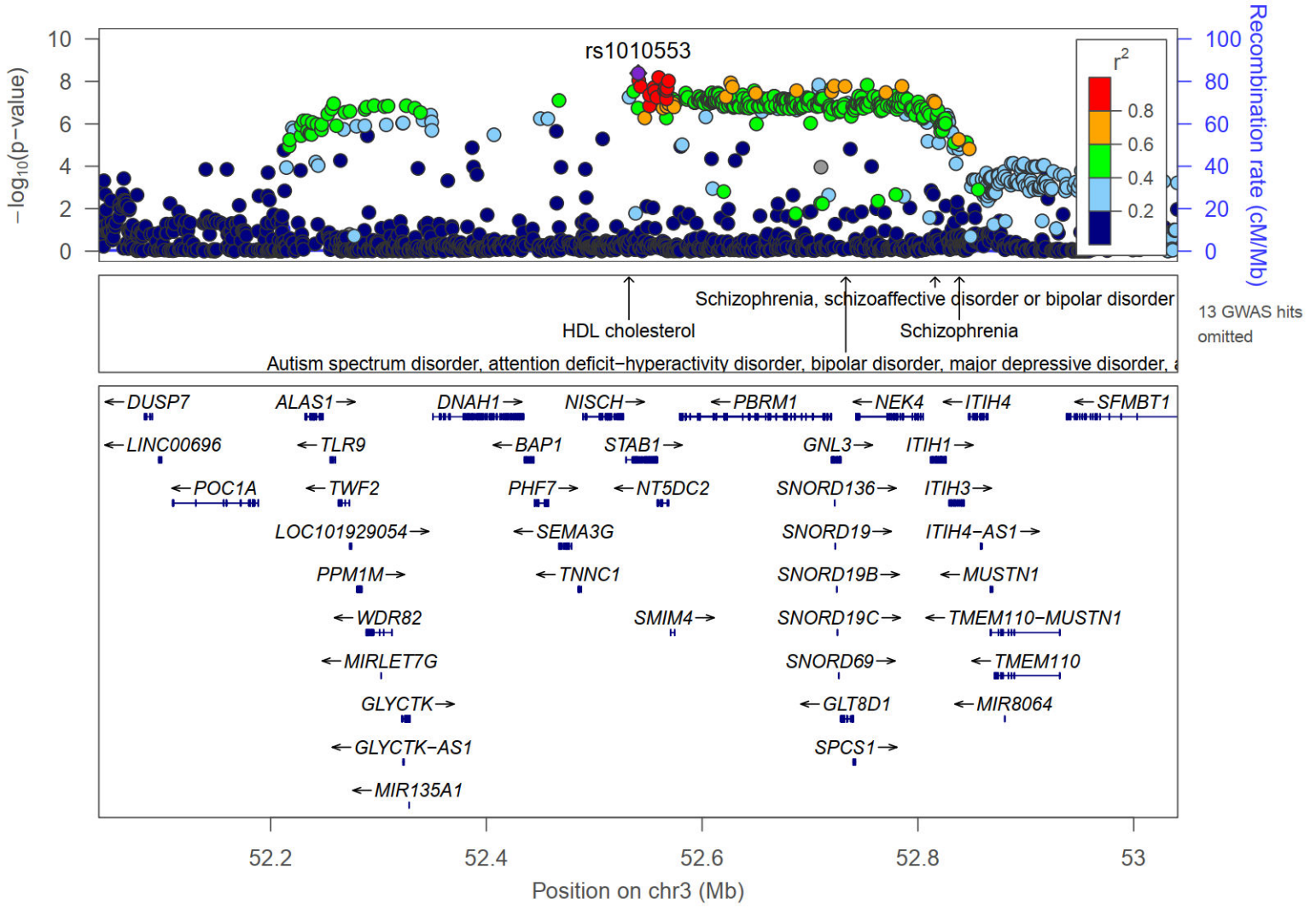
Supplementary Figure 1: Workflow of the project

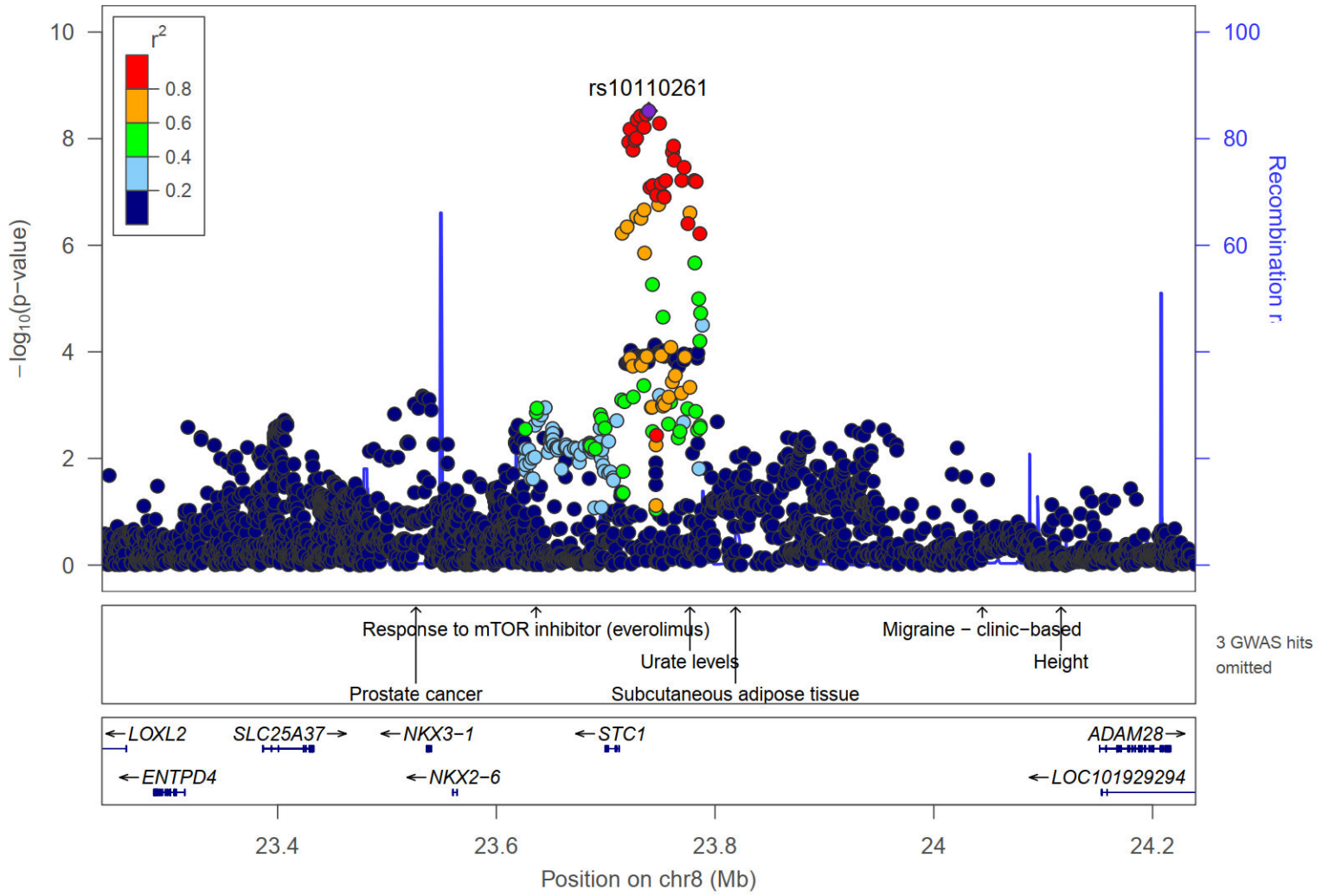


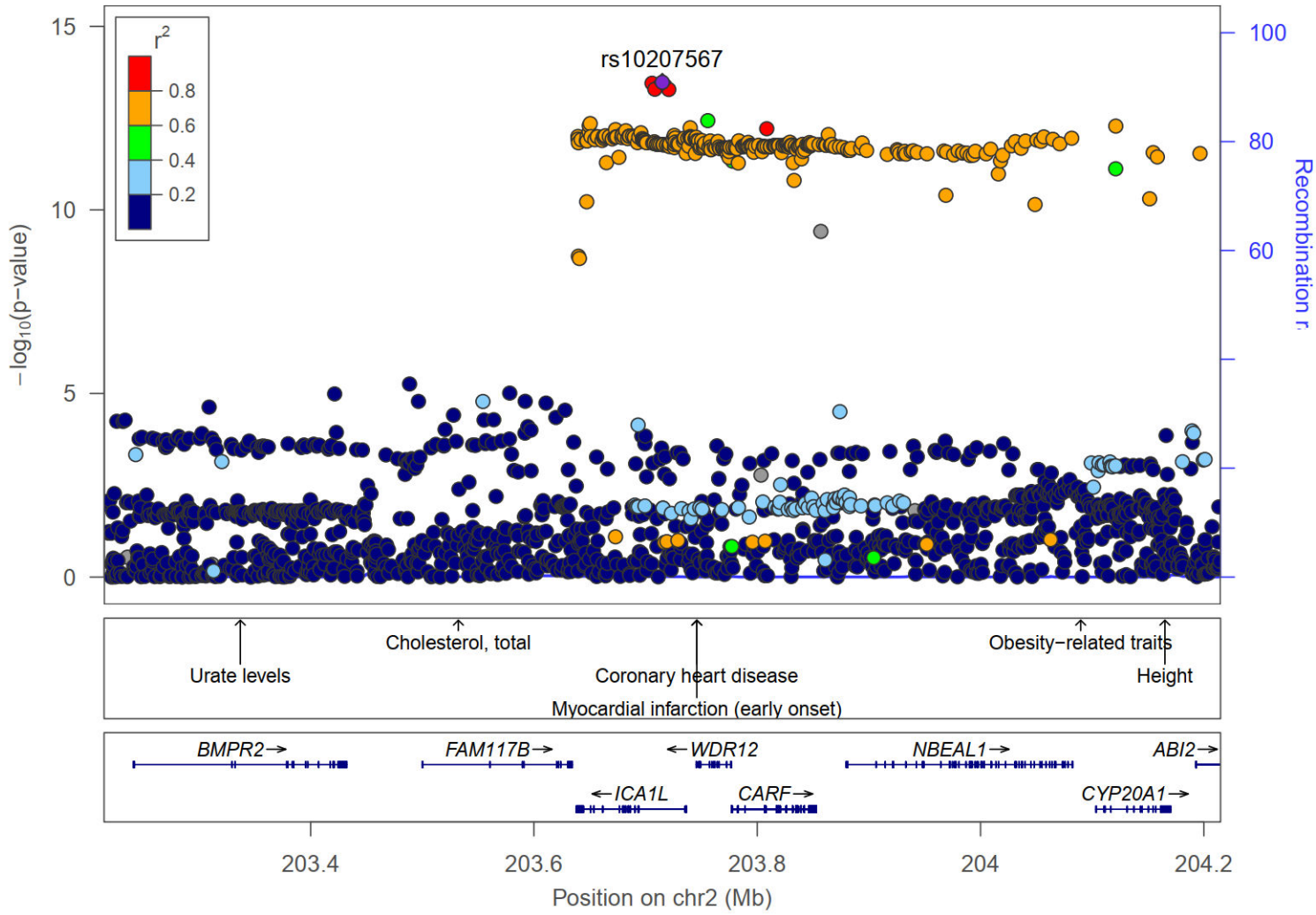
Overview of the analysis workflow for trans-ethnic (a), European ancestry-specific (b), and diabetes-specific (c) genome-wide association meta-analyses (GWAMA). The Venn diagram in panel (d) shows the number of overlapping loci between the different GWAMA.

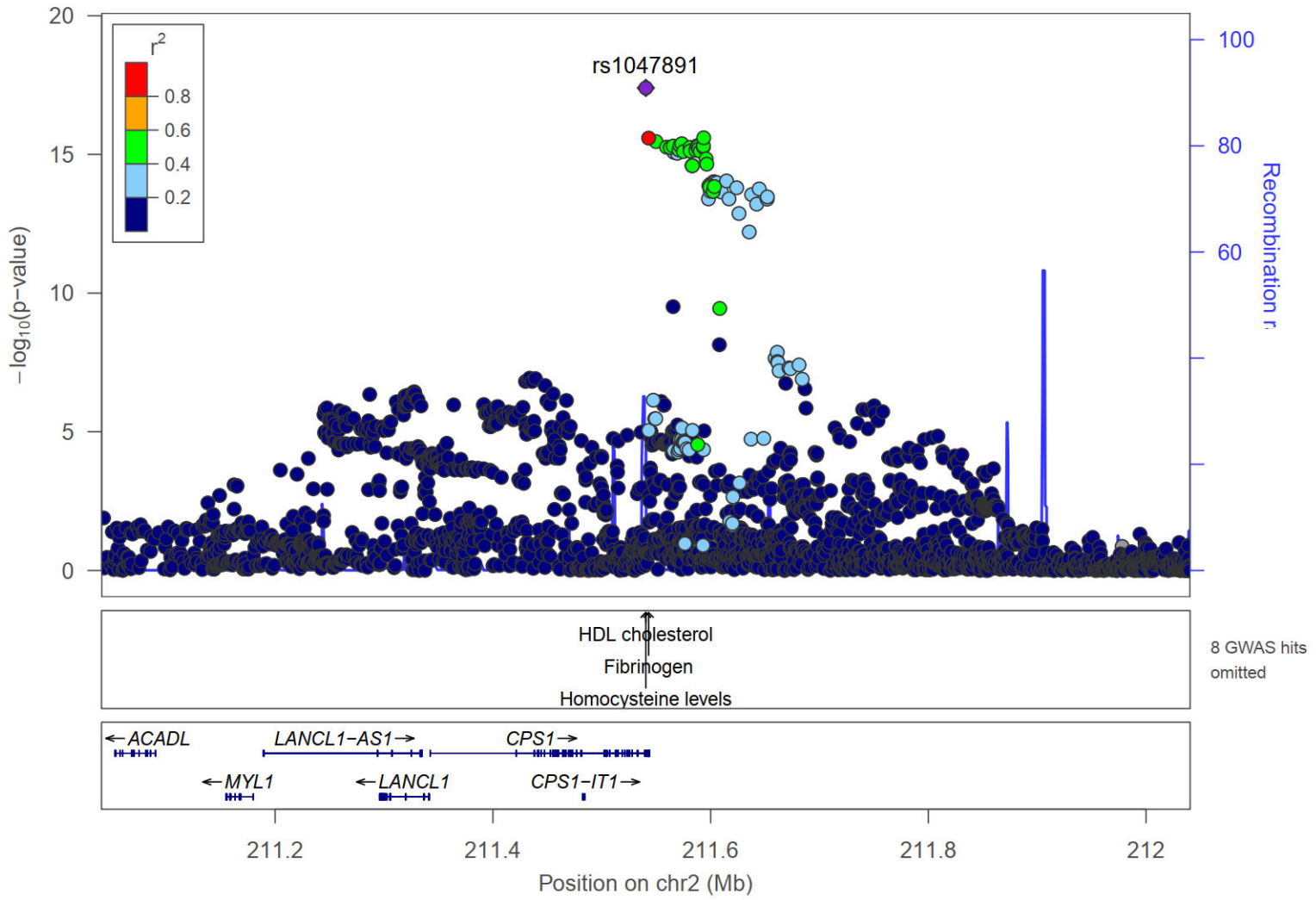
Supplementary Figure 2: Regional association plots for loci identified in trans-ethnic GWAS meta-analysis of UACR

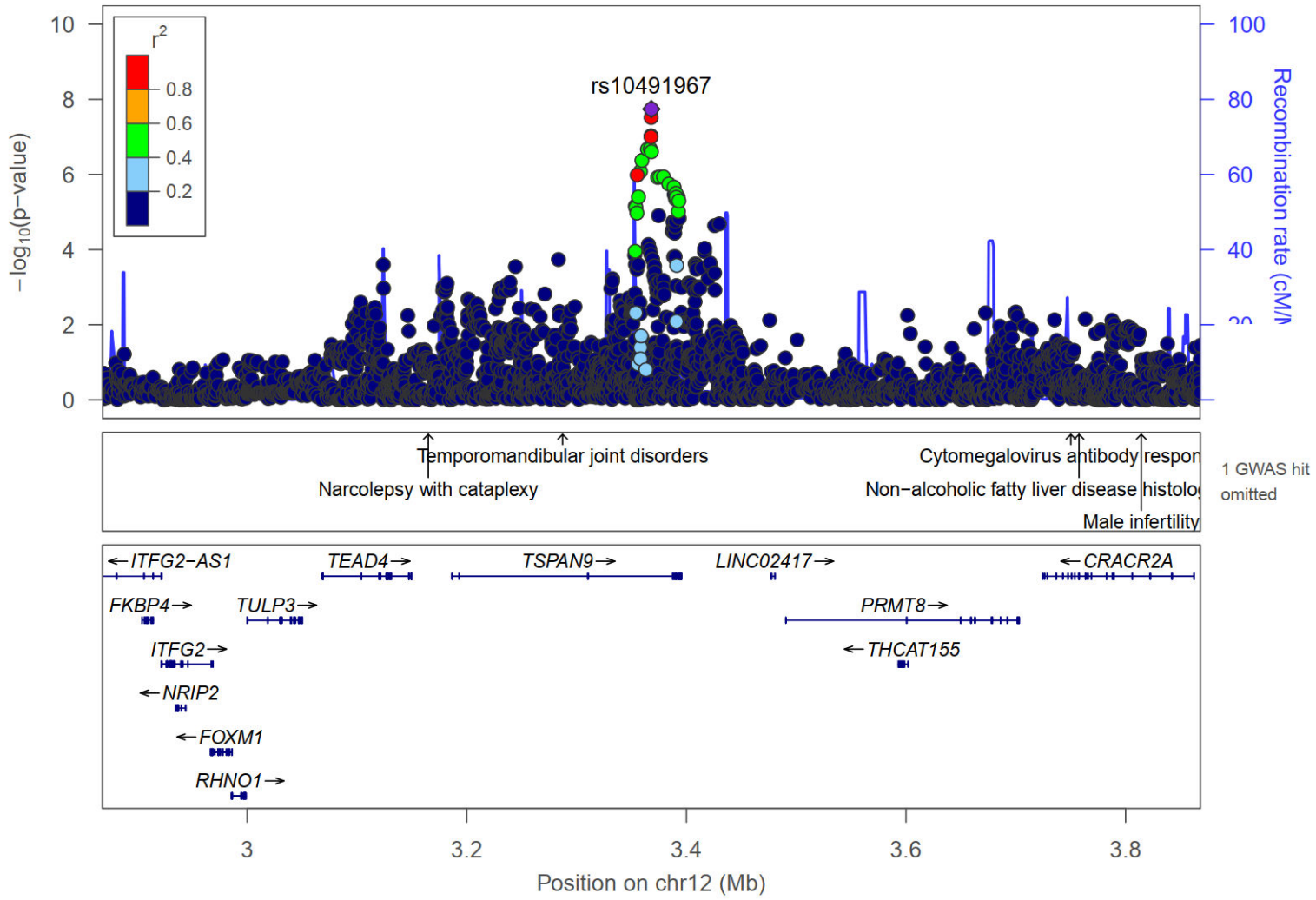

rs10023335
r²
0.8
0.6
0.4
0.2
−log10(p−value)
14
12
10
8
6
4
2
0
Glomerular filtration rate
Glomerular filtration rate
Renal function−related traits (eGRFcrea)
10 GWAS hits omitted
NAAA
NUP54
FAM47E
CCDC158
SHROOM3
SOWAHB
SDAD1
SCARB2
STBD1
MIR4450
LOC101928809
FAM47E−STBD1
MIR548AH
CXCL9
ART3
CXCL10
CXCL11
77
77.2
77.4
77.6
77.8
Position on chr4 (Mb)

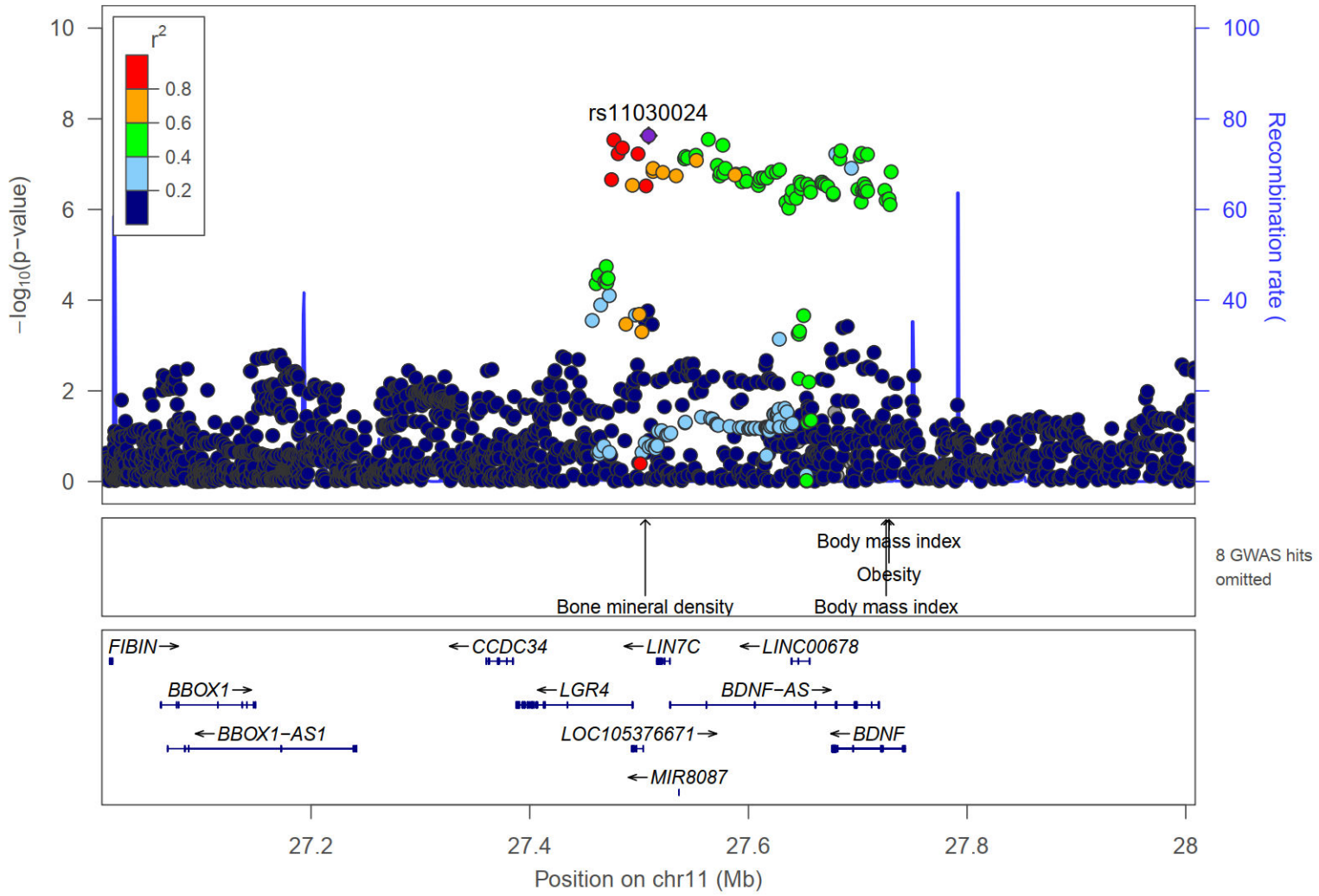

rs1010553
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
HDL cholesterol
Schizophrenia, schizoaffective disorder or bipolar disorder
Schizophrenia
13 GWAS hits omitted
Autism spectrum disorder, attention deficit−hyperactivity disorder, bipolar disorder, major depressive disorder,
DUSP7
ALAS1
DNAH1
NISCH
PBRM1
NEK4
ITIH4
SFMBT1
LINC00696
TLR9
BAP1
STAB1
GNL3
ITIH1
POC1A
TWF2
PHF7
NT5DC2
SNORD136
ITIH3
LOC101929054
SEMA3G
SNORD19
ITIH4−AS1
PPM1M
TNNC1
SNORD19B
MUSTN1
WDR82
SMIM4
SNORD19C
TMEM110−MUSTN1
MIRLET7G
SNORD69
TMEM110
GLYCTK
GLT8D1
MIR8064
GLYCTK−AS1
SPCS1
MIR135A1
Position on chr3 (Mb)

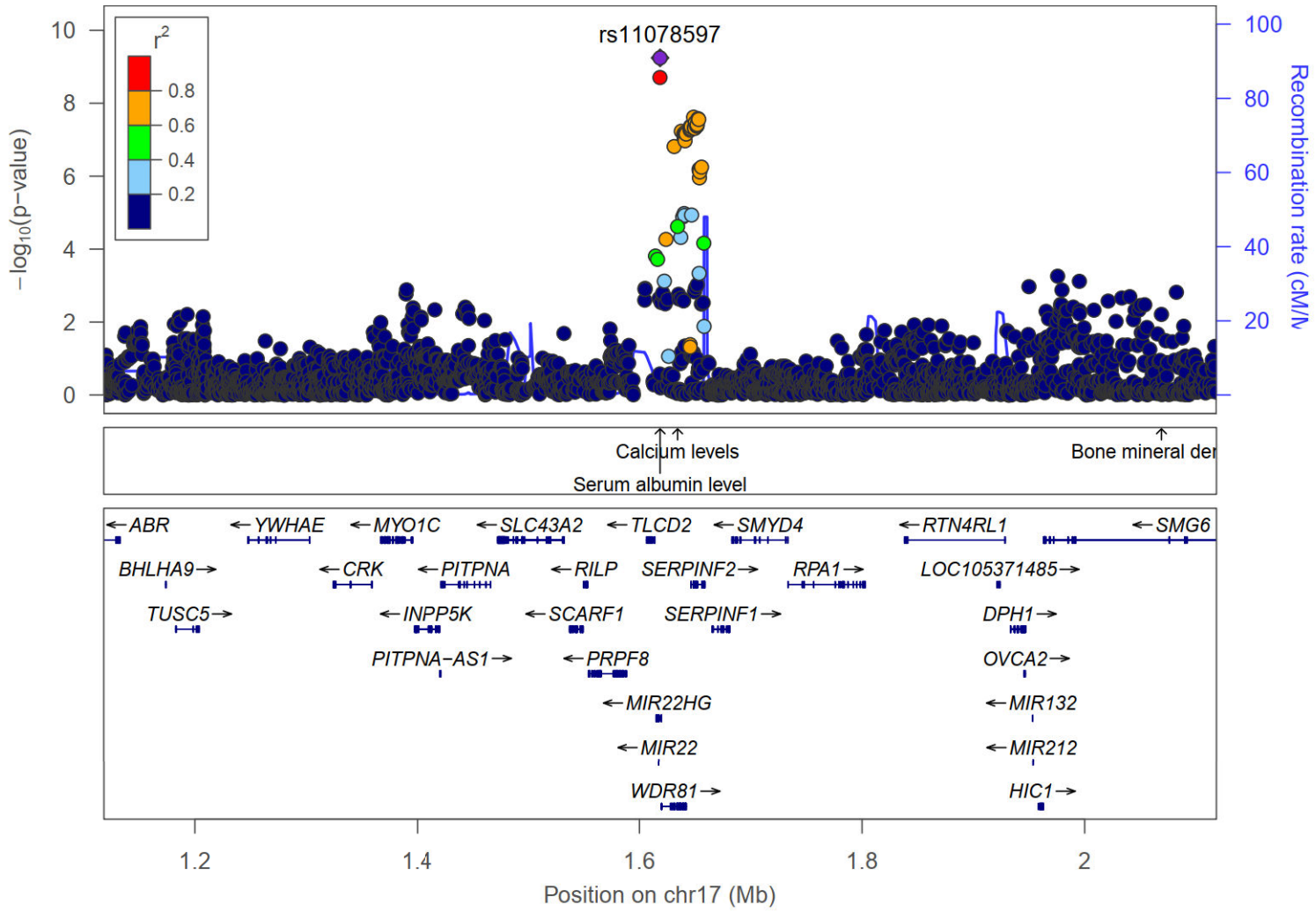

r2
0.8
0.6
0.4
0.2
rs10110261
−log10(p−value)
Recombination r
Response to mTOR inhibitor (everolimus)
Prostate cancer
Urate levels
Subcutaneous adipose tissue
Migraine − clinic−based
Height
3 GWAS hits
omitted
←LOXL2
SLC25A37→
←NKX3−1
←STC1
ADAM28→
←ENTPD4
←NKX2−6
←LOC101929294
Position on chr8 (Mb)

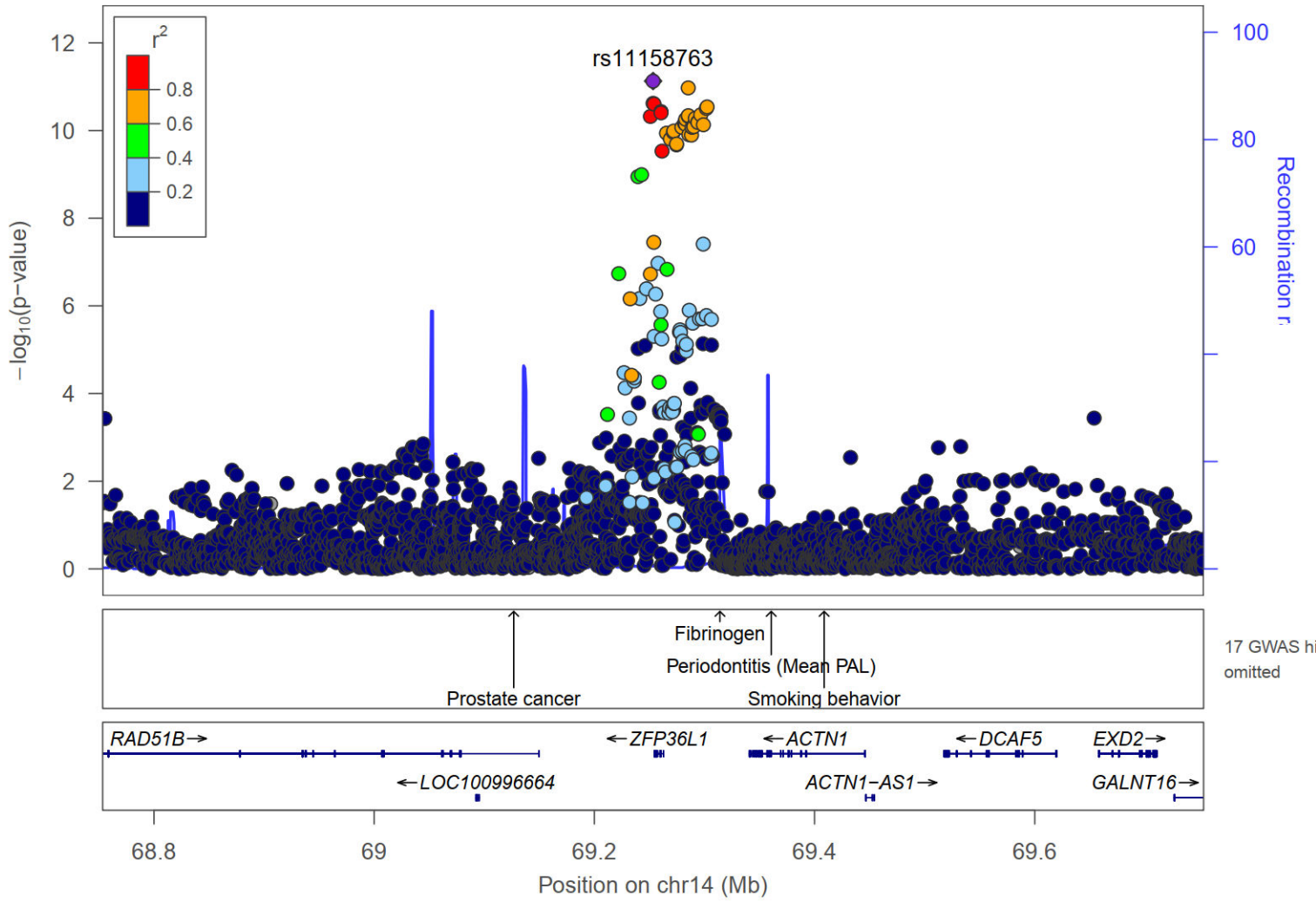

r2
0.8
0.6
0.4
0.2
rs10207567
15
10
5
0
100
80
60
−log10(p−value)
Recombination r
Urate levels
Cholesterol, total
Coronary heart disease
Myocardial infarction (early onset)
Obesity−related traits
Height
BMPR2→
FAM117B→
←WDR12
NBEAL1→
ABI2→
←ICA1L
CARF→
CYP20A1→
203.4
203.6
203.8
204
204.2
Position on chr2 (Mb)

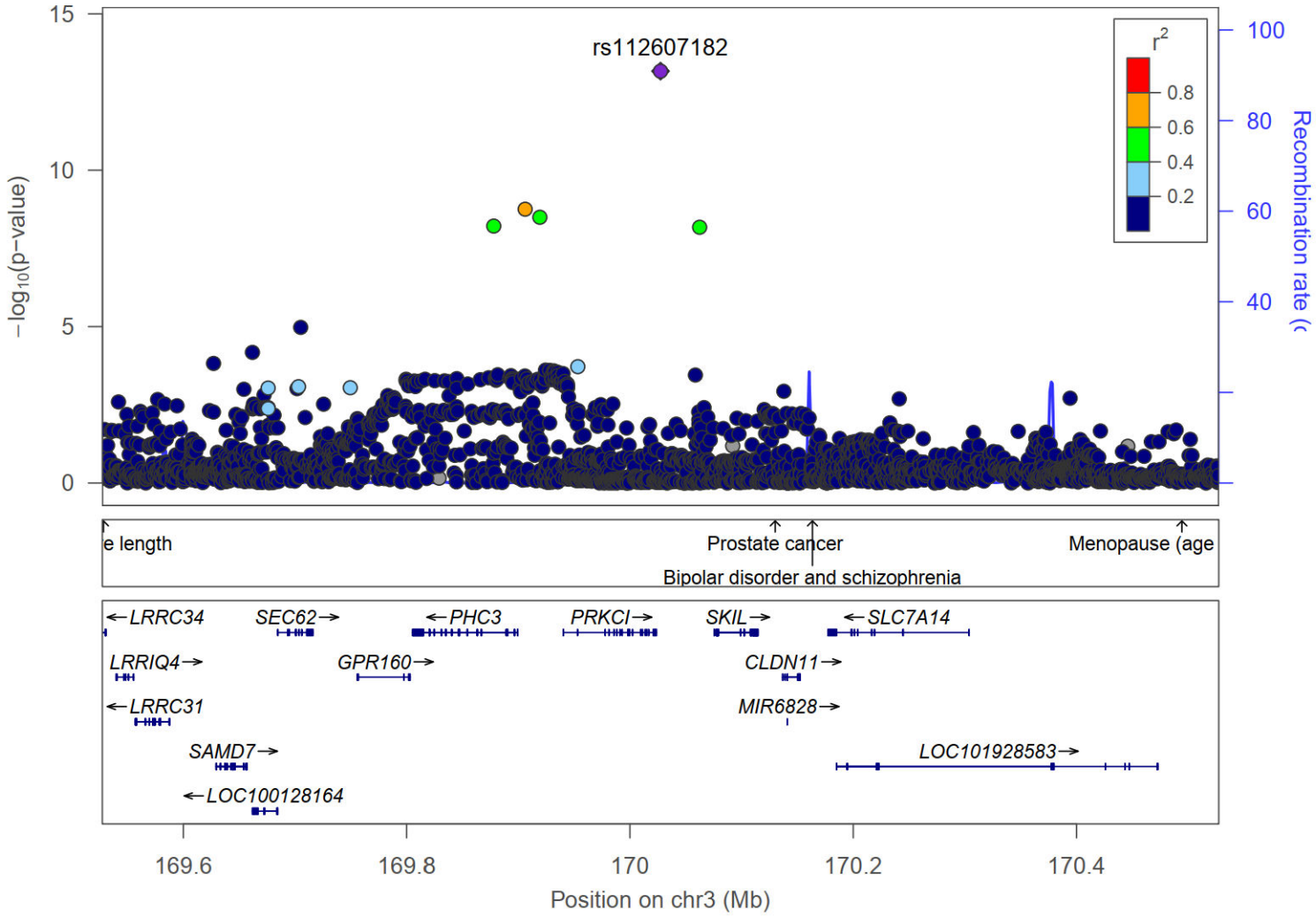

r2
0.8
0.6
0.4
0.2
rs1047891
20
15
10
5
0
−log10(p−value)
100
80
60
Recombination r
HDL cholesterol
Fibrinogen
Homocysteine levels
8 GWAS hits
omitted
←ACADL
LANCL1−AS1→
CPS1→
←MYL1
←LANCL1
CPS1−IT1→
211.2
211.4
211.6
211.8
212
Position on chr2 (Mb)

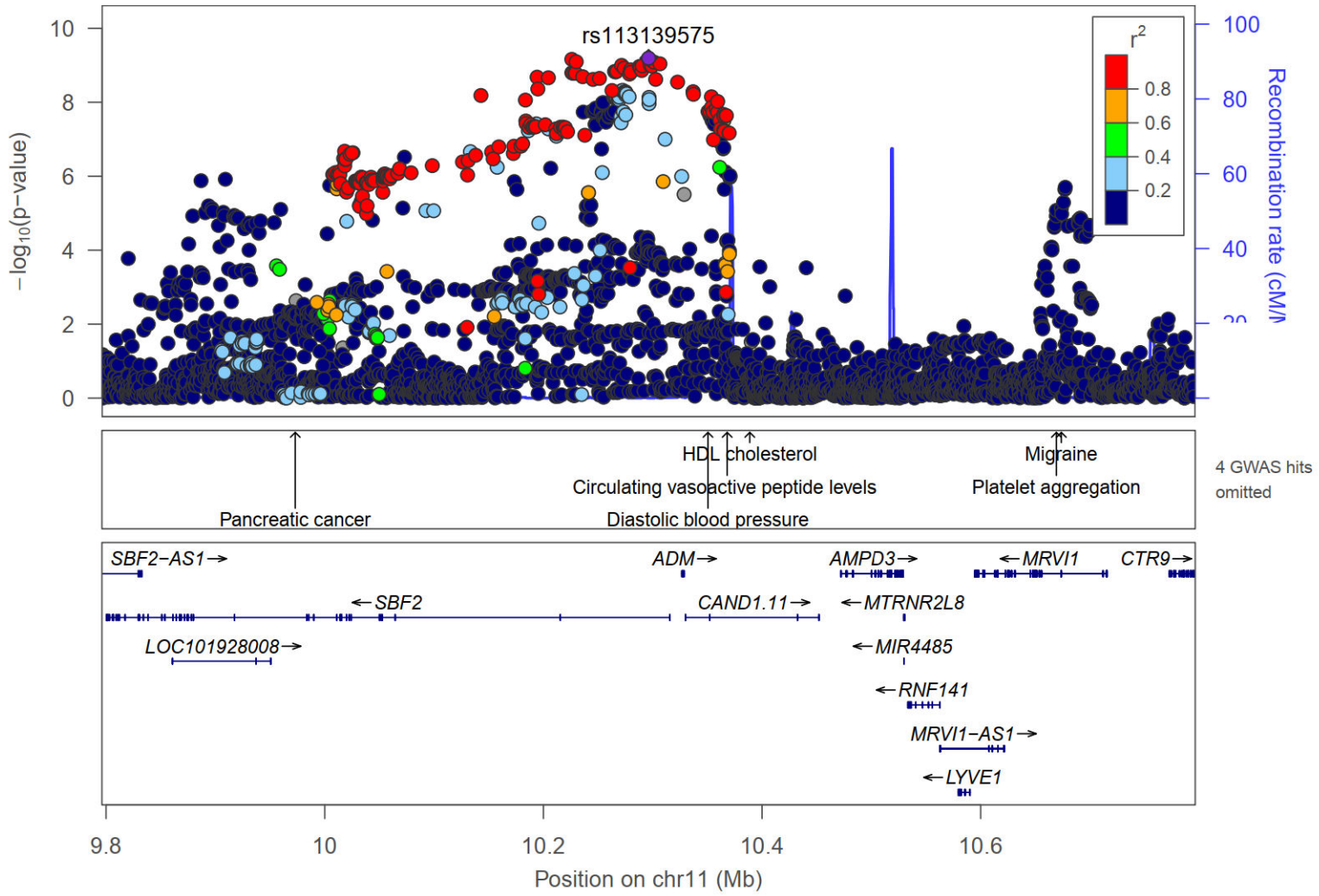

r²
0.8
0.6
0.4
0.2
rs10491967
−log10(p−value)
Recombination rate (cM/
Temporomandibular joint disorders
Narcolepsy with cataplexy
Cytomegalovirus antibody respon
Non−alcoholic fatty liver disease histolo
Male infertility
1 GWAS hit
omitted
ITFG2−AS1
TEAD4
TSPAN9
LINC02417
CRACR2A
FKBP4
TULP3
PRMT8
ITFG2
THCAT155
NRIP2
FOXM1
RHNO1
Position on chr12 (Mb)

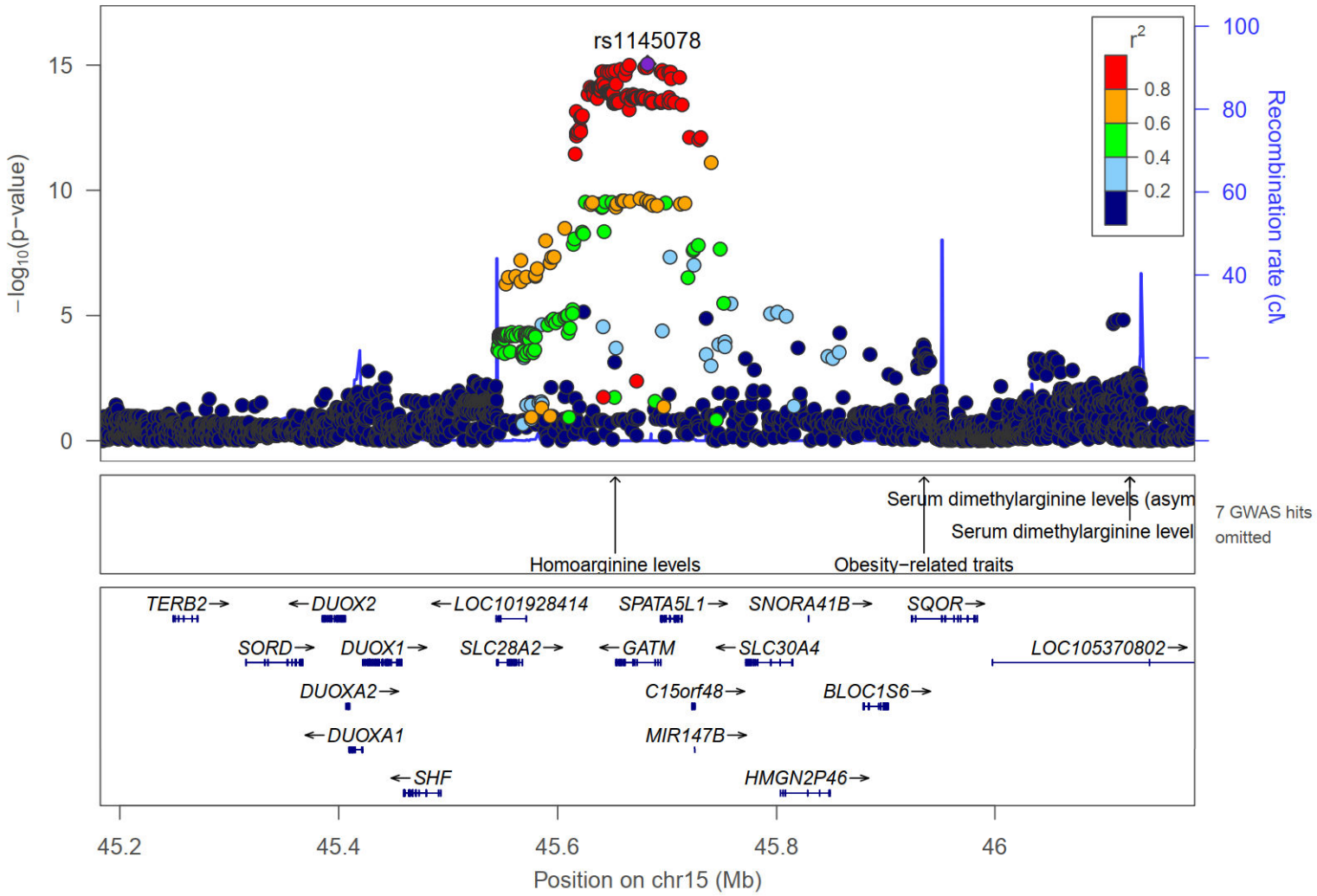

r2
0.8
0.6
0.4
0.2
rs11030024
−log10(p−value)
Recombination rate (
10
8
6
4
2
0
100
80
60
40
Body mass index
Obesity
Bone mineral density
Body mass index
8 GWAS hits
omitted
FIBIN→
←CCDC34
←LIN7C
←LINC00678
BBOX1→
←LGR4
BDNF−AS→
←BBOX1−AS1
LOC105376671→
←BDNF
←MIR8087
27.2
27.4
27.6
27.8
28
Position on chr11 (Mb)

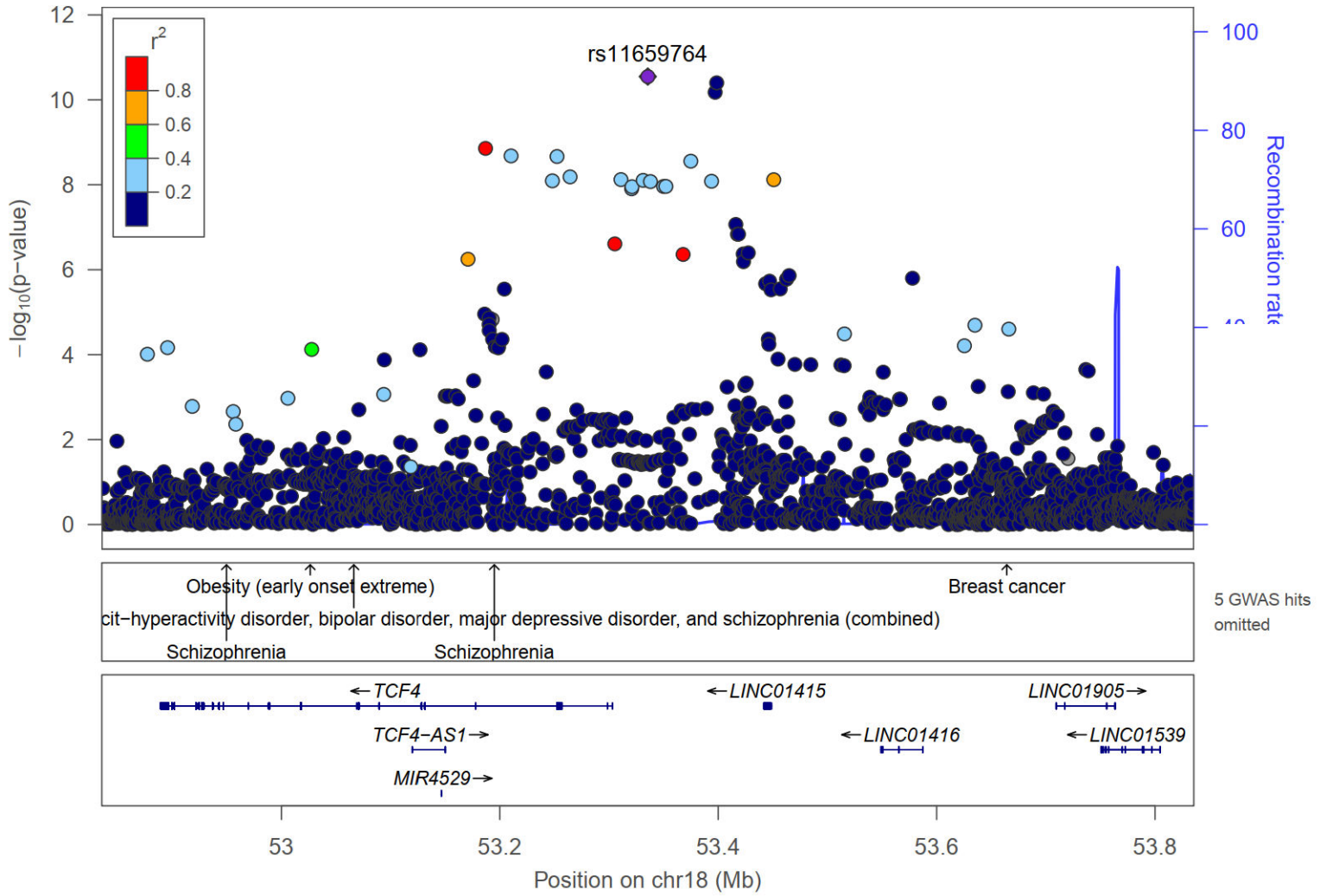

rs11078597
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/M
Calcium levels
Serum albumin level
Bone mineral den
ABR
YWHAE
MYO1C
SLC43A2
TLCD2
SMYD4
RTN4RL1
SMG6
BHLHA9
CRK
PITPNA
RILP
SERPINF2
RPA1
LOC105371485
TUSC5
INPP5K
SCARF1
SERPINF1
DPH1
PITPNA−AS1
PRPF8
OVCA2
MIR22HG
MIR132
MIR22
MIR212
WDR81
HIC1
Position on chr17 (Mb)

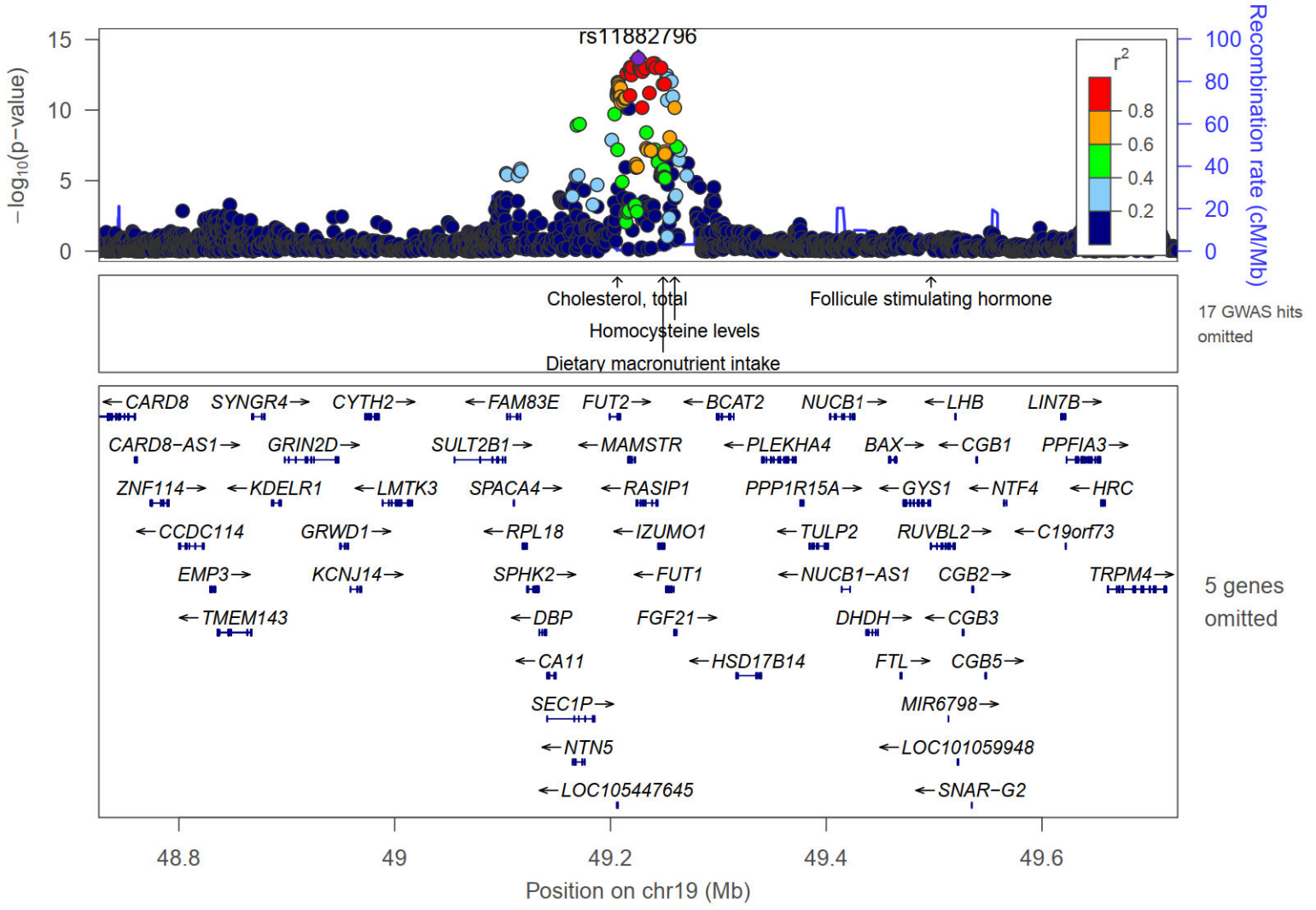

r2
0.8
0.6
0.4
0.2
rs11158763
−log10(p−value)
Recombination r
17 GWAS hits
omitted
Fibrinogen
Periodontitis (Mean PAL)
Prostate cancer
Smoking behavior
RAD51B→
←ZFP36L1
←ACTN1
←DCAF5
EXD2→
←LOC100996664
ACTN1−AS1→
GALNT16→
Position on chr14 (Mb)

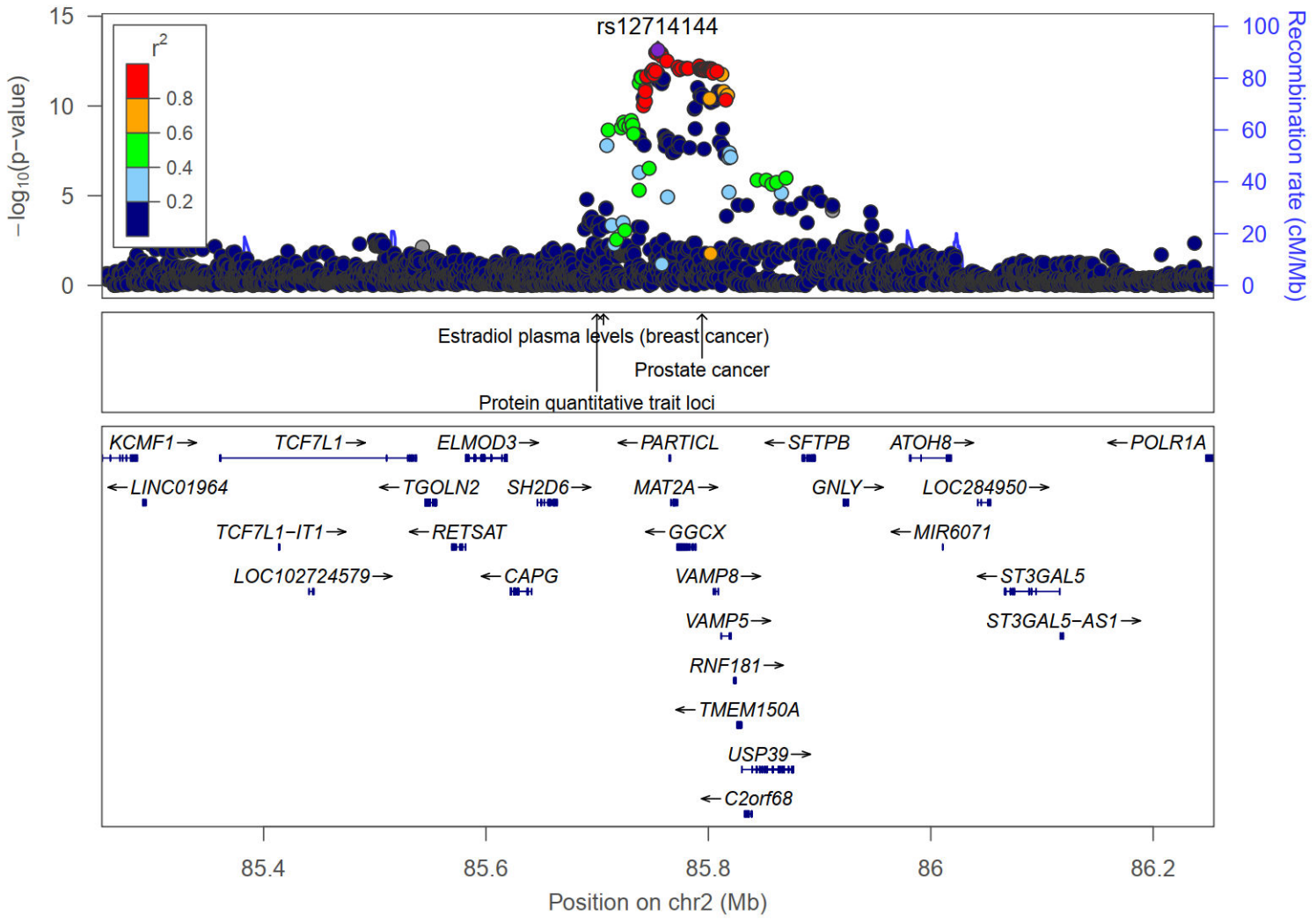

rs112607182
r2
0.8
0.6
0.4
0.2
15
10
5
0
100
80
60
40
−log10(p−value)
Recombination rate (
e length
Prostate cancer
Menopause (age
Bipolar disorder and schizophrenia
LRRC34
SEC62
PHC3
PRKCI
SKIL
SLC7A14
LRRIQ4
GPR160
CLDN11
LRRC31
MIR6828
SAMD7
LOC101928583
LOC100128164
169.6
169.8
170
170.2
170.4
Position on chr3 (Mb)

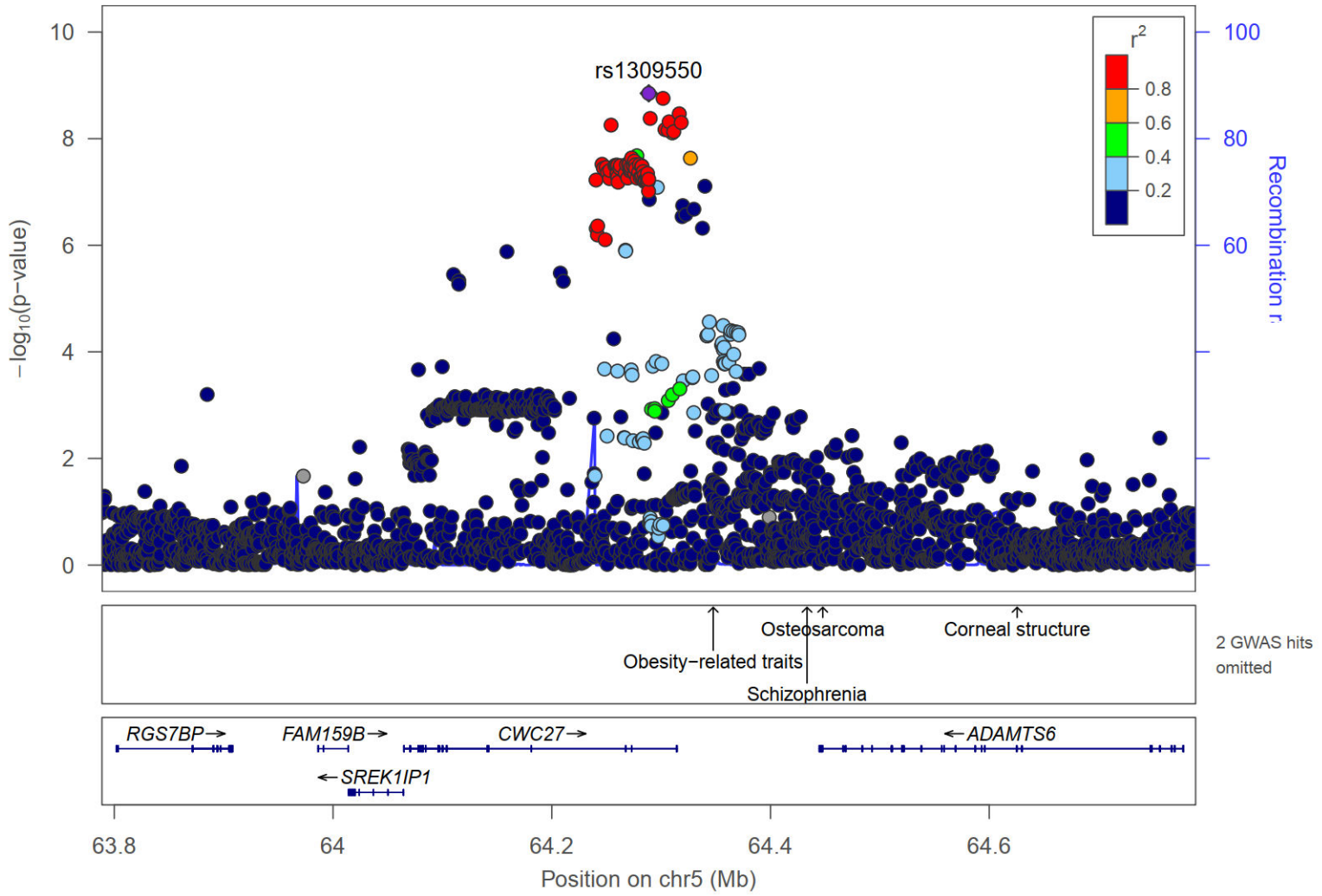

rs113139575
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/
Pancreatic cancer
HDL cholesterol
Circulating vasoactive peptide levels
Diastolic blood pressure
Migraine
Platelet aggregation
4 GWAS hits omitted
SBF2−AS1→
ADM→
AMPD3→
←MRVI1
CTR9→
←SBF2
CAND1.11→
←MTRNR2L8
LOC101928008→
←MIR4485
←RNF141
MRVI1−AS1→
←LYVE1
Position on chr11 (Mb)

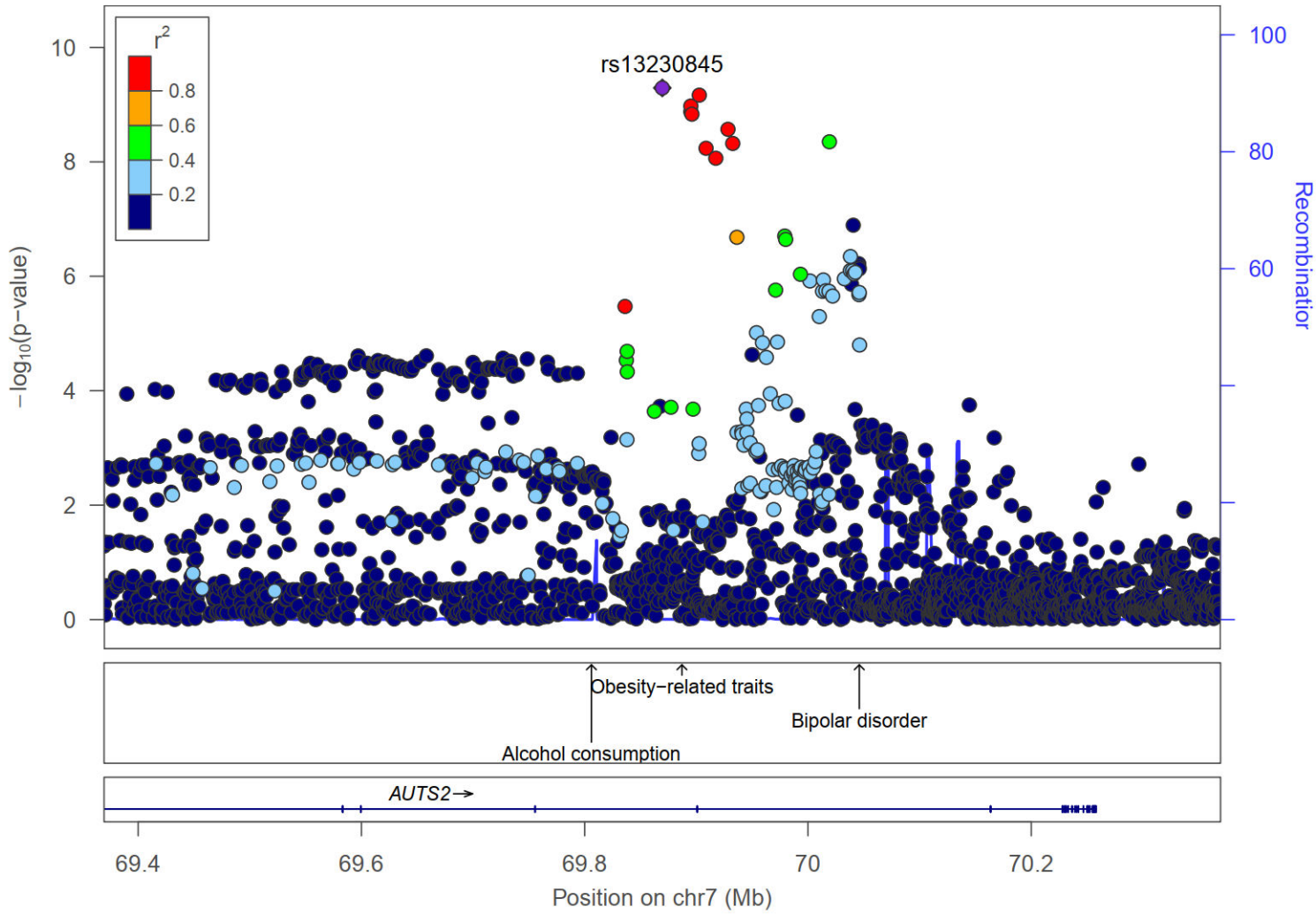

rs1145078
r2
0.8
0.6
0.4
0.2
100
80
60
40
Recombination rate (cM
15
10
5
0
−log10(p−value)
Homoarginine levels
Obesity−related traits
Serum dimethylarginine levels (asym
Serum dimethylarginine level
7 GWAS hits
omitted
TERB2→
←DUOX2
←LOC101928414
SPATA5L1→
SNORA41B→
SQOR→
SORD→
DUOX1→
SLC28A2→
←GATM
←SLC30A4
LOC105370802→
DUOXA2→
C15orf48→
BLOC1S6→
←DUOXA1
MIR147B→
←SHF
HMGN2P46→
45.2
45.4
45.6
45.8
46
Position on chr15 (Mb)

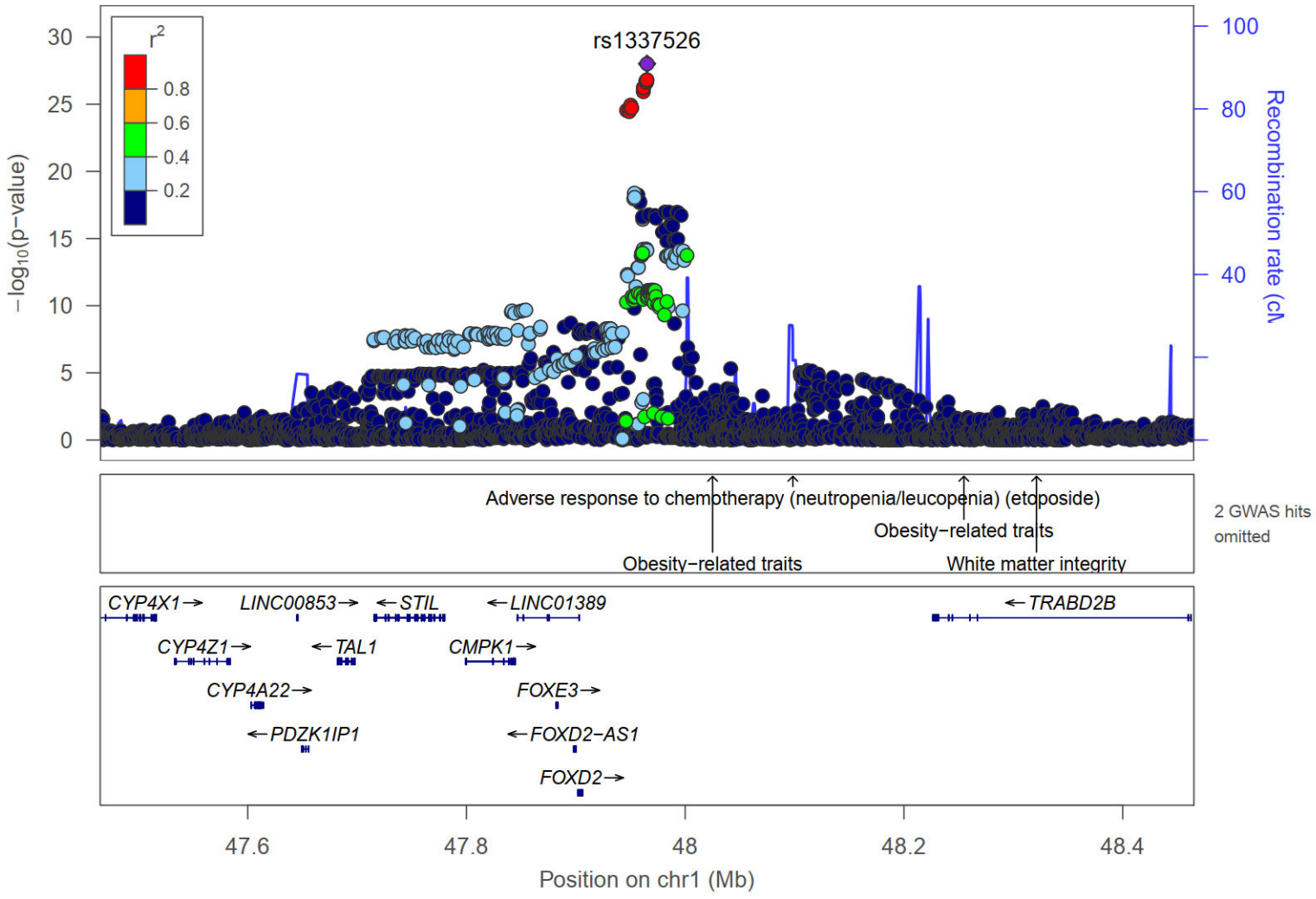

rs11659764
r2
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate
Obesity (early onset extreme)
Breast cancer
cit−hyperactivity disorder, bipolar disorder, major depressive disorder, and schizophrenia (combined)
Schizophrenia
Schizophrenia
5 GWAS hits omitted
TCF4
LINC01415
LINC01905
TCF4−AS1
LINC01416
LINC01539
MIR4529
Position on chr18 (Mb)

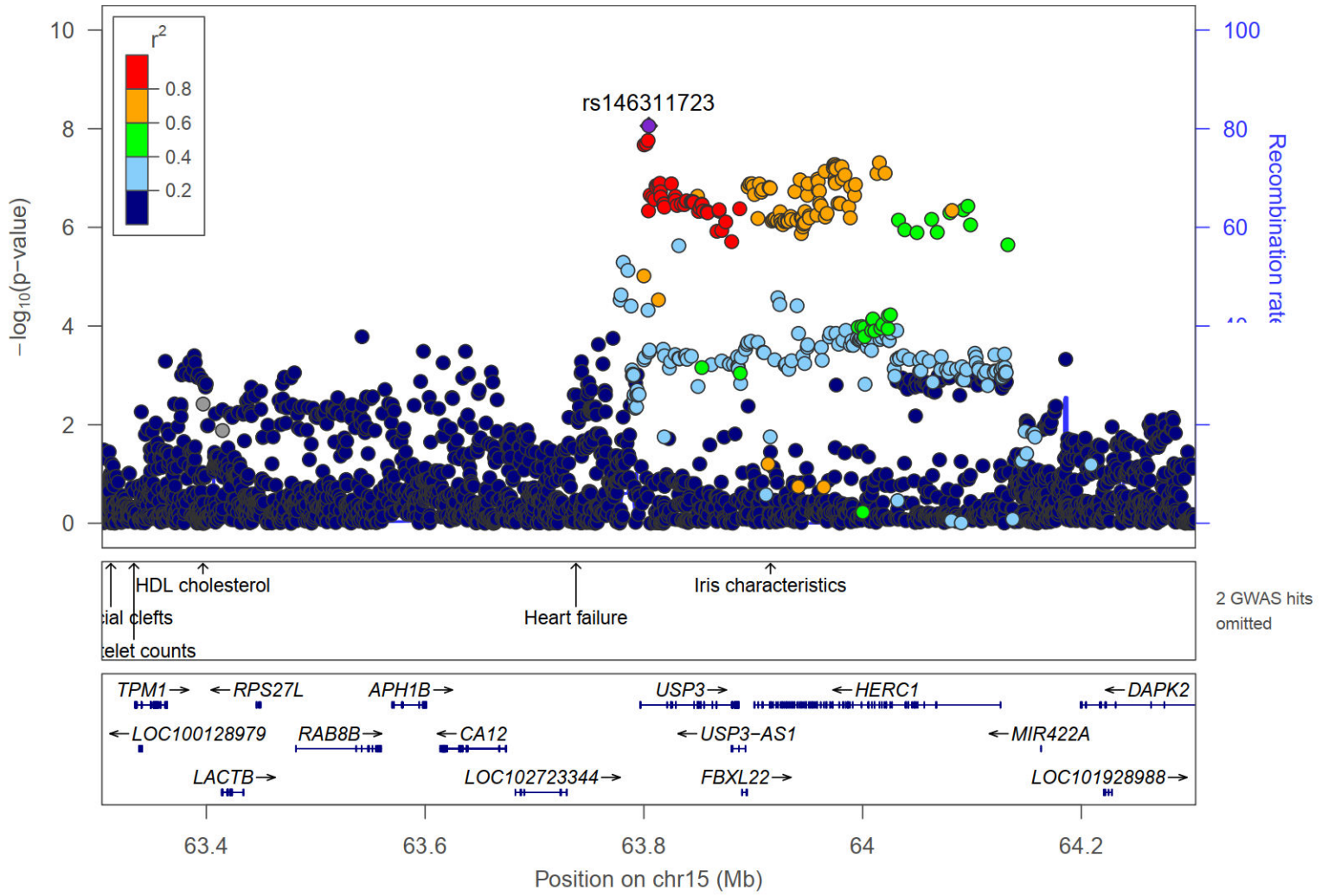

rs11882796
$-\log_{10}$(p-value)
Recombination rate (cM/Mb)
r^2
0.8
0.6
0.4
0.2
Cholesterol, total
Homocysteine levels
Dietary macronutrient intake
Follicule stimulating hormone
17 GWAS hits omitted
CARD8 SYNGR4 CYTH2 FAM83E FUT2 BCAT2 NUCB1 LHB LIN7B
CARD8-AS1 GRIN2D SULT2B1 MAMSTR PLEKHA4 BAX CGB1 PPFIA3
ZNF114 KDELR1 LMTK3 SPACA4 RASIP1 PPP1R15A GYS1 NTF4 HRC
CCDC114 GRWD1 RPL18 IZUMO1 TULP2 RUVBL2 C19orf73
EMP3 KCNJ14 SPHK2 FUT1 NUCB1-AS1 CGB2 TRPM4
TMEM143 DBP FGF21 DHDH CGB3
CA11 HSD17B14 FTL CGB5
SEC1P MIR6798
NTN5 LOC101059948
LOC105447645 SNAR-G2
5 genes omitted
48.8
49
49.2
49.4
49.6
Position on chr19 (Mb)

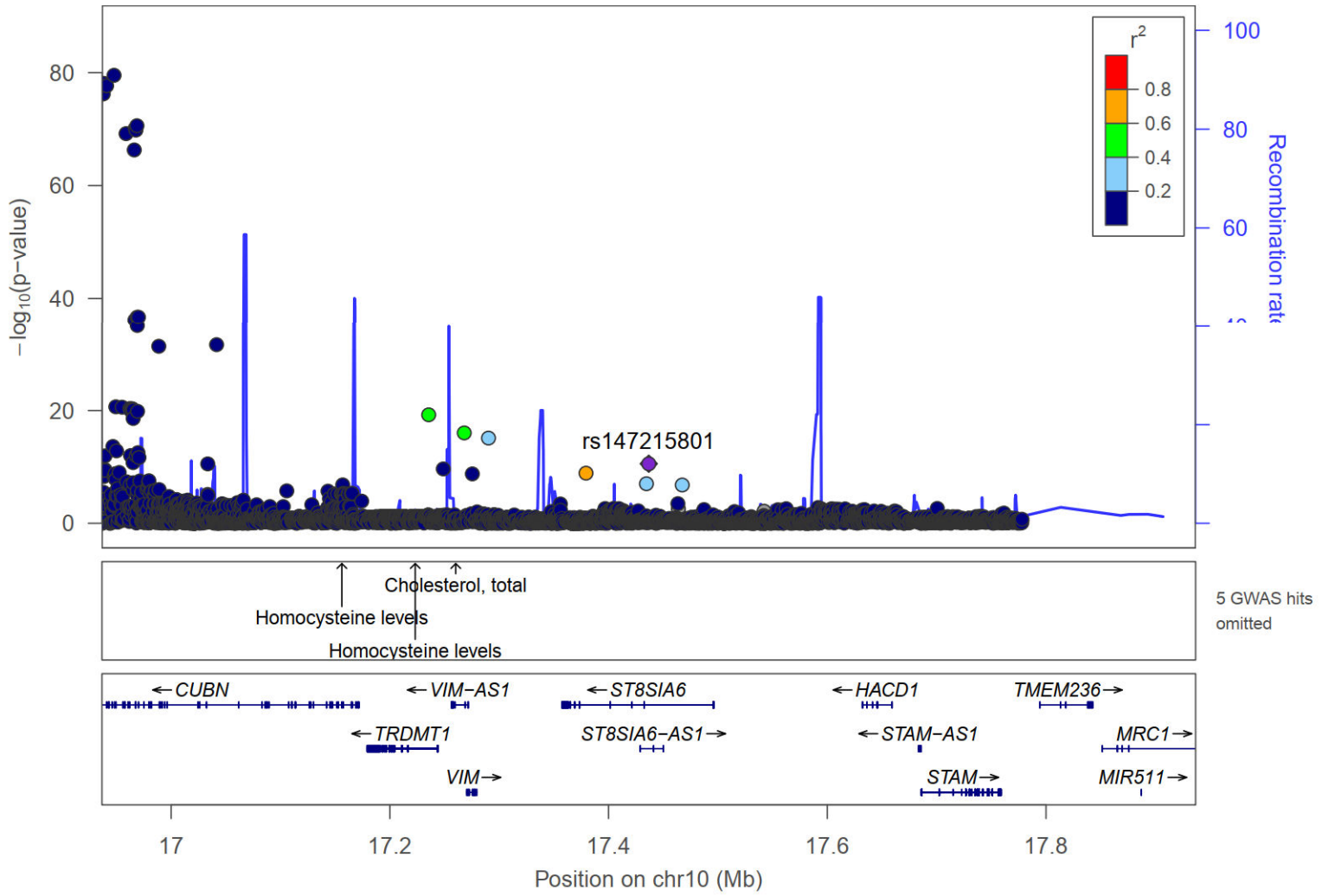

rs12714144
r2
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
Estradiol plasma levels (breast cancer)
Prostate cancer
Protein quantitative trait loci
KCMF1→
TCF7L1→
ELMOD3→
←PARTICL
←SFTPB
ATOH8→
←POLR1A
←LINC01964
←TGOLN2
SH2D6→
MAT2A→
GNLY→
LOC284950→
TCF7L1−IT1→
←RETSAT
←GGCX
←MIR6071
LOC102724579→
←CAPG
VAMP8→
←ST3GAL5
VAMP5→
ST3GAL5−AS1→
RNF181→
←TMEM150A
USP39→
←C2orf68
85.4
85.6
85.8
86
86.2
Position on chr2 (Mb)

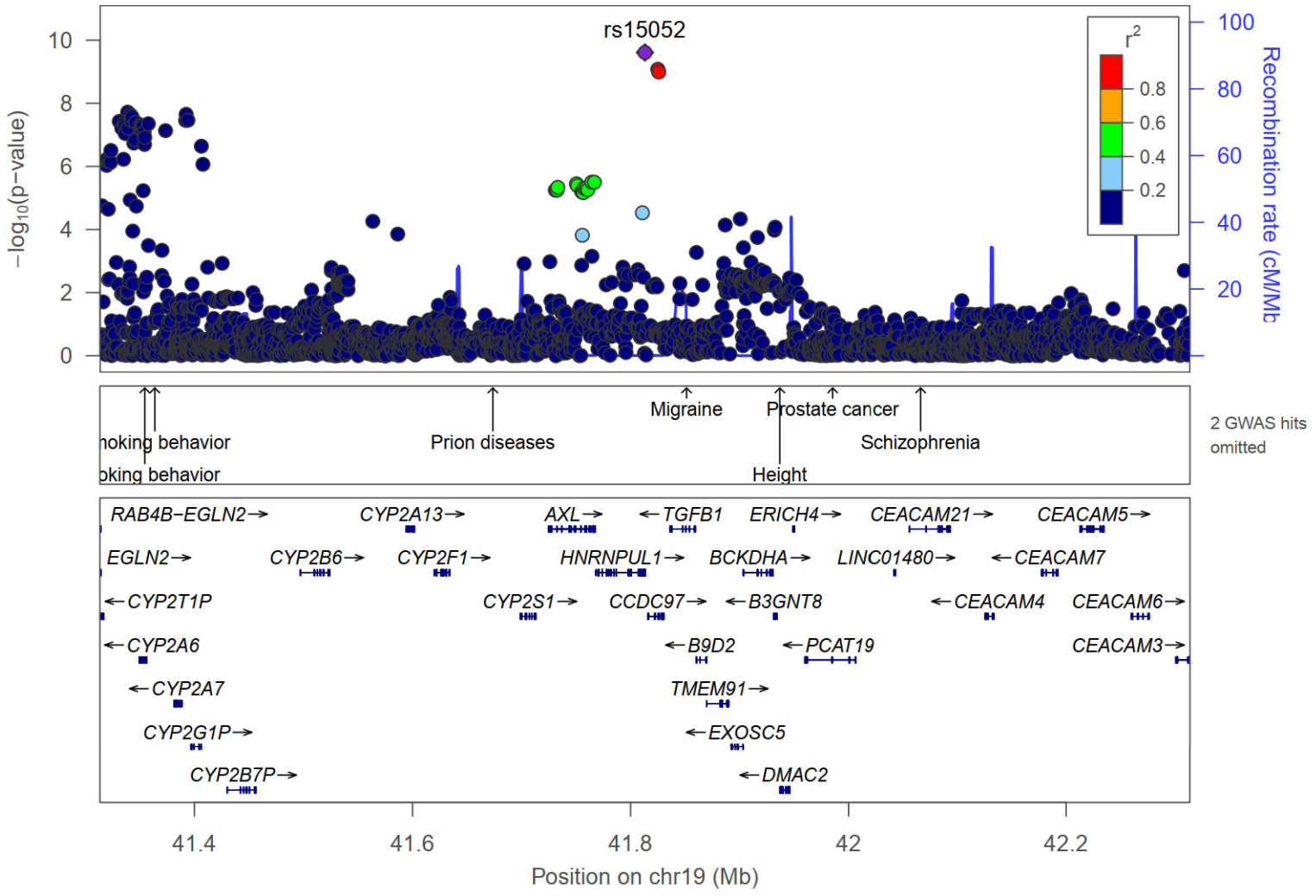

rs1309550
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination r
Obesity−related traits
Osteosarcoma
Schizophrenia
Corneal structure
2 GWAS hits
omitted
RGS7BP
FAM159B
CWC27
ADAMTS6
SREK1IP1
Position on chr5 (Mb)

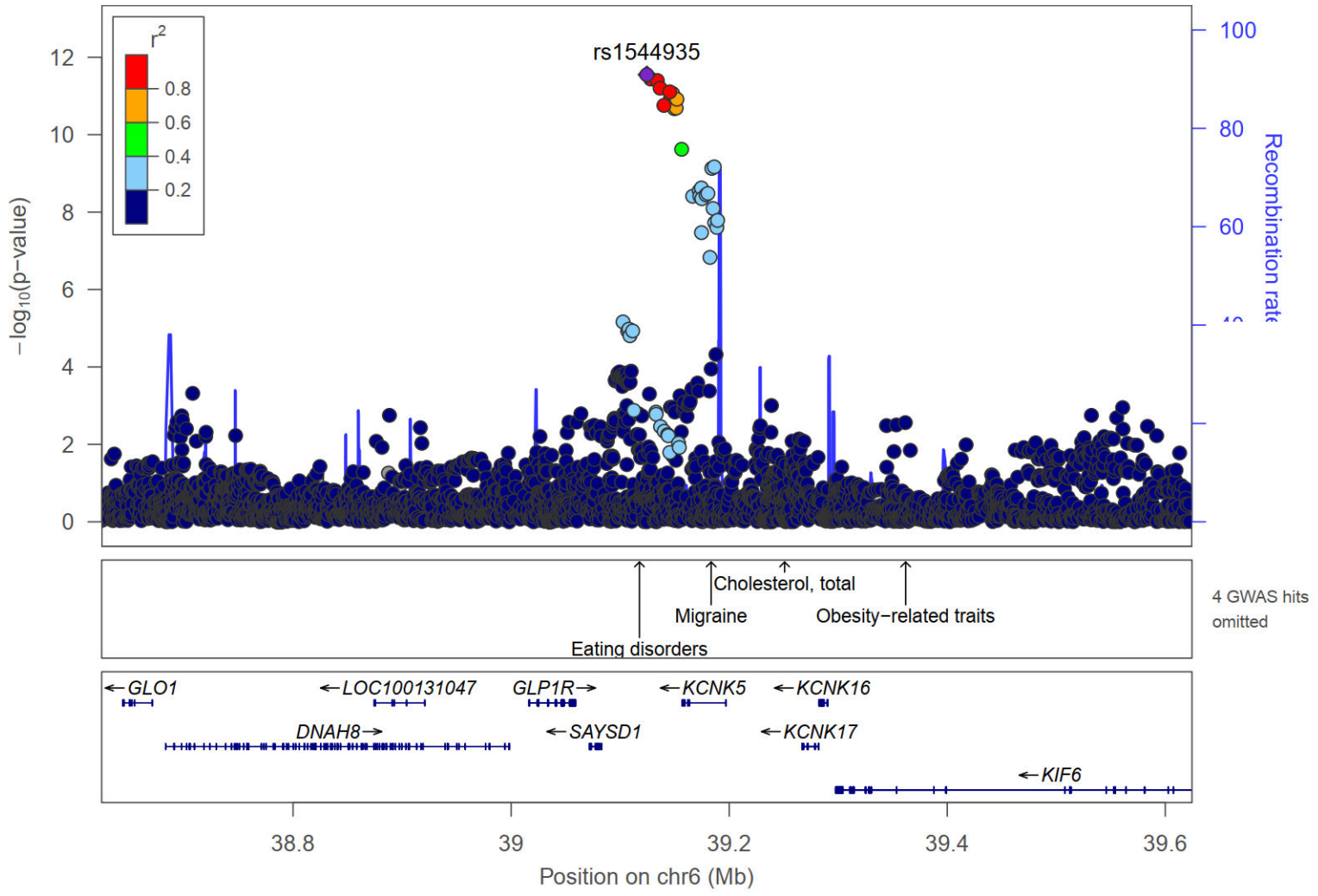

r2
0.8
0.6
0.4
0.2
rs13230845
10
8
6
4
2
0
−log10(p−value)
100
80
60
Recombinatior
Obesity−related traits
Bipolar disorder
Alcohol consumption
AUTS2→
69.4
69.6
69.8
70
70.2
Position on chr7 (Mb)

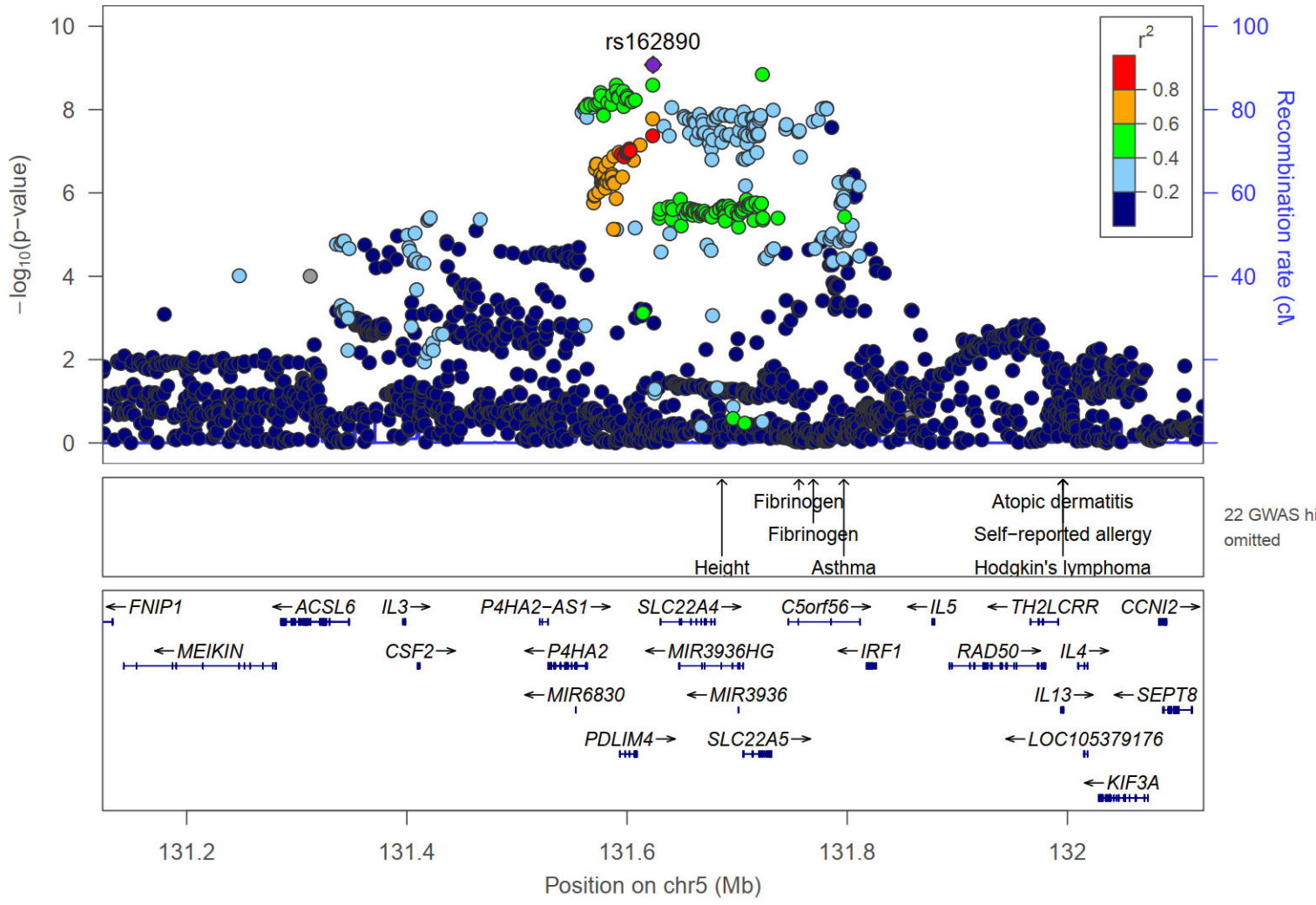

rs1337526
r2
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM
Adverse response to chemotherapy (neutropenia/leucopenia) (etoposide)
Obesity−related traits
Obesity−related traits
White matter integrity
2 GWAS hits omitted
CYP4X1
LINC00853
STIL
LINC01389
TRABD2B
CYP4Z1
TAL1
CMPK1
CYP4A22
FOXE3
PDZK1IP1
FOXD2−AS1
FOXD2
47.6
47.8
48
48.2
48.4
Position on chr1 (Mb)

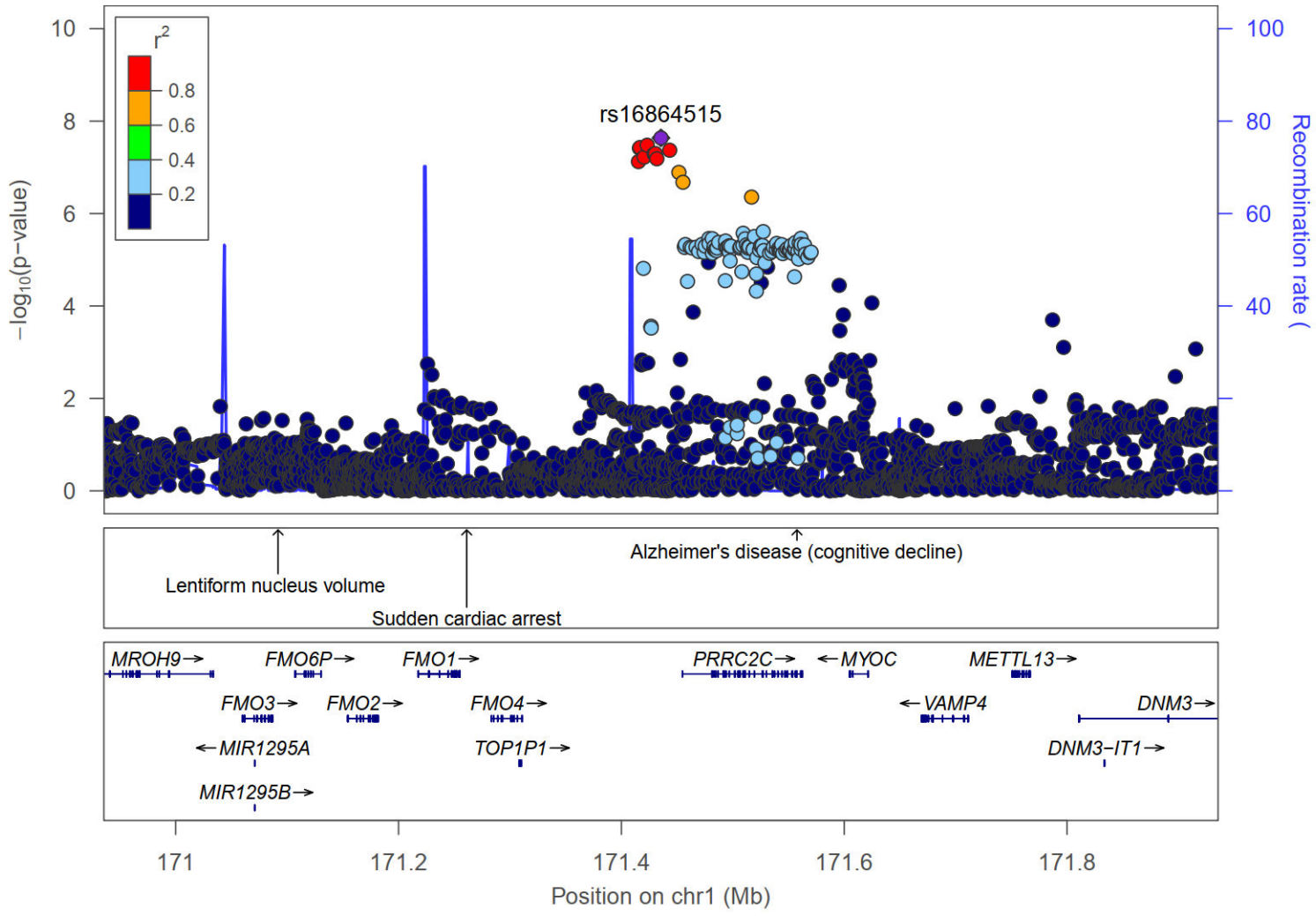

r²
0.8
0.6
0.4
0.2
rs146311723
−log10(p−value)
Recombination rate
HDL cholesterol
Heart failure
Iris characteristics
2 GWAS hits omitted
TPM1→
←RPS27L
APH1B→
USP3→
←HERC1
←DAPK2
←LOC100128979
RAB8B→
←CA12
←USP3−AS1
←MIR422A
LACTB→
LOC102723344→
FBXL22→
LOC101928988→
63.4
63.6
63.8
64
64.2
Position on chr15 (Mb)

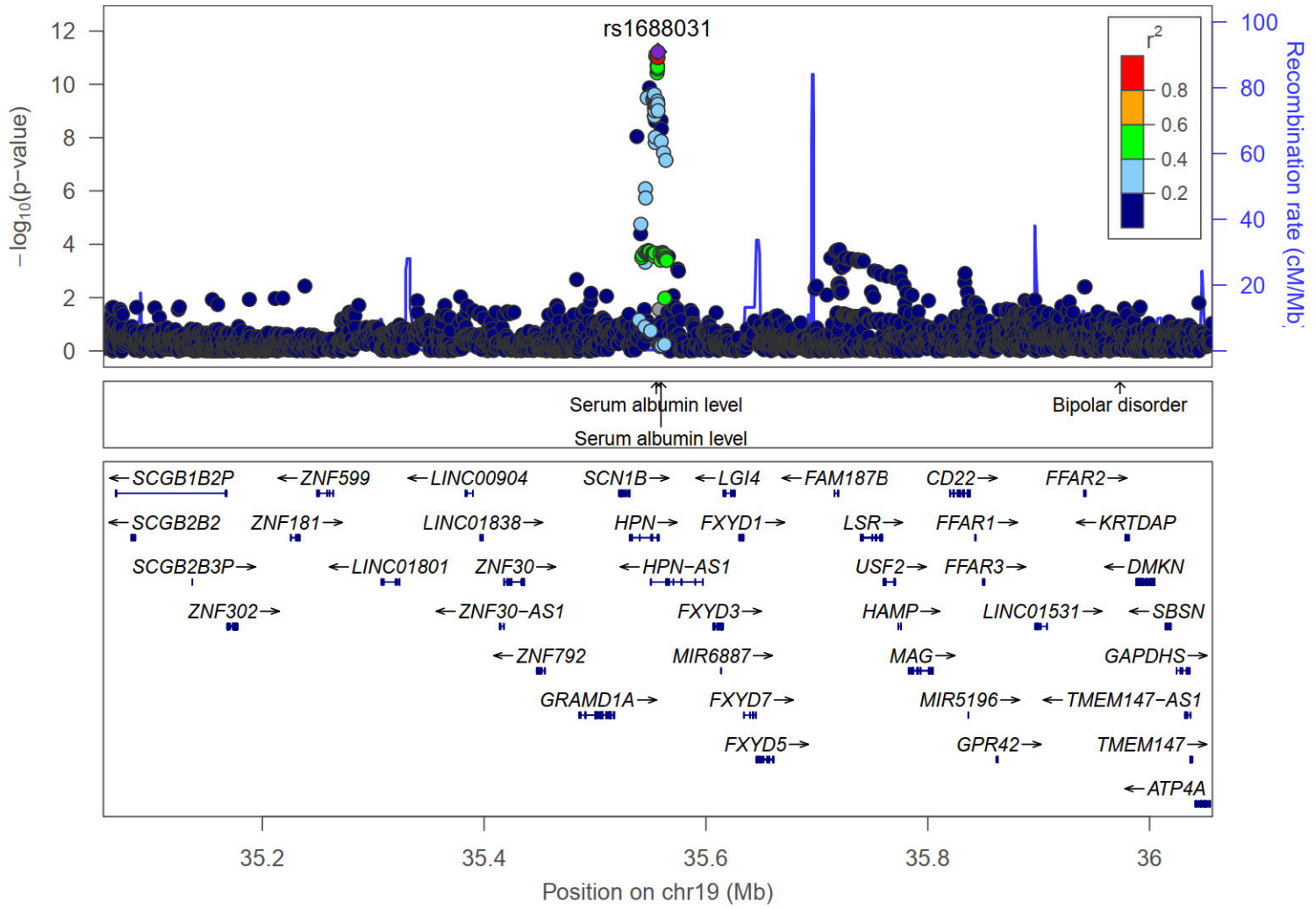

r²
0.8
0.6
0.4
0.2
100
80
60
40
20
0
−log10(p−value)
Recombination rate
rs147215801
Cholesterol, total
Homocysteine levels
Homocysteine levels
5 GWAS hits
omitted
←CUBN
←VIM−AS1
←ST8SIA6
←HACD1
TMEM236→
←TRDMT1
ST8SIA6−AS1→
←STAM−AS1
MRC1→
VIM→
STAM→
MIR511→
17
17.2
17.4
17.6
17.8
Position on chr10 (Mb)

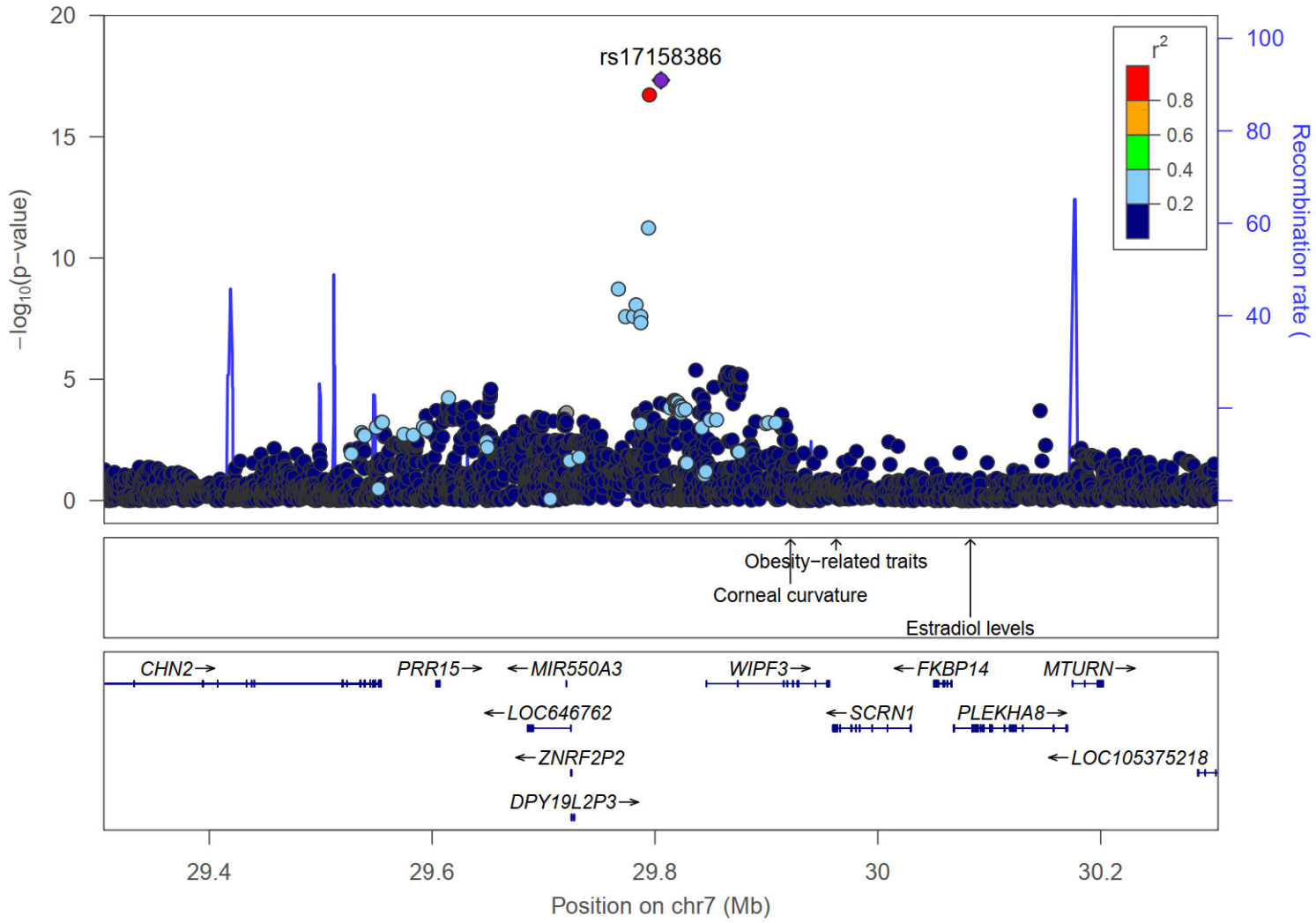

rs15052
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb
Migraine
Prostate cancer
Prion diseases
Schizophrenia
Height
2 GWAS hits omitted
RAB4B−EGLN2
CYP2A13
AXL
TGFB1
ERICH4
CEACAM21
CEACAM5
EGLN2
CYP2B6
CYP2F1
HNRNPUL1
BCKDHA
LINC01480
CEACAM7
CYP2T1P
CYP2S1
CCDC97
B3GNT8
CEACAM4
CEACAM6
CYP2A6
B9D2
PCAT19
CEACAM3
CYP2A7
TMEM91
CYP2G1P
EXOSC5
CYP2B7P
DMAC2
41.4
41.6
41.8
42
42.2
Position on chr19 (Mb)

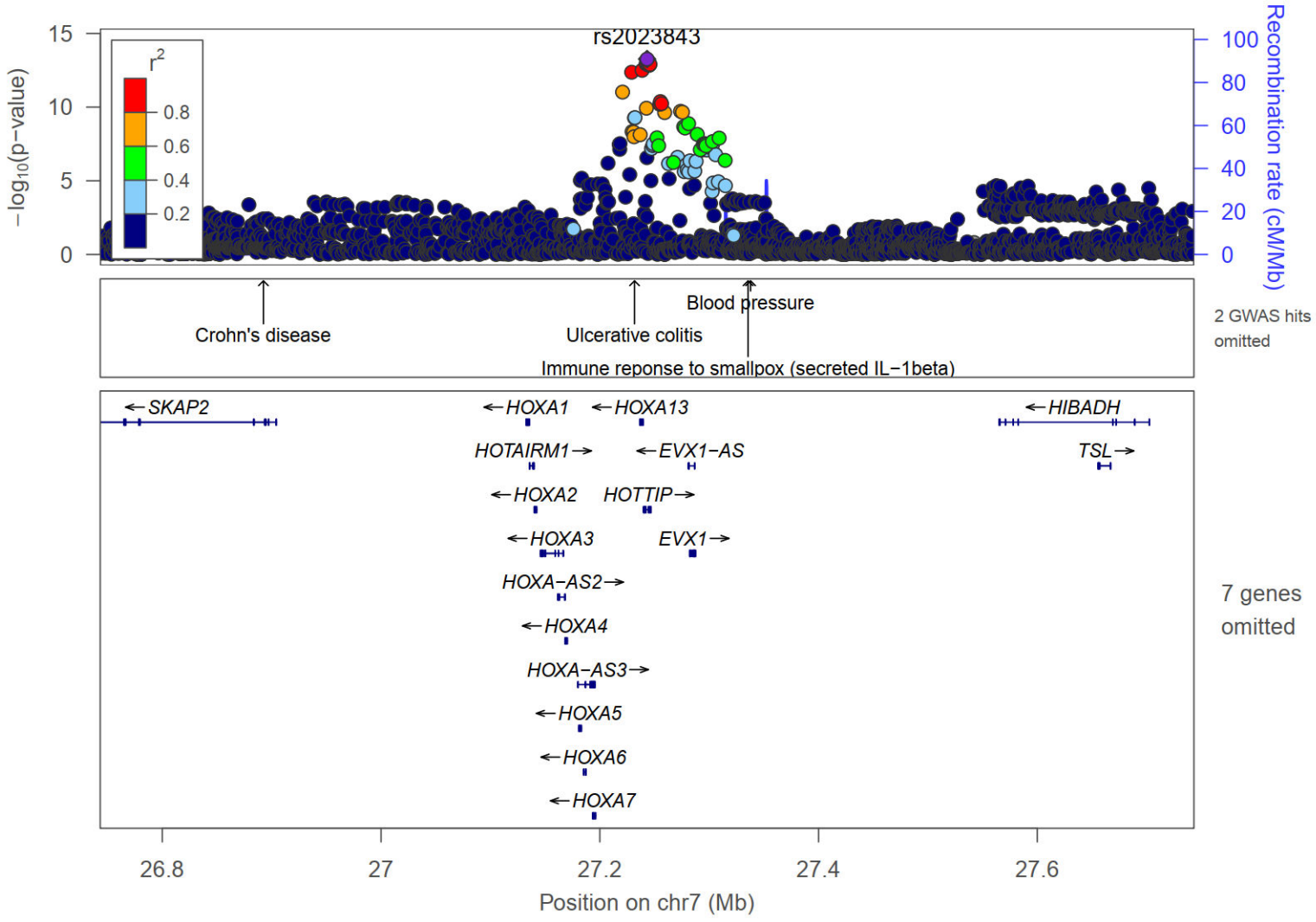

r2
0.8
0.6
0.4
0.2
rs1544935
−log10(p−value)
Recombination rate
Cholesterol, total
Migraine
Obesity−related traits
Eating disorders
4 GWAS hits omitted
GLO1
LOC100131047
GLP1R
KCNK5
KCNK16
DNAH8
SAYSD1
KCNK17
KIF6
Position on chr6 (Mb)

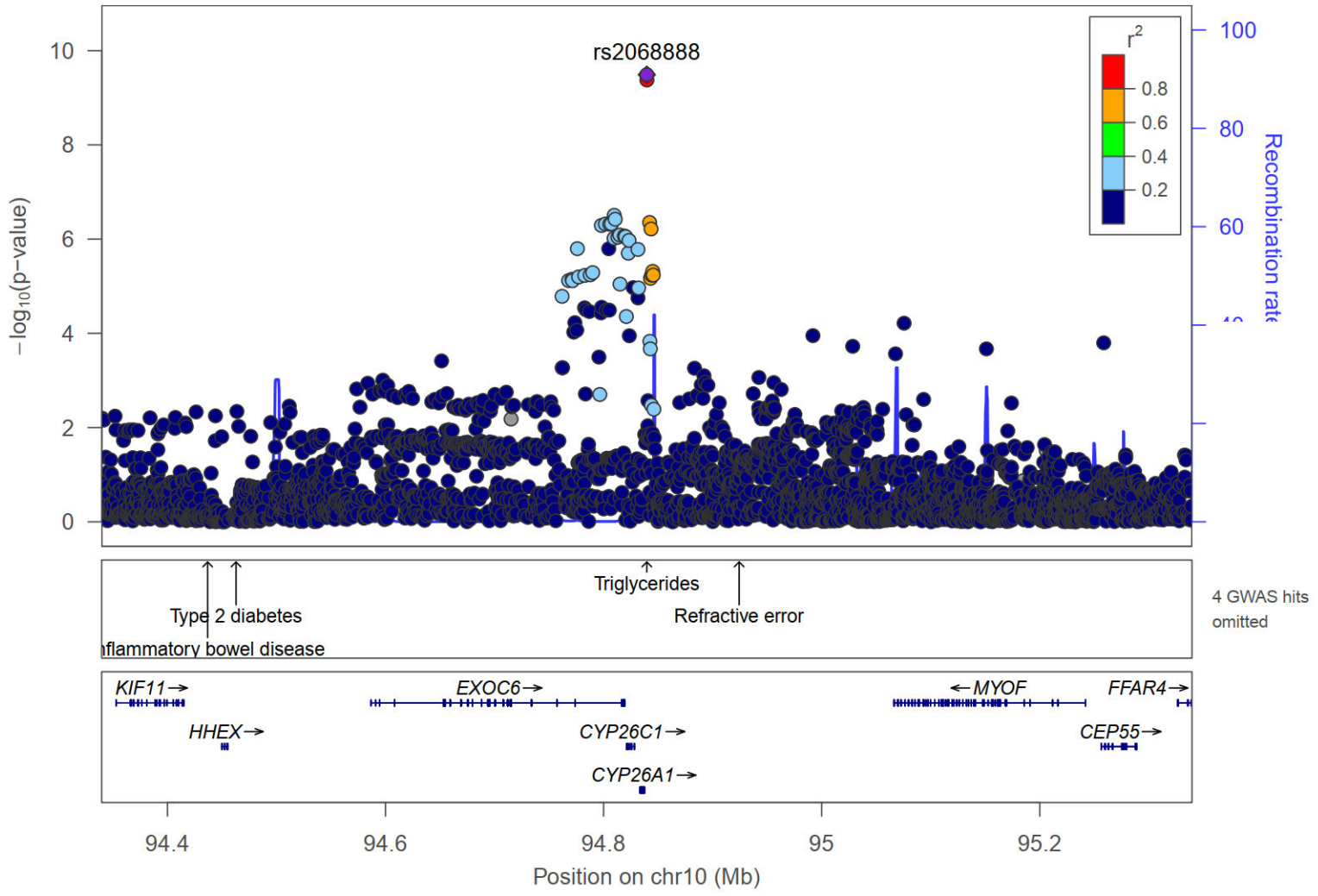

rs162890
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM
Height
Fibrinogen
Fibrinogen
Asthma
Atopic dermatitis
Self−reported allergy
Hodgkin's lymphoma
22 GWAS hits omitted
FNIP1
ACSL6
IL3
P4HA2−AS1
SLC22A4
C5orf56
IL5
TH2LCRR
CCNI2
MEIKIN
CSF2
P4HA2
MIR3936HG
IRF1
RAD50
IL4
MIR6830
MIR3936
IL13
SEPT8
PDLIM4
SLC22A5
LOC105379176
KIF3A
131.2
131.4
131.6
131.8
132
Position on chr5 (Mb)

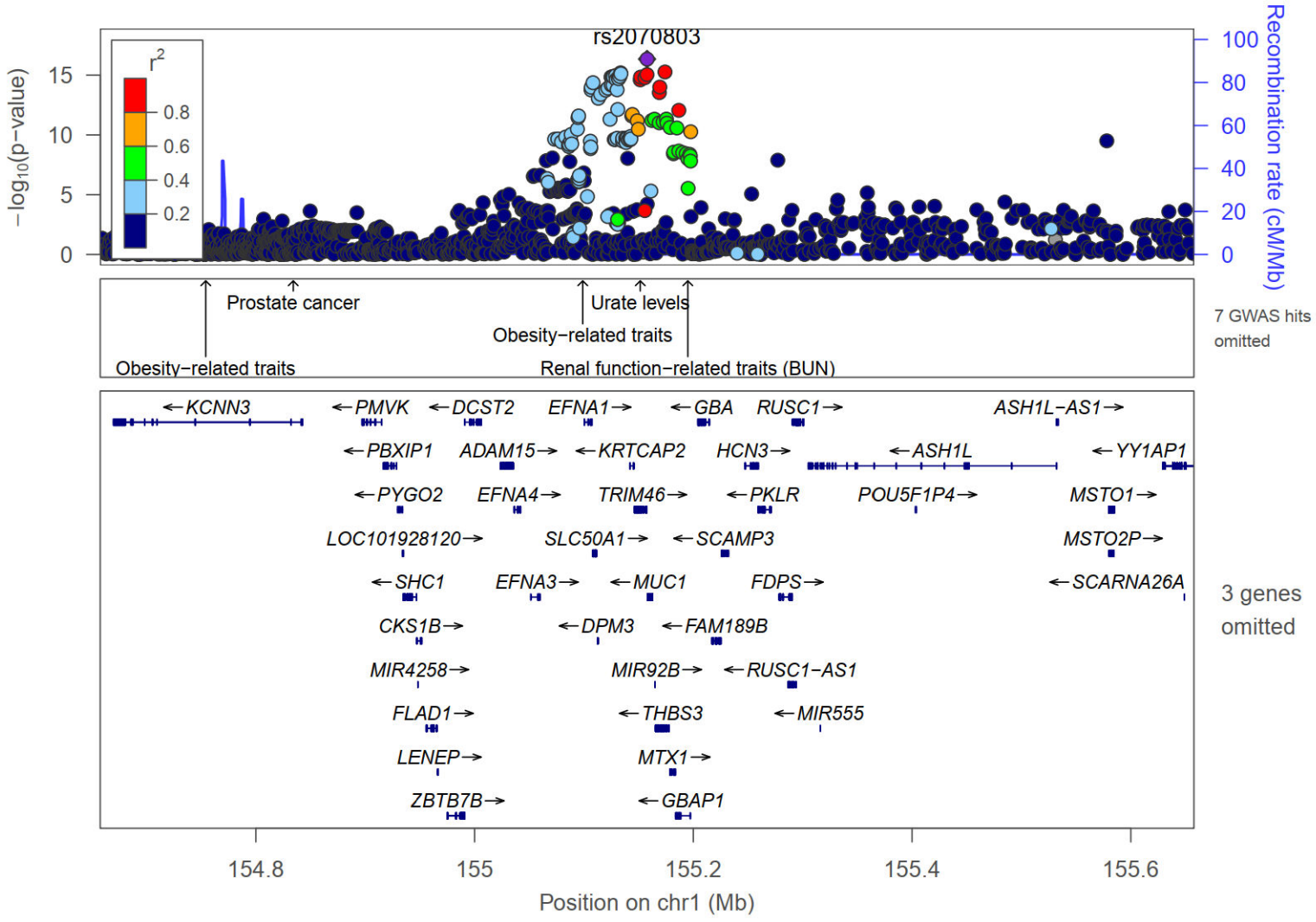

r2
0.8
0.6
0.4
0.2
rs16864515
−log10(p−value)
Recombination rate (
Lentiform nucleus volume
Sudden cardiac arrest
Alzheimer's disease (cognitive decline)
MROH9→
FMO6P→
FMO1→
PRRC2C→
←MYOC
METTL13→
FMO3→
FMO2→
FMO4→
←VAMP4
DNM3→
←MIR1295A
TOP1P1→
DNM3−IT1→
MIR1295B→
171
171.2
171.4
171.6
171.8
Position on chr1 (Mb)

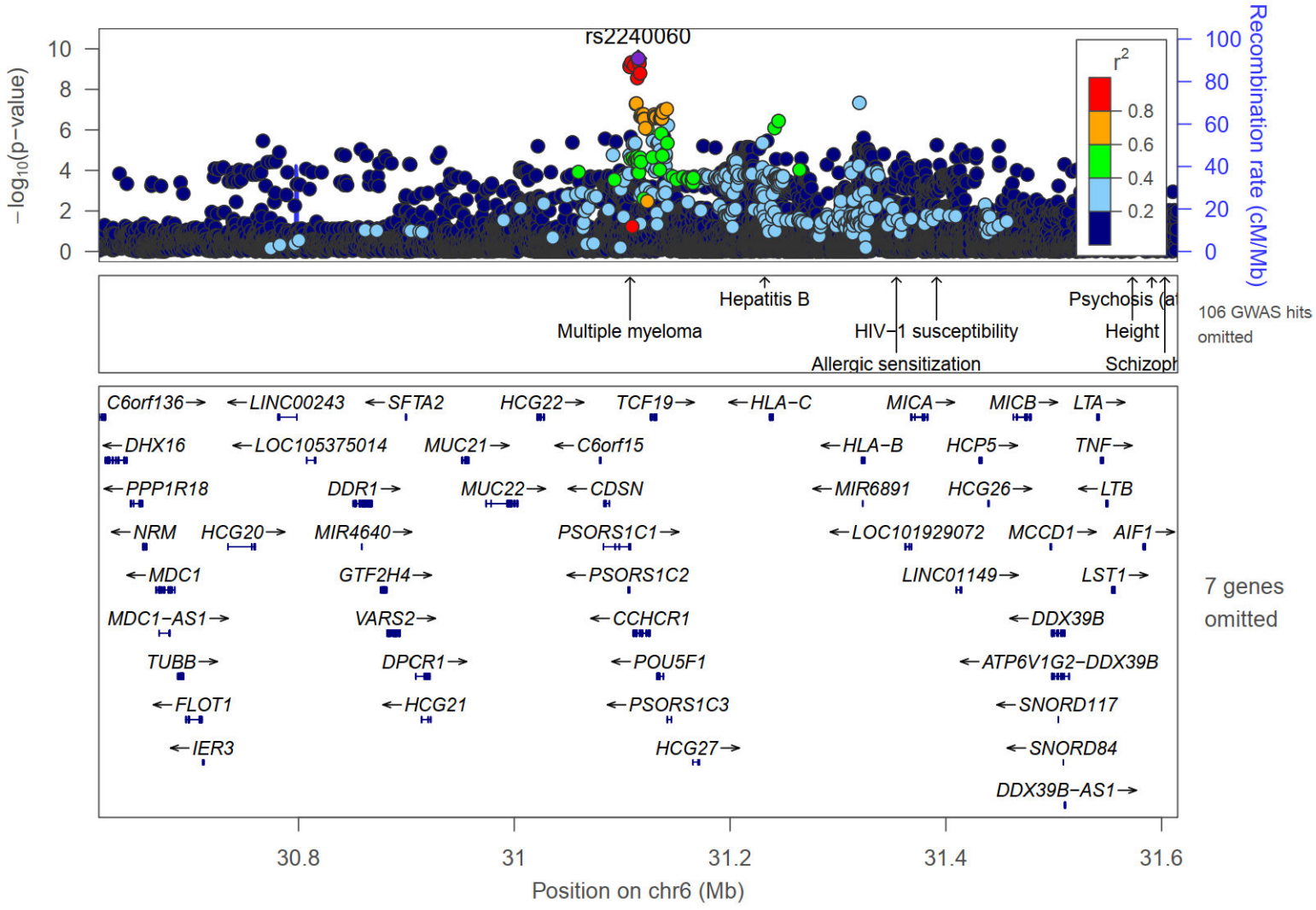

rs1688031
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
Serum albumin level
Serum albumin level
Bipolar disorder
←SCGB1B2P
←ZNF599
←LINC00904
SCN1B→
←LGI4
←FAM187B
CD22→
FFAR2→
←SCGB2B2
ZNF181→
LINC01838→
HPN→
FXYD1→
LSR→
FFAR1→
←KRTDAP
SCGB2B3P→
←LINC01801
ZNF30→
←HPN−AS1
USF2→
FFAR3→
←DMKN
ZNF302→
←ZNF30−AS1
FXYD3→
HAMP→
LINC01531→
←SBSN
←ZNF792
MIR6887→
MAG→
GAPDHS→
GRAMD1A→
FXYD7→
MIR5196→
←TMEM147−AS1
FXYD5→
GPR42→
TMEM147→
←ATP4A
35.2
35.4
35.6
35.8
36
Position on chr19 (Mb)

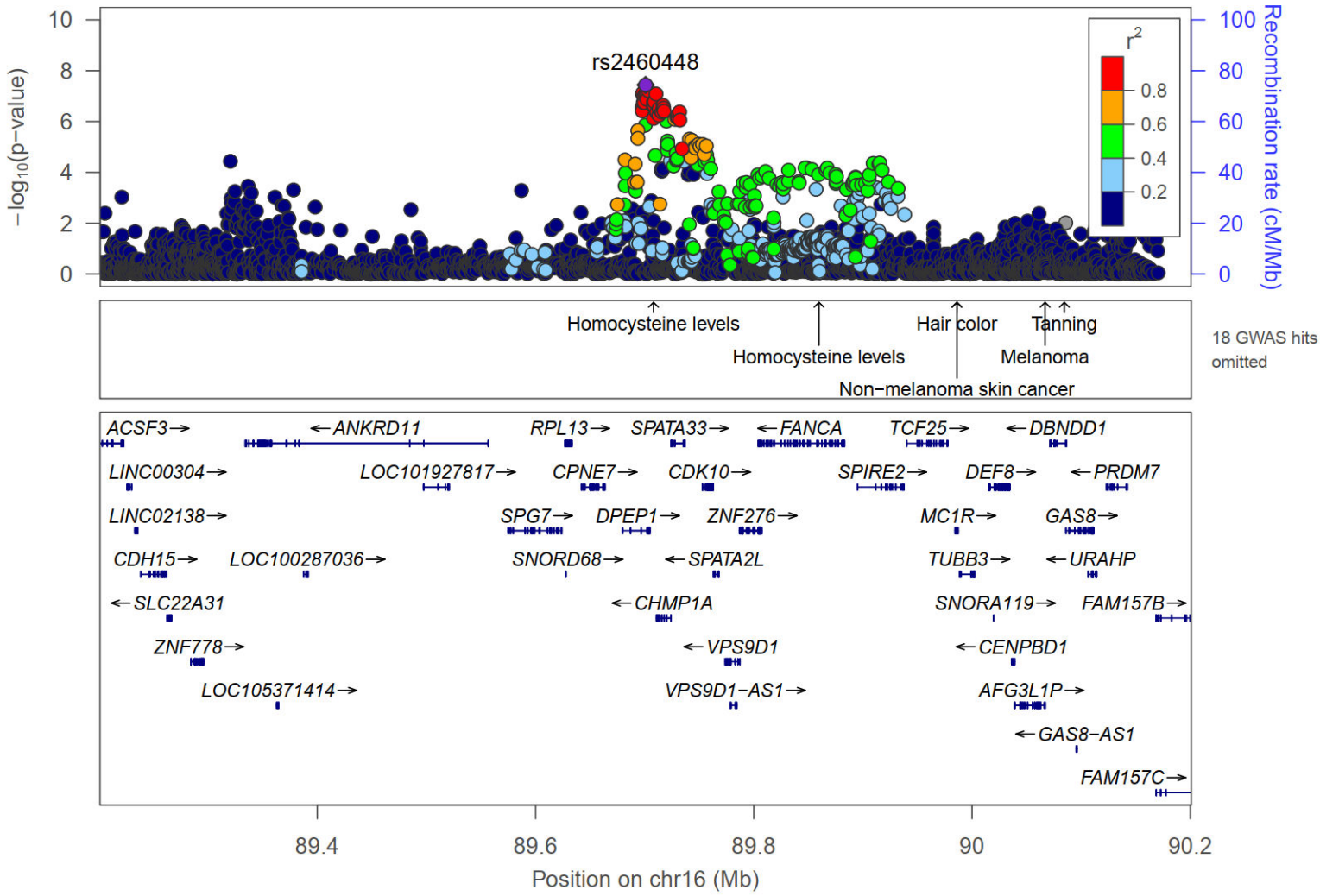

rs17158386
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (
Obesity−related traits
Corneal curvature
Estradiol levels
CHN2→
PRR15→
←MIR550A3
WIPF3→
←FKBP14
MTURN→
←LOC646762
←SCRN1
PLEKHA8→
←ZNRF2P2
←LOC105375218
DPY19L2P3→
Position on chr7 (Mb)

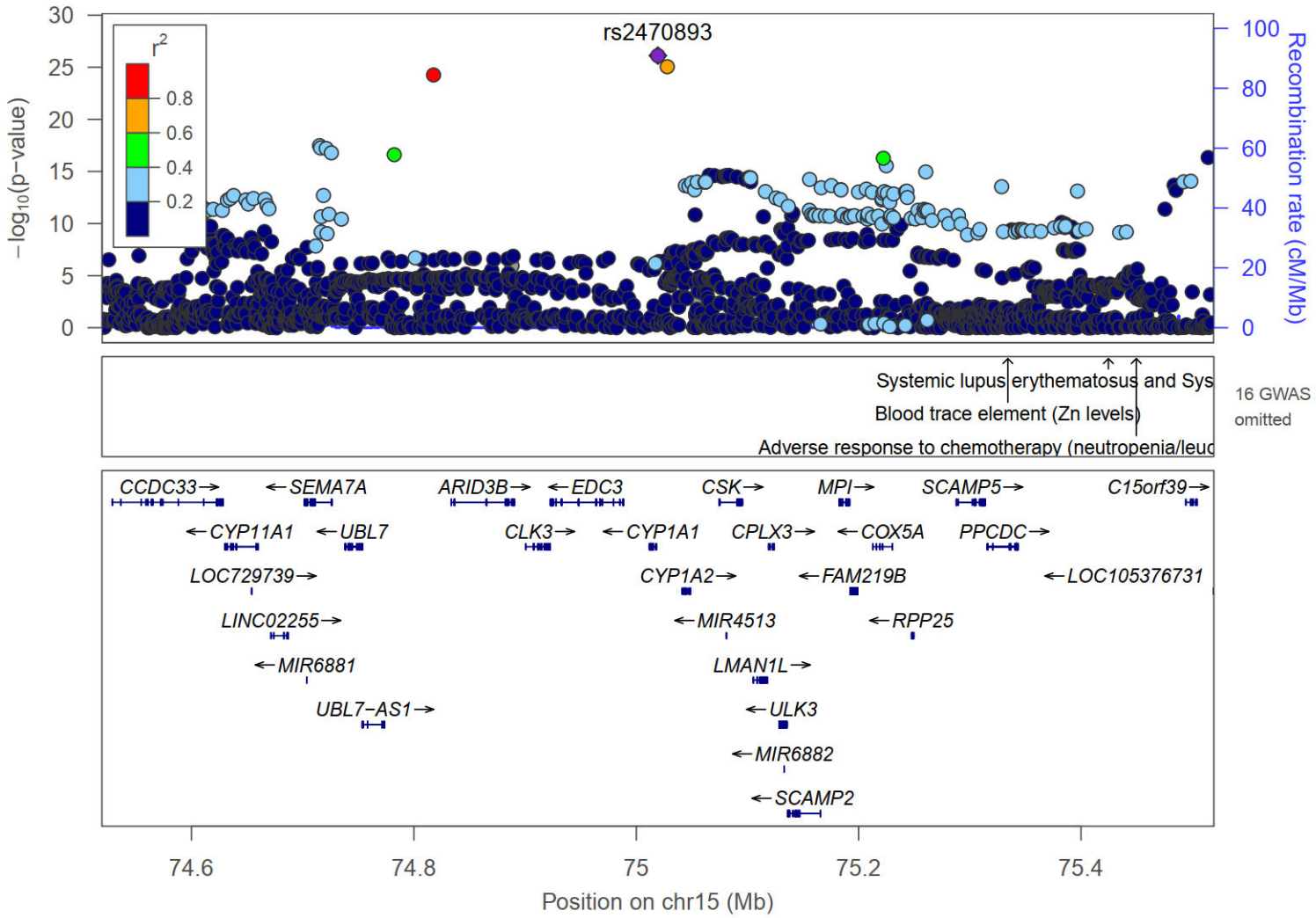

rs2023843
r2
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
Crohn's disease
Ulcerative colitis
Blood pressure
Immune reponse to smallpox (secreted IL−1beta)
2 GWAS hits omitted
SKAP2
HOXA1
HOXA13
HIBADH
HOTAIRM1
EVX1−AS
TSL
HOXA2
HOTTIP
HOXA3
EVX1
HOXA−AS2
HOXA4
HOXA−AS3
HOXA5
HOXA6
HOXA7
7 genes omitted
Position on chr7 (Mb)

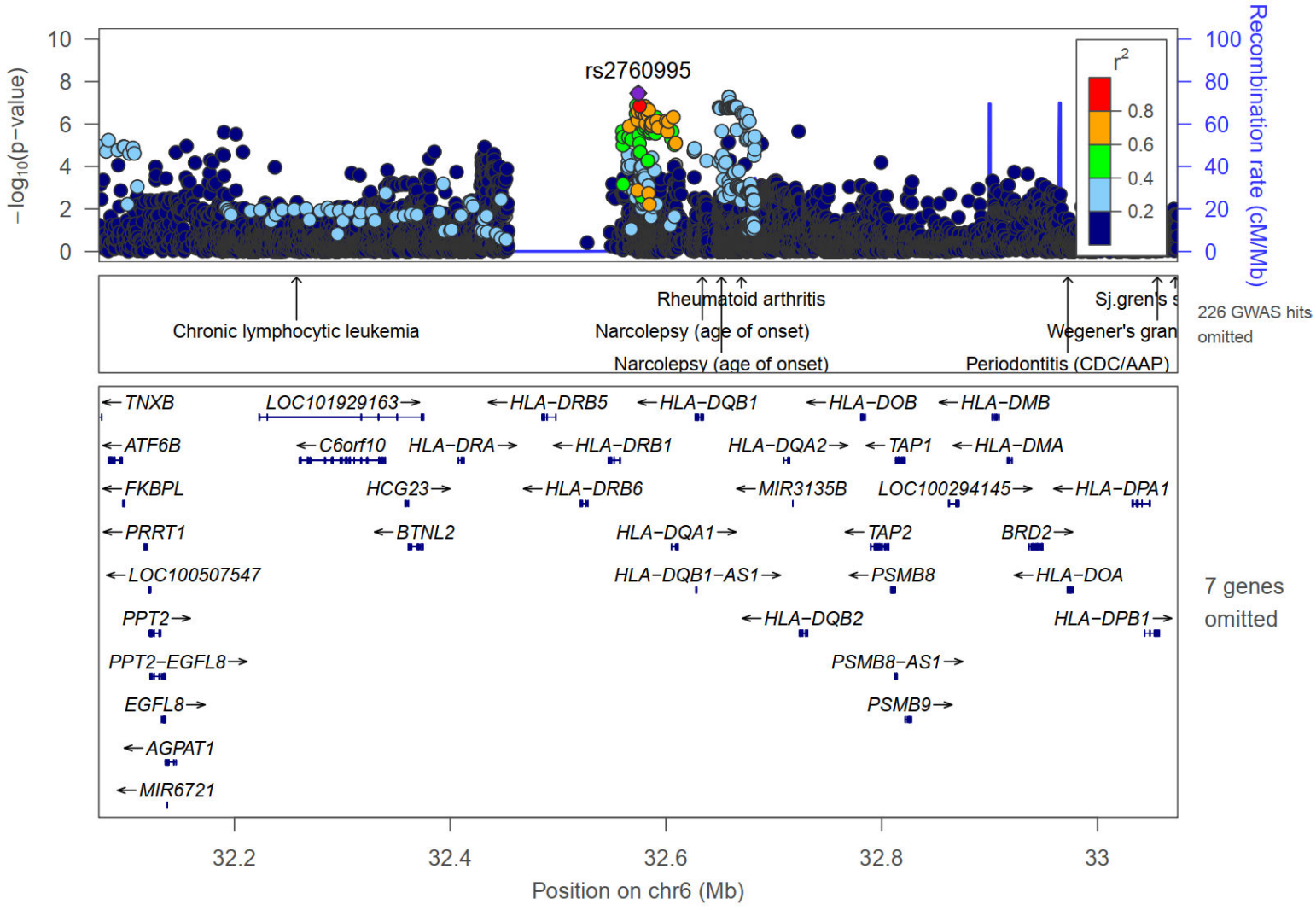

rs2068888
r²
0.8
0.6
0.4
0.2
100
80
60
Recombination rate
10
8
6
4
2
0
−log10(p−value)
Triglycerides
Refractive error
Type 2 diabetes
nflammatory bowel disease
4 GWAS hits
omitted
KIF11→
EXOC6→
←MYOF
FFAR4→
HHEX→
CYP26C1→
CEP55→
CYP26A1→
94.4
94.6
94.8
95
95.2
Position on chr10 (Mb)

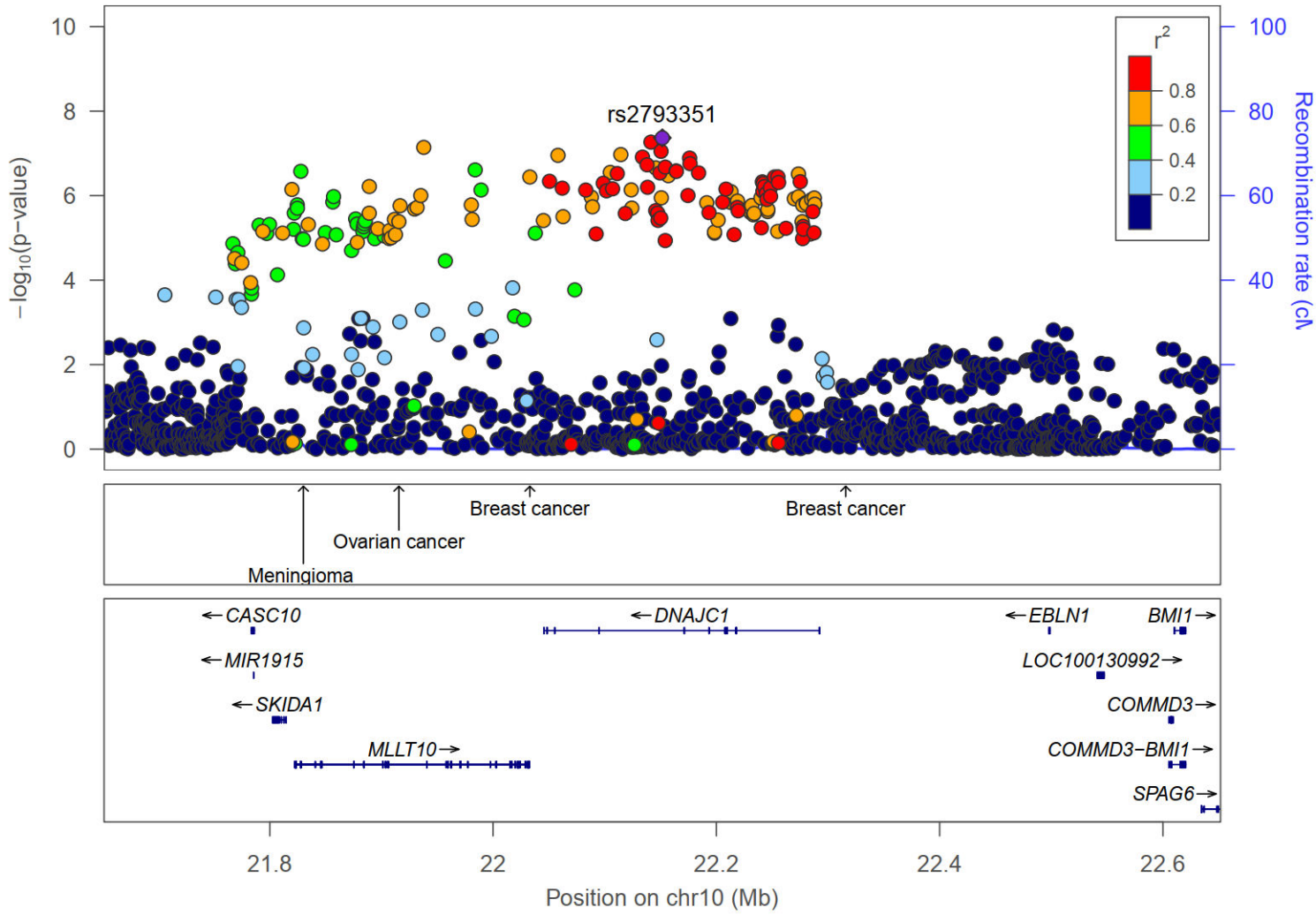

rs2070803
r²
0.8
0.6
0.4
0.2
−log10(p−value)
15
10
5
0
Recombination rate (cM/Mb)
100
80
60
40
20
0
Prostate cancer
Urate levels
Obesity−related traits
Obesity−related traits
Renal function−related traits (BUN)
7 GWAS hits omitted
←KCNN3
←PMVK
←DCST2
EFNA1→
←GBA
RUSC1→
ASH1L−AS1→
←PBXIP1
ADAM15→
←KRTCAP2
HCN3→
←ASH1L
←YY1AP1
←PYGO2
EFNA4→
TRIM46→
←PKLR
POU5F1P4→
MSTO1→
LOC101928120→
SLC50A1→
←SCAMP3
MSTO2P→
←SHC1
EFNA3→
←MUC1
FDPS→
←SCARNA26A
CKS1B→
←DPM3
←FAM189B
MIR4258→
MIR92B→
←RUSC1−AS1
FLAD1→
←THBS3
←MIR555
LENEP→
MTX1→
ZBTB7B→
←GBAP1
3 genes omitted
154.8
155
155.2
155.4
155.6
Position on chr1 (Mb)

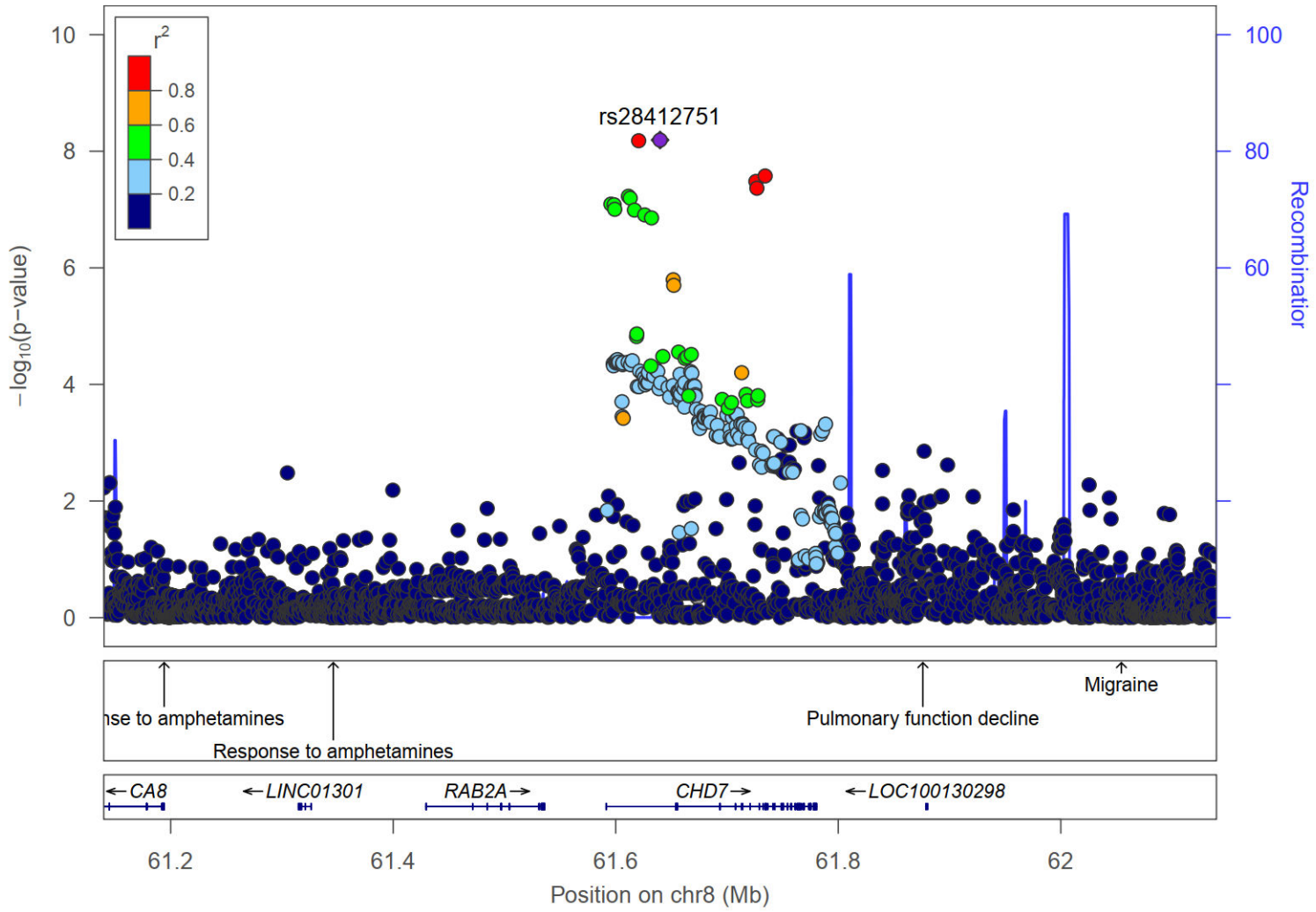

rs2240060
$-\log_{10}$(p-value)
Recombination rate (cM/Mb)
r^2
0.8
0.6
0.4
0.2
Multiple myeloma
Hepatitis B
HIV−1 susceptibility
Allergic sensitization
Height
106 GWAS hits omitted
C6orf136→ ←LINC00243 ←SFTA2 HCG22→ TCF19→ ←HLA−C MICA→ MICB→ LTA→
←DHX16 ←LOC105375014 MUC21→ ←C6orf15 ←HLA−B HCP5→ TNF→
←PPP1R18 DDR1→ MUC22→ ←CDSN ←MIR6891 HCG26→ ←LTB
←NRM HCG20→ MIR4640→ PSORS1C1→ ←LOC101929072 MCCD1→ AIF1→
←MDC1 GTF2H4→ ←PSORS1C2 LINC01149→ LST1→
MDC1−AS1→ VARS2→ ←CCHCR1 ←DDX39B
TUBB→ DPCR1→ ←POU5F1 ←ATP6V1G2−DDX39B
←FLOT1 ←HCG21 ←PSORS1C3 ←SNORD117
←IER3 HCG27→ ←SNORD84
DDX39B−AS1→
7 genes omitted
30.8
31
31.2
31.4
31.6
Position on chr6 (Mb)

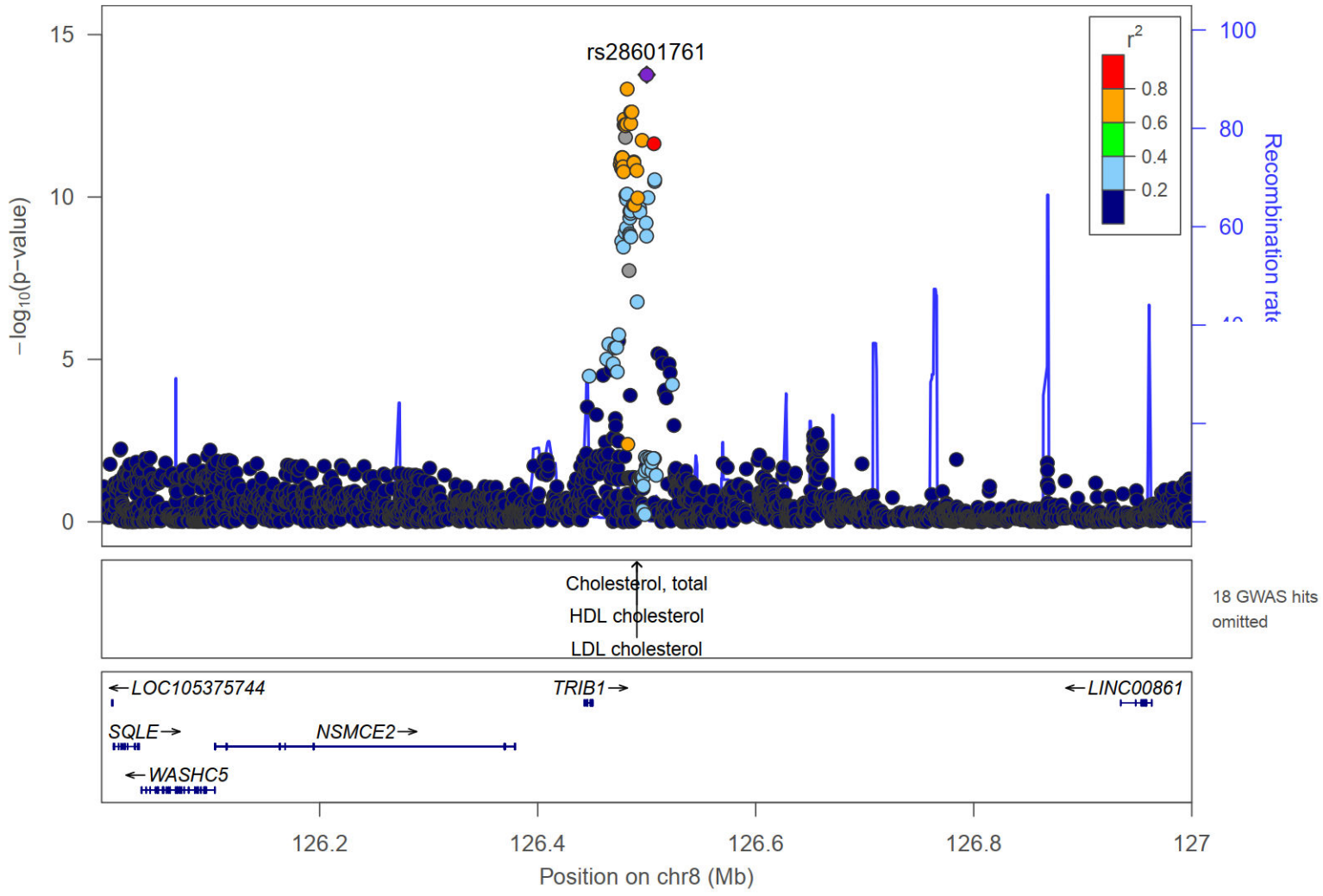

rs2460448
r2
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
Homocysteine levels
Homocysteine levels
Hair color
Tanning
Melanoma
Non−melanoma skin cancer
18 GWAS hits omitted
ACSF3→
←ANKRD11
RPL13→
SPATA33→
←FANCA
TCF25→
←DBNDD1
LINC00304→
LOC101927817→
CPNE7→
CDK10→
SPIRE2→
DEF8→
←PRDM7
LINC02138→
SPG7→
DPEP1→
ZNF276→
MC1R→
GAS8→
CDH15→
LOC100287036→
SNORD68→
←SPATA2L
TUBB3→
←URAHP
←SLC22A31
←CHMP1A
SNORA119→
FAM157B→
ZNF778→
←VPS9D1
←CENPBD1
LOC105371414→
VPS9D1−AS1→
AFG3L1P→
←GAS8−AS1
FAM157C→
89.4
89.6
89.8
90
90.2
Position on chr16 (Mb)

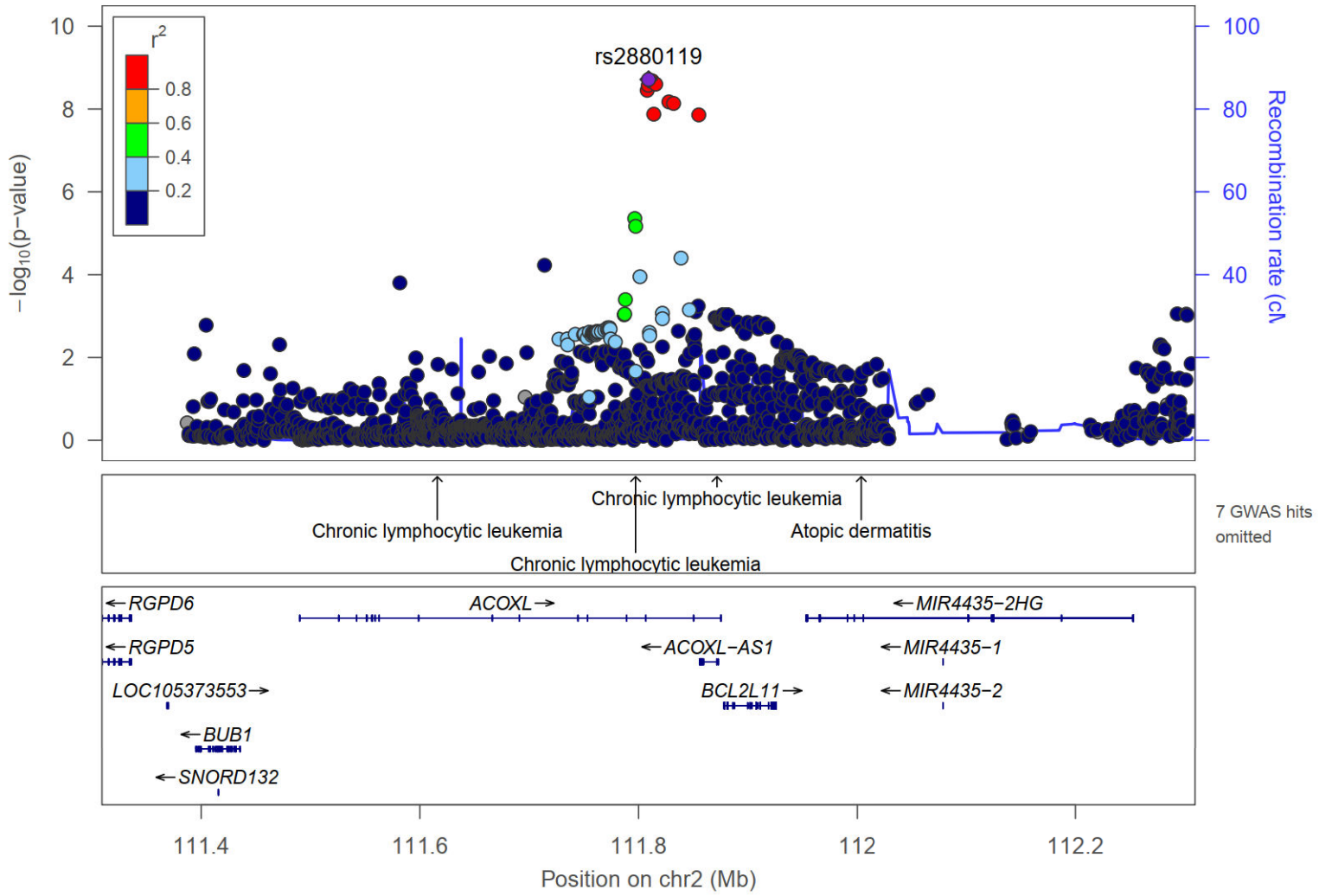

rs2470893
r2
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
Systemic lupus erythematosus and Sys
Blood trace element (Zn levels)
Adverse response to chemotherapy (neutropenia/leuc
16 GWAS hits omitted
CCDC33→
←SEMA7A
ARID3B→
←EDC3
CSK→
MPI→
SCAMP5→
C15orf39→
←CYP11A1
←UBL7
CLK3→
←CYP1A1
CPLX3→
←COX5A
PPCDC→
LOC729739→
CYP1A2→
←FAM219B
←LOC105376731
LINC02255→
←MIR4513
←RPP25
←MIR6881
LMAN1L→
UBL7−AS1→
←ULK3
←MIR6882
←SCAMP2
74.6
74.8
75
75.2
75.4
Position on chr15 (Mb)

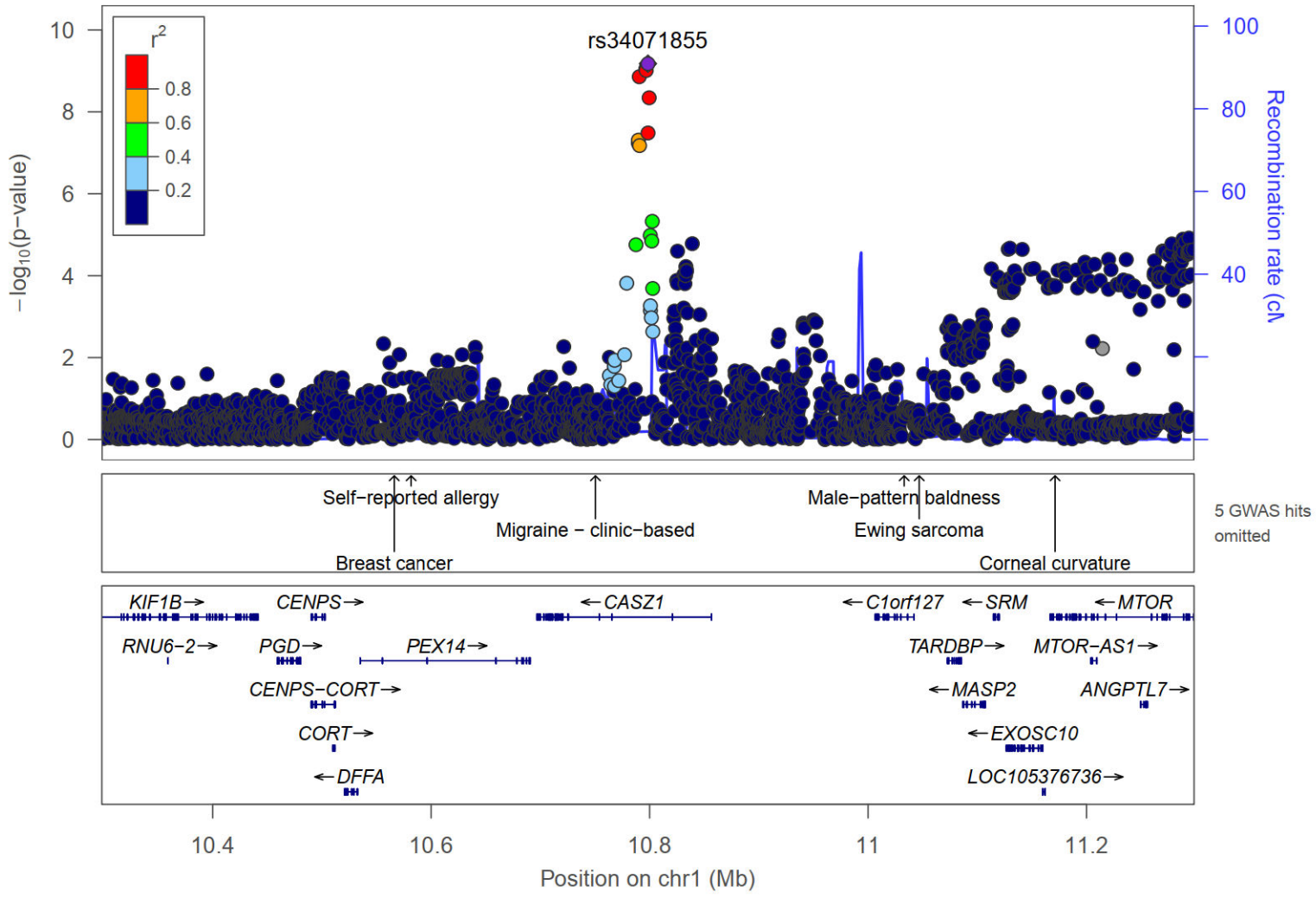

rs2760995
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
Chronic lymphocytic leukemia
Rheumatoid arthritis
Narcolepsy (age of onset)
Narcolepsy (age of onset)
Periodontitis (CDC/AAP)
226 GWAS hits omitted
TNXB
LOC101929163
HLA−DRB5
HLA−DQB1
HLA−DOB
HLA−DMB
ATF6B
C6orf10
HLA−DRA
HLA−DRB1
HLA−DQA2
TAP1
HLA−DMA
FKBPL
HCG23
HLA−DRB6
MIR3135B
LOC100294145
HLA−DPA1
PRRT1
BTNL2
HLA−DQA1
TAP2
BRD2
LOC100507547
HLA−DQB1−AS1
PSMB8
HLA−DOA
PPT2
HLA−DQB2
HLA−DPB1
PPT2−EGFL8
PSMB8−AS1
EGFL8
PSMB9
AGPAT1
MIR6721
7 genes omitted
32.2
32.4
32.6
32.8
33
Position on chr6 (Mb)

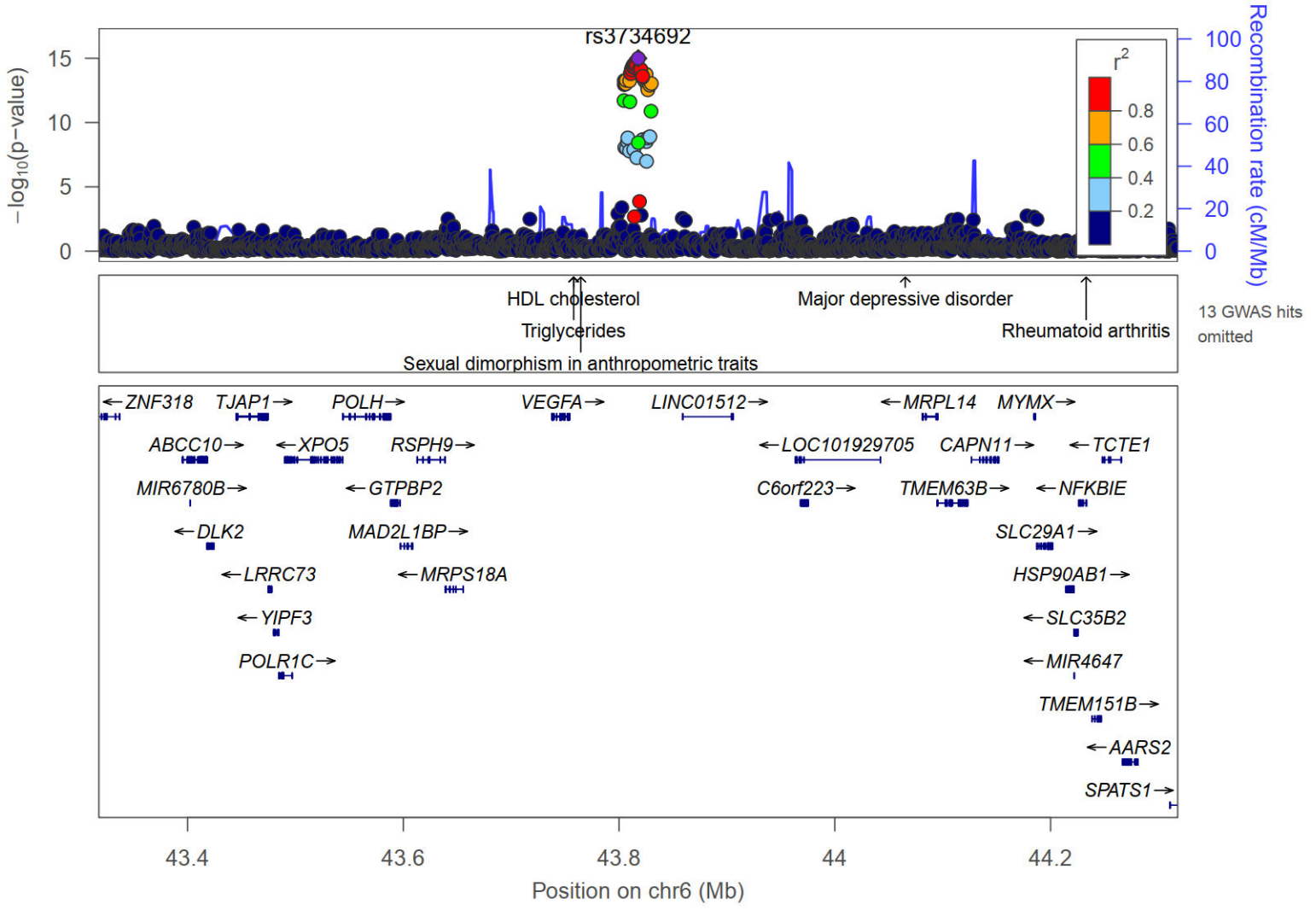

rs2793351
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM
Meningioma
Ovarian cancer
Breast cancer
Breast cancer
CASC10
MIR1915
SKIDA1
MLLT10
DNAJC1
EBLN1
BMI1
LOC100130992
COMMD3
COMMD3−BMI1
SPAG6
Position on chr10 (Mb)

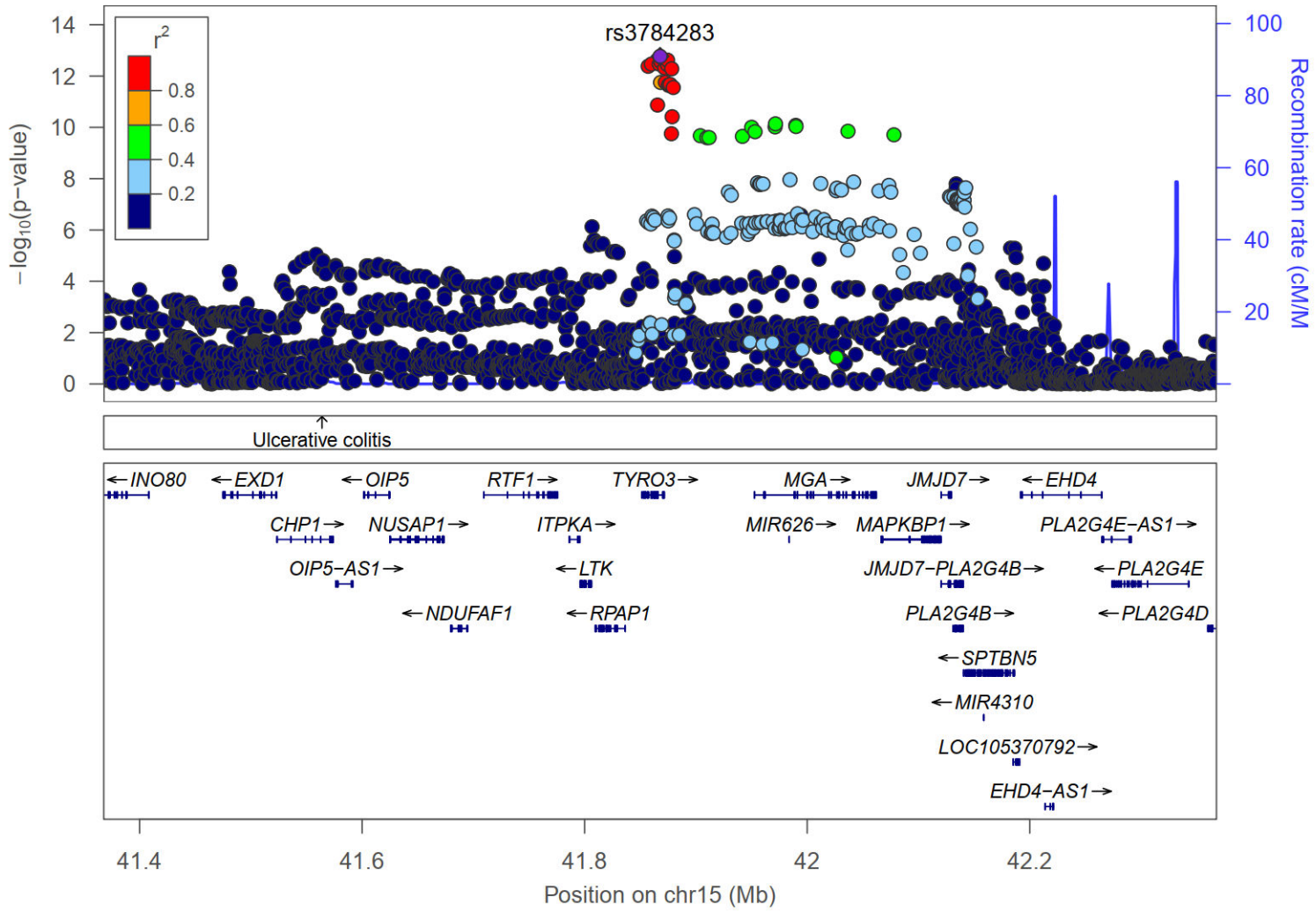

r2
0.8
0.6
0.4
0.2
rs28412751
−log10(p−value)
Recombinatior
10
8
6
4
2
0
100
80
60
Migraine
Pulmonary function decline
Response to amphetamines
CA8
LINC01301
RAB2A
CHD7
LOC100130298
61.2
61.4
61.6
61.8
62
Position on chr8 (Mb)

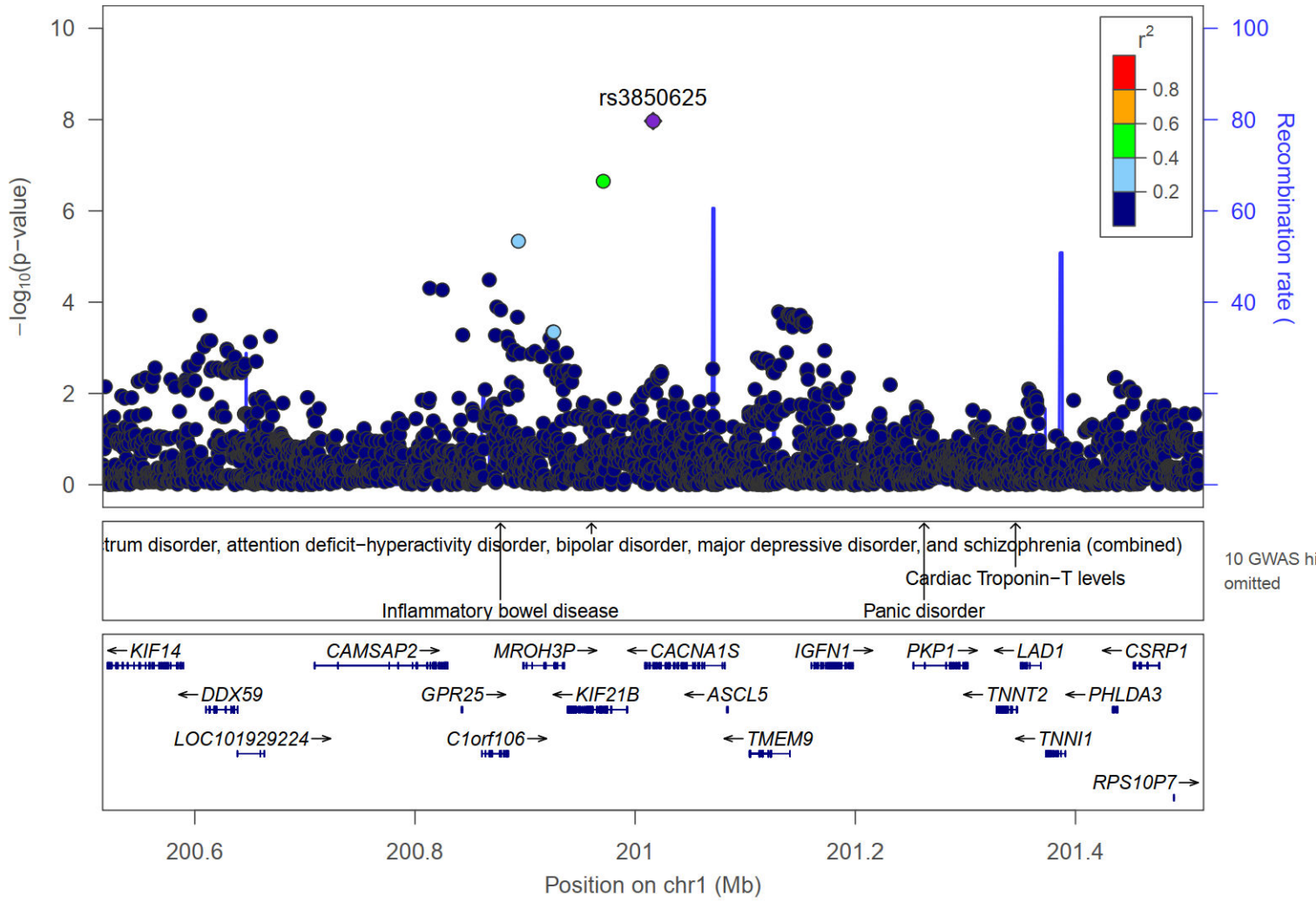

rs28601761
r²
0.8
0.6
0.4
0.2
15
10
5
0
100
80
60
−log10(p−value)
Recombination rate
Cholesterol, total
HDL cholesterol
LDL cholesterol
18 GWAS hits omitted
←LOC105375744
TRIB1→
←LINC00861
SQLE→
NSMCE2→
←WASHC5
126.2
126.4
126.6
126.8
127
Position on chr8 (Mb)

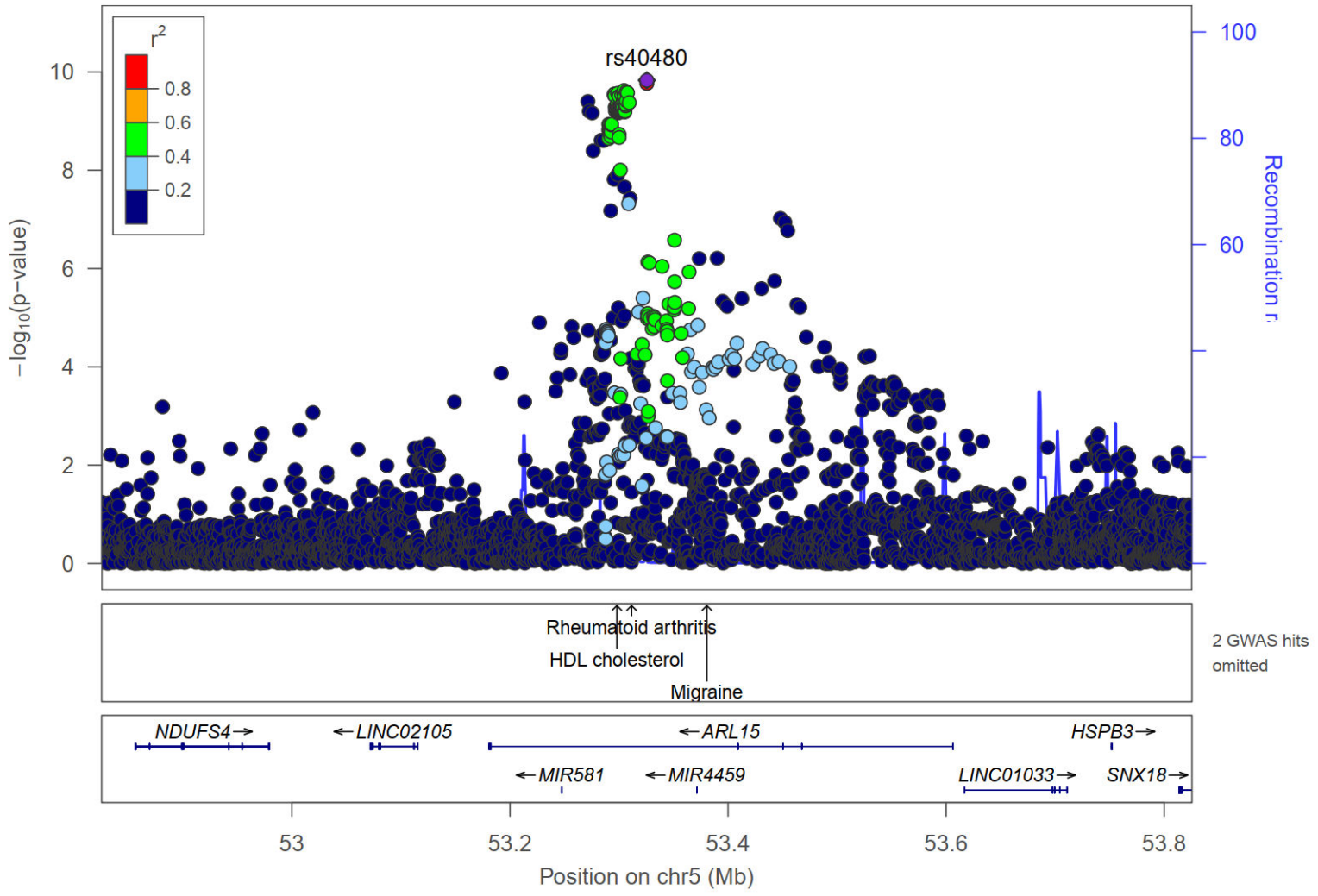

r2
0.8
0.6
0.4
0.2
rs2880119
−log10(p−value)
Recombination rate (cM
Chronic lymphocytic leukemia
Chronic lymphocytic leukemia
Chronic lymphocytic leukemia
Atopic dermatitis
7 GWAS hits omitted
RGPD6
RGPD5
LOC105373553
BUB1
SNORD132
ACOXL
ACOXL−AS1
BCL2L11
MIR4435−2HG
MIR4435−1
MIR4435−2
Position on chr2 (Mb)

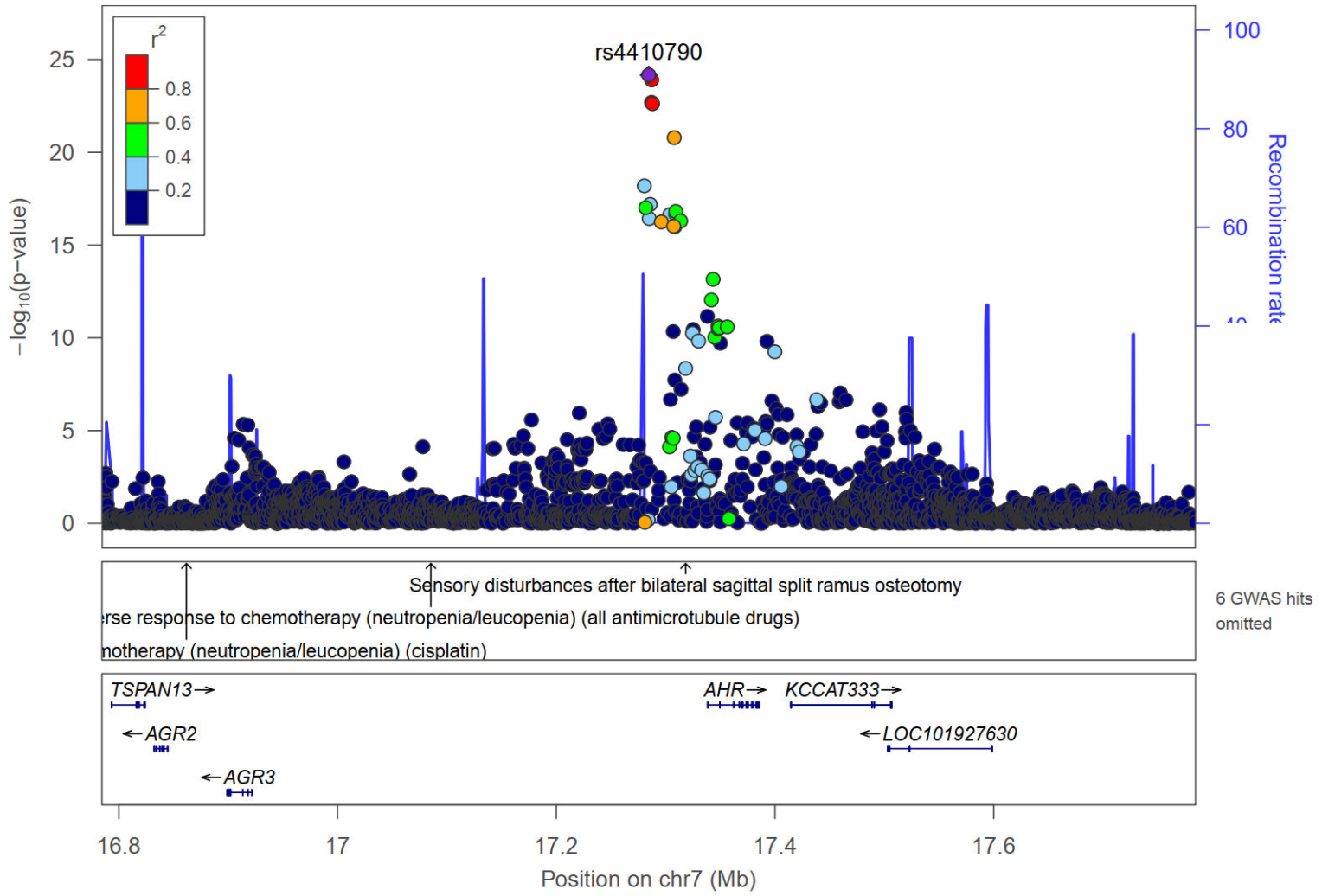

rs34071855
r2
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM
Self−reported allergy
Migraine − clinic−based
Male−pattern baldness
Ewing sarcoma
Breast cancer
Corneal curvature
5 GWAS hits omitted
KIF1B→
CENPS→
←CASZ1
←C1orf127
←SRM
←MTOR
RNU6−2→
PGD→
PEX14→
TARDBP→
MTOR−AS1→
CENPS−CORT→
←MASP2
ANGPTL7→
CORT→
←EXOSC10
←DFFA
LOC105376736→
Position on chr1 (Mb)

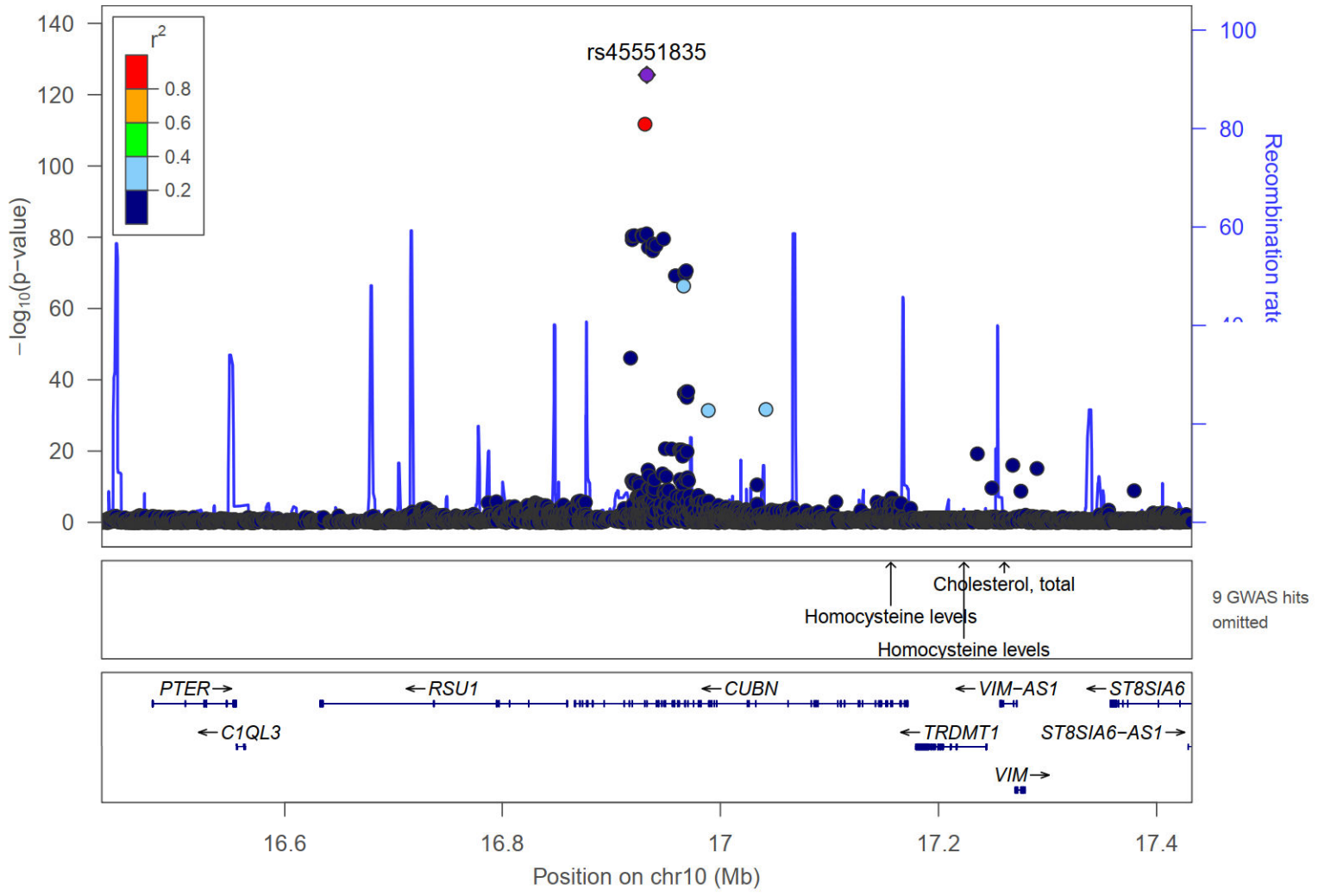

rs3734692
$-\log_{10}$(p-value)
15
10
5
0
r^2
0.8
0.6
0.4
0.2
100
80
60
40
20
0
Recombination rate (cM/Mb)
HDL cholesterol
Triglycerides
Sexual dimorphism in anthropometric traits
Major depressive disorder
Rheumatoid arthritis
13 GWAS hits omitted
ZNF318
TJAP1
POLH
VEGFA
LINC01512
MRPL14
MYMX
ABCC10
XPO5
RSPH9
LOC101929705
CAPN11
TCTE1
MIR6780B
GTPBP2
C6orf223
TMEM63B
NFKBIE
DLK2
MAD2L1BP
SLC29A1
LRRC73
MRPS18A
HSP90AB1
YIPF3
SLC35B2
POLR1C
MIR4647
TMEM151B
AARS2
SPATS1
43.4
43.6
43.8
44
44.2
Position on chr6 (Mb)

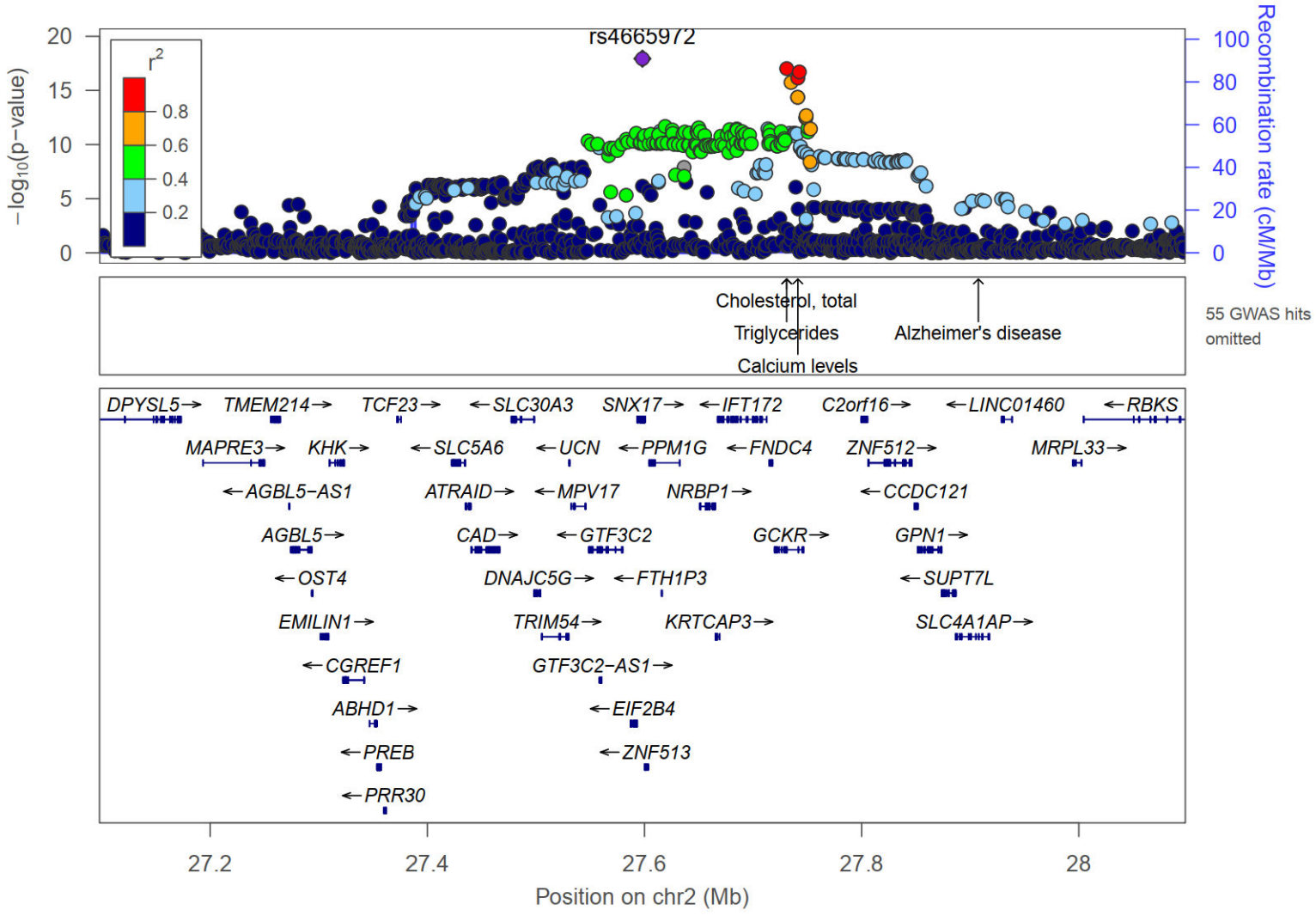

rs3784283
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/M
Ulcerative colitis
←INO80
←EXD1
←OIP5
RTF1→
TYRO3→
MGA→
JMJD7→
←EHD4
CHP1→
NUSAP1→
ITPKA→
MIR626→
MAPKBP1→
PLA2G4E−AS1→
OIP5−AS1→
←LTK
JMJD7−PLA2G4B→
←PLA2G4E
←NDUFAF1
←RPAP1
PLA2G4B→
←PLA2G4D
←SPTBN5
←MIR4310
LOC105370792→
EHD4−AS1→
41.4
41.6
41.8
42
42.2
Position on chr15 (Mb)

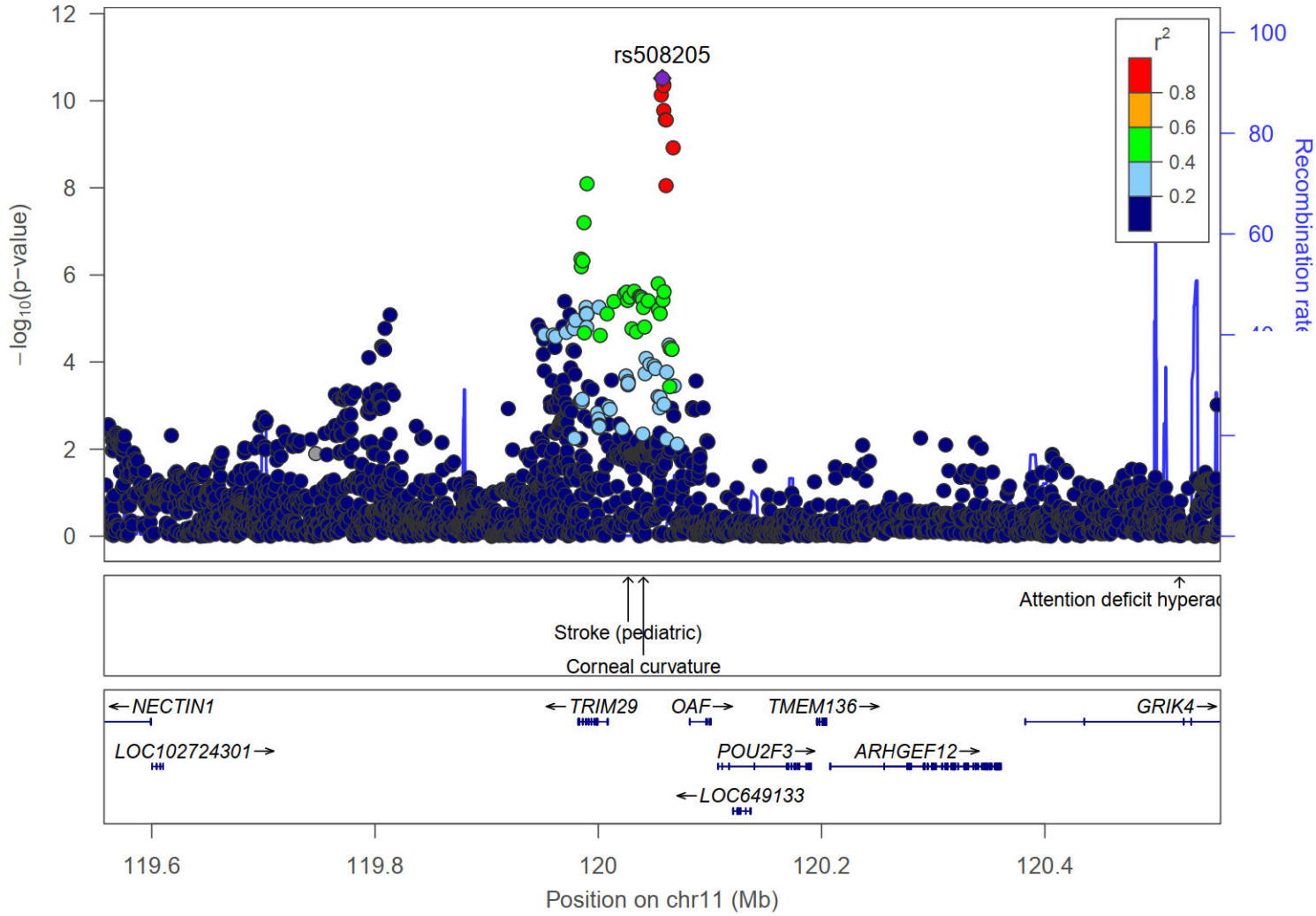

rs3850625
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (
10
8
6
4
2
0
100
80
60
40
trum disorder, attention deficit−hyperactivity disorder, bipolar disorder, major depressive disorder, and schizophrenia (combined)
Cardiac Troponin−T levels
Inflammatory bowel disease
Panic disorder
10 GWAS hits omitted
←KIF14
CAMSAP2→
MROH3P→
←CACNA1S
IGFN1→
PKP1→
←LAD1
←CSRP1
←DDX59
GPR25→
←KIF21B
←ASCL5
←TNNT2
←PHLDA3
LOC101929224→
C1orf106→
←TMEM9
←TNNI1
RPS10P7→
200.6
200.8
201
201.2
201.4
Position on chr1 (Mb)

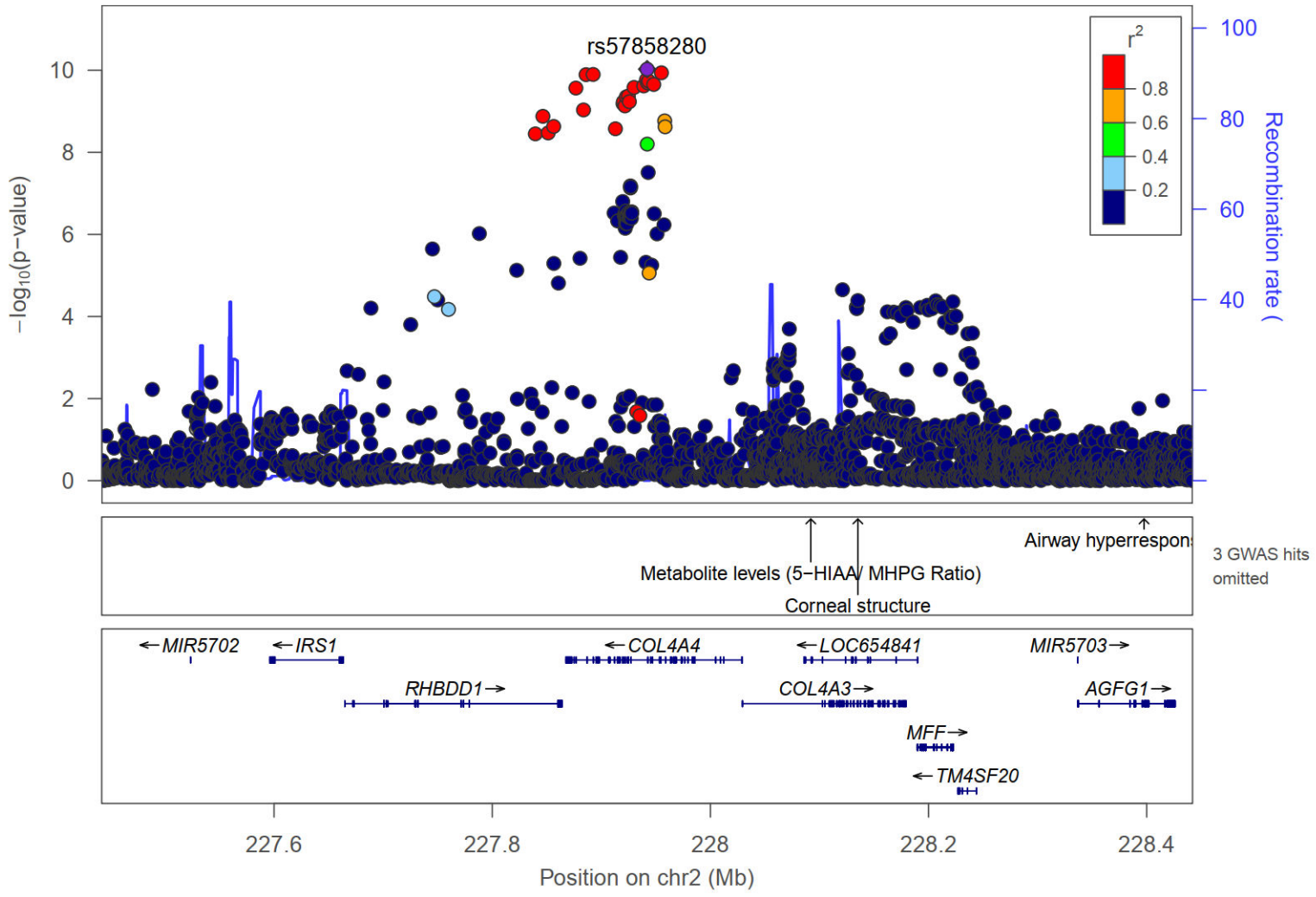

r2
0.8
0.6
0.4
0.2
rs40480
−log10(p−value)
Recombination r
Rheumatoid arthritis
HDL cholesterol
Migraine
2 GWAS hits
omitted
NDUFS4
LINC02105
ARL15
HSPB3
MIR581
MIR4459
LINC01033
SNX18
Position on chr5 (Mb)

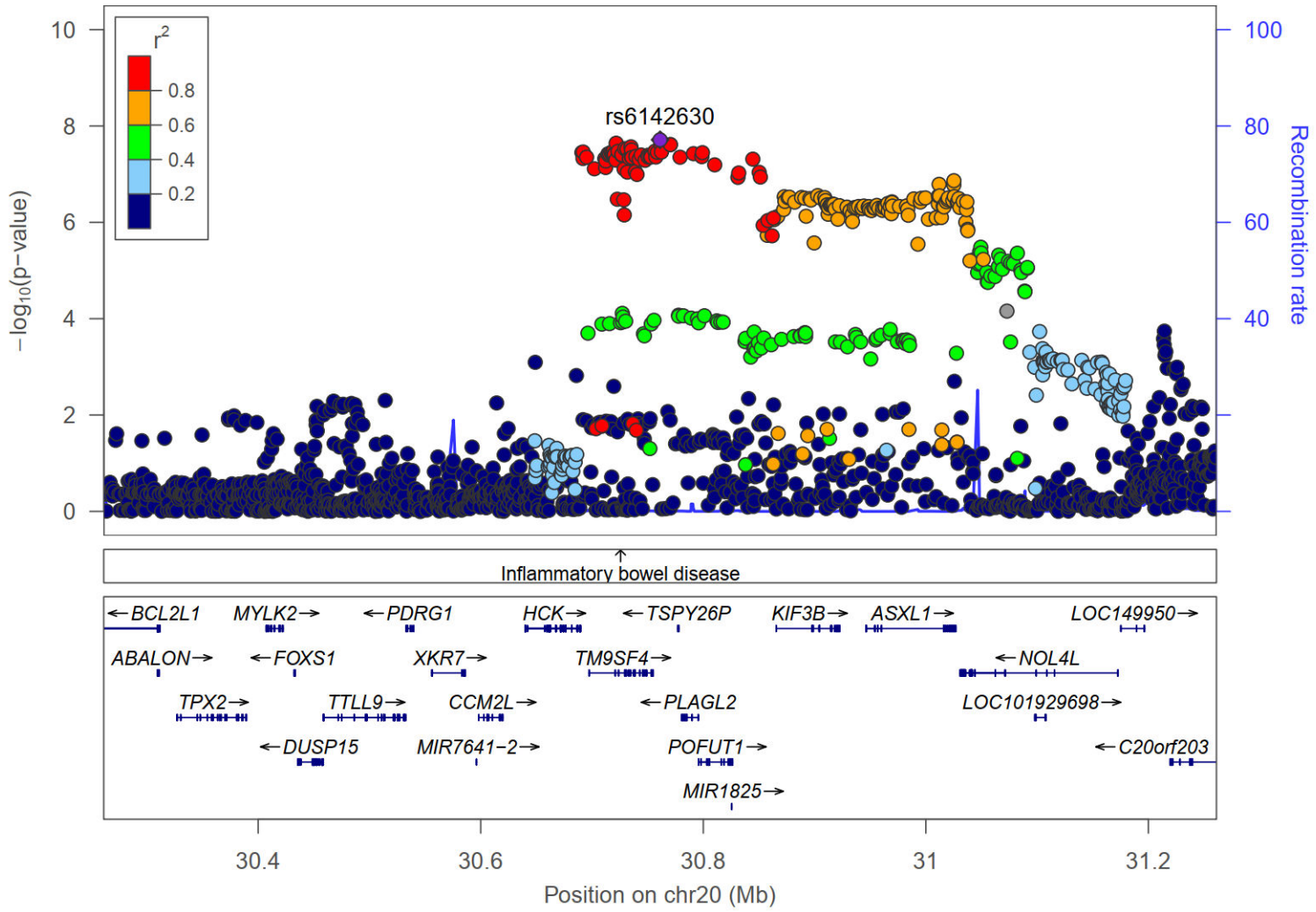

r²
0.8
0.6
0.4
0.2
rs4410790
−log10(p−value)
Recombination rate
Sensory disturbances after bilateral sagittal split ramus osteotomy
rse response to chemotherapy (neutropenia/leucopenia) (all antimicrotubule drugs)
notherapy (neutropenia/leucopenia) (cisplatin)
6 GWAS hits omitted
TSPAN13
AGR2
AGR3
AHR
KCCAT333
LOC101927630
Position on chr7 (Mb)

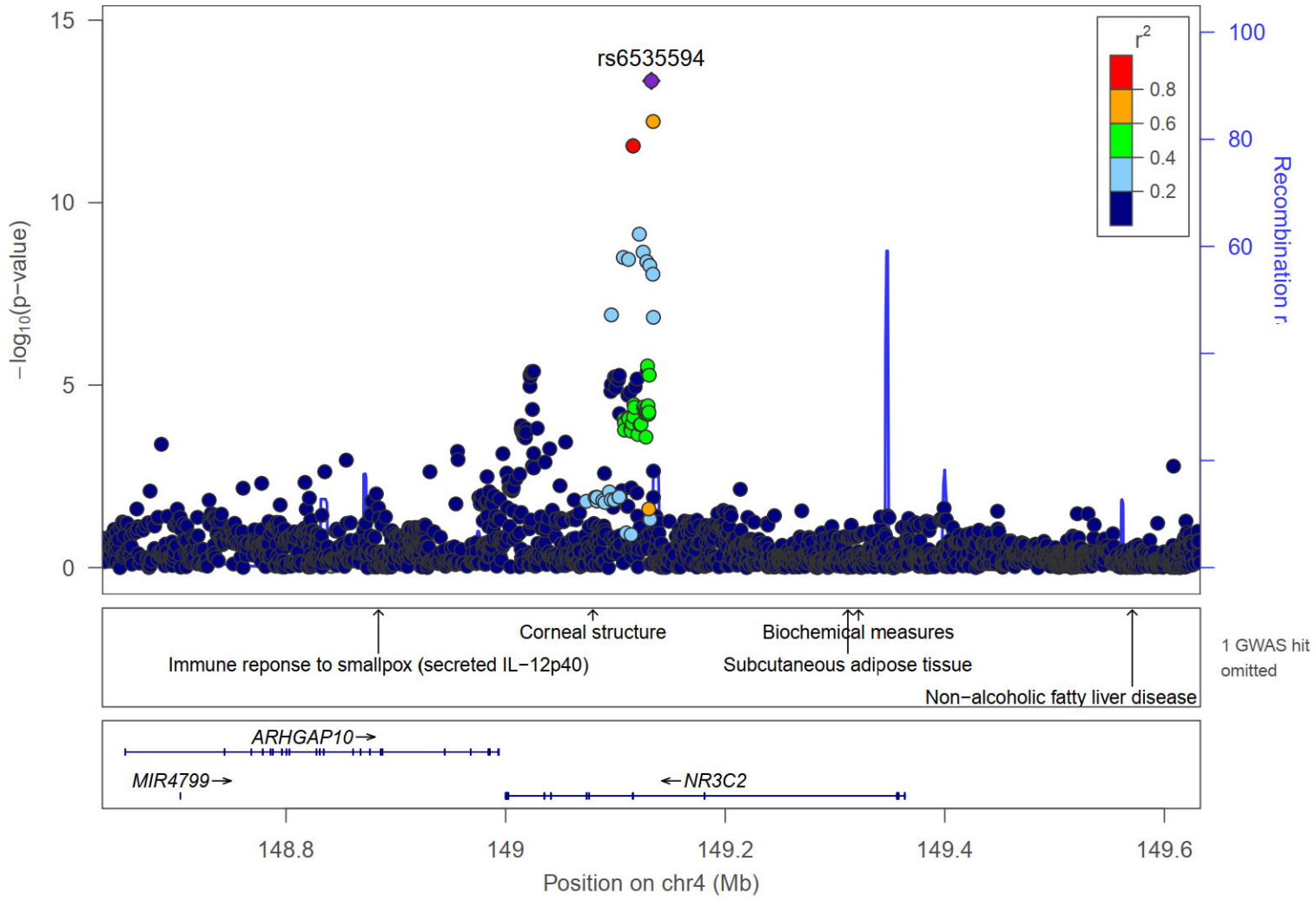

rs45551835
r2
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate
Cholesterol, total
Homocysteine levels
Homocysteine levels
9 GWAS hits omitted
PTER
RSU1
CUBN
VIM−AS1
ST8SIA6
C1QL3
TRDMT1
ST8SIA6−AS1
VIM
Position on chr10 (Mb)

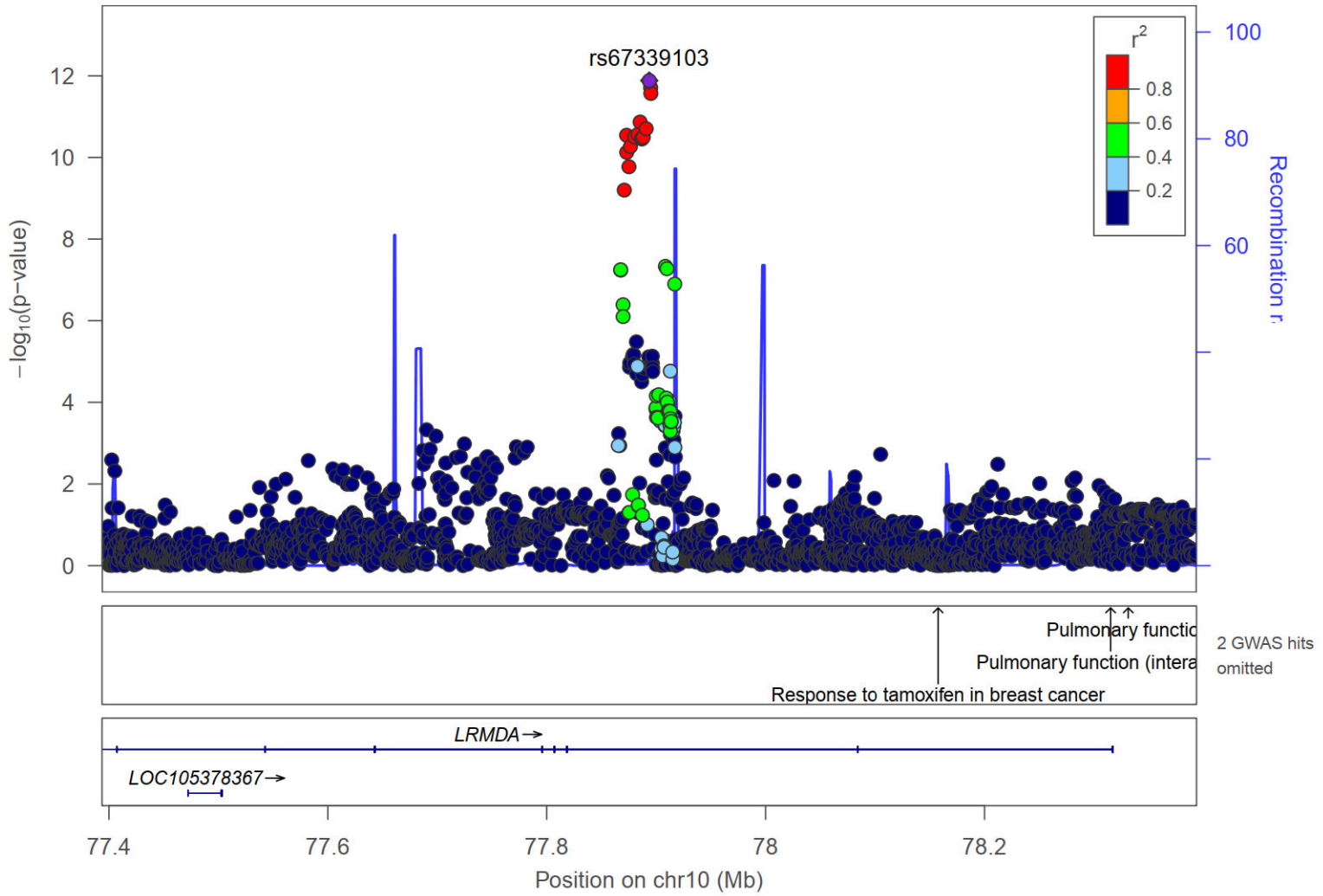

rs4665972
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
Cholesterol, total
Triglycerides
Calcium levels
Alzheimer's disease
55 GWAS hits omitted
DPYSL5→ TMEM214→ TCF23→ ←SLC30A3 SNX17→ ←IFT172 C2orf16→ ←LINC01460 ←RBKS
MAPRE3→ KHK→ ←SLC5A6 ←UCN ←PPM1G ←FNDC4 ZNF512→ MRPL33→
←AGBL5-AS1 ATRAID→ ←MPV17 NRBP1→ ←CCDC121
AGBL5→ CAD→ ←GTF3C2 GCKR→ GPN1→
←OST4 DNAJC5G→ ←FTH1P3 ←SUPT7L
EMILIN1→ TRIM54→ KRTCAP3→ SLC4A1AP→
←CGREF1 GTF3C2-AS1→
ABHD1→ ←EIF2B4
←PREB ←ZNF513
←PRR30
27.2
27.4
27.6
27.8
28
Position on chr2 (Mb)

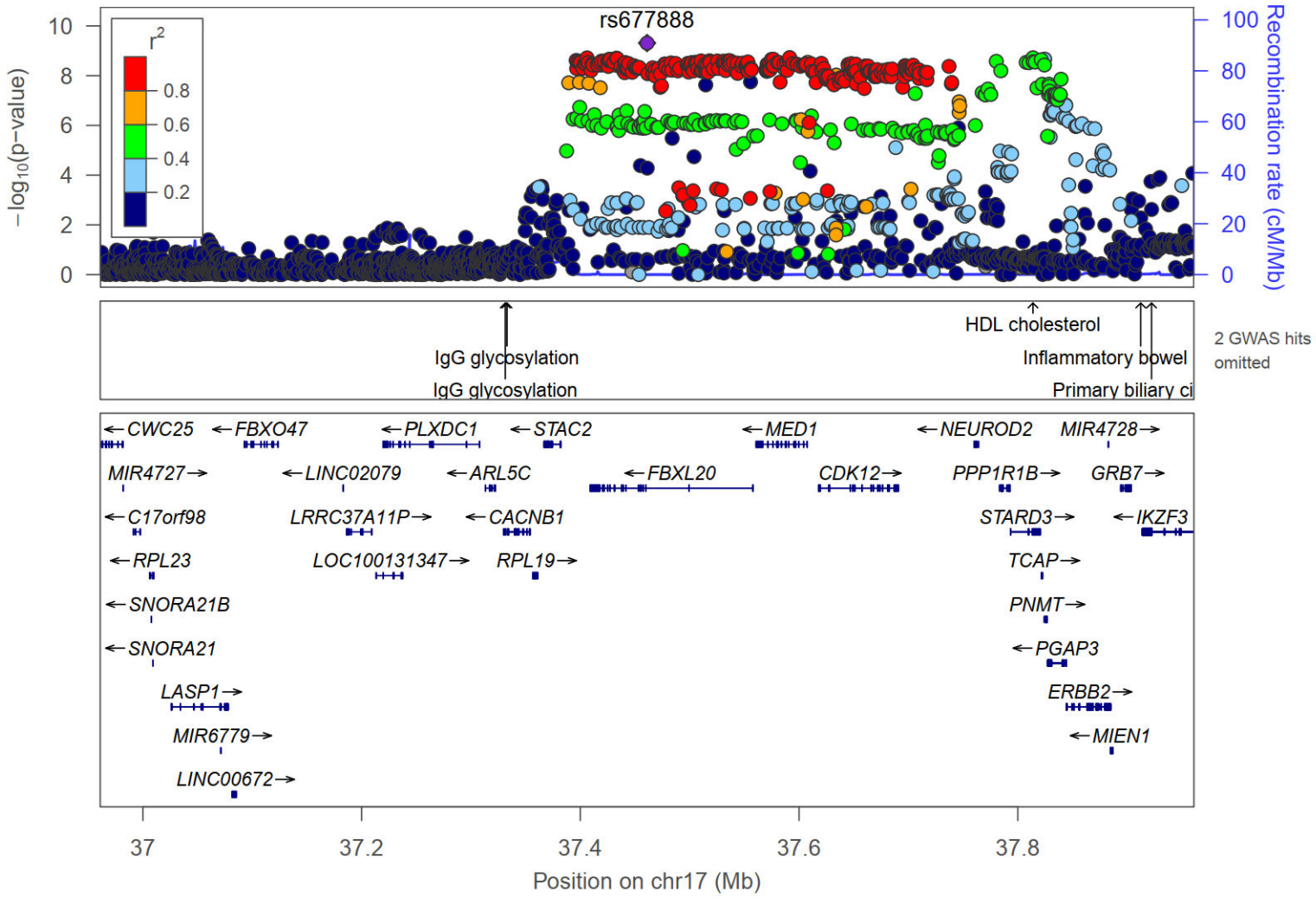

rs508205
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate
Stroke (pediatric)
Corneal curvature
Attention deficit hyperac
NECTIN1
TRIM29
OAF
TMEM136
GRIK4
LOC102724301
POU2F3
ARHGEF12
LOC649133
119.6
119.8
120
120.2
120.4
Position on chr11 (Mb)

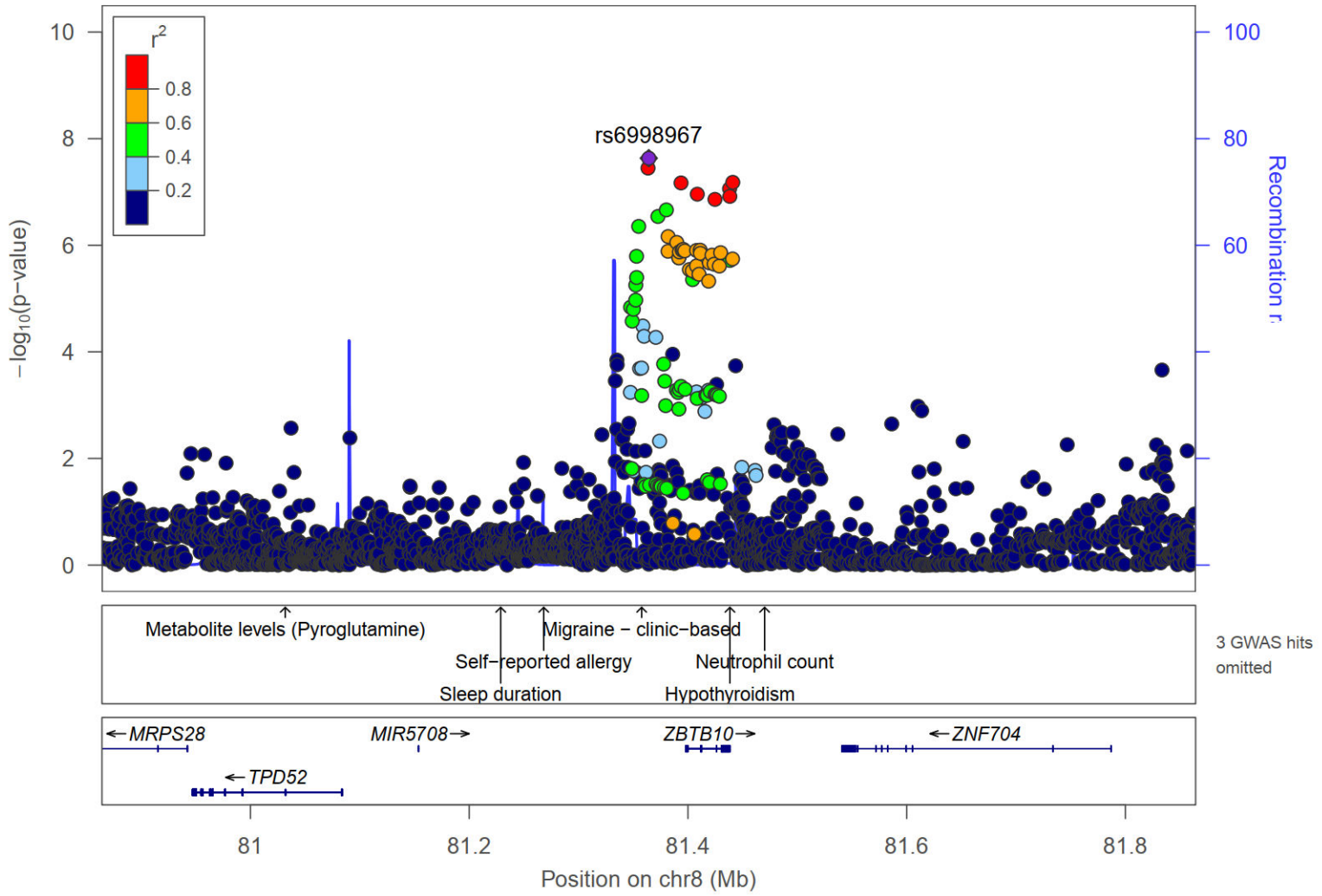

rs57858280
r²
0.8
0.6
0.4
0.2
100
80
60
40
Recombination rate (
10
8
6
4
2
0
−log10(p−value)
Airway hyperrespons
Metabolite levels (5−HIAA/ MHPG Ratio)
Corneal structure
3 GWAS hits
omitted
←MIR5702
←IRS1
←COL4A4
←LOC654841
MIR5703→
RHBDD1→
COL4A3→
AGFG1→
MFF→
←TM4SF20
227.6
227.8
228
228.2
228.4
Position on chr2 (Mb)

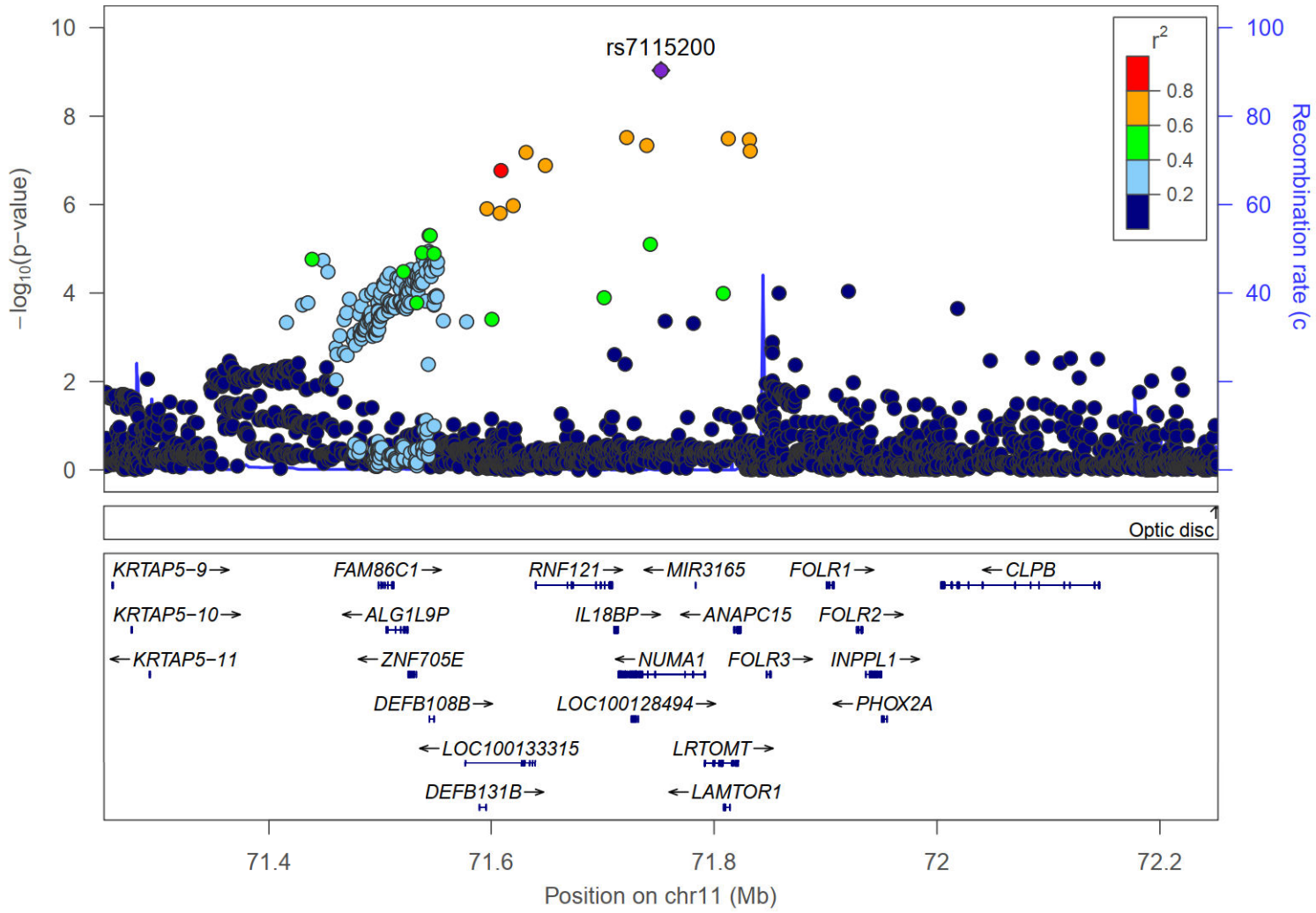

r2
0.8
0.6
0.4
0.2
rs6142630
−log10(p−value)
Recombination rate
Inflammatory bowel disease
←BCL2L1
MYLK2→
←PDRG1
HCK→
←TSPY26P
KIF3B→
ASXL1→
LOC149950→
ABALON→
←FOXS1
XKR7→
TM9SF4→
←NOL4L
TPX2→
TTLL9→
CCM2L→
←PLAGL2
LOC101929698→
←DUSP15
MIR7641−2→
POFUT1→
←C20orf203
MIR1825→
Position on chr20 (Mb)

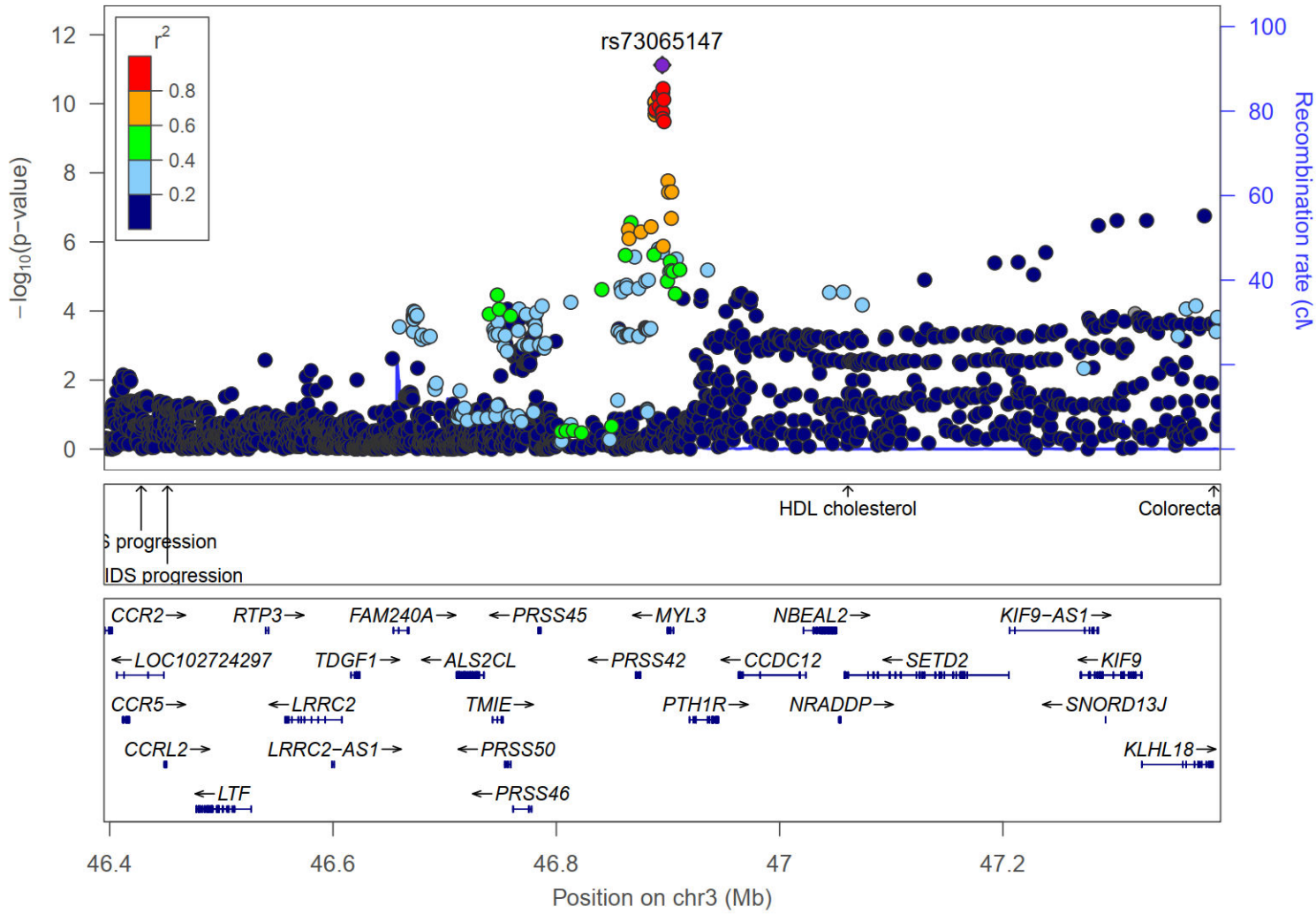

rs6535594
r2
0.8
0.6
0.4
0.2
15
10
5
0
100
80
60
−log10(p−value)
Recombination r
Corneal structure
Biochemical measures
Immune reponse to smallpox (secreted IL−12p40)
Subcutaneous adipose tissue
Non−alcoholic fatty liver disease
1 GWAS hit
omitted
ARHGAP10→
MIR4799→
←NR3C2
148.8
149
149.2
149.4
149.6
Position on chr4 (Mb)

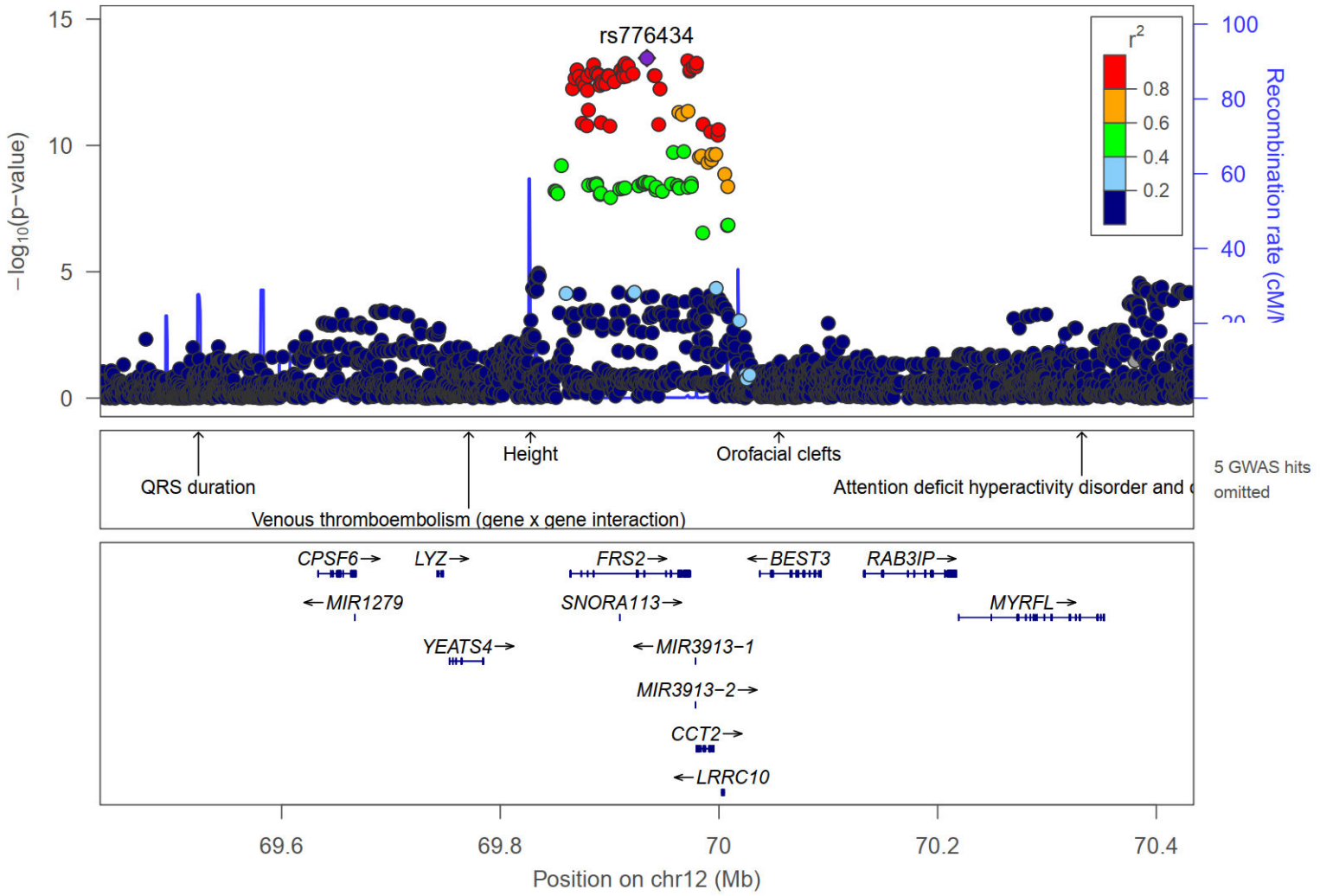

rs67339103
r²
0.8
0.6
0.4
0.2
100
80
60
Recombination r
12
10
8
6
4
2
0
−log10(p−value)
Pulmonary functic
Pulmonary function (intera
2 GWAS hits
omitted
Response to tamoxifen in breast cancer
LRMDA
LOC105378367
77.4
77.6
77.8
78
78.2
Position on chr10 (Mb)

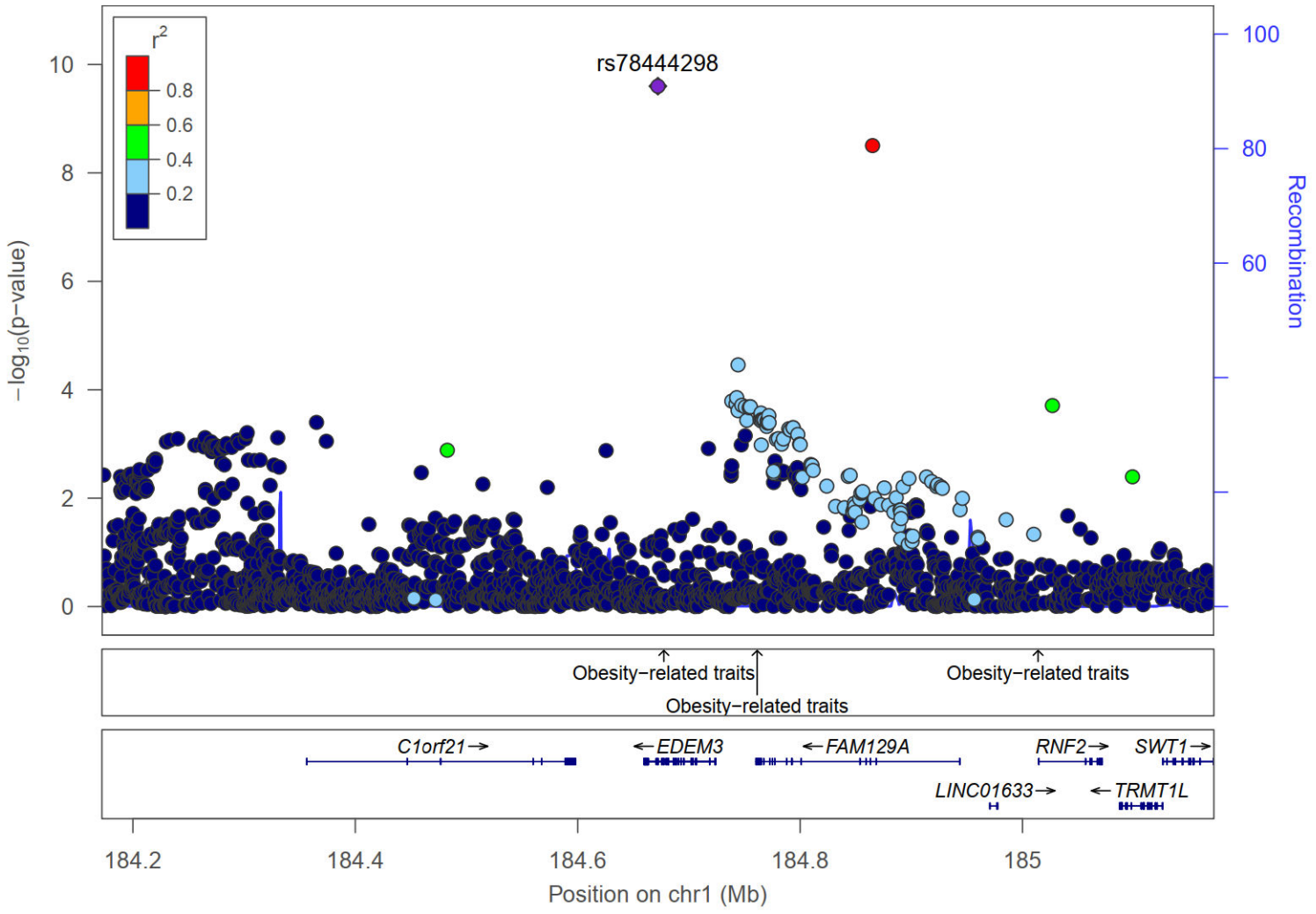

rs677888
r2
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
IgG glycosylation
IgG glycosylation
HDL cholesterol
Inflammatory bowel
Primary biliary ci
2 GWAS hits
omitted
CWC25
FBXO47
PLXDC1
STAC2
MED1
NEUROD2
MIR4728
MIR4727
LINC02079
ARL5C
FBXL20
CDK12
PPP1R1B
GRB7
C17orf98
LRRC37A11P
CACNB1
STARD3
IKZF3
RPL23
LOC100131347
RPL19
TCAP
SNORA21B
PNMT
SNORA21
PGAP3
LASP1
ERBB2
MIR6779
MIEN1
LINC00672
Position on chr17 (Mb)

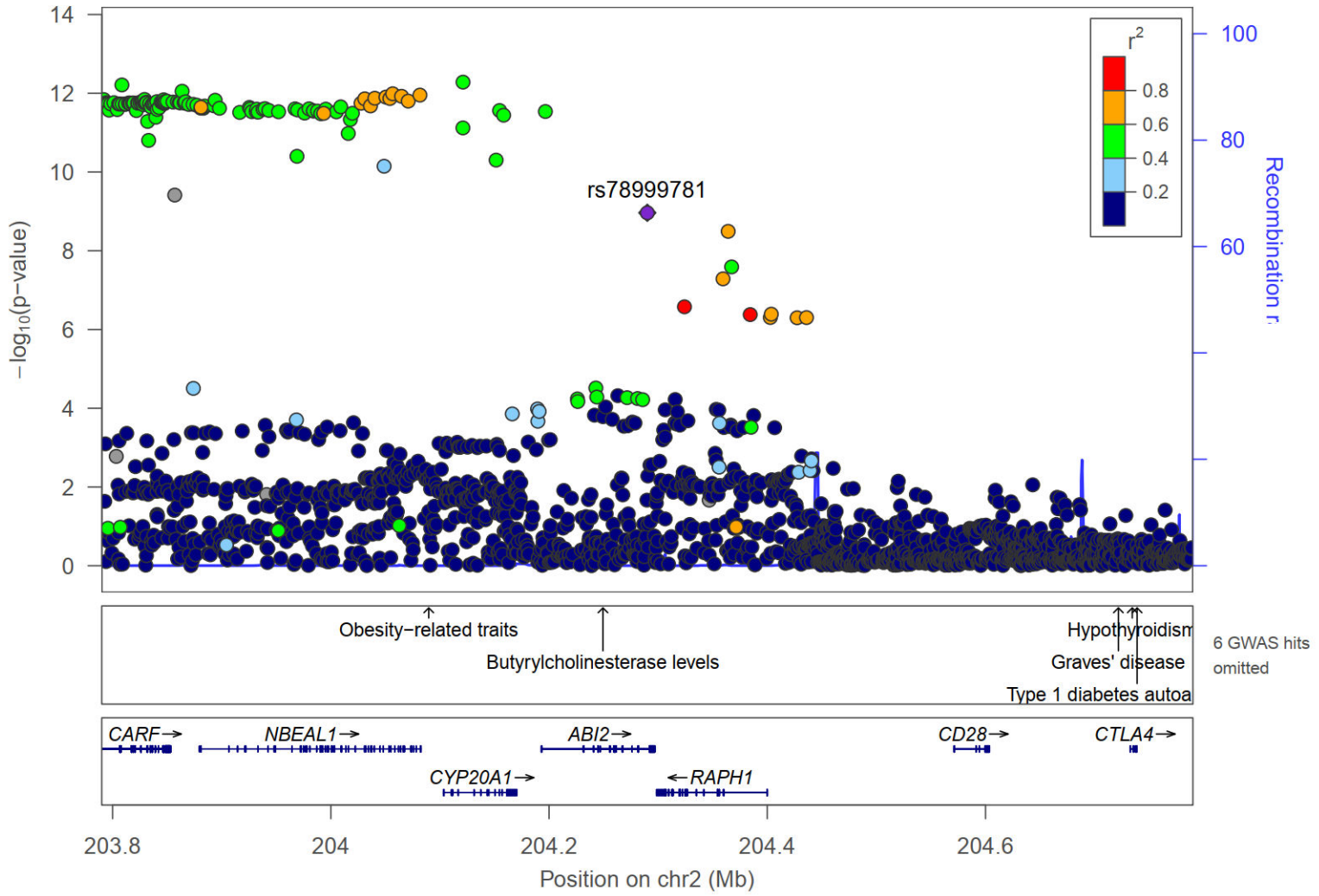

r2
0.8
0.6
0.4
0.2
rs6998967
−log10(p−value)
Recombination r
10
8
6
4
2
0
100
80
60
Metabolite levels (Pyroglutamine)
Self−reported allergy
Migraine − clinic−based
Sleep duration
Neutrophil count
Hypothyroidism
3 GWAS hits
omitted
MRPS28
MIR5708
ZBTB10
ZNF704
TPD52
81
81.2
81.4
81.6
81.8
Position on chr8 (Mb)

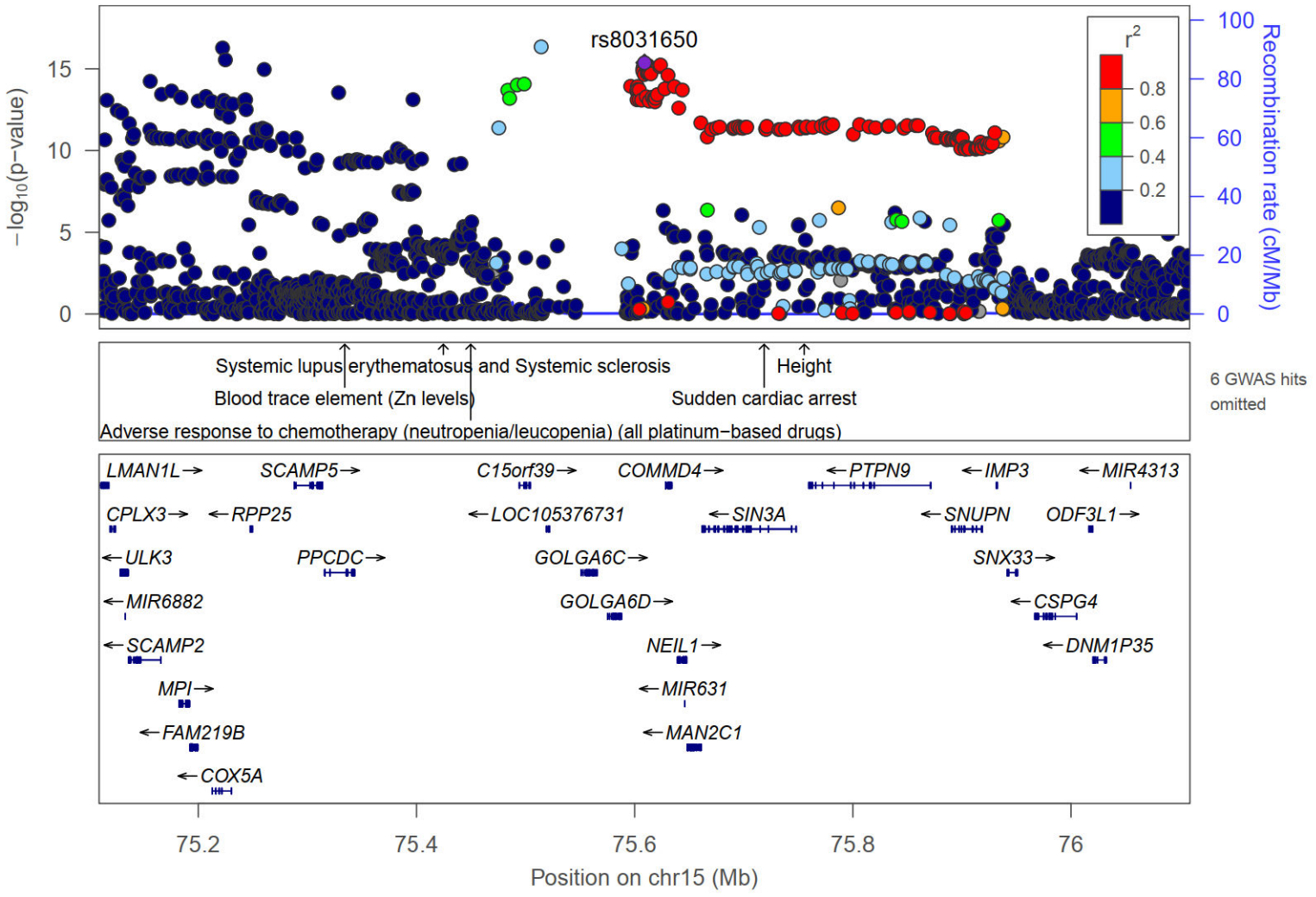

rs7115200
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (c
10
8
6
4
2
0
100
80
60
40
Optic disc
KRTAP5−9→
FAM86C1→
RNF121→
←MIR3165
FOLR1→
←CLPB
KRTAP5−10→
←ALG1L9P
IL18BP→
←ANAPC15
FOLR2→
←KRTAP5−11
←ZNF705E
←NUMA1
FOLR3→
INPPL1→
DEFB108B→
LOC100128494→
←PHOX2A
←LOC100133315
LRTOMT→
DEFB131B→
←LAMTOR1
71.4
71.6
71.8
72
72.2
Position on chr11 (Mb)

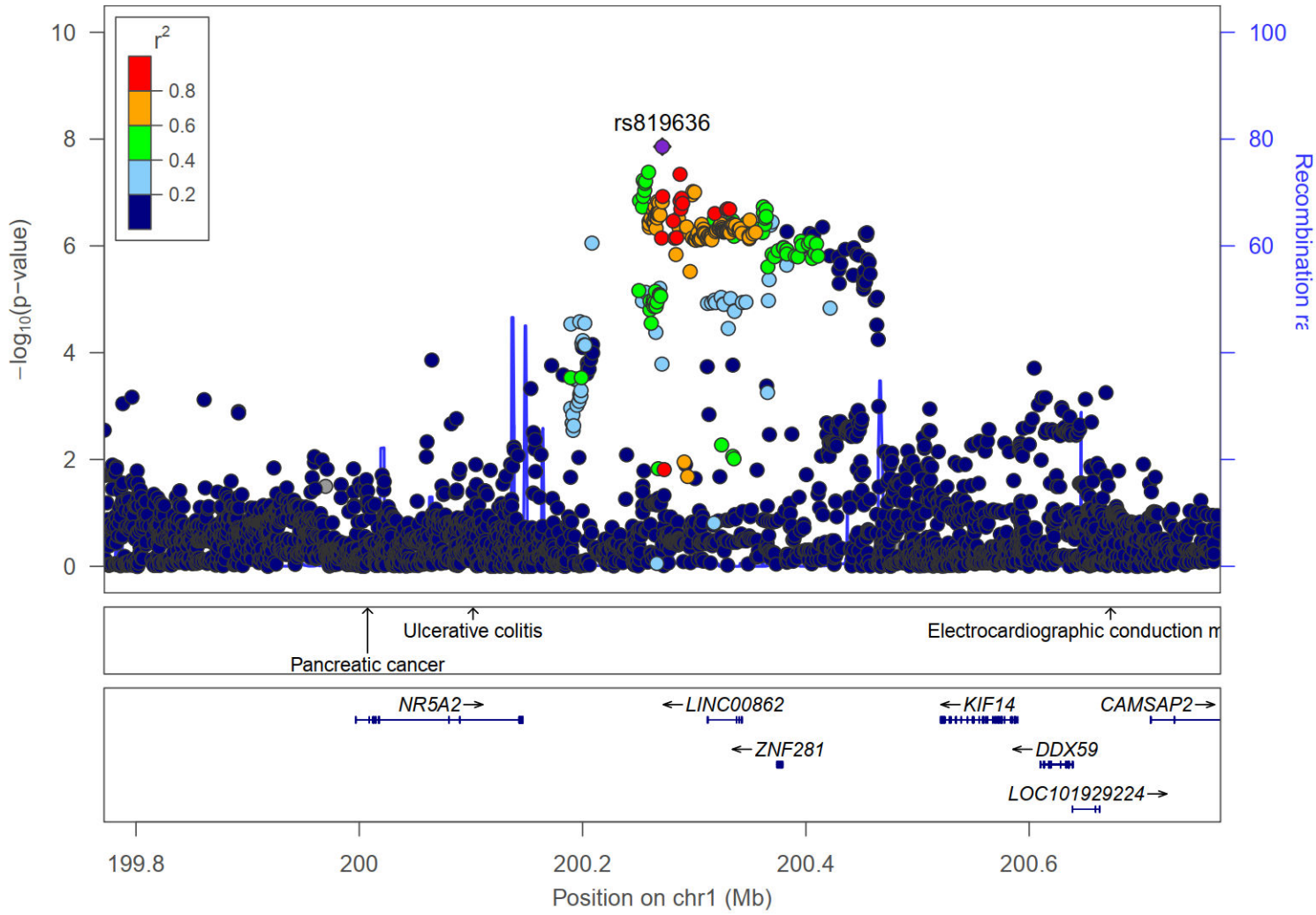

rs73065147
r2
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM
HDL cholesterol
Colorecta
progression
IDS progression
CCR2→
RTP3→
FAM240A→
←PRSS45
←MYL3
NBEAL2→
KIF9−AS1→
←LOC102724297
TDGF1→
←ALS2CL
←PRSS42
←CCDC12
←SETD2
←KIF9
CCR5→
←LRRC2
TMIE→
PTH1R→
NRADDP→
←SNORD13J
CCRL2→
LRRC2−AS1→
←PRSS50
KLHL18→
←LTF
←PRSS46
46.4
46.6
46.8
47
47.2
Position on chr3 (Mb)


rs776434
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/
15
10
5
0
100
80
60
40
QRS duration
Venous thromboembolism (gene x gene interaction)
Height
Orofacial clefts
Attention deficit hyperactivity disorder and
5 GWAS hits
omitted
CPSF6→
LYZ→
FRS2→
←BEST3
RAB3IP→
←MIR1279
SNORA113→
MYRFL→
YEATS4→
←MIR3913−1
MIR3913−2→
CCT2→
←LRRC10
69.6
69.8
70
70.2
70.4
Position on chr12 (Mb)


r2
0.8
0.6
0.4
0.2
rs78444298
10
8
6
4
2
0
−log10(p−value)
100
80
60
Recombination
Obesity−related traits
Obesity−related traits
Obesity−related traits
C1orf21→
←EDEM3
←FAM129A
RNF2→
SWT1→
LINC01633→
←TRMT1L
184.2
184.4
184.6
184.8
185
Position on chr1 (Mb)

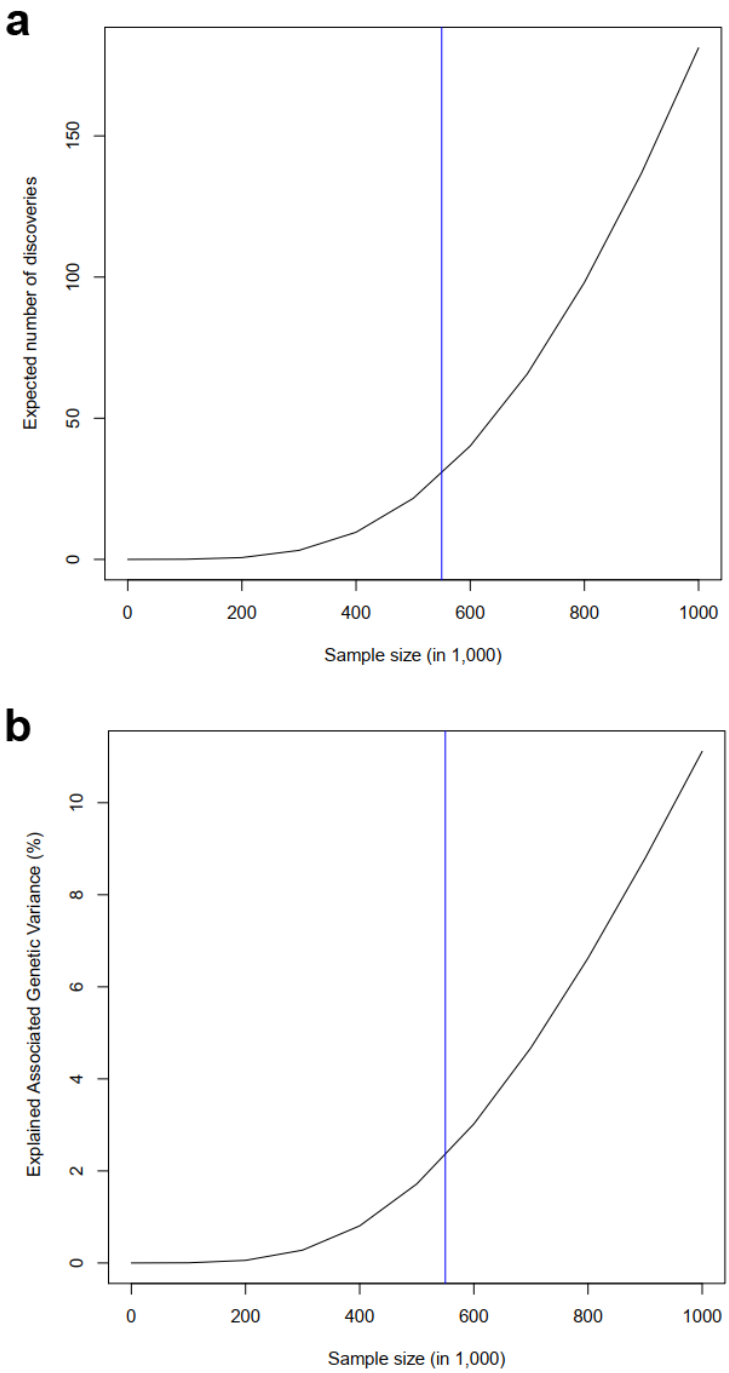

rs78999781
r2
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination r
Obesity−related traits
Butyrylcholinesterase levels
Hypothyroidism
Graves' disease
Type 1 diabetes autoa
6 GWAS hits
omitted
CARF
NBEAL1
ABI2
CD28
CTLA4
CYP20A1
RAPH1
Position on chr2 (Mb)


rs8031650
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
15
10
5
0
100
80
60
40
20
0
Systemic lupus erythematosus and Systemic sclerosis
Height
Blood trace element (Zn levels)
Sudden cardiac arrest
Adverse response to chemotherapy (neutropenia/leucopenia) (all platinum−based drugs)
6 GWAS hits
omitted
LMAN1L→
SCAMP5→
C15orf39→
COMMD4→
←PTPN9
←IMP3
←MIR4313
CPLX3→
←RPP25
←LOC105376731
←SIN3A
←SNUPN
ODF3L1→
←ULK3
PPCDC→
GOLGA6C→
SNX33→
←MIR6882
GOLGA6D→
←CSPG4
←SCAMP2
NEIL1→
←DNM1P35
MPI→
←MIR631
←FAM219B
←MAN2C1
←COX5A
75.2
75.4
75.6
75.8
76
Position on chr15 (Mb)


r²
0.8
0.6
0.4
0.2
rs819636
−log10(p−value)
Recombination ra
Pancreatic cancer
Ulcerative colitis
Electrocardiographic conduction m
NR5A2→
←LINC00862
←KIF14
CAMSAP2→
←ZNF281
←DDX59
LOC101929224→
199.8
200
200.2
200.4
200.6
Position on chr1 (Mb)

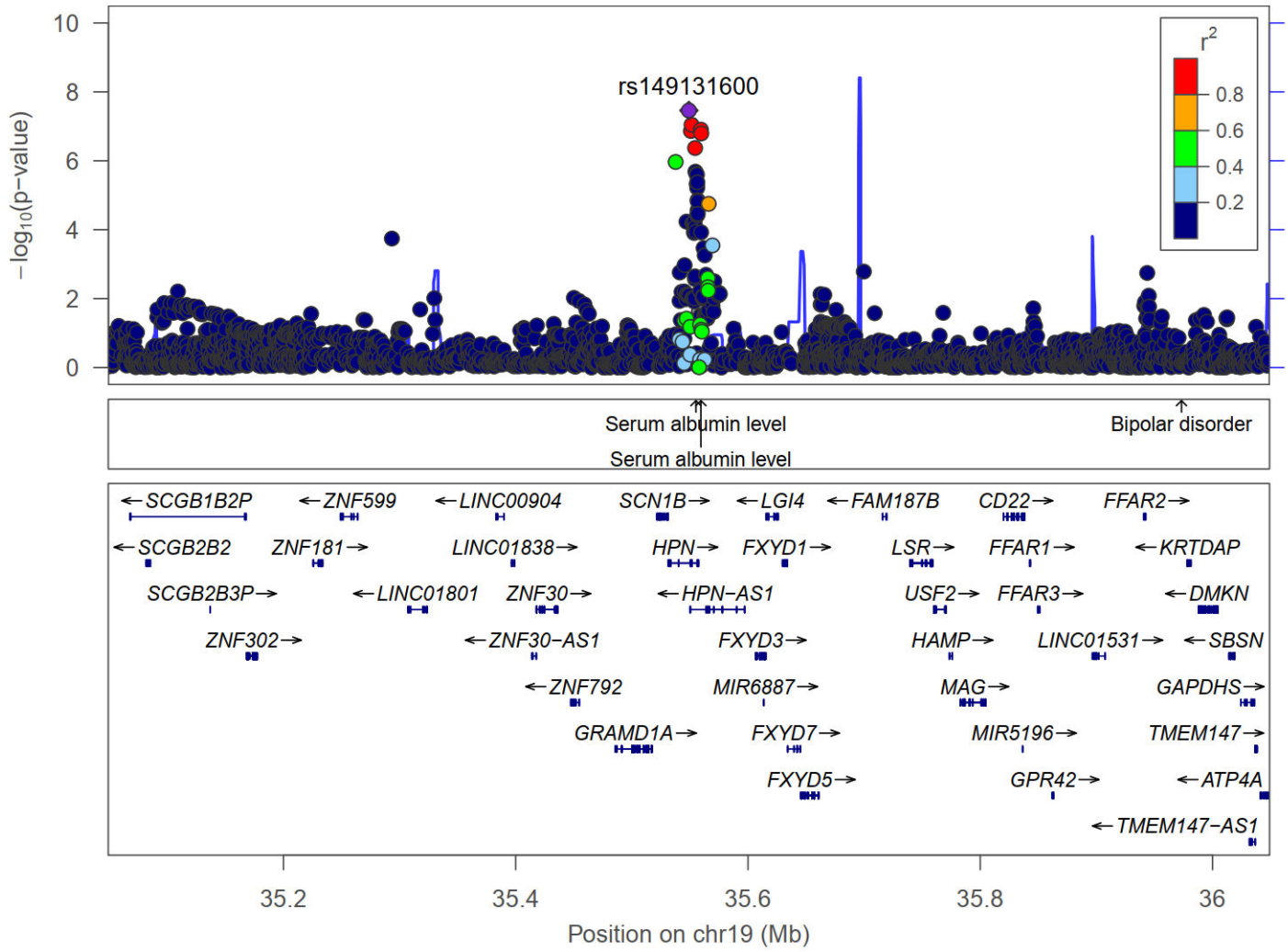
Regional association plots are shown for all genome-wide significant index SNPs. The dots are plotted on the y-axis according to their meta-analysis association p-value, and colored according to their correlation r^2 with the index SNP estimated based on the 1000 Genomes EUR reference samples (gray for missing data). Plots were generated using the stand-alone version 1.3 of LocusZoom[2]. Genetic positions refer to GRCh37/hg19 coordinates.

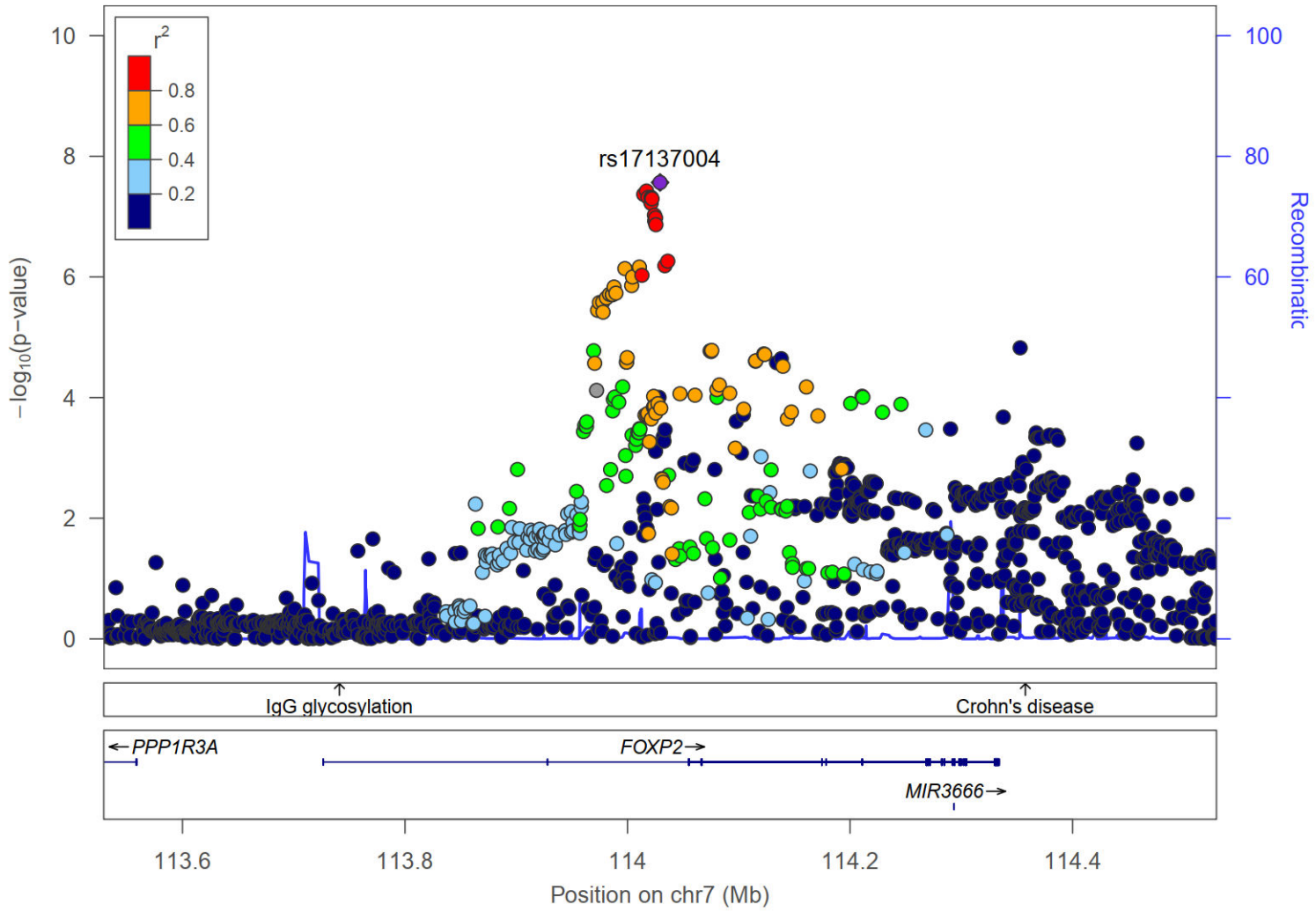
Supplementary Figure 3: Expected number of discoveries at increasing GWAS discovery sample sizes.

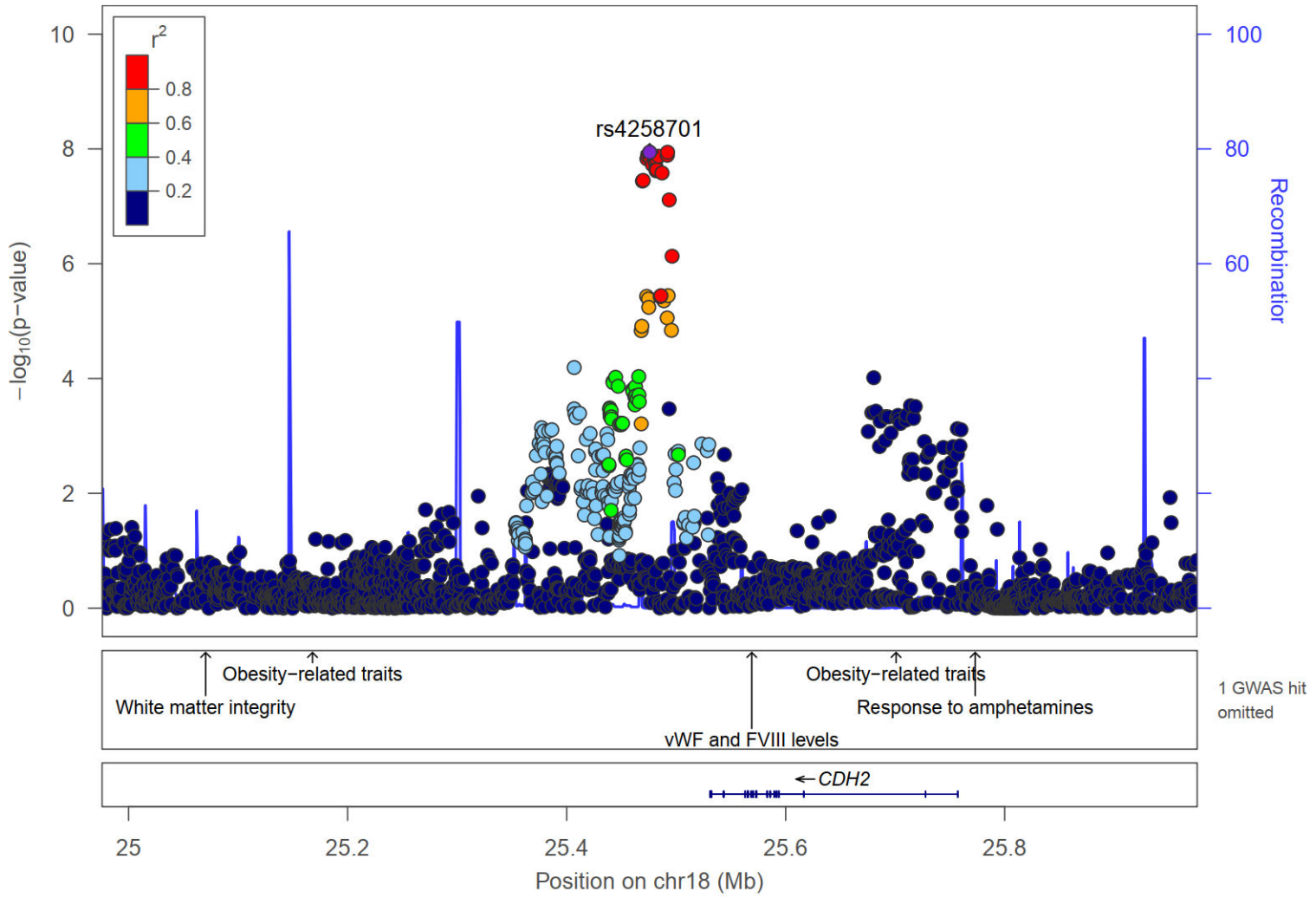


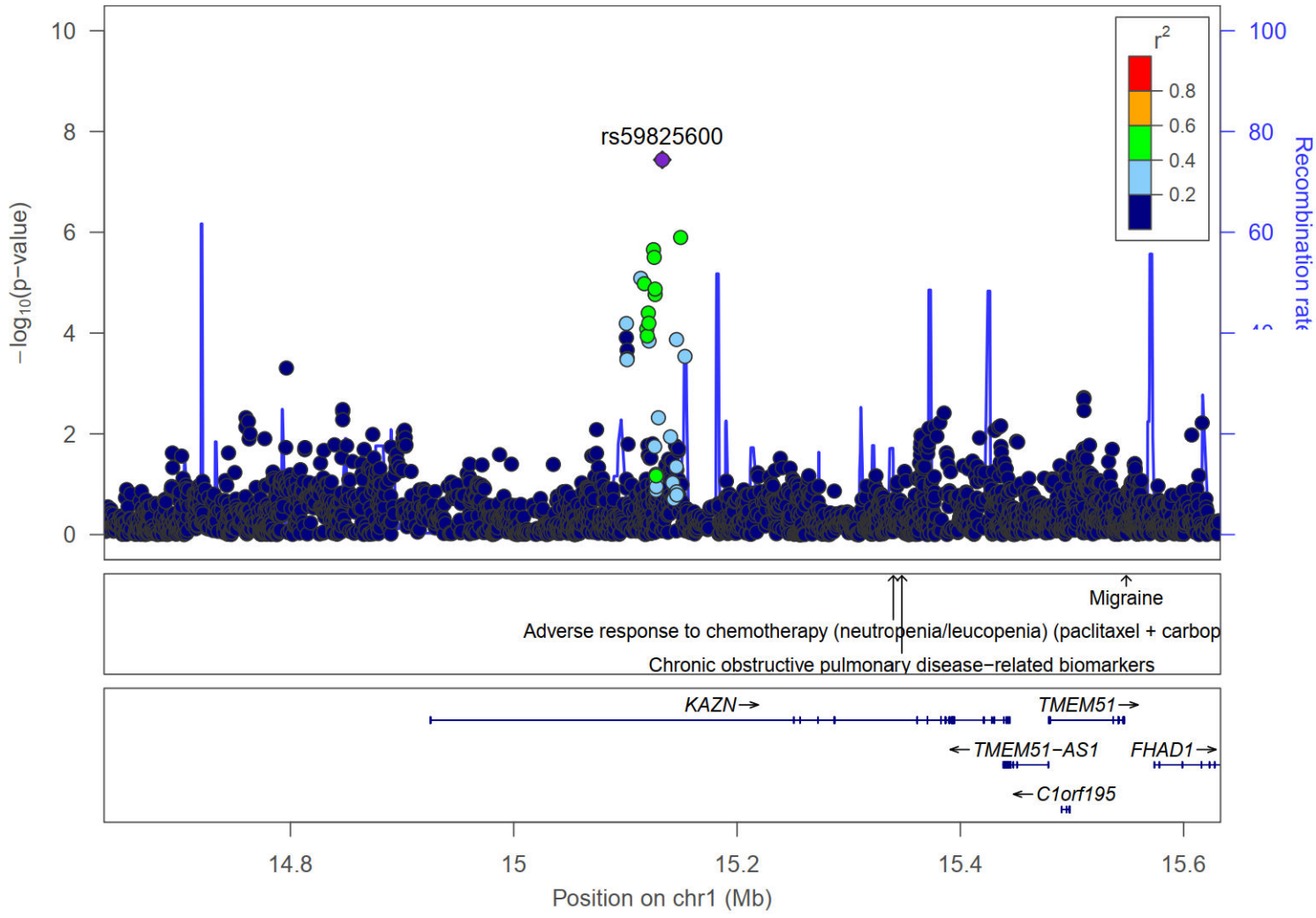
The panels show the estimate the number of expected discoveries (a) and the corresponding percentage of GWAS heritability explained (b) with increases in sample size using the summary statistics of our UACR trans-ethnic meta-analysis as input. The vertical blue line marks the number of predicted discoveries for UACR at the current sample size and may represent an underestimate because of many SNPs with small effects.

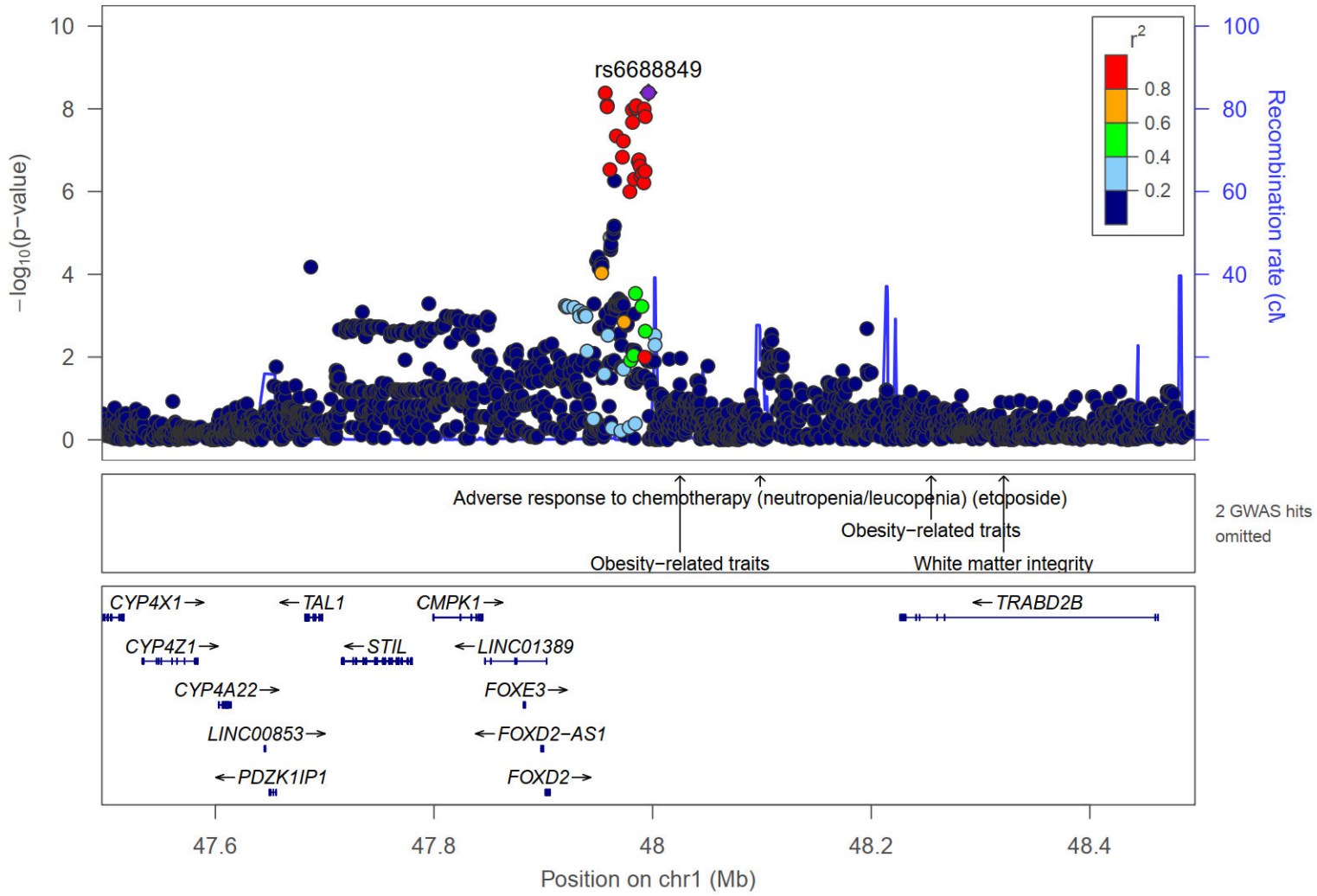
Supplementary Figure 4: Regional association plots for loci identified in trans-ethnic GWAS meta-analysis of UACR among individuals with diabetes

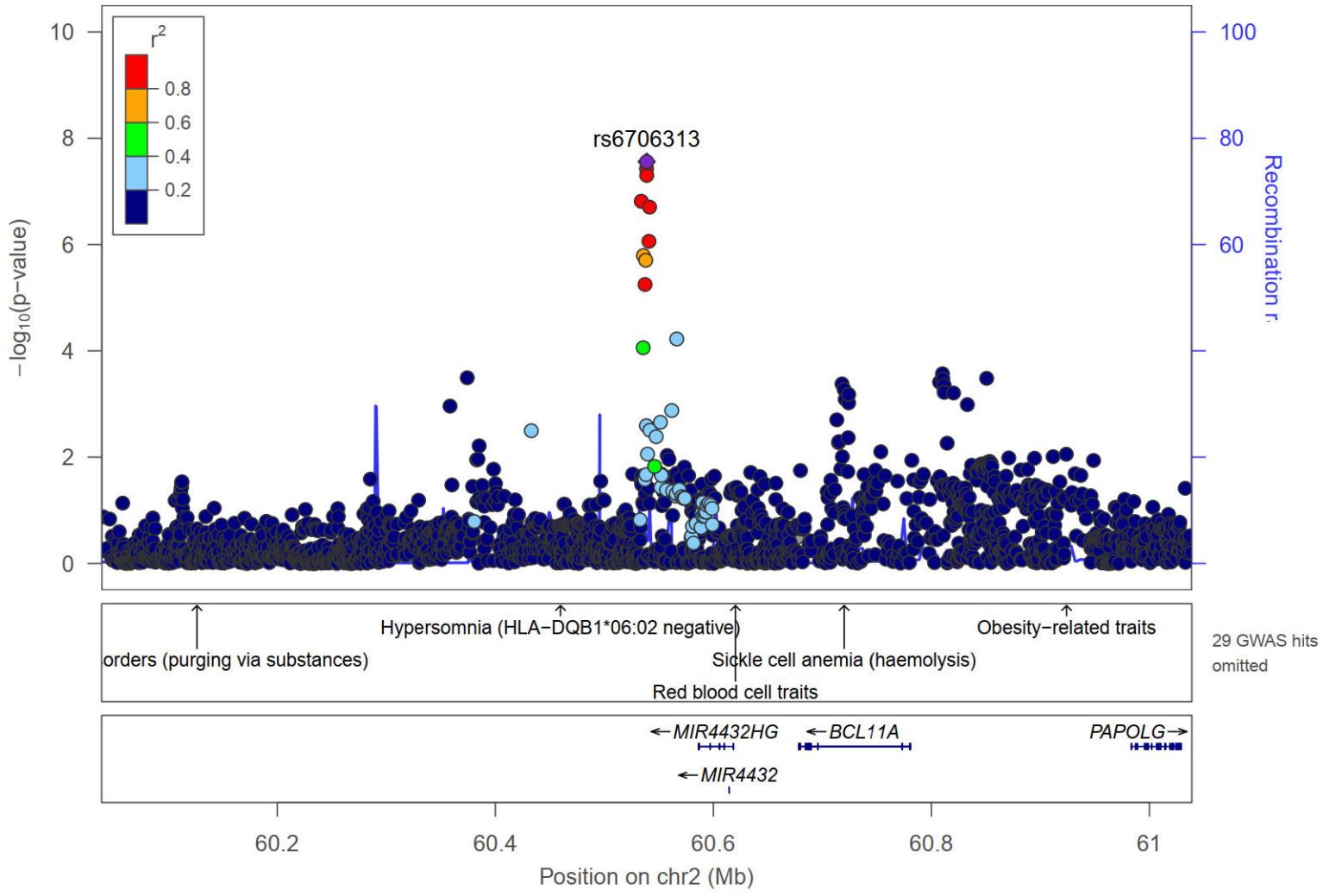

rs149131600
r2
0.8
0.6
0.4
0.2
−log10(p−value)
10
8
6
4
2
0
Serum albumin level
Bipolar disorder
Serum albumin level
←SCGB1B2P
←ZNF599
←LINC00904
SCN1B→
←LGI4
←FAM187B
CD22→
FFAR2→
←SCGB2B2
ZNF181→
LINC01838→
HPN→
FXYD1→
LSR→
FFAR1→
←KRTDAP
SCGB2B3P→
←LINC01801
ZNF30→
←HPN−AS1
USF2→
FFAR3→
←DMKN
ZNF302→
←ZNF30−AS1
FXYD3→
HAMP→
LINC01531→
←SBSN
←ZNF792
MIR6887→
MAG→
GAPDHS→
GRAMD1A→
FXYD7→
MIR5196→
TMEM147→
FXYD5→
GPR42→
←ATP4A
←TMEM147−AS1
35.2
35.4
35.6
35.8
36
Position on chr19 (Mb)

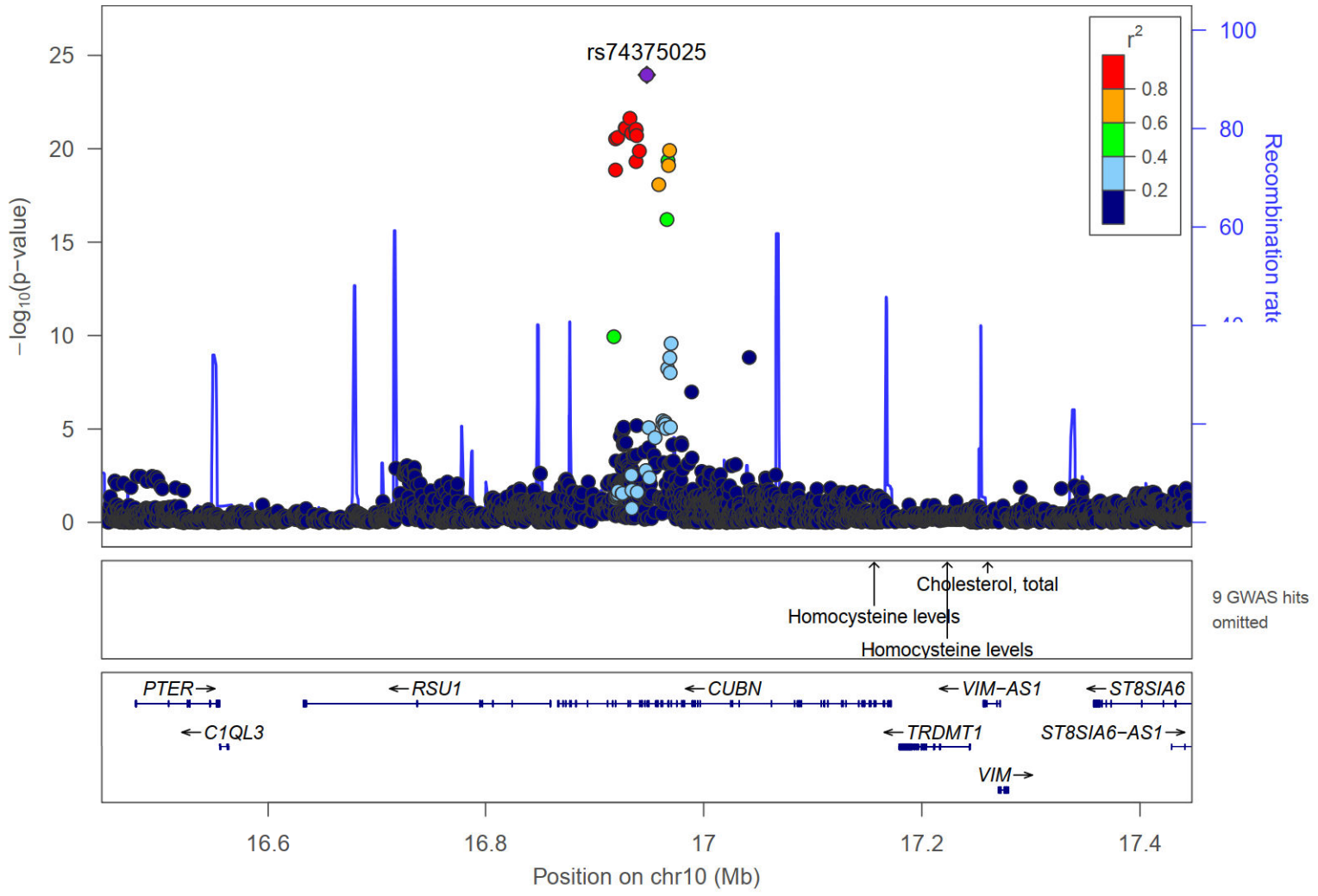

r2
0.8
0.6
0.4
0.2
rs17137004
−log10(p−value)
Recombinatic
IgG glycosylation
Crohn's disease
PPP1R3A
FOXP2
MIR3666
Position on chr7 (Mb)

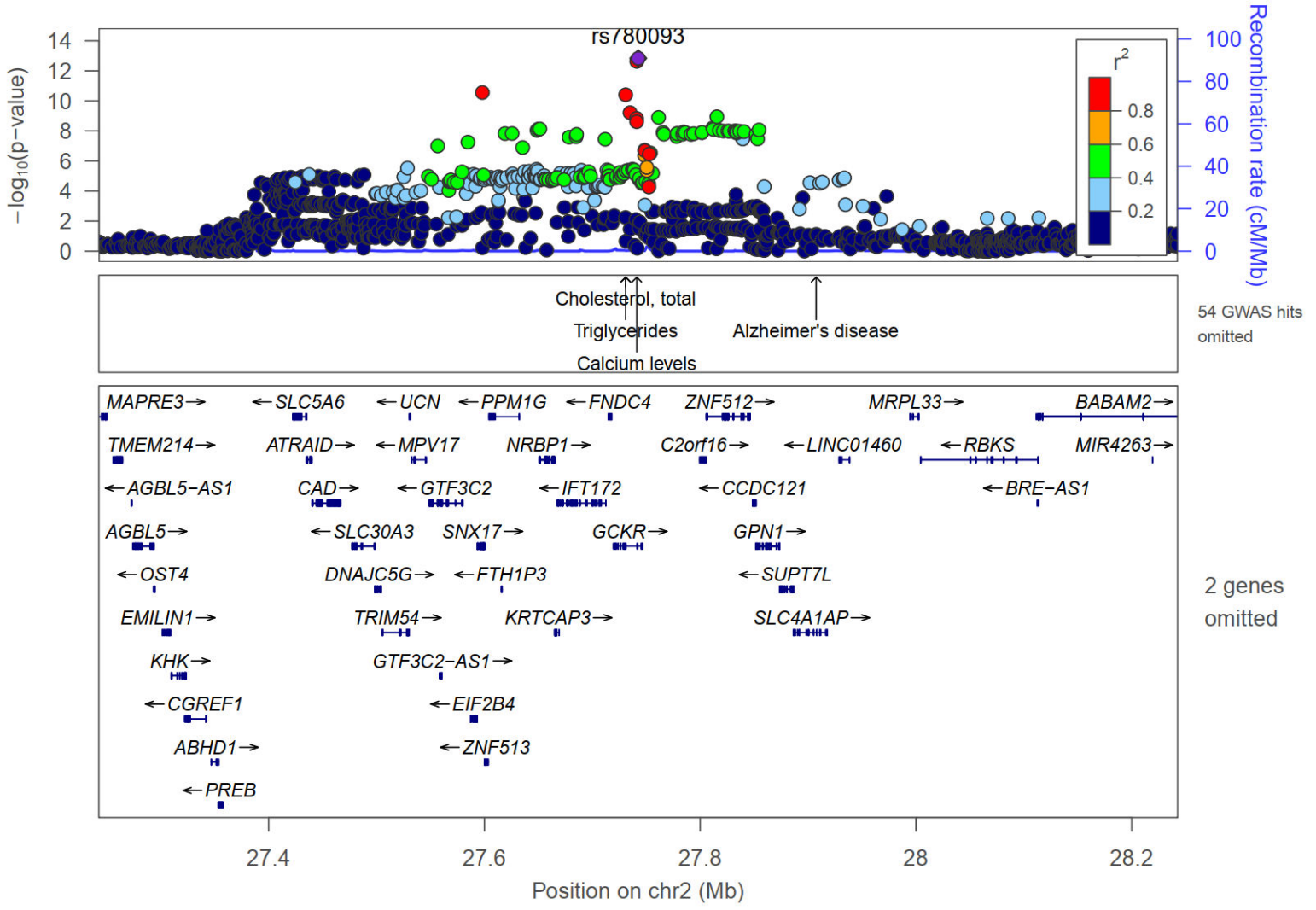

r²
0.8
0.6
0.4
0.2
rs4258701
−log10(p−value)
Recombination
10
8
6
4
2
0
100
80
60
Obesity−related traits
White matter integrity
vWF and FVIII levels
Obesity−related traits
Response to amphetamines
1 GWAS hit
omitted
CDH2
25
25.2
25.4
25.6
25.8
Position on chr18 (Mb)


rs59825600
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate
Migraine
Adverse response to chemotherapy (neutropenia/leucopenia) (paclitaxel + carbop
Chronic obstructive pulmonary disease−related biomarkers
KAZN
TMEM51
TMEM51−AS1
FHAD1
C1orf195
Position on chr1 (Mb)


rs6688849
r2
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM
10
8
6
4
2
0
100
80
60
40
Adverse response to chemotherapy (neutropenia/leucopenia) (etoposide)
Obesity−related traits
Obesity−related traits
White matter integrity
2 GWAS hits omitted
CYP4X1→
←TAL1
CMPK1→
←TRABD2B
CYP4Z1→
←STIL
←LINC01389
CYP4A22→
FOXE3→
LINC00853→
←FOXD2−AS1
←PDZK1IP1
FOXD2→
47.6
47.8
48
48.2
48.4
Position on chr1 (Mb)

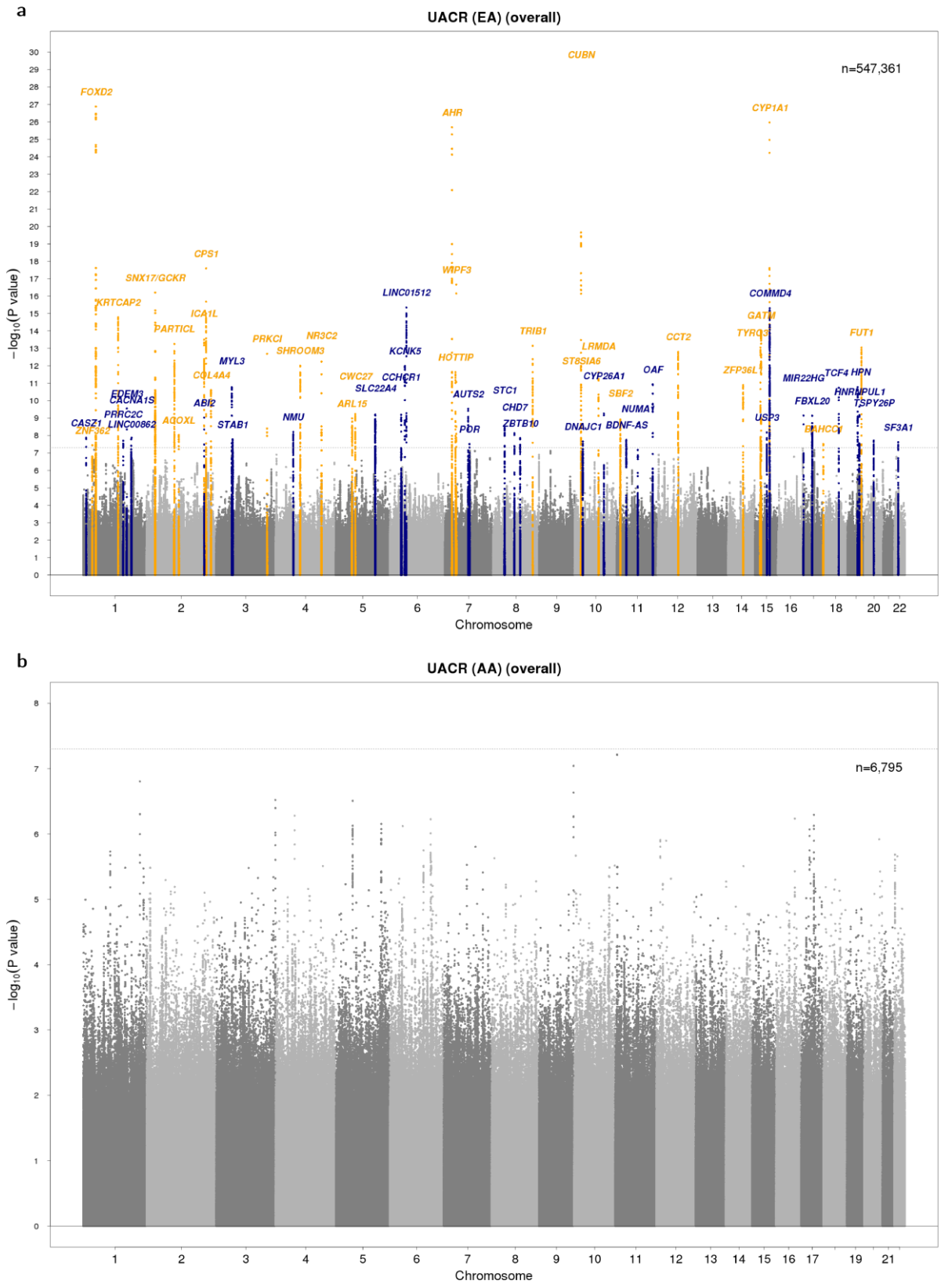

r2
0.8
0.6
0.4
0.2
rs6706313
−log10(p−value)
Recombination r
10
8
6
4
2
0
100
80
60
orders (purging via substances)
Hypersomnia (HLA−DQB1*06:02 negative)
Sickle cell anemia (haemolysis)
Obesity−related traits
Red blood cell traits
29 GWAS hits
omitted
MIR4432HG
BCL11A
PAPOLG
MIR4432
60.2
60.4
60.6
60.8
61
Position on chr2 (Mb)

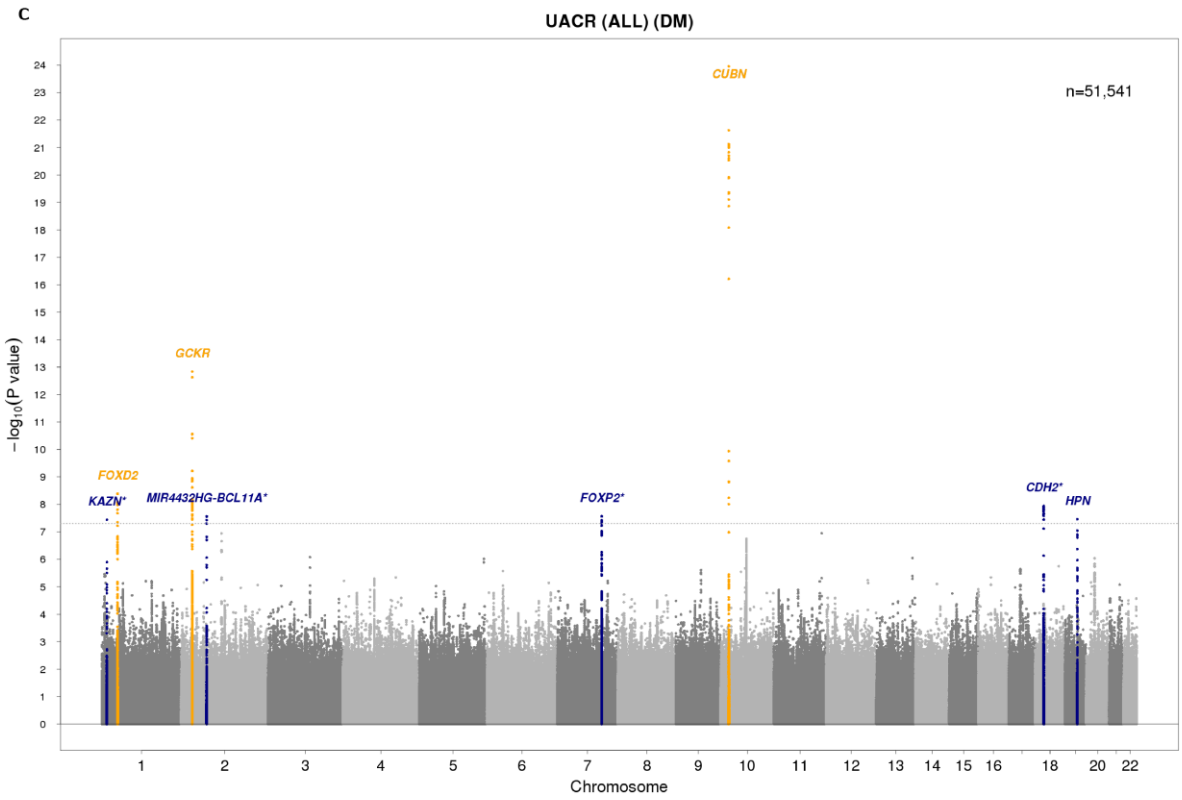

rs74375025
r²
0.8
0.6
0.4
0.2
100
80
60
Recombination rate
25
20
15
10
5
0
−log10(p−value)
Cholesterol, total
Homocysteine levels
Homocysteine levels
9 GWAS hits
omitted
PTER→
←RSU1
←CUBN
←VIM−AS1
←ST8SIA6
←C1QL3
←TRDMT1
ST8SIA6−AS1→
VIM→
16.6
16.8
17
17.2
17.4
Position on chr10 (Mb)


rs780093
−log10(p−value)
Recombination rate (cM/Mb)
r2
0.8
0.6
0.4
0.2
Cholesterol, total
Triglycerides
Calcium levels
Alzheimer's disease
54 GWAS hits omitted
MAPRE3→ ←SLC5A6 ←UCN ←PPM1G ←FNDC4 ZNF512→ MRPL33→ BABAM2→
TMEM214→ ATRAID→ ←MPV17 NRBP1→ C2orf16→ ←LINC01460 ←RBKS MIR4263→
←AGBL5-AS1 CAD→ ←GTF3C2 ←IFT172 ←CCDC121 ←BRE-AS1
AGBL5→ ←SLC30A3 SNX17→ GCKR→ GPN1→
←OST4 DNAJC5G→ ←FTH1P3 ←SUPT7L
EMILIN1→ TRIM54→ KRTCAP3→ SLC4A1AP→
KHK→ GTF3C2-AS1→
←CGREF1 ←EIF2B4
ABHD1→ ←ZNF513
←PREB
2 genes omitted
27.4
27.6
27.8
28
28.2
Position on chr2 (Mb)

Regional association plots are shown for all genome-wide significant index SNPs. The dots are plotted on the y-axis according to their meta-analysis association p-value, and colored according to their correlation r^2 with the index SNP estimated based on the 1000 Genomes EUR reference samples (gray for missing data). Plots were generated using the stand-alone version 1.3 of LocusZoom[2]. Genetic positions refer to GRCh37/hg19 coordinates.

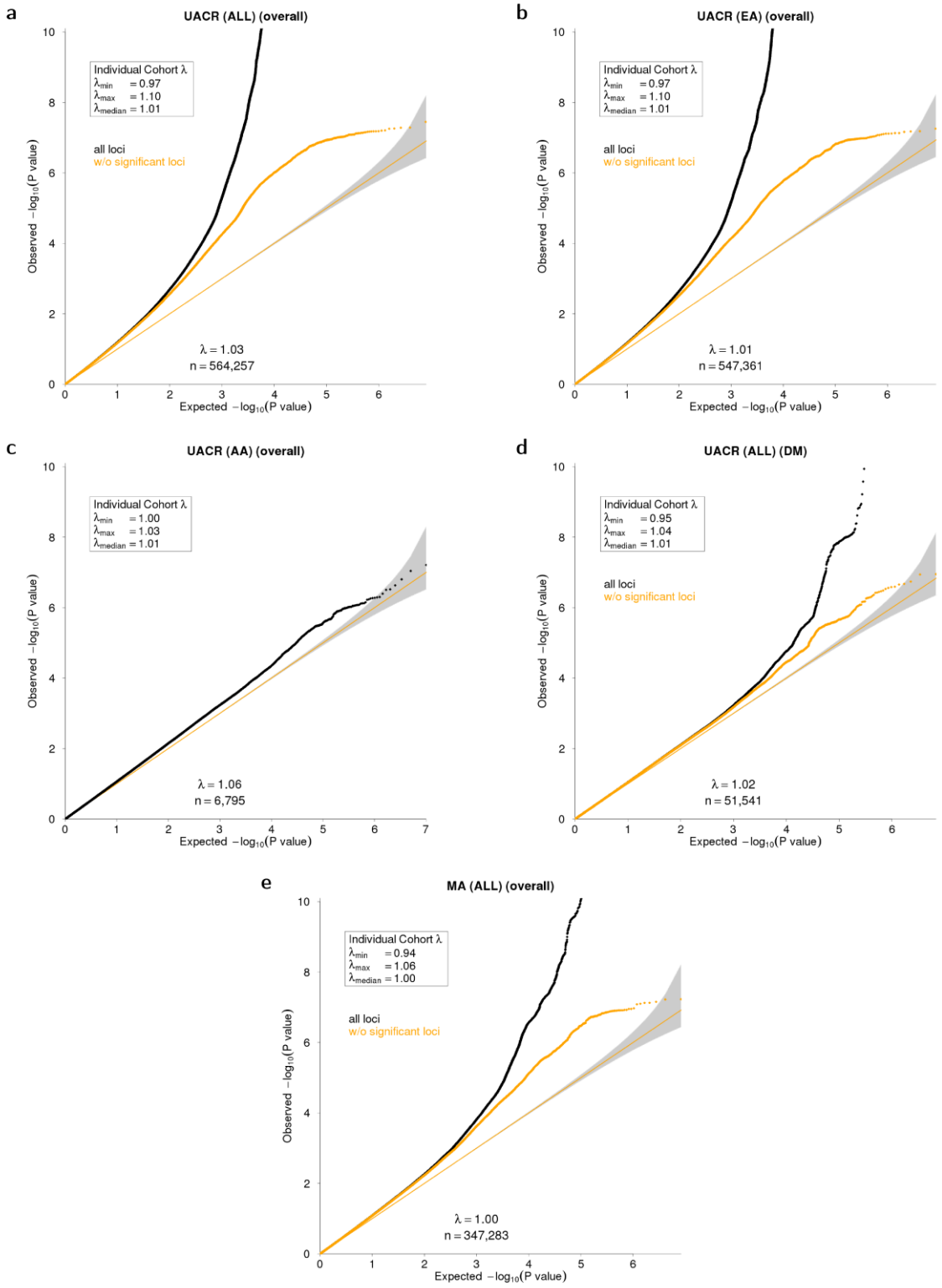
Supplementary Figure 5: Manhattan plots for all secondary GWAS meta-analyses





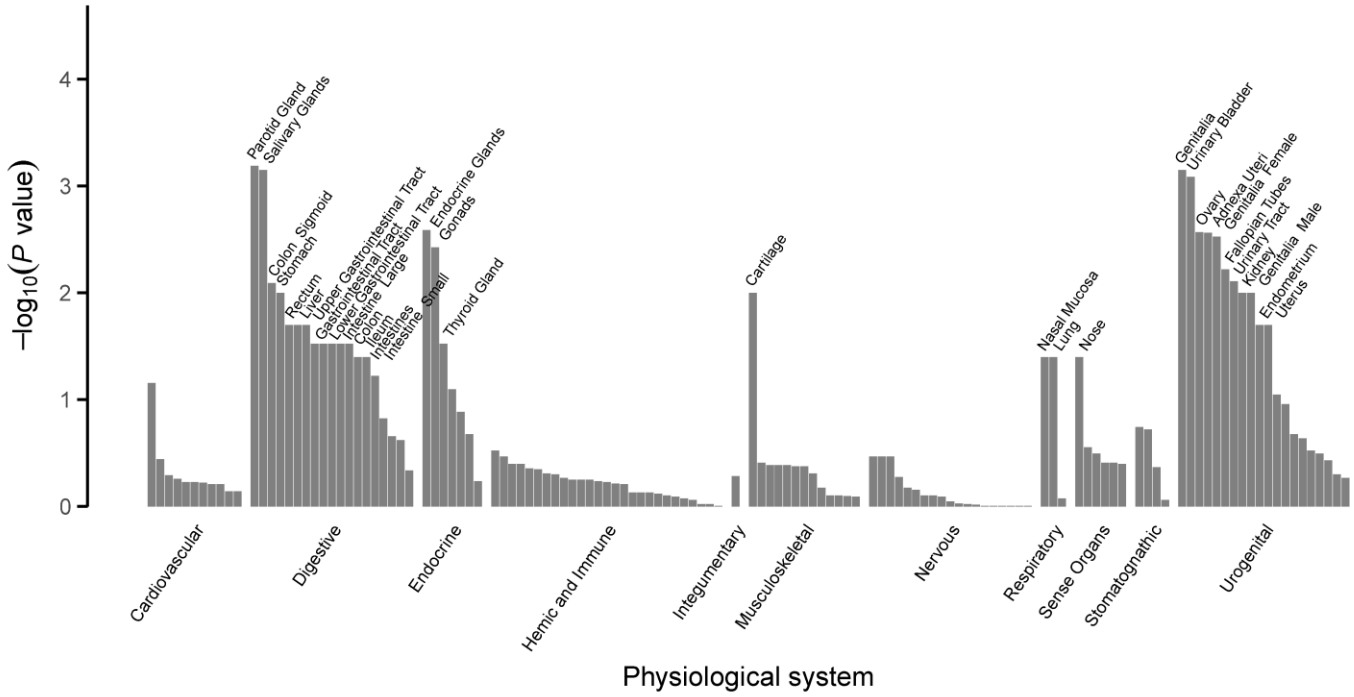
Manhattan plots of the GWAS meta-analysis results for UACR in individuals of European ancestry (a), in individuals of African ancestry (b), and among trans-ethnic individuals with diabetes (c). SNPs are plotted on the x-axis according to their position on each chromosome with the -$\log_{10}$(p-value) of the meta-analysis association test on the y-axis. The solid horizontal line indicates the threshold for genome-wide significance, $5x10^{-8}$. The labels show the closest gene. New loci are colored in blue, previously published UACR loci in orange. Genomic loci in panel (c) that are specific for individuals with diabetes are marked with an asterisk.

Supplementary Figure 6: QQ plots plots for all GWAS meta-analyses



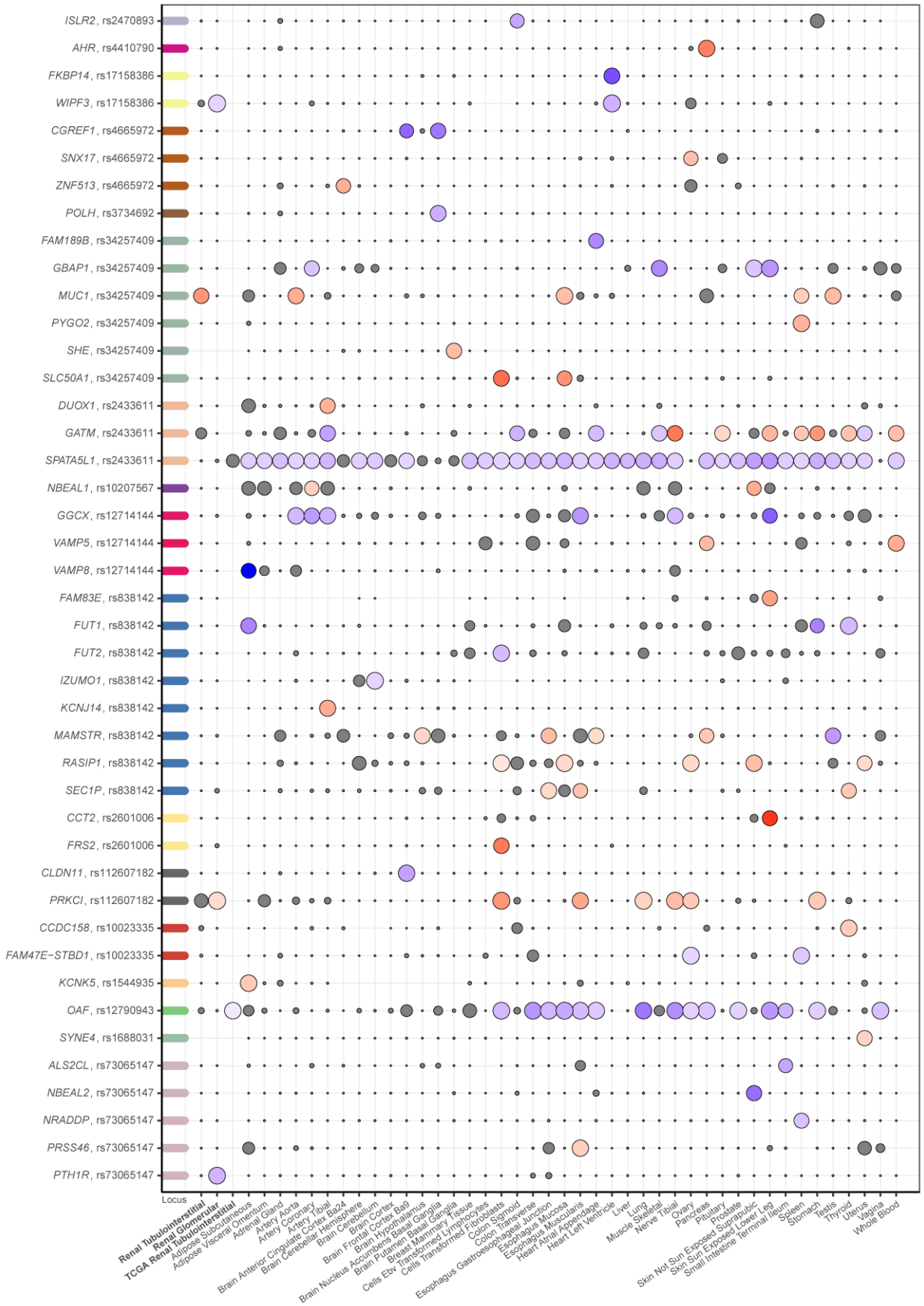
Quantile-quantile (QQ) plots of the GWAS meta-analysis results for UACR in the trans-ethnic sample (a), in individuals of European ancestry (b), in individuals of African ancestry (c), among trans-ethnic individuals with diabetes (d), and for trans-ethnic microalbuminuria meta-analysis (e). The observed p-values of the meta-analysis association test are plotted on the y-axis against their expected distribution under the null hypothesis of no association on the x-axis. Results for all SNPs are shown in black, and results after removal of loci (±500kb of index SNP) genome-wide significantly ($p<5x10^{-8}$) associated with the trait are shown in yellow (the African ancestry GWAS revealed no genome-wide significant associations). Gray bands represent 95% confidence intervals. λ: lambda, genomic control parameter; n: sample size.

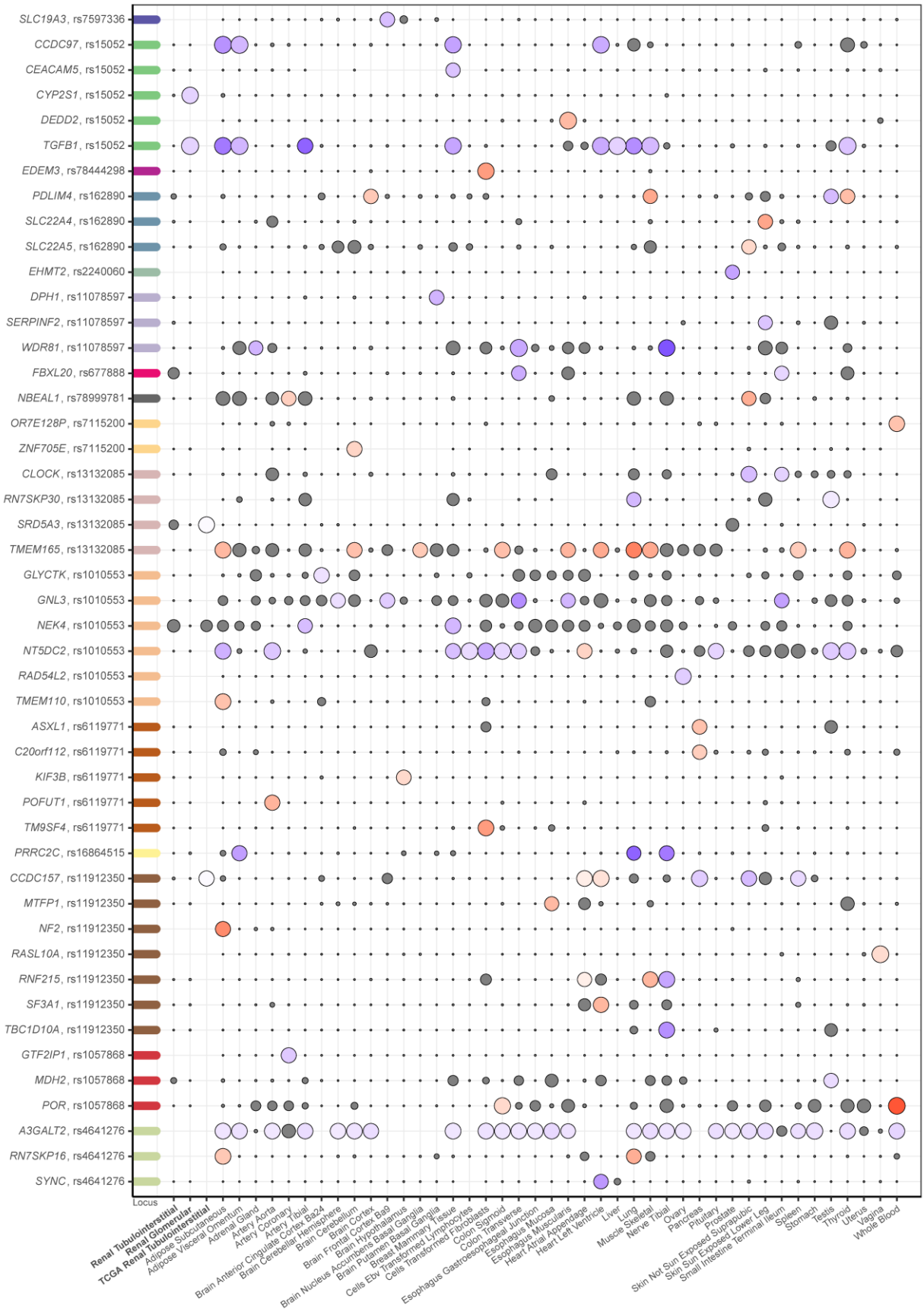
Supplementary Figure 7: Enrichment analysis results for physiological system where UACR-associated genes are highly expressed

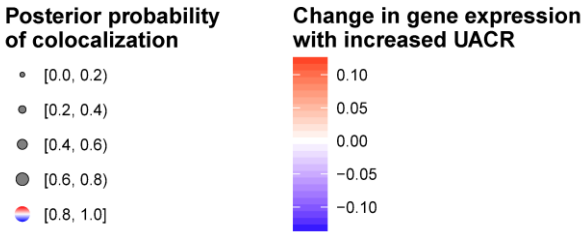


Results for enrichment of physiological systems based on the trans-ethnic UACR GWAS meta-analysis obtained by DEPICT software are shown. The x-axis is labeled by MeSH first level terms. Nominally significant associations ($p<0.05$) are labeled in the figure. The y-axis represents the $-\log_{10}$(p-value) of the enrichment test implemented in DEPICT.

Supplementary Figure 8: Co-localization of UACR-association signals with gene expression in *cis* across 47 human tissues

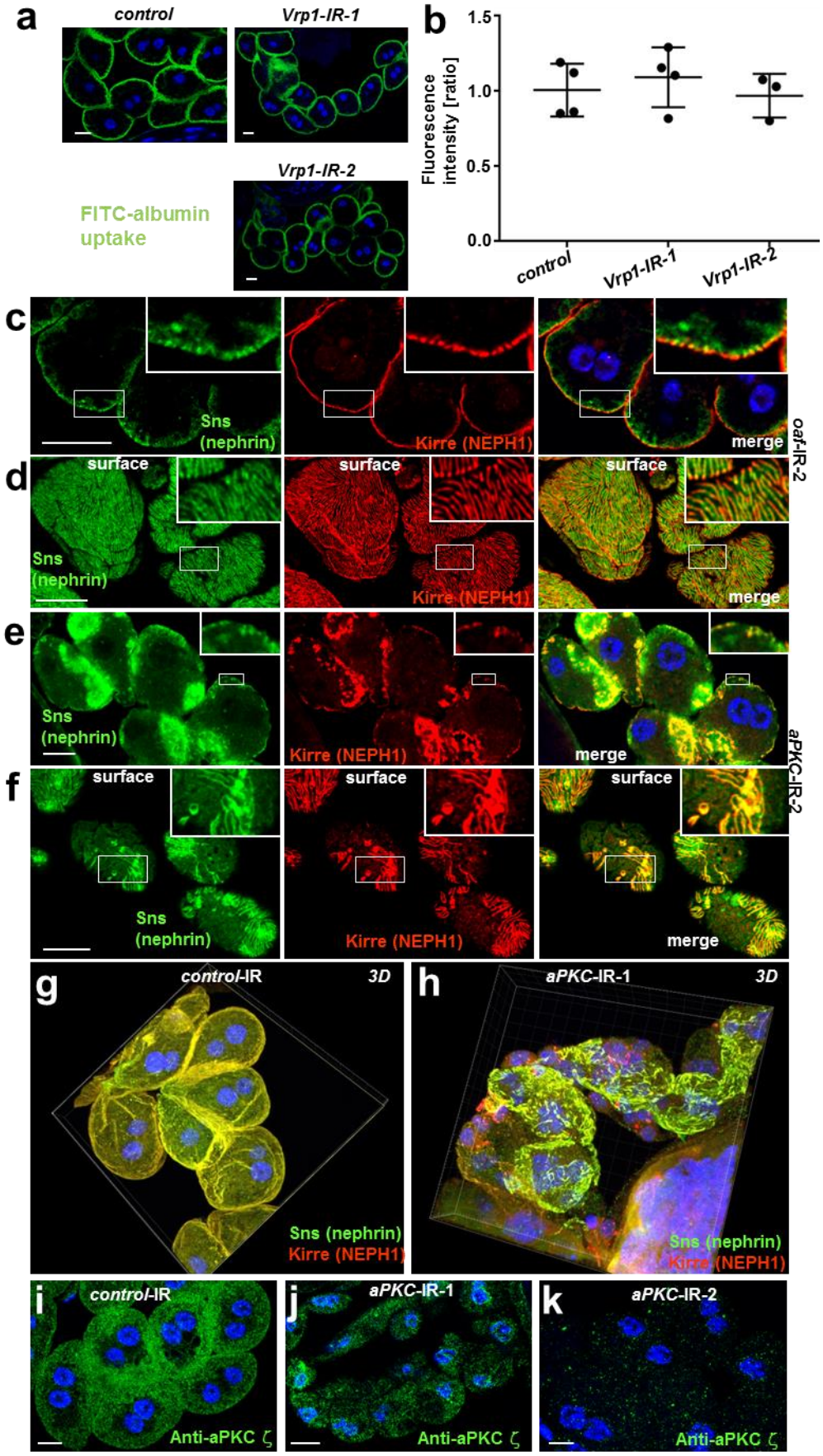



SLC19A3, rs7597336
CCDC97, rs15052
CEACAM5, rs15052
CYP2S1, rs15052
DEDD2, rs15052
TGFB1, rs15052
EDEM3, rs78444298
PDLIM4, rs162890
SLC22A4, rs162890
SLC22A5, rs162890
EHMT2, rs2240060
DPH1, rs11078597
SERPINF2, rs11078597
WDR81, rs11078597
FBXL20, rs677888
NBEAL1, rs78999781
OR7E128P, rs7115200
ZNF705E, rs7115200
CLOCK, rs13132085
RN7SKP30, rs13132085
SRD5A3, rs13132085
TMEM165, rs13132085
GLYCTK, rs1010553
GNL3, rs1010553
NEK4, rs1010553
NT5DC2, rs1010553
RAD54L2, rs1010553
TMEM110, rs1010553
ASXL1, rs6119771
C20orf112, rs6119771
KIF3B, rs6119771
POFUT1, rs6119771
TM9SF4, rs6119771
PRRC2C, rs16864515
CCDC157, rs11912350
MTFP1, rs11912350
NF2, rs11912350
RASL10A, rs11912350
RNF215, rs11912350
SF3A1, rs11912350
TBC1D10A, rs11912350
GTF2IP1, rs1057868
MDH2, rs1057868
POR, rs1057868
A3GALT2, rs4641276
RN7SKP16, rs4641276
SYNC, rs4641276
Locus
Renal Tubulointerstitial
Renal Glomerular
TCGA Renal Tubulointerstitial
Adipose Subcutaneous
Adipose Visceral Omentum
Adrenal Gland
Artery Aorta
Artery Coronary
Artery Tibial
Brain Anterior Cingulate Cortex BA24
Brain Cerebellar Hemisphere
Brain Cerebellum
Brain Cortex
Brain Frontal Cortex BA9
Brain Hypothalamus
Brain Nucleus Accumbens Basal Ganglia
Brain Putamen Basal Ganglia
Breast Mammary Tissue
Cells Ebv Transformed Lymphocytes
Cells Transformed Fibroblasts
Colon Sigmoid
Colon Transverse
Esophagus Gastroesophageal Junction
Esophagus Mucosa
Esophagus Muscularis
Heart Atrial Appendage
Heart Left Ventricle
Liver
Lung
Muscle Skeletal
Nerve Tibial
Ovary
Pancreas
Pituitary
Prostate
Skin Not Sun Exposed Suprapubic
Skin Sun Exposed Lower Leg
Small Intestine Terminal Ileum
Spleen
Stomach
Testis
Thyroid
Uterus
Vagina
Whole Blood



The plot shows genes whose expression levels in any tested tissues co-localized with the UACR association signal with a posterior probability of ≥80%. Genes and their respective index SNP are shown on the y-axis. Co-localization across tissues (x-axis) is illustrated as dots, where the size of the dots indicates the posterior probability of the co-localization. The change in UACR is color-coded relative to the change in gene expression, or gray in case of a posterior probability <0.80. Kidney tissues are labeled in bold.

Supplementary Figure 9: The *Drosophila OAF* and *PRKCI* are both required for nephrocyte function and PRKCI-RNAi affects slit diaphragm formation



(a) Garland cell nephrocytes were exposed to FITC-albumin. Nephrocytes expressing control-RNAi exhibit intense endocytosis of FITC-albumin. Expression of *Vrp1*-RNAi has no significant effect on FITC-albumin uptake. (b) Quantitation of fluorescence intensity from FITC-albumin uptake is shown for the indicated genotypes. Values are presented as mean±standard deviation of the ratio to a control experiment. Statistical significance was calculated using ANOVA and Dunnett's *post hoc* analysis. A statistically significant difference (defined as $p<0.05$) was not observed (N=4 for *Vrp1*-RNAi-1, N=3 for *Vrp1*-RNAi-2).
(c) Staining the slit diaphragm proteins Sns (ortholog of nephrin) and Kirre (ortholog of NEPH1) in nephrocytes expressing *oaf*-RNAi-2 shows regular formation of slit diaphragms on the entire nephrocyte surface. (d) Tangential sections through the surface of control nephrocytes reveals the regular fingerprint-like pattern of slit diaphragm proteins.
(e-f) Expression of *aPKC*-RNAi-2 results in an clustered and irregular pattern of slit diaphragm proteins (inset in e) and a complete loss of slit diaphragm protein from distinct areas on the cell surface (insets f).
3D reconstructions from sequential confocal sections of nephrocytes expressing (g) control-RNAi and (h) *aPKC*-RNAi are shown. The surface is completely covered but slit diaphragm protein in the control but upon silencing aPKC large gaps appear.
(i-k) Staining control garland cell nephrocytes using anti-aPKC ζ, an antibody that is known to detect Drosophila aPKC, reveals a punctate staining pattern that is concentrated at the periphery of the cell including the membrane (i). Expression of *aPKC*-RNAi-1 (j) and *aPKC*-RNAi-2 (k) results in a distinct reduction of the antibody signal from the cell surface and periphery. This indicates a successful knockdown of aPKC on the protein level. Images were recorded at identical settings of the confocal microscope.
All scale bars represent 10 μm.

Supplementary Table 1: Association results of the UACR genetic risk score quartiles with microalbuminuria in the UKBB

Quartile	Effect	SE	Odds ratio (95% CI)	P-value	N cases	N controls
I			reference		6,281	54,096
II	0.159	0.019	1.17 (1.13-1.22)	2.24E-17	7,001	51,618
III	0.282	0.018	1.33 (1.28-1.38)	7.45E-53	7,583	49,799
IV	0.527	0.018	1.69 (1.64-1.75)	3.04E-191	9,149	47,224

Supplementary Table 2: Association results of the genetic risk score (GRS) analyses of UACR and it's risk factors

Exposure	Outcome	N SNPs	Effect	SE	OR (95% CI)	P-value	N cases	N total	Interpretation of effect
UACR	CAD	57	0.003	0.085	1.00 (0.85-1.18)	0.975	60,801	184,305	change in log(OR) of CAD per SD unit increase of log(UACR)
UACR	HF	59	0.398	0.158	1.49 (1.09-2.03)	0.012	6,065	408,313	change in log(OR) of HF per SD unit increase of log(UACR)
UACR	HTN	59	0.386	0.041	1.47 (1.36-1.59)	**2.38E-21**	226,011	408,539	change in log(OR) of HTN per SD unit increase of log(UACR)
UACR	Stroke	57	0.145	0.074	1.16 (1.00-1.34)	0.049	67,162	521,612	change in log(OR) of Stroke per SD unit increase of log(UACR)
DBP	UACR	319	0.007	0.001	-	**1.23E-24**	-	757,601	change of SD unit of log(UACR) per mm Hg DBP increase
SBP	UACR	244	0.008	0.001	-	**3.52E-63**	-	757,601	change of SD unit of log(UACR) per mm Hg SBP increase
T2DM	UACR	138	0.018	0.003	-	**1.01E-10**	62,892	659,316	change of SD unit of log(UACR) per unit increase in T2DM GRS

N SNPs gives the number of SNPs included in the genetic risk score. Significant P-values are marked bold.
N cases: number of cases; N total: total sample size of the non-UACR trait; OR [95% CI]: Odds ratio with 95% confidence interval; SD: standard deviation

CAD: coronary artery disease[3]

HF: heart failure (assessed in the UK BioBank)

HTN: hypertention (assessed in the UK BioBank)

Stroke: any stroke[4]

DBP, SBP: diastolic and systolic blood pressure[5]

T2DM: type 2 diabetes[6]

Supplementary Table 3: Evidence for additional candidate causal genes at UACR-associated variants

Gene	SNP	credible set size	variant PP	functional consequence	CADD	DHS	Brief summary of literature and gene function
EDEM3	rs78444298	2	0.92	p.Pro746Ser (NP_079467.3)	24.6	-	The protein encoded by the ER Degradation Enhancing Alpha-Mannosidase Like Protein 3 (EDEM3) gene belongs to a group of proteins that accelerate degradation of misfolded glycoproteins in the ER. It catalyzes mannose trimming of N-glycans. This variant has been reported in an exome chip study of eGFR (PMID: 27920155).
CUBN	rs45551835	1	1.00	p.Ala2914Val (NP_001072.2)	34.0	-	The cubilin gene (*CUBN*) has been reported in the first GWAS of UACR (PMID: 21355061) and has been replicated many times since. The encoded cubilin protein is important for reabsorption of filtered albumin in the proximal tubule. *CUBN* KO mice lose albumin in the urine (PMID: 21926402). Rare mutations cause aut-rec megaloblastic anemia-1, Finnish type (#261100). Patients show low-molecular weight proteinuria (PMID: 11717447).
CPS1	rs1047891	15	0.96	p.Thr1412Asn (NP_001116105.1)	22.1	-	Carbamoyl-Phosphate Synthase 1 (*CPS1*) encodes a key enzyme of the urea cycle that is important to remove excess urea. Rare mutations cause aut-rec carbamoylphosphate synthetase I deficiency (#237300). GWAS locus for eGFR (PMID: 20383146) and many other quantitative biomarkers. This variant has been reported to associate with hyperammonemia after valproate therapy (PMID: 23997965).
GCKR	rs1260326	5	0.09	p.Leu446Pro (NP_001477.2)	0.1	1*	The Glucokinase Regulator (*GCKR*) gene encodes a regulatory protein inhibiting glucokinase in pancreatic islet cells and liver. Has been identified in previous GWAS of serum albumin (PMID: 23022100), glycated albumin (PMID: 29844224) and multiple other cardiometabolic traits including diabetes.

This table includes all genes supported by missense variants with high posterior probability (>0.5) of association, or missense variants mapping into small credible sets of size ≤5.
1*: ENCODE kidney

Supplementary Table 4: Results of the trans-eQTL analysis

SNP meta-analysis	SNP Chr:Position (b37)	SNP p-value meta-analysis	Max. Posterior Probability meta-analysis	LD between SNP and eQTL-SNP (r^2)	eQTL-SNP	eQTL-SNP Chr:Position (b37)	eQTL-Gene	Chr eQTL Gene	Tissue source of eQTL study	p-value eQTL	inter-chromo-somal trans-eQTL
rs12714144	2:85754578	5.5E-14	0.194	0.97	chr2:85753464:D	2:85753464	*DPEP3*	16	*1	1.29E-14	yes
rs12714144	2:85754578	5.5E-14	0.194	0.97	2:85753464:TTTG_	2:85753464	*DPEP3*	16	*2	5.51E-11	yes
rs2240060	6:31114900	6.4E-10	0.183	1	rs115017941	6:31115604	*BTN3A2*	6	*1	3.08E-08	no
rs2240060	6:31114900	6.4E-10	0.183	1	6:31108485	6:31108485	*BTN3A2*	6	*2	2.70E-11	no
rs2240060	6:31114900	6.4E-10	0.183	1	rs115017941	6:31115604	*HLA-DRB1*	6	*1	3.21E-126	no
rs2240060	6:31114900	6.4E-10	0.183	1	6:31108485	6:31108485	*HLA-DRB1*	6	*2	1.82E-63	no

*1: PBMC and Whole Blood, LIFE A1&B3 study[7–9]

*2: Whole Blood, Framingham Heart Study[10]

Supplementary Table 5: Co-localization results of UACR association signals with those from associations with plasma protein levels

UACR SNP	UACR SNP chr	UACR SNP position	protein name	protein SNP	protein SNP chr	protein SNP position	protein SNP type	LD (r^2)	No. SNPs	PP H4 abf
rs12790943	11	120058623	OAF.6414.8.3	rs508205	11	120057343	conditional_hit	0.90	1526	0.99
rs1010553	3	52540773	AP4M1.10076.1.3	rs12493107	3	52706724	top_sentinel	0.50	1163	0.68
rs162890	5	131623658	C1QTNF5.7810.20.3	rs11955347	5	131567924	top_sentinel	0.41	1398	0.62
rs838142	19	49252151	CCL25.14068.29.3	rs35106244	19	49203829	top_sentinel	0.22	1492	0.55
rs838142	19	49252151	ALPI.10463.23.3	rs679574	19	49206108	top_sentinel	0.23	1492	0.53
rs12790943	11	120058623	OAF.6414.8.3	rs117554512	11	120098329	top_sentinel	0.00	1527	0.42
rs838142	19	49252151	FUT3.4548.4.2	rs679574	19	49206108	top_sentinel	0.23	1492	0.35
rs838142	19	49252151	FGF19.2762.30.2	rs601338	19	49206674	top_sentinel	0.24	1492	0.31
rs838142	19	49252151	GOLM1.8983.7.3	rs601338	19	49206674	top_sentinel	0.24	1492	0.27
rs838142	19	49252151	FAM177A1.8039.41.3	rs679574	19	49206108	top_sentinel	0.23	1492	0.26
rs838142	19	49252151	CCL15.14109.15.3	rs681343	19	49206462	top_sentinel	0.24	1492	0.25
rs838142	19	49252151	FAM3D.13102.1.3	rs601338	19	49206674	top_sentinel	0.24	1492	0.22
rs6119771	20	30770375	POFUT1.5634.39.3	rs35968884	20	30818823	conditional_hit	0.00	814	0.06
rs2240060	6	31114900	CREB3L4.11308.8.3	rs41558819	6	31324166	conditional_hit	0.00	6890	0.016
rs2240060	6	31114900	LRPAP1.3640.14.3	rs28572463	6	31209854	conditional_hit	0.01	6890	0.002
rs56043834	19	41331149	MIA.2687.2.1	rs2604877	19	41275048	top_sentinel	0.01	1672	0.0005
rs1010553	3	52540773	SEMA3G.5628.21.3	rs13091025	3	52467324	conditional_hit	0.11	1162	0.0003
rs35572189	17	79419025	ENTHD2.7947.19.3	rs61745945	17	79205421	top_sentinel	0.00	1858	0.0003
rs2240060	6	31114900	LRPAP1.8829.4.3	6:31149622	6	31149622	conditional_hit	0.01	6890	0.0002
rs56043834	19	41331149	MIA.2687.2.1	rs34532358	19	41288723	conditional_hit	0.08	1660	7.0E-05
rs2240060	6	31114900	GNLY.3195.50.2	rs558163186	6	31253305	top_sentinel	0.06	6891	2.1E-05
rs6119771	20	30770375	POFUT1.5634.39.3	rs76143353	20	30815755	top_sentinel	0.04	815	2.0E-05
rs15052	19	41813375	B3GNT8.9297.12.3	rs557663478	19	41933790	top_sentinel	0.00	1303	1.7E-05
rs12714144	2	85754578	GNLY.3195.50.2	rs10169536	2	85912860	conditional_hit	0.02	1503	1.6E-05
rs15052	19	41813375	B3GNT2.7980.72.3	rs67047091	19	41938684	top_sentinel	0.00	1303	1.5E-05
rs2240060	6	31114900	GZMA.3440.7.2	rs10569394	6	31240246	top_sentinel	0.06	6891	1.4E-05
rs7115200	11	71752160	STAB1.14599.18.3	rs139130389	11	71850156	top_sentinel	0.00	1417	1.4E-05
rs1010553	3	52540773	SEMA3G.5628.21.3	rs2016575	3	52477080	top_sentinel	0.06	1163	1.3E-05
rs7115200	11	71752160	CST8.10572.65.3	rs139130389	11	71850156	top_sentinel	0.00	1417	1.2E-05
rs2240060	6	31114900	LRPAP1.3640.14.3	rs41552714	6	31324756	top_sentinel	0.01	6891	2.1E-06
rs2240060	6	31114900	LRPAP1.8829.4.3	rs41552714	6	31324756	top_sentinel	0.01	6891	2.1E-06
rs2240060	6	31114900	CREB3L4.11308.8.3	rs9295987	6	31349844	top_sentinel	0.02	6891	1.6E-06
rs2240060	6	31114900	LILRB1.5090.49.2	rs141232332	6	31075601	top_sentinel	0.14	6891	1.5E-06
rs12790943	11	120058623	IL25.4137.57.2	rs2508490	11	120099679	top_sentinel	0.01	1527	4.1E-08
rs12714144	2	85754578	GNLY.3195.50.2	rs17430897	2	85912962	conditional_hit	0.01	1504	2.6E-10
rs12714144	2	85754578	GNLY.3195.50.2	rs12151621	2	85934499	top_sentinel	0.00	1505	1.3E-10
rs3734692	6	43817791	VEGFA.14032.2.3	rs6921438	6	43925607	top_sentinel	0.00	1507	1.2E-12
rs3734692	6	43817791	VEGFA.2597.8.3	rs6921438	6	43925607	top_sentinel	0.00	1507	1.2E-12

PP: posterior probability; LD: linkage disequilibrium; PP H4 abf: posterior probability of the H4 test (one common causal variant of trait and pQTL association)

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