

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

Teumer *et al.*

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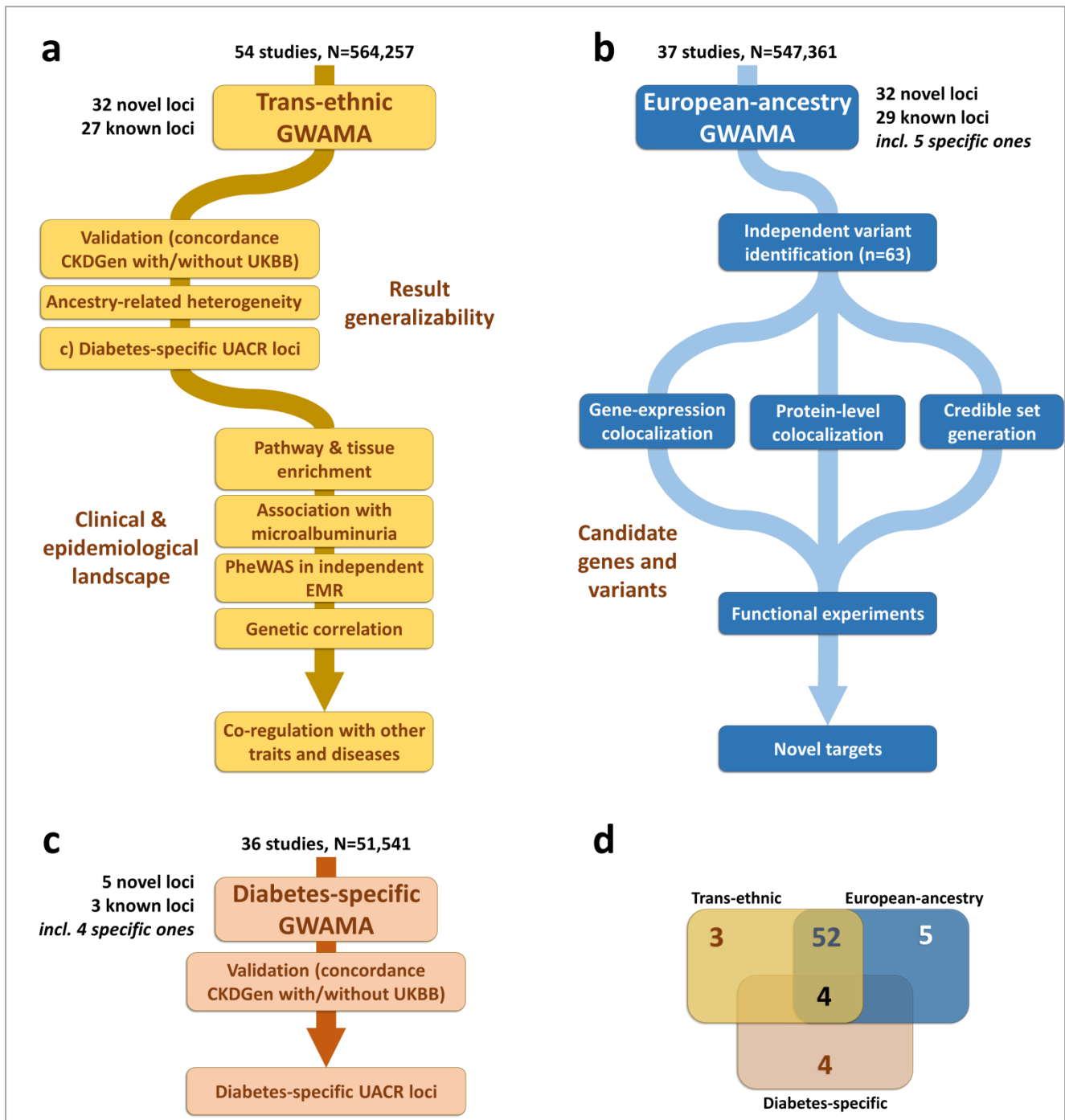
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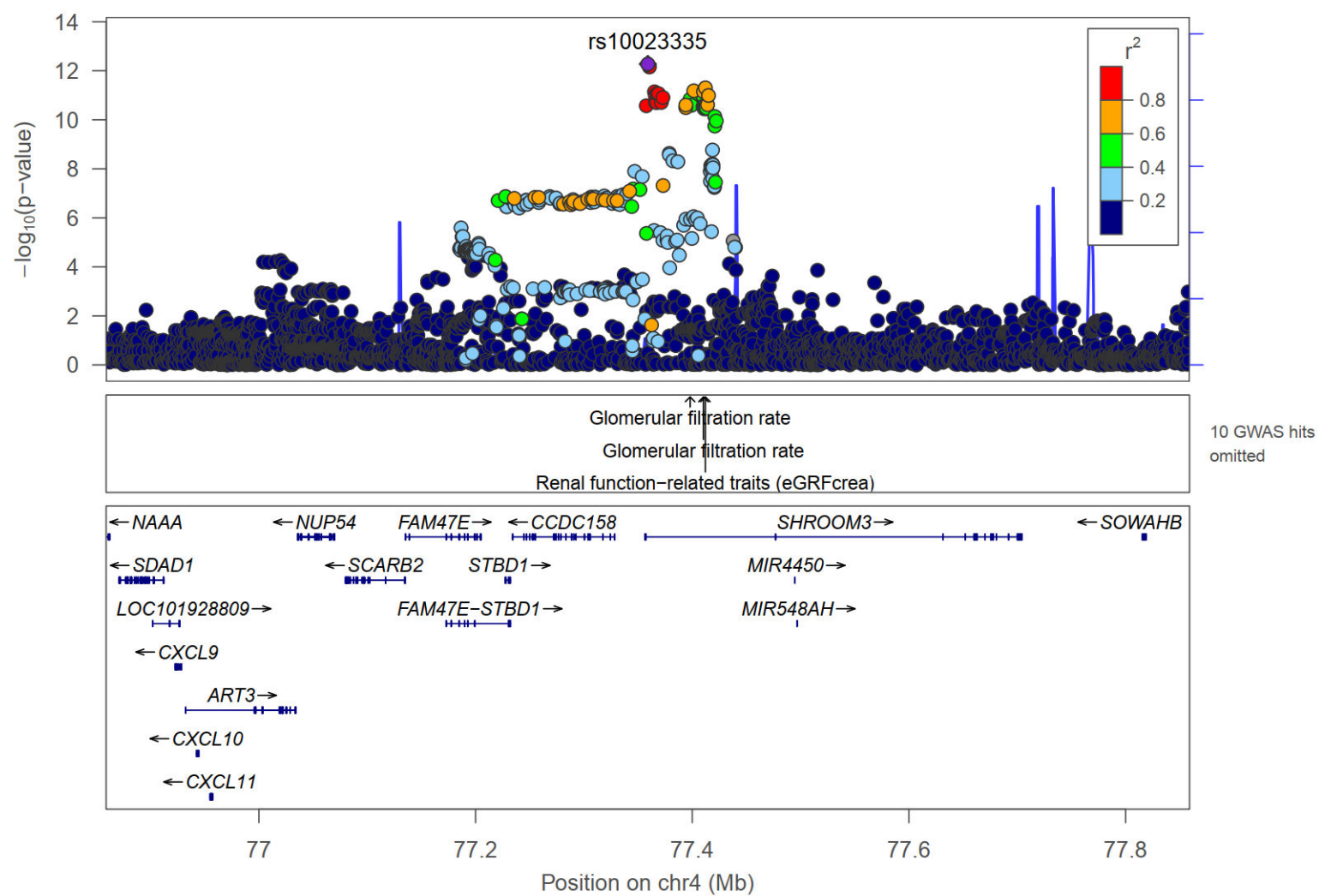
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 238 Psychiatric Genetics Unit, Group of Psychiatry, Mental Health and Addictions, Vall d'Hebron Research Institute (VHIR), Universitat Autònoma de Barcelona, Biomedical Network Research Centre on Mental Health (CIBERSAM), Barcelona, Spain
 239 Department of Neurology, IMIM-Hospital del Mar, and Universitat Autònoma de Barcelona, Spain
 240 IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain
 241 National Institute for Health Research Comprehensive Biomedical Research Centre, Guy's & St. Thomas' NHS Foundation Trust and King's College London, London, UK
 242 Division of Health and Social Care Research, King's College London, London, UK
 243 FIMM-Institute for Molecular Medicine Finland, Helsinki, Finland
 244 THL-National Institute for Health and Welfare, Helsinki, Finland
 245 Iwate Tohoku Medical Megabank Organization, Iwate Medical University, Iwate, Japan
 246 BHF Glasgow Cardiovascular Research Centre, Faculty of Medicine, Glasgow, UK
 247 deCODE Genetics/Amgen, Inc., Reykjavik, Iceland
 248 Icelandic Heart Association, Reykjavik, Iceland
 249 Institute of Biomedicine, the Sahlgrenska Academy at University of Gothenburg, Goteborg, Sweden
 250 Department of Epidemiology, University of Maryland School of Medicine, Baltimore, MD, USA
 251 Institute of Cardiovascular and Medical Sciences, Faculty of Medicine, University of Glasgow, Glasgow, UK
 252 Chair of Genetic Epidemiology, IBE, Faculty of Medicine, LMU Munich, Germany
 253 Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, Nagoya, Japan
 254 Department of Epidemiology, Nagoya University Graduate School of Medicine, Nagoya, Japan
 255 University Medicine Greifswald, Institute for Community Medicine, SHIP-KEF, Greifswald, Germany
 256 Department of Neurology, Caen University Hospital, Caen, France
 257 University of Caen Normandy, Caen, France
 258 Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, Netherlands
 259 Landspítali University Hospital, Reykjavik, Iceland
 260 Survey Research Center, University of Michigan, Ann Arbor, MI, USA
 261 University of Virginia Department of Neurology, Charlottesville, VA, USA

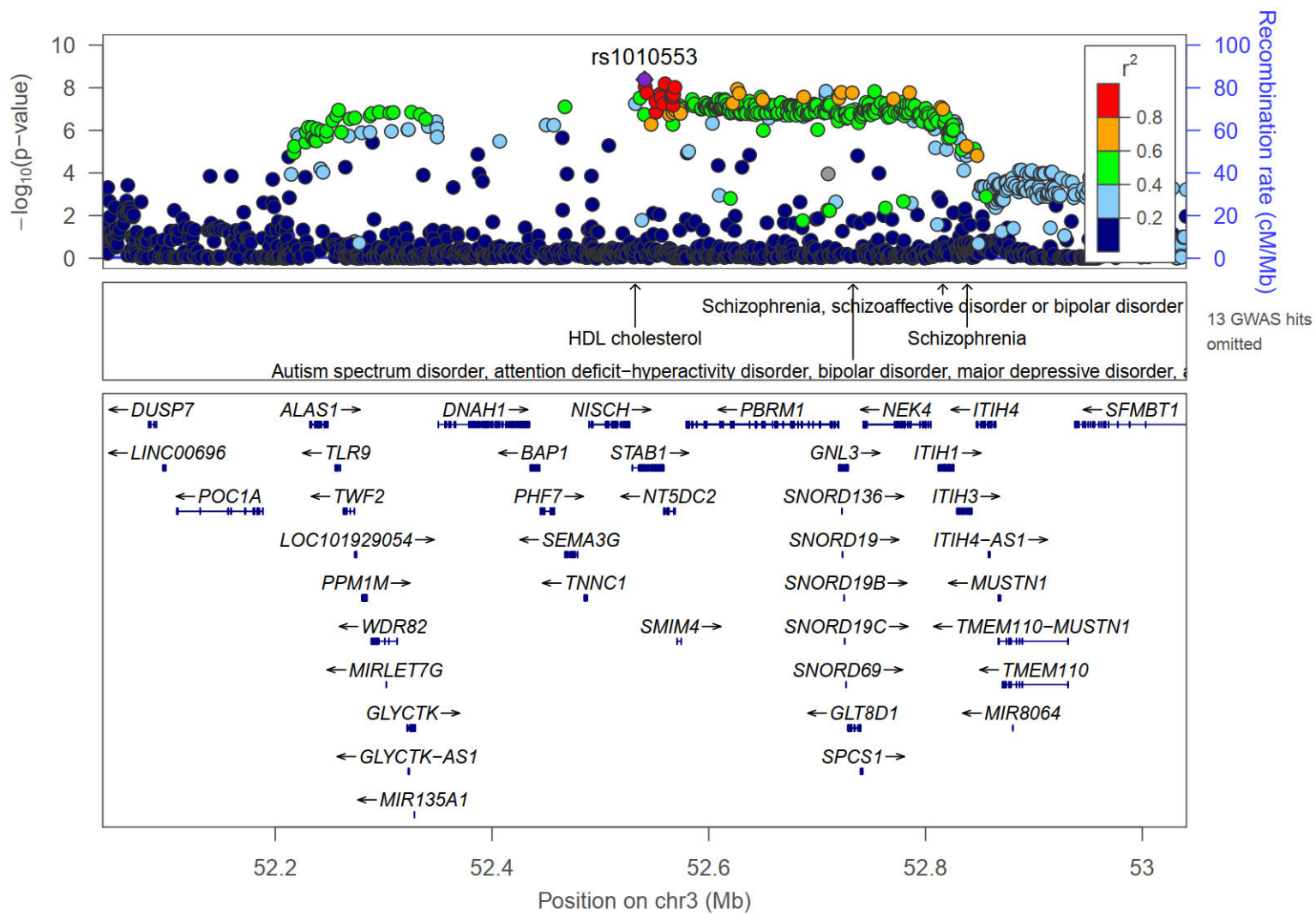
Supplementary Figure 1: Workflow of the project

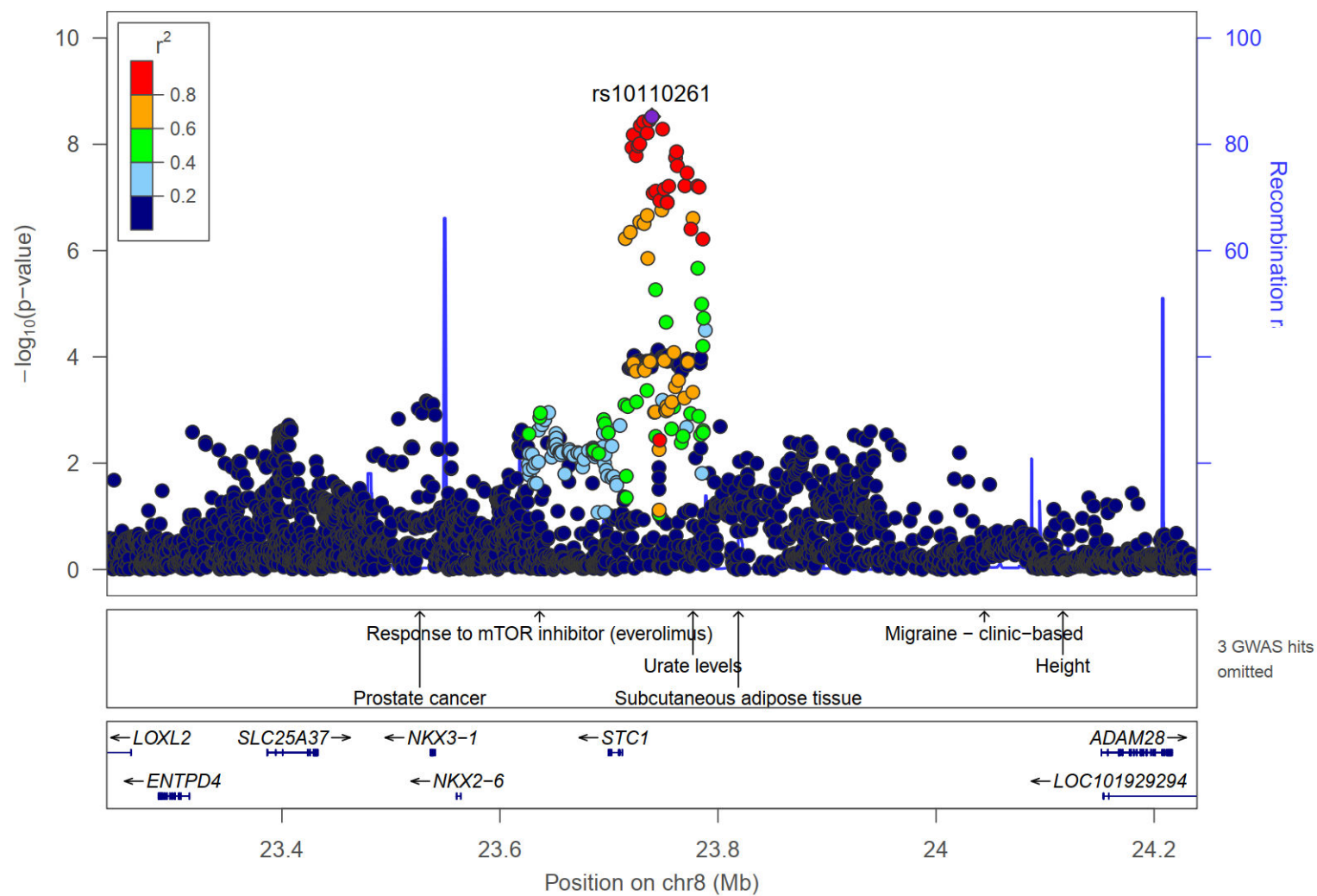


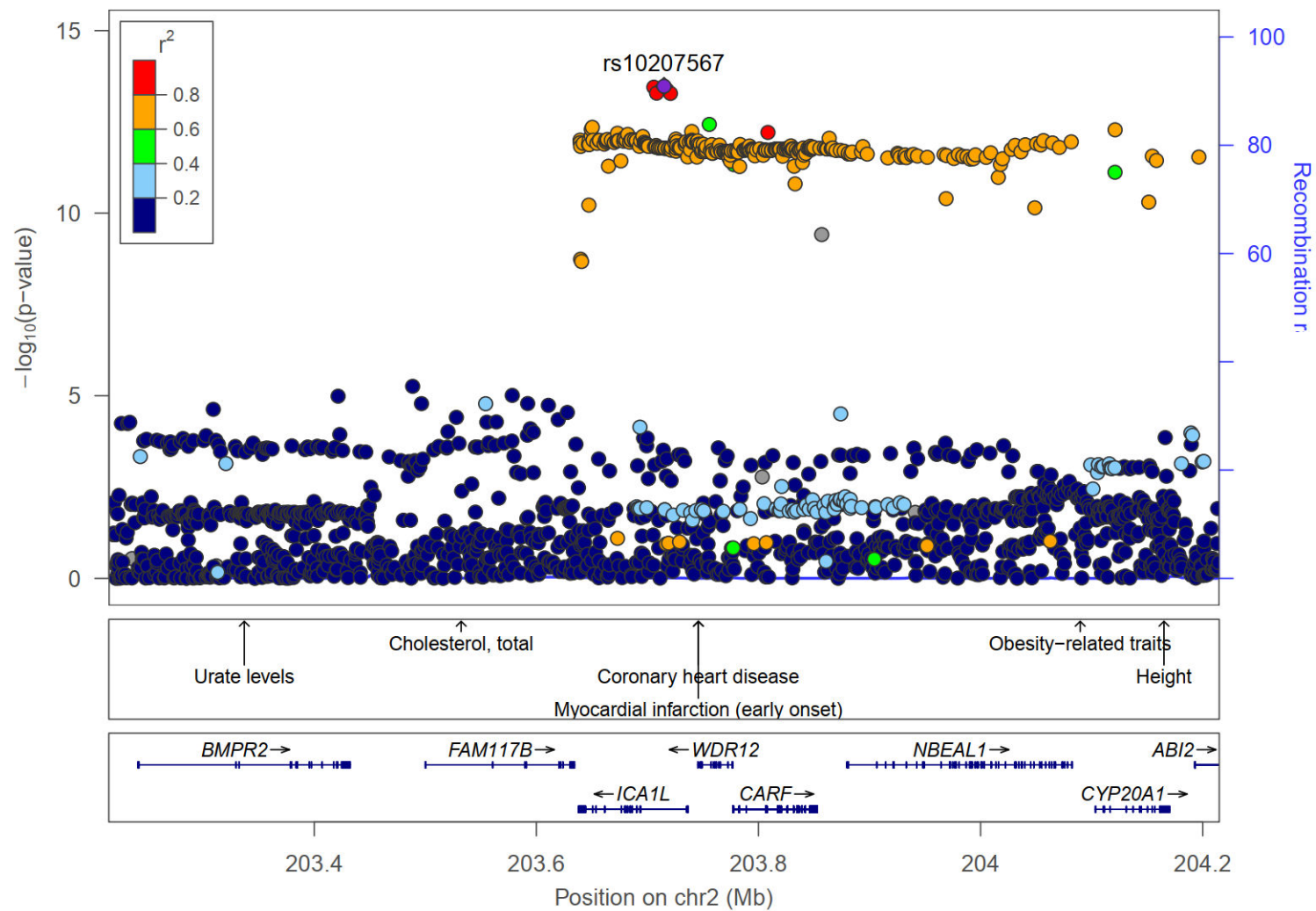
Overview of the analysis workflow for trans-ethnic (a), European ancestry-specific (b), and diabetes-specific (c) genome-wide association meta-analyses (GWAMA). The Venn diagram in panel (d) shows the number of overlapping loci between the different GWAMA.

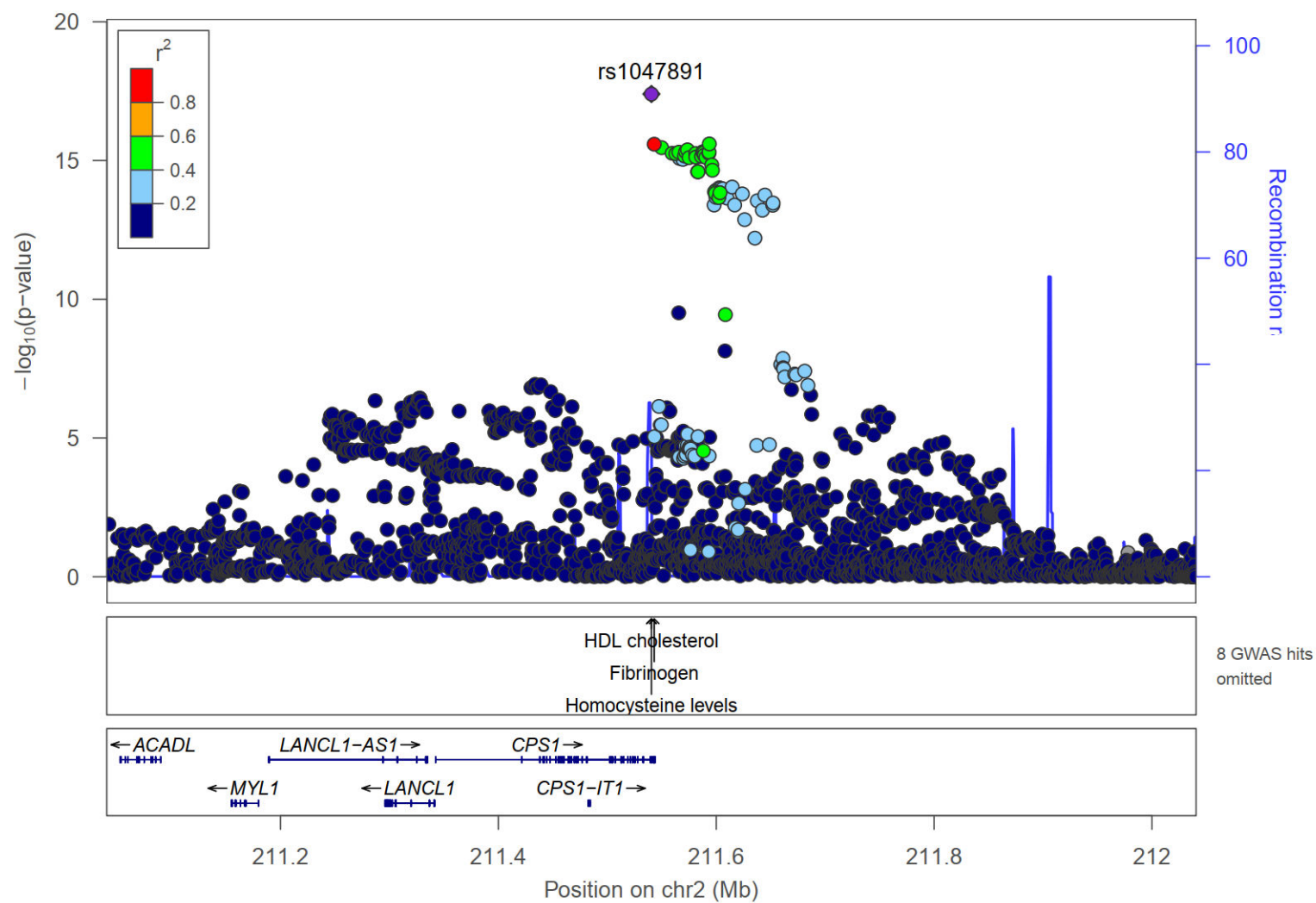
Supplementary Figure 2: Regional association plots for loci identified in trans-ethnic GWAS meta-analysis of UACR

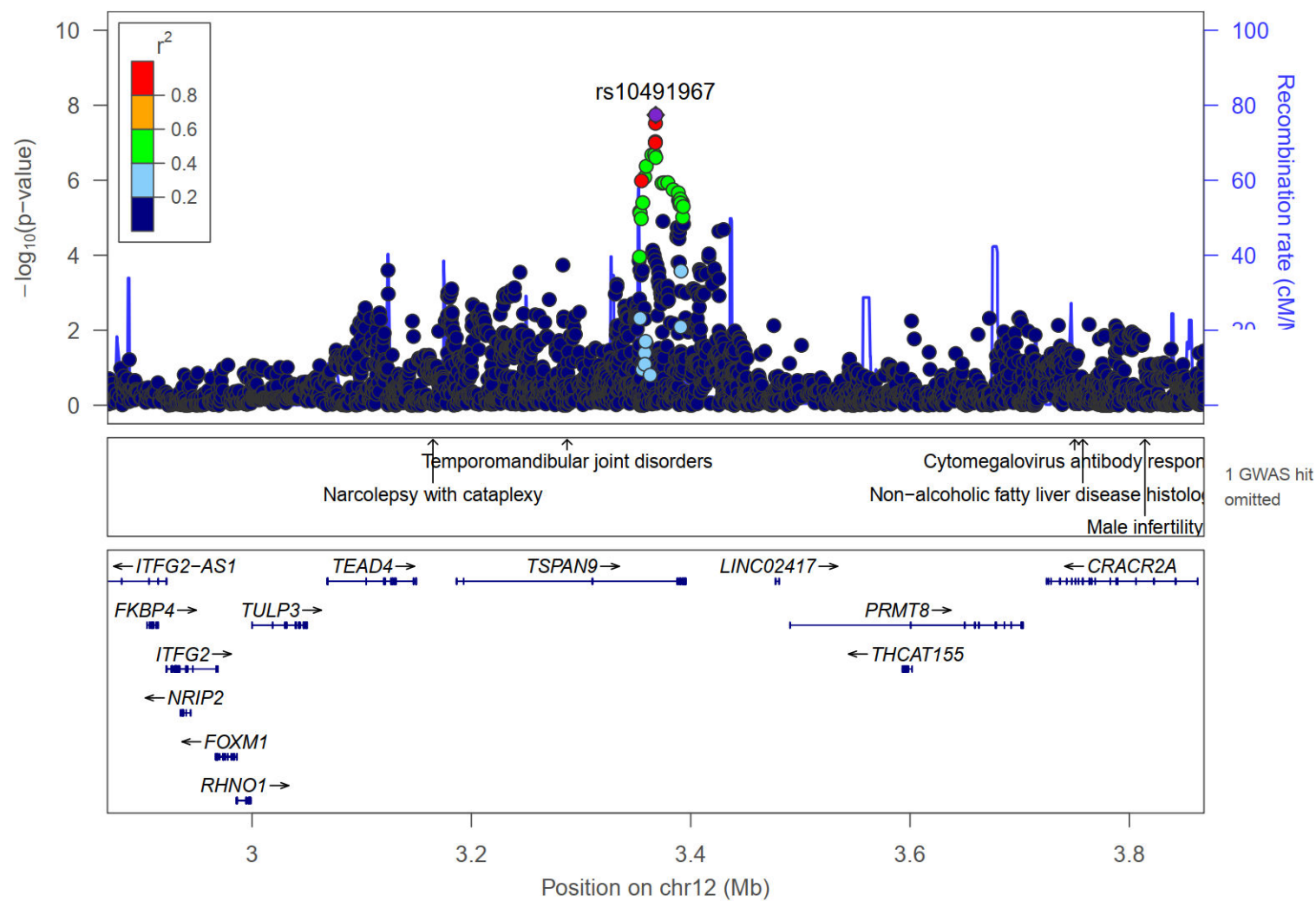


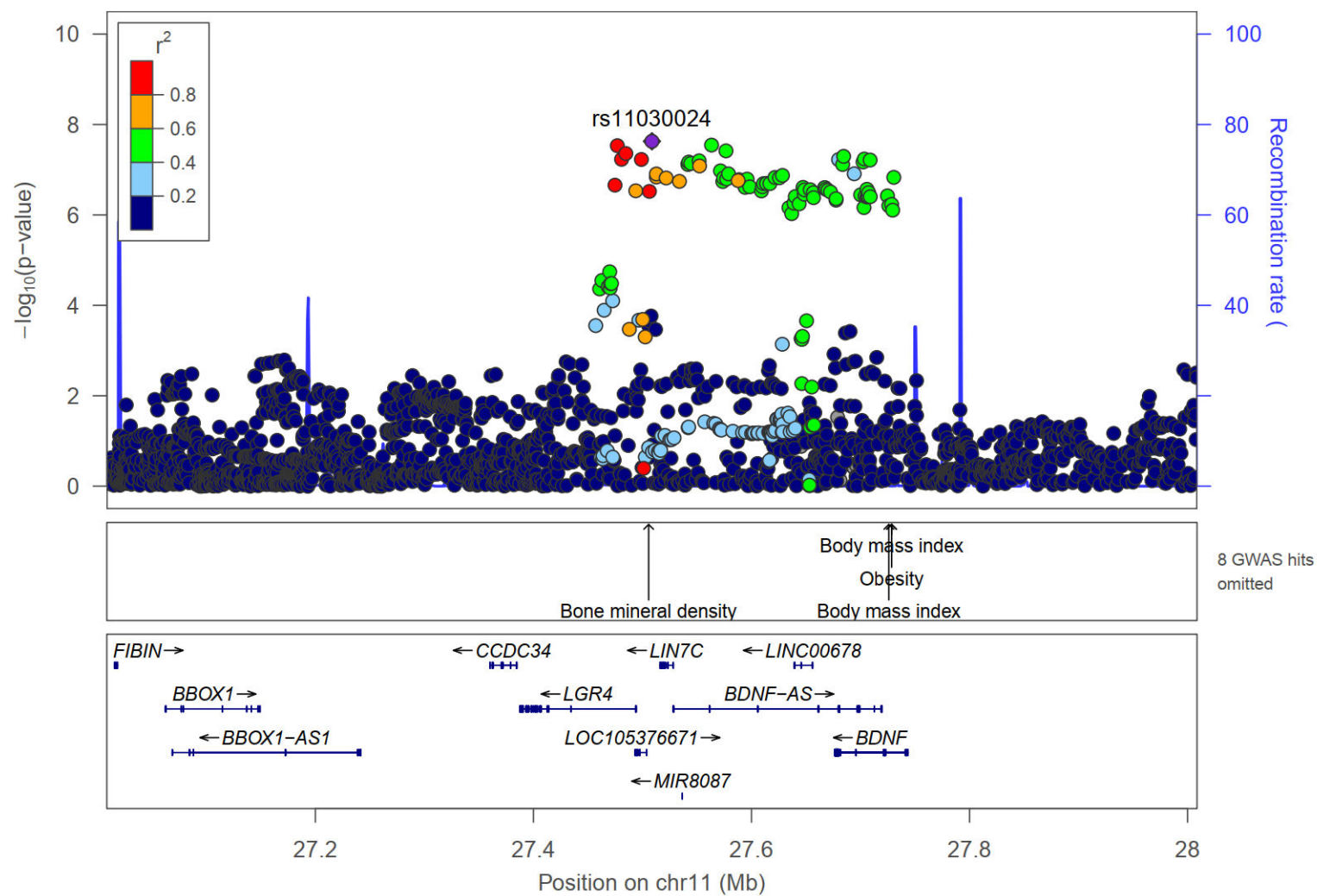


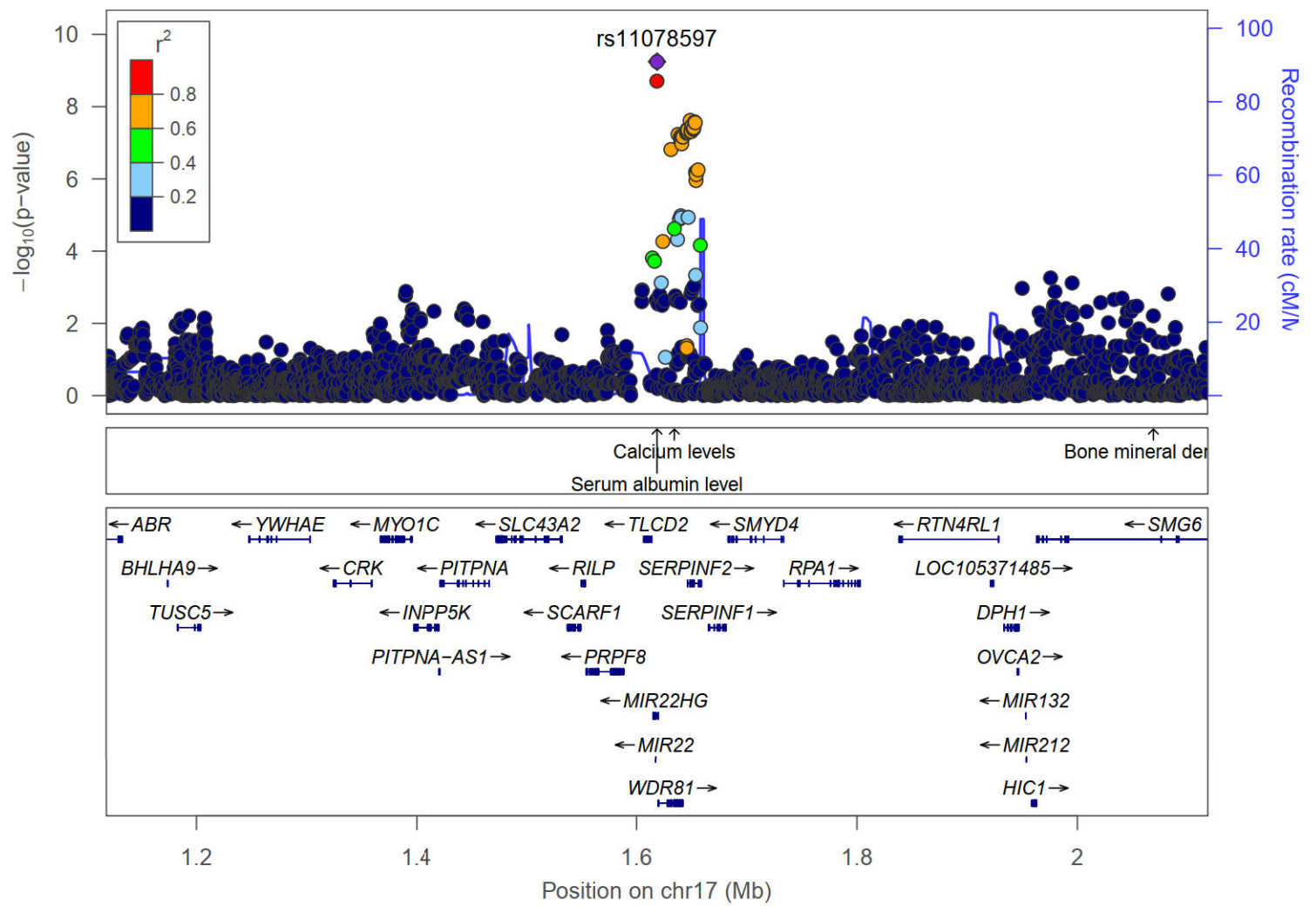


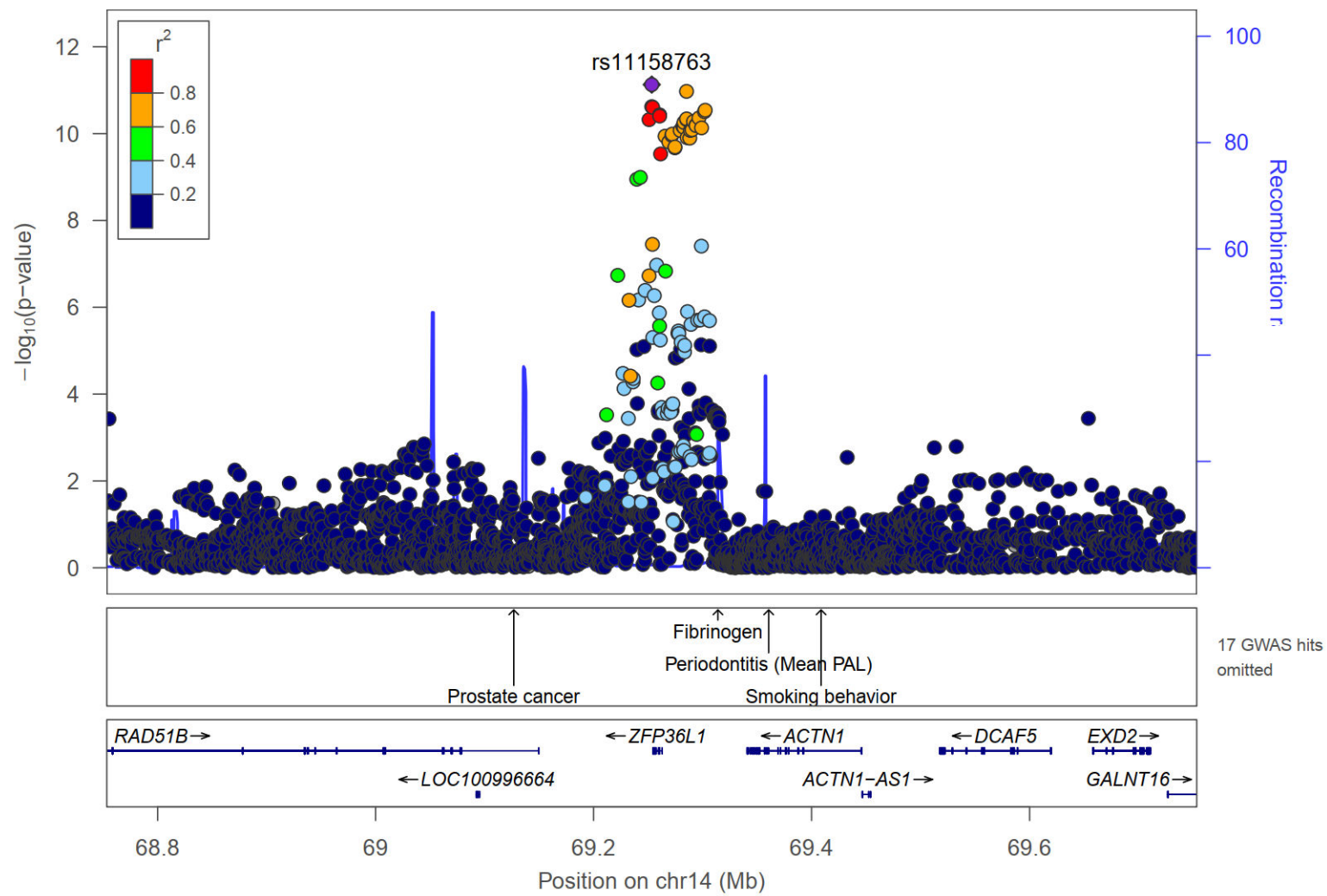


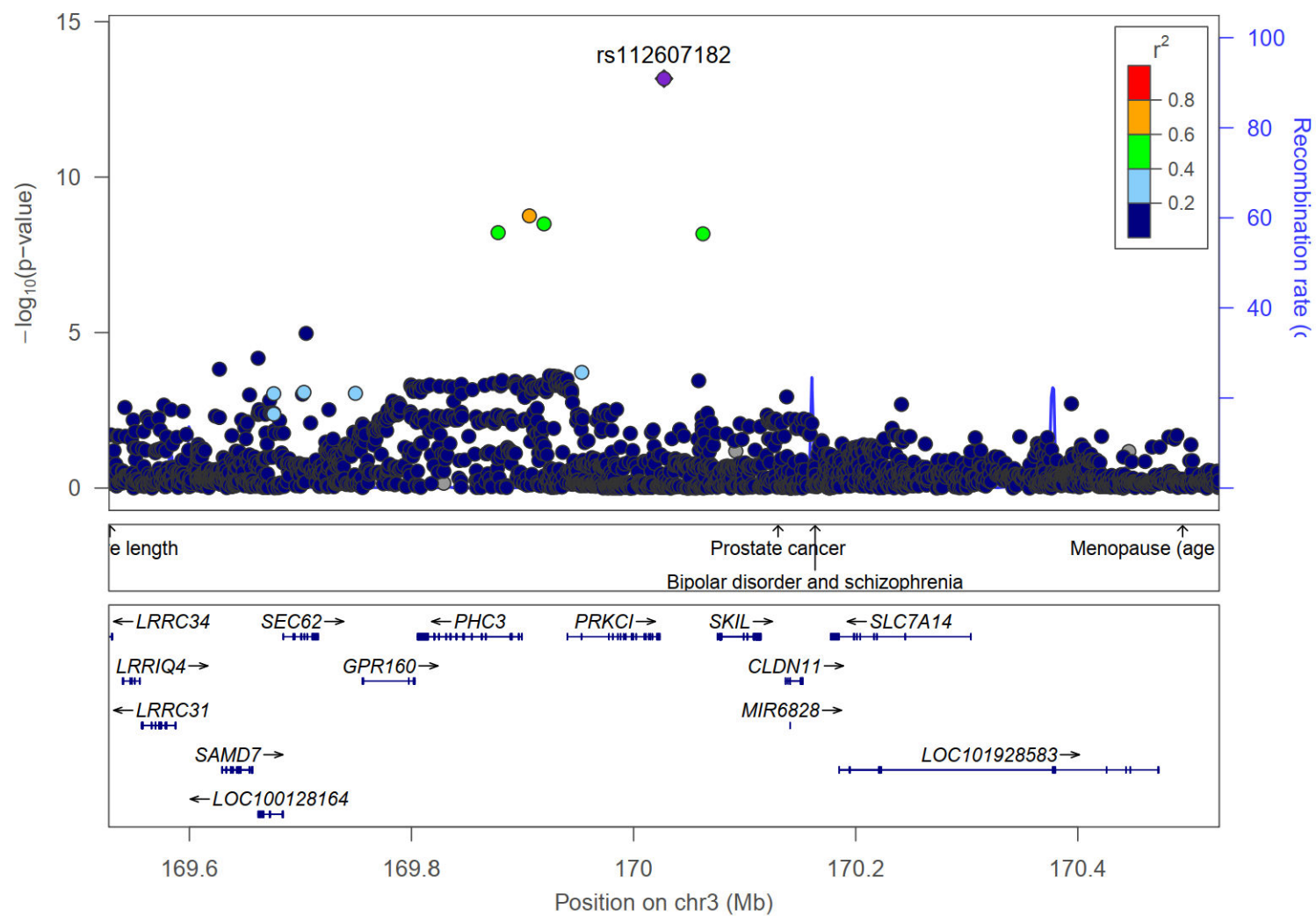


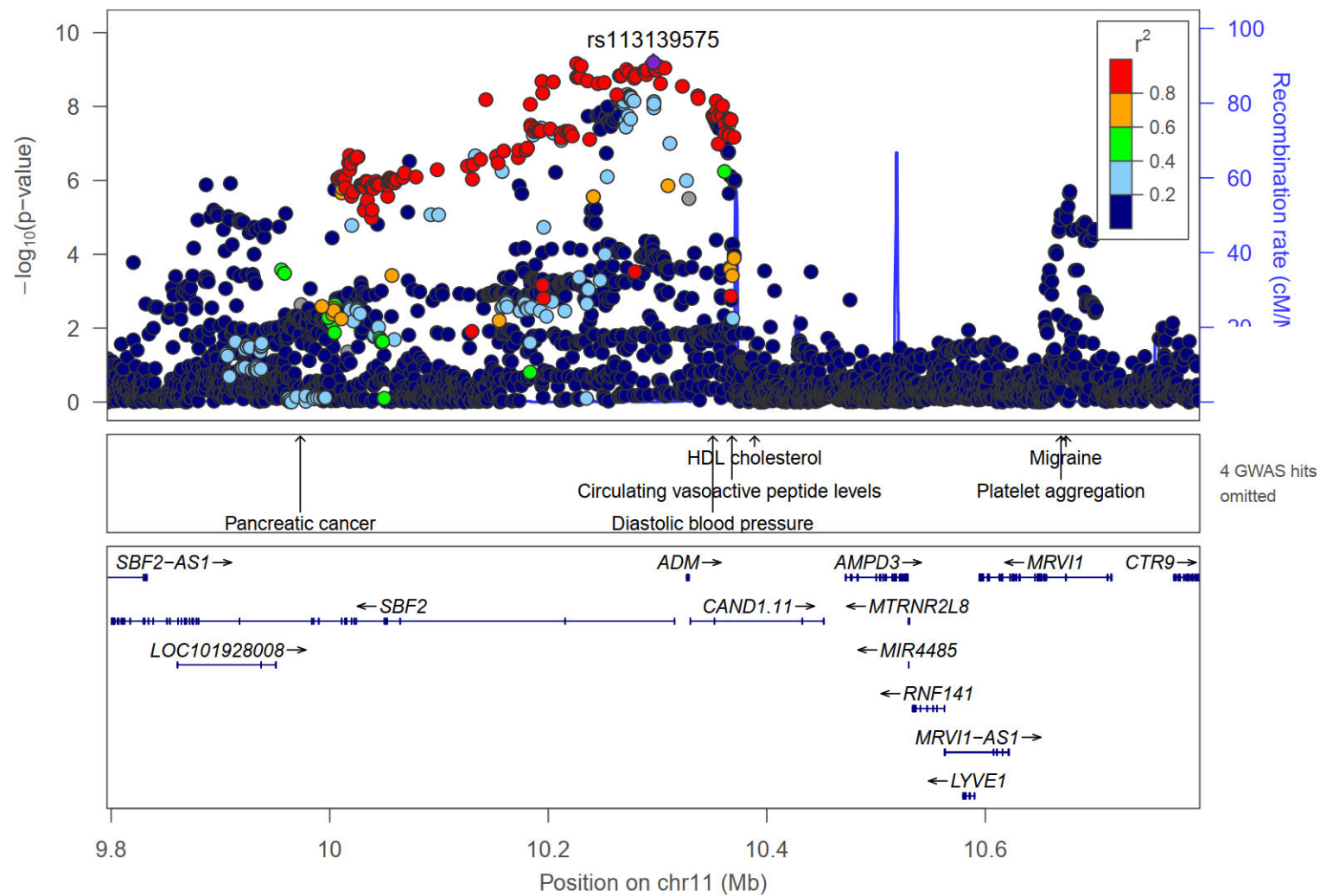


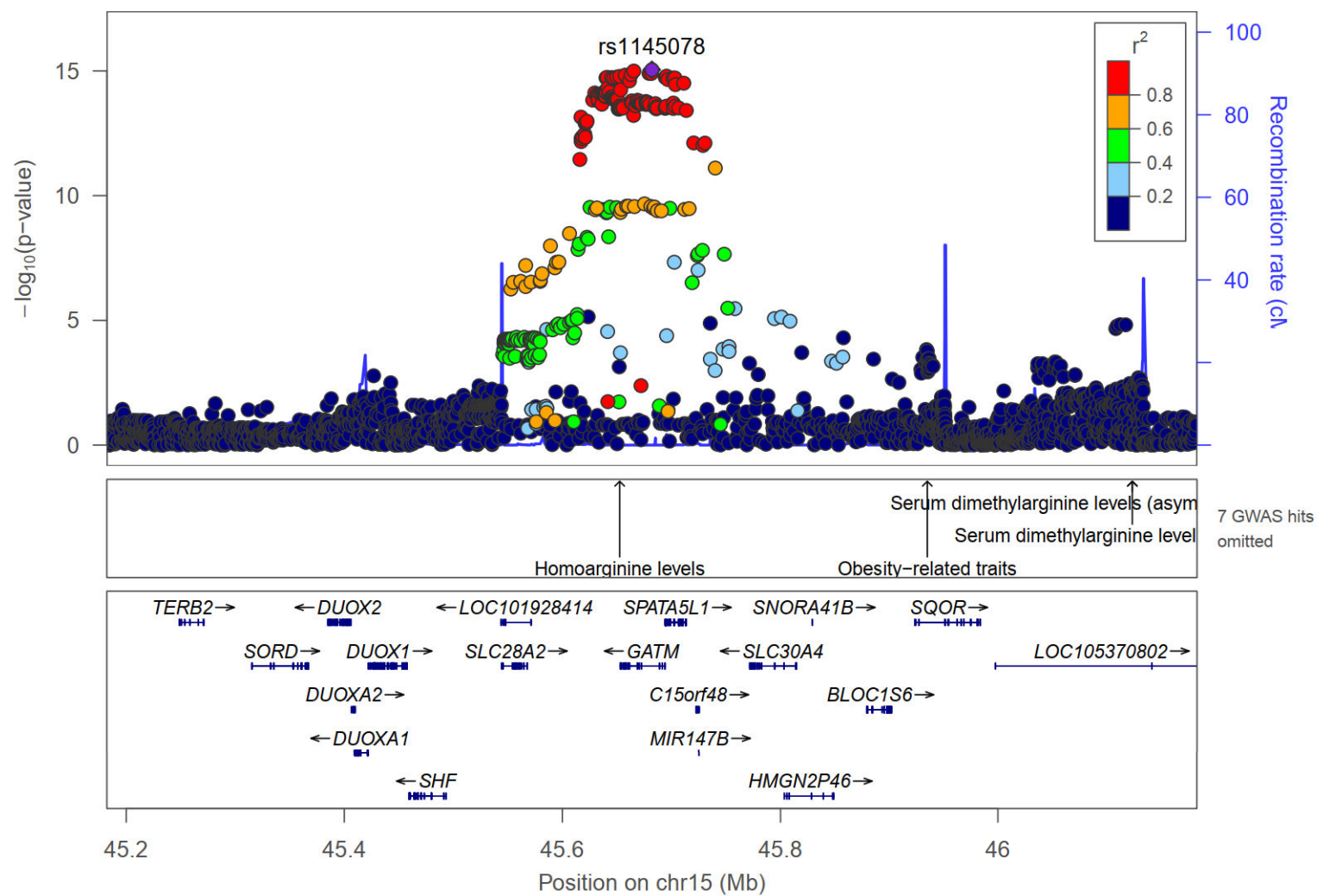


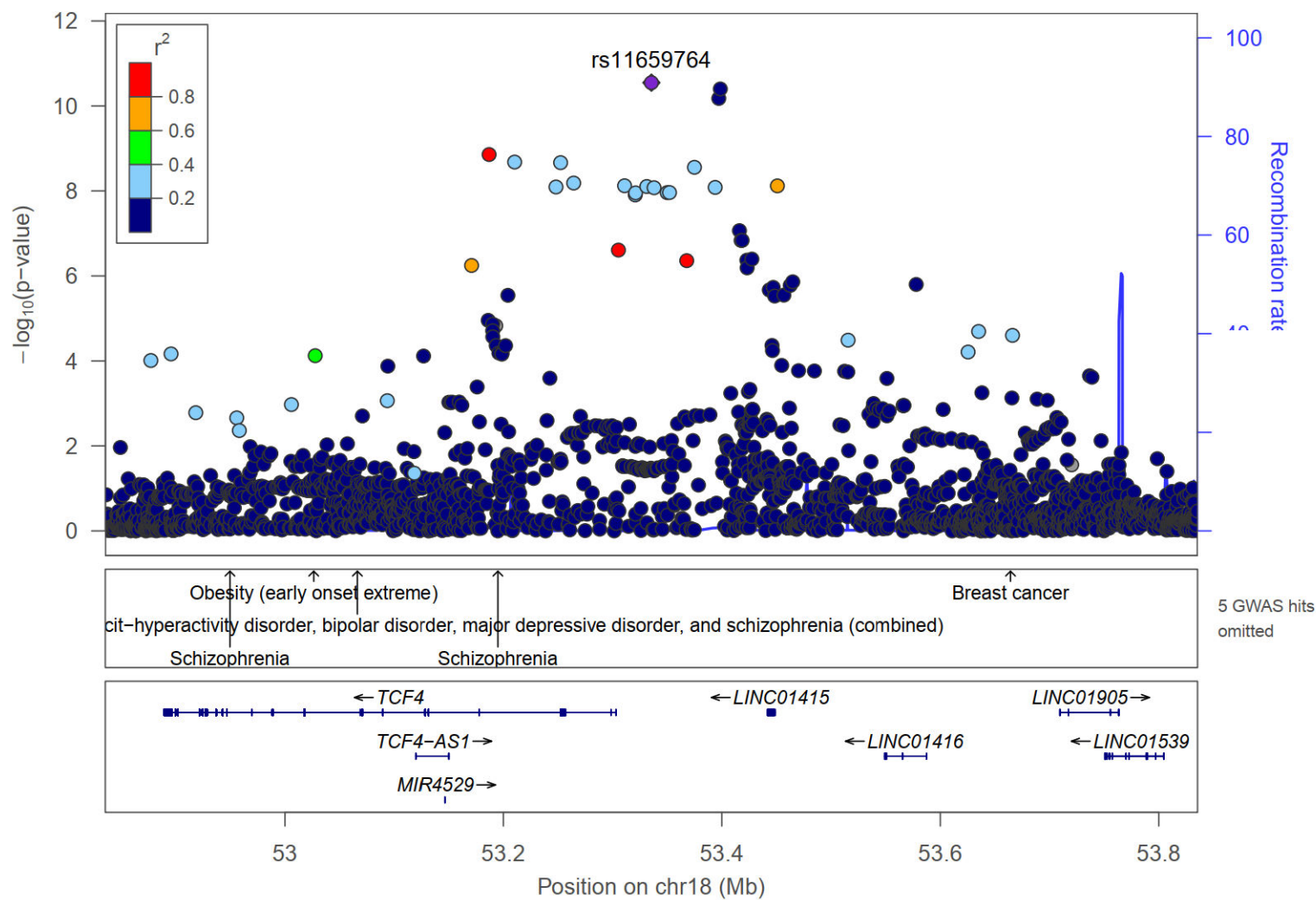


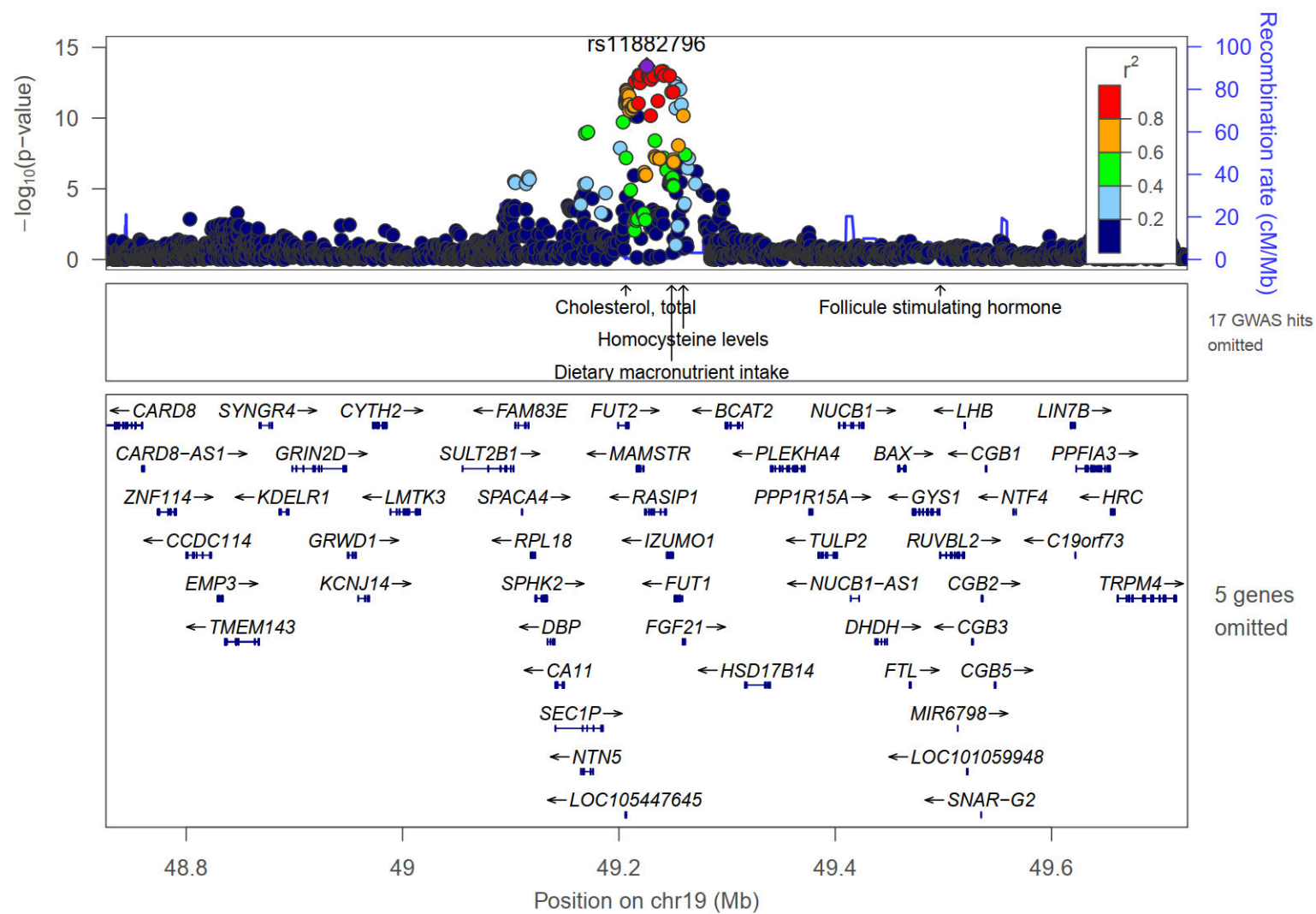


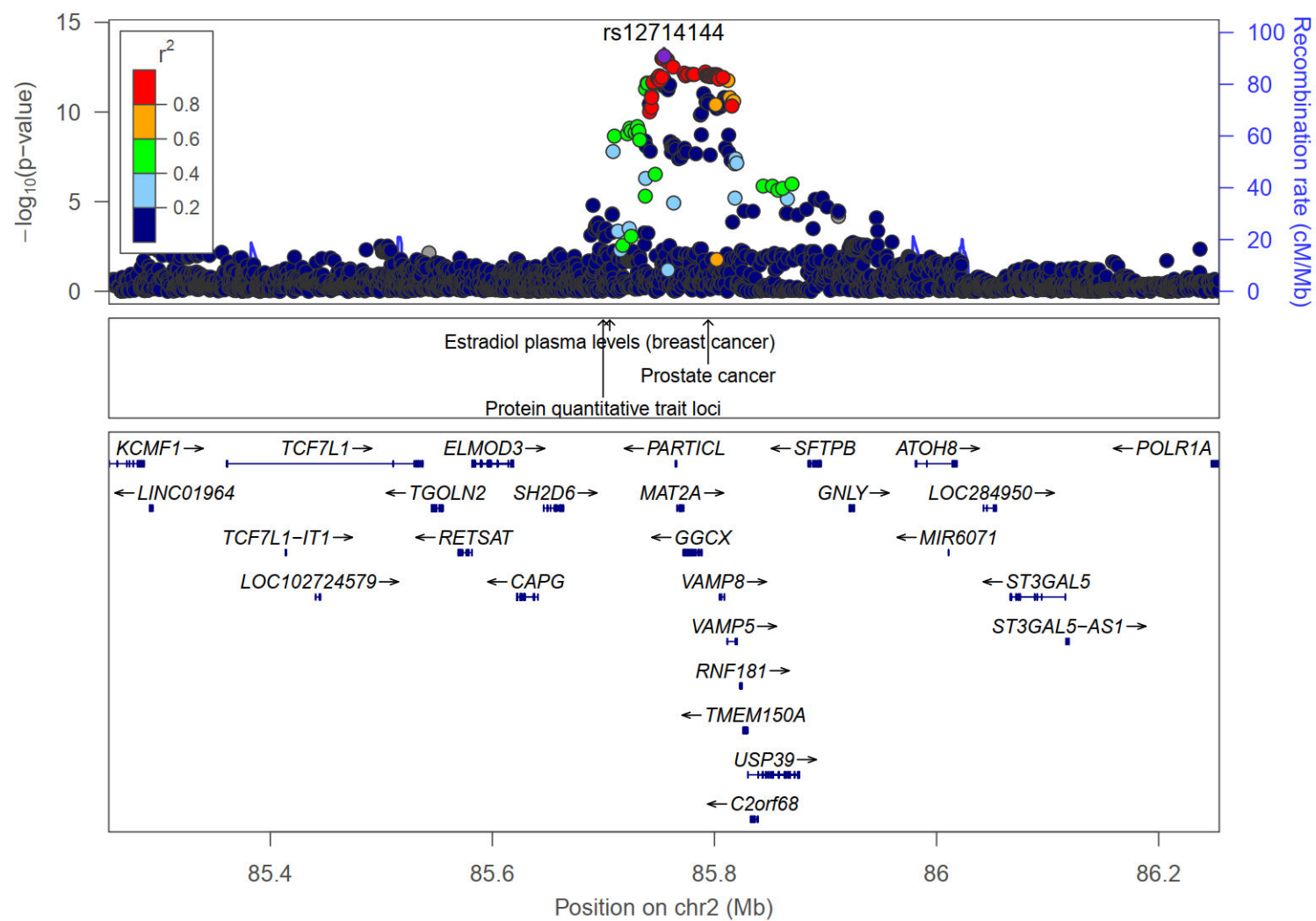


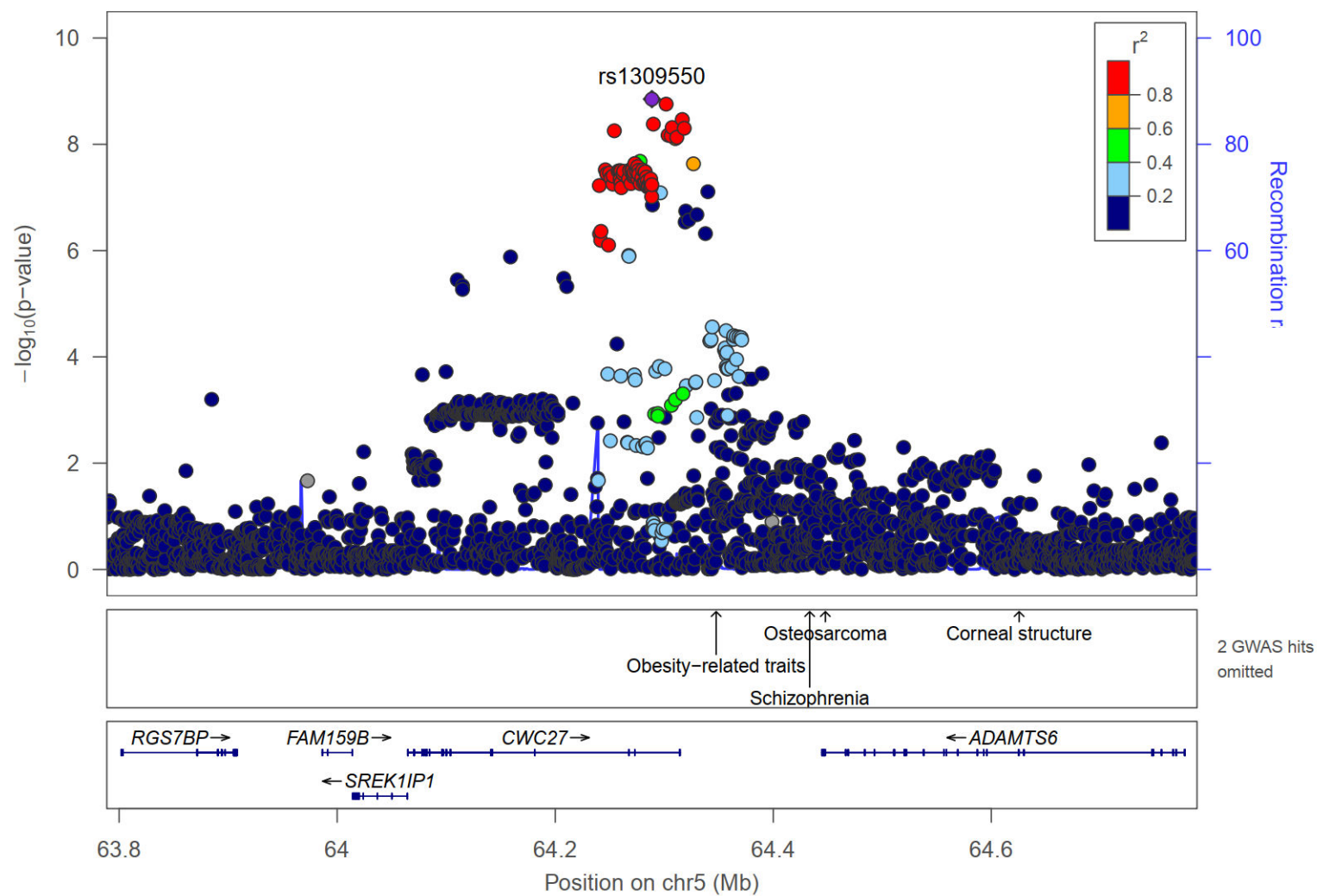


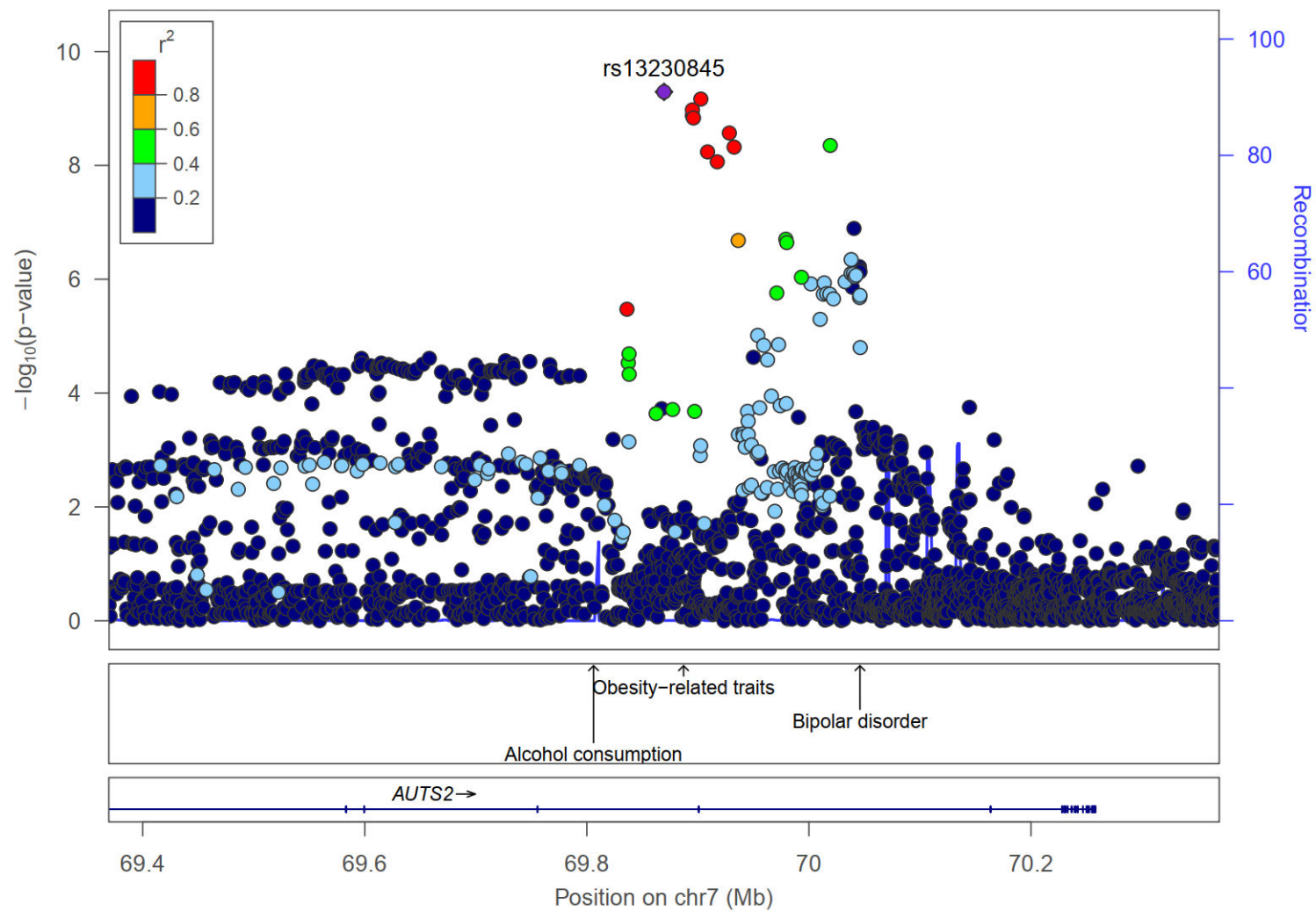


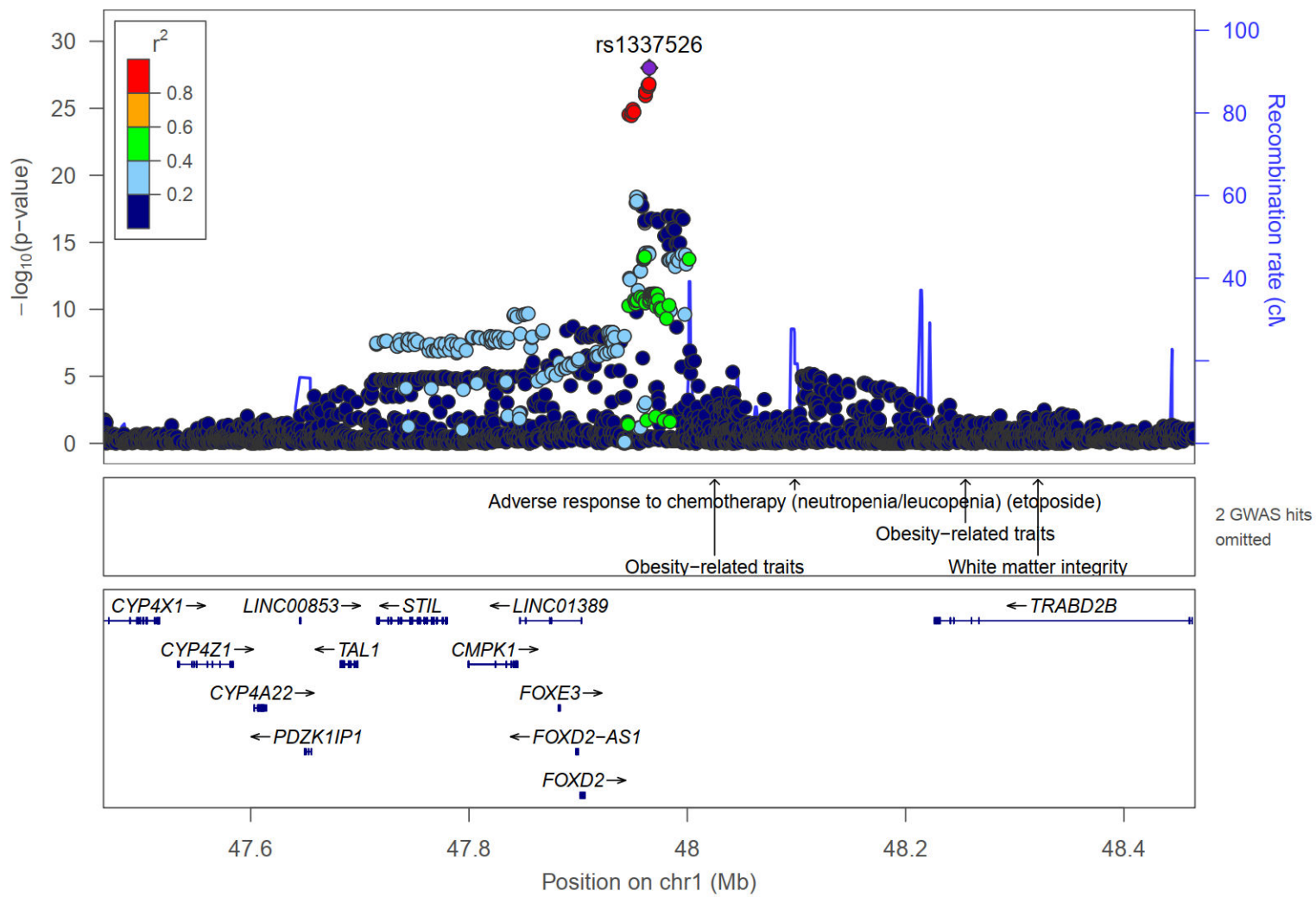


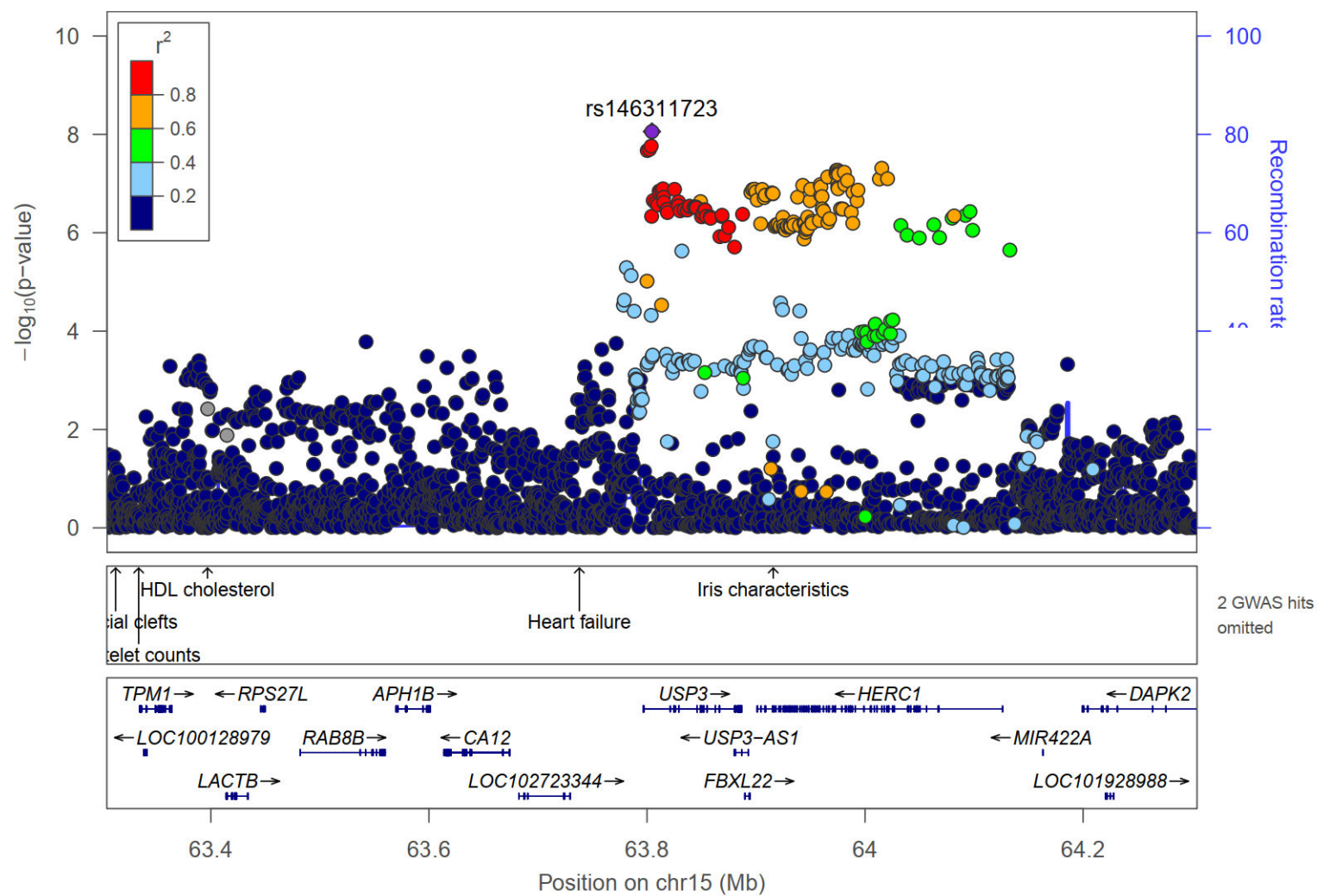


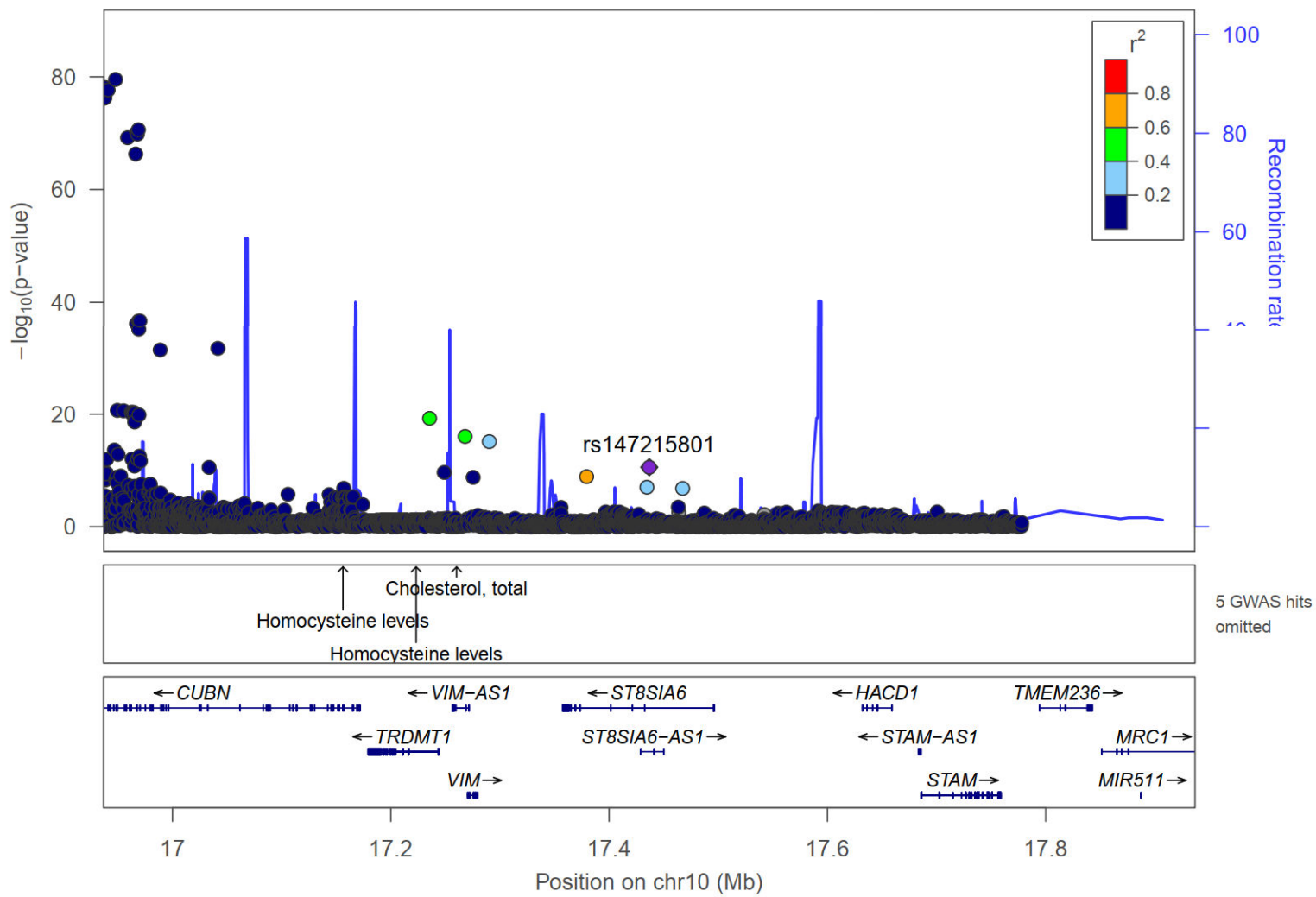


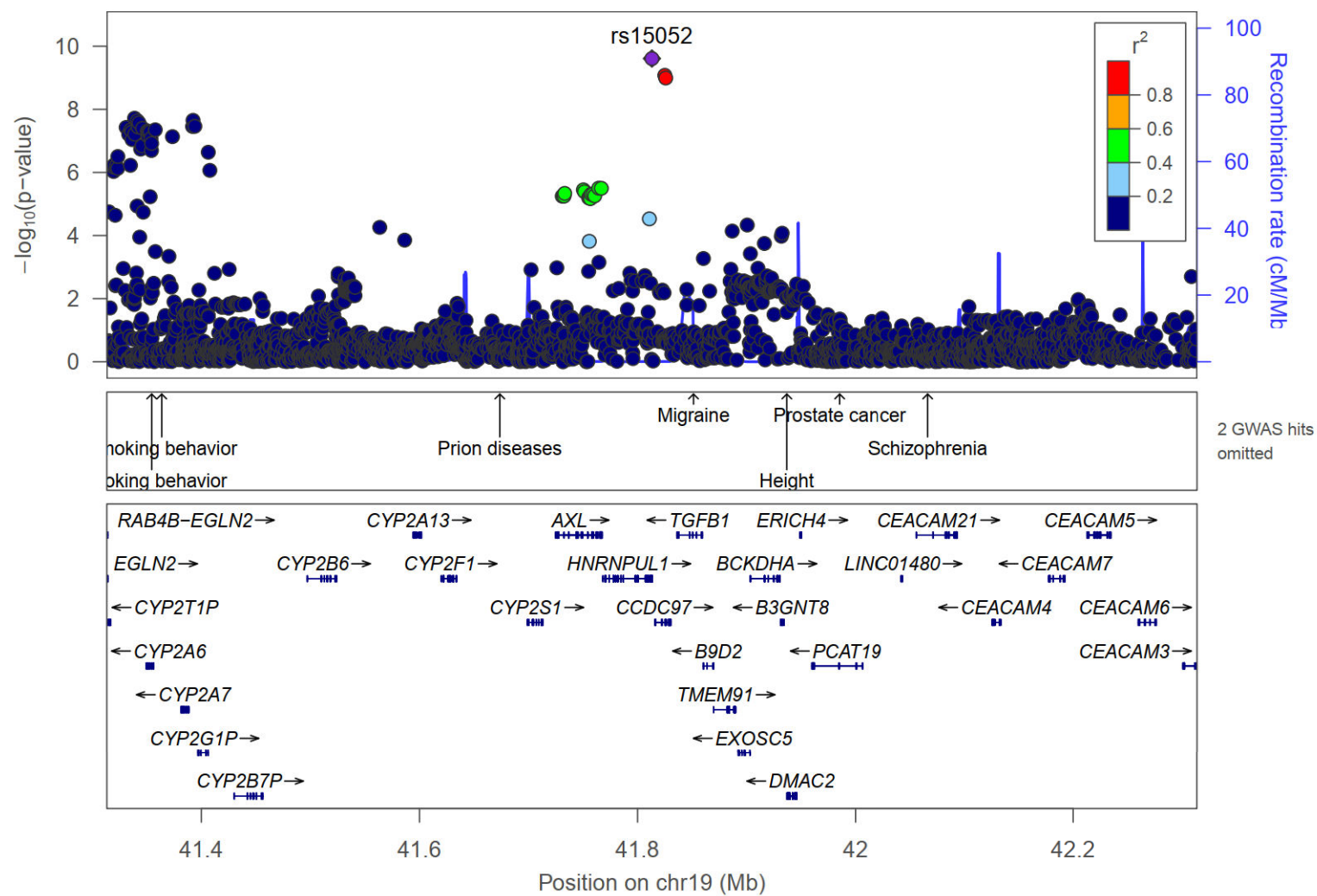


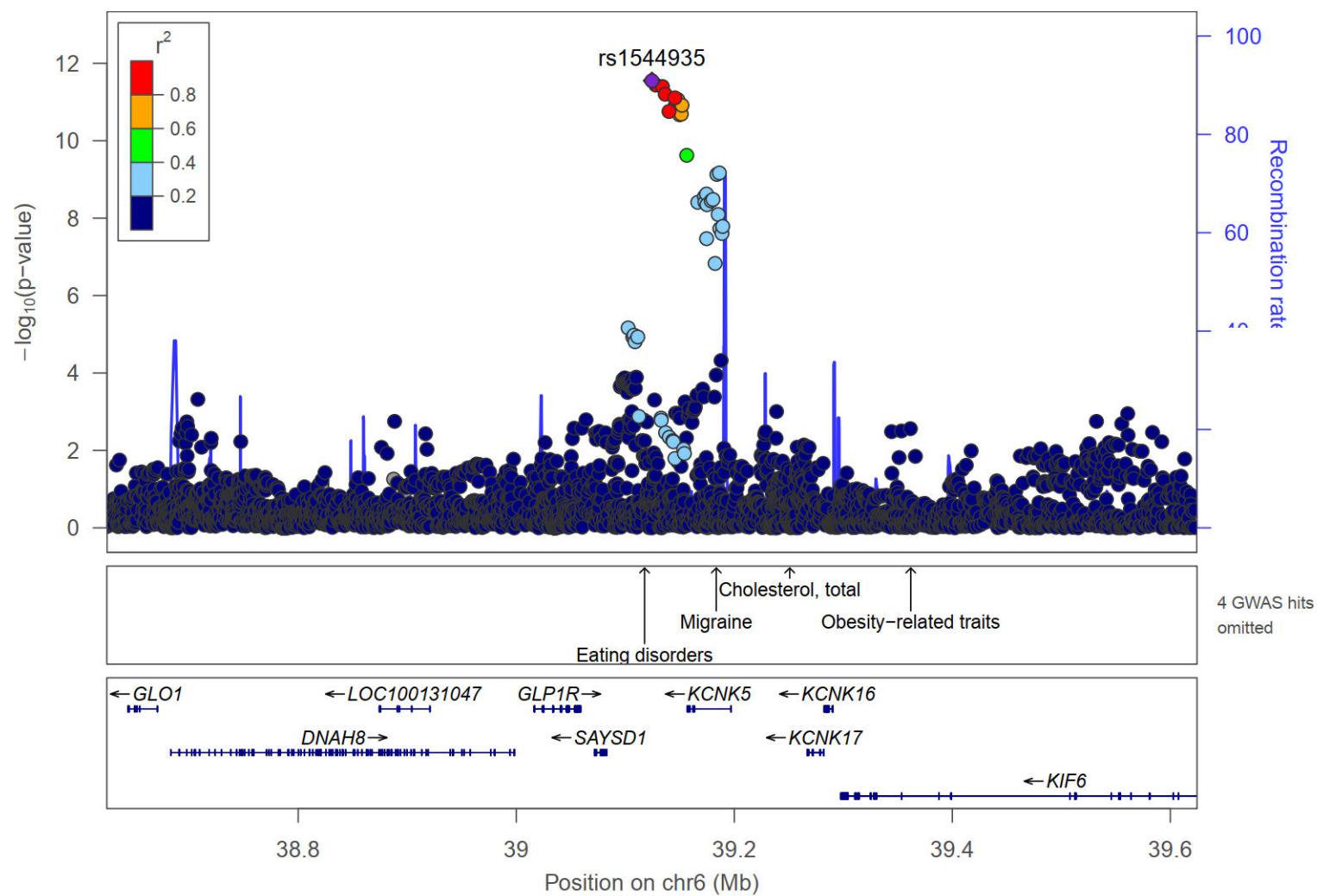


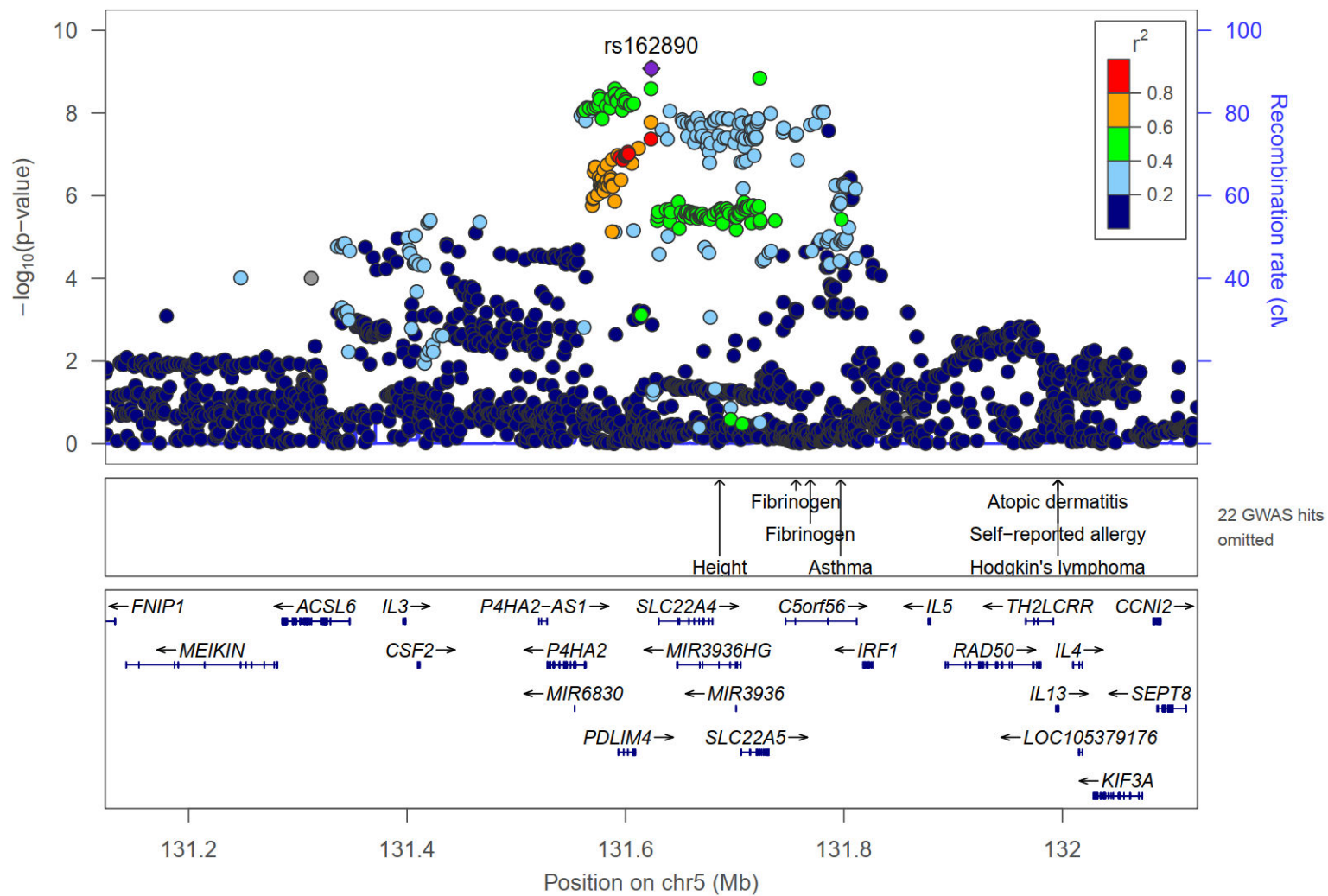


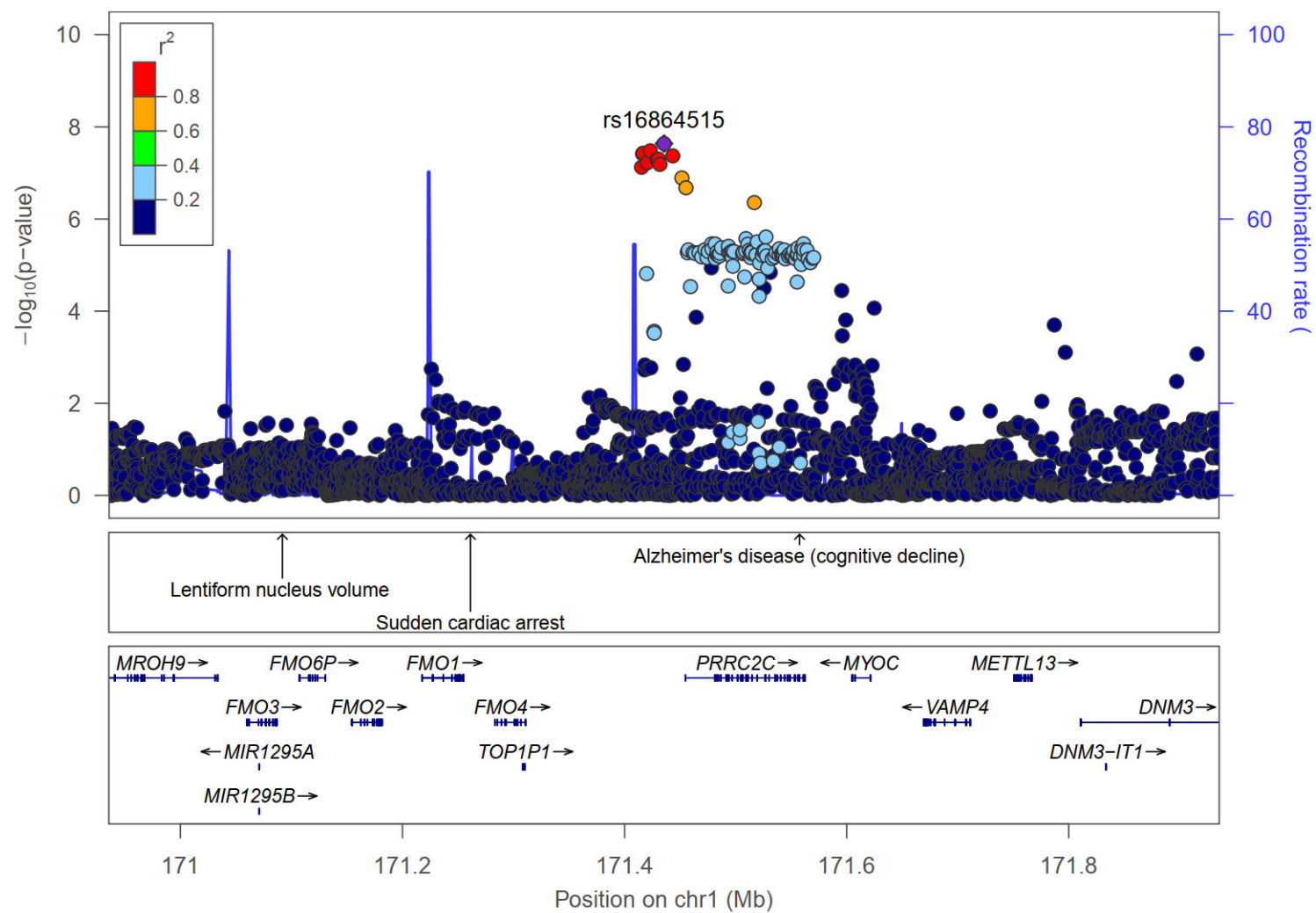


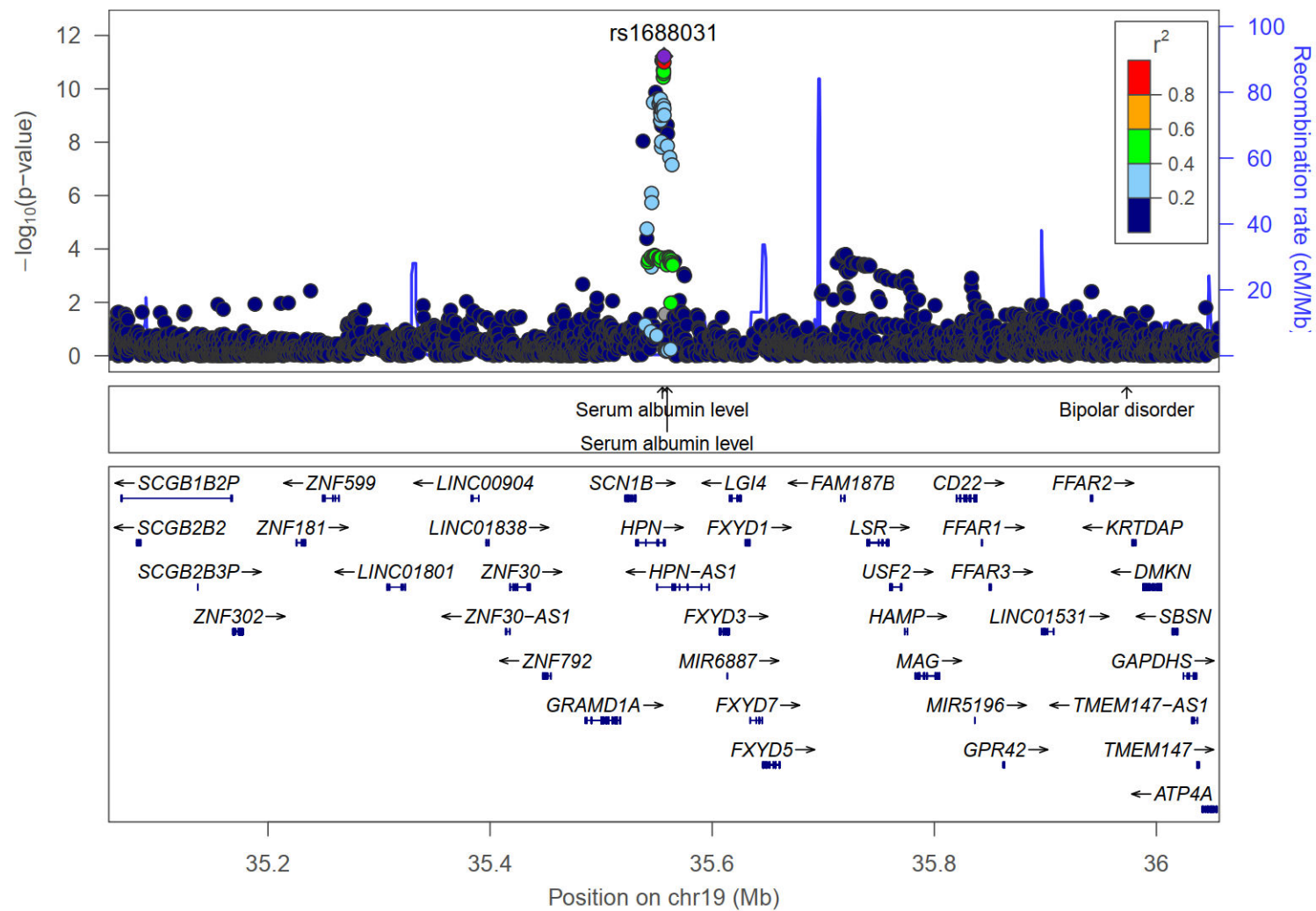


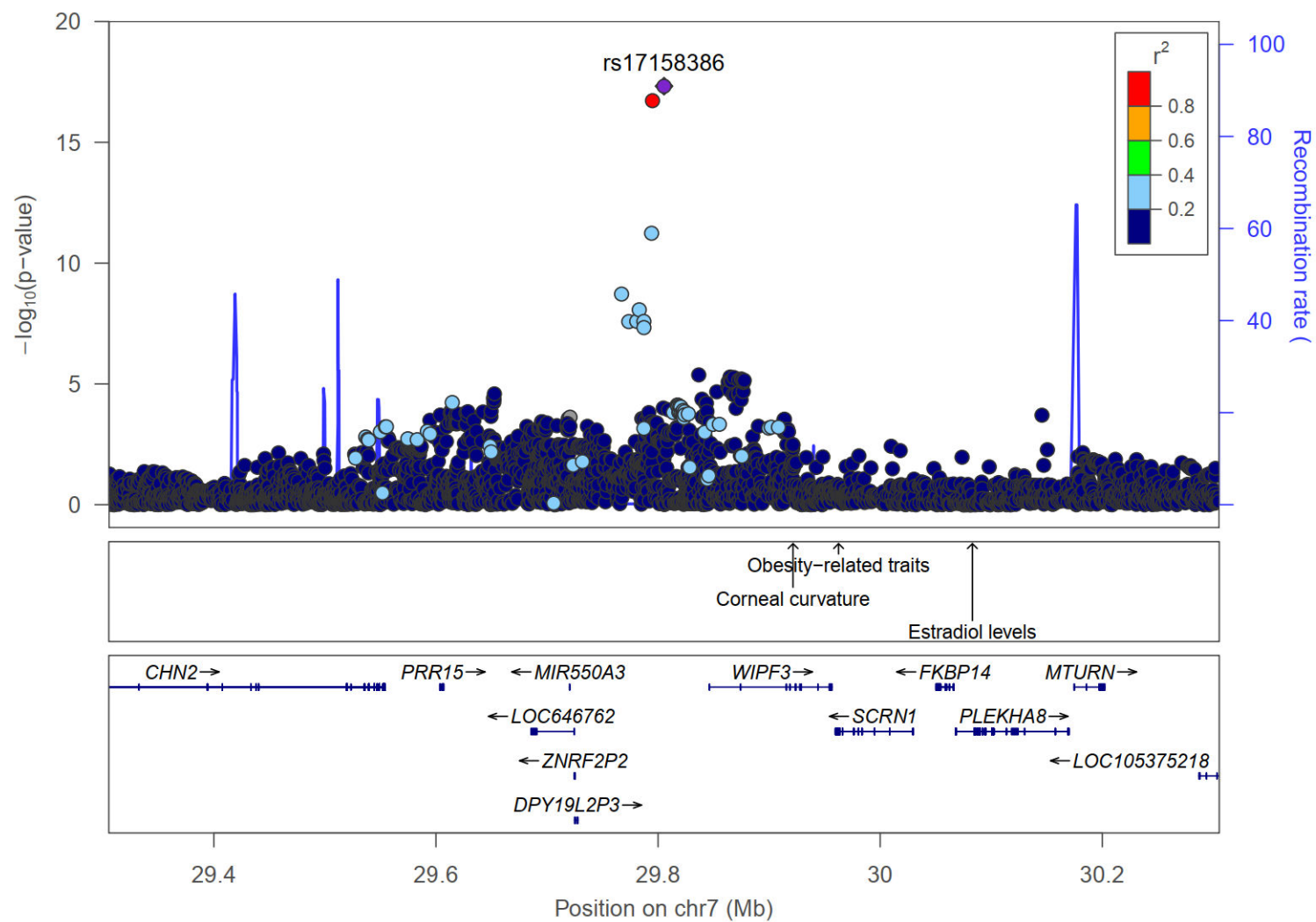


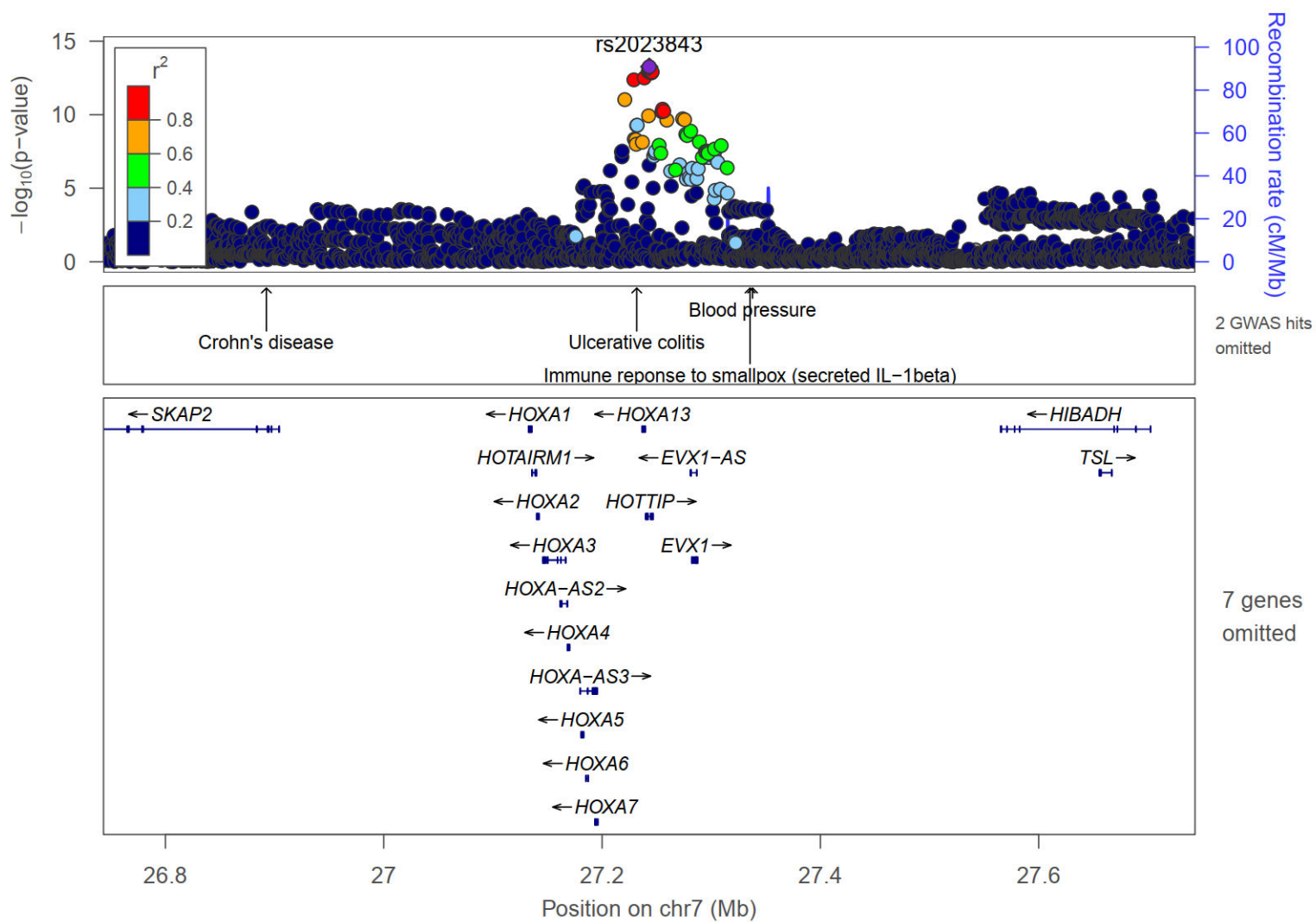


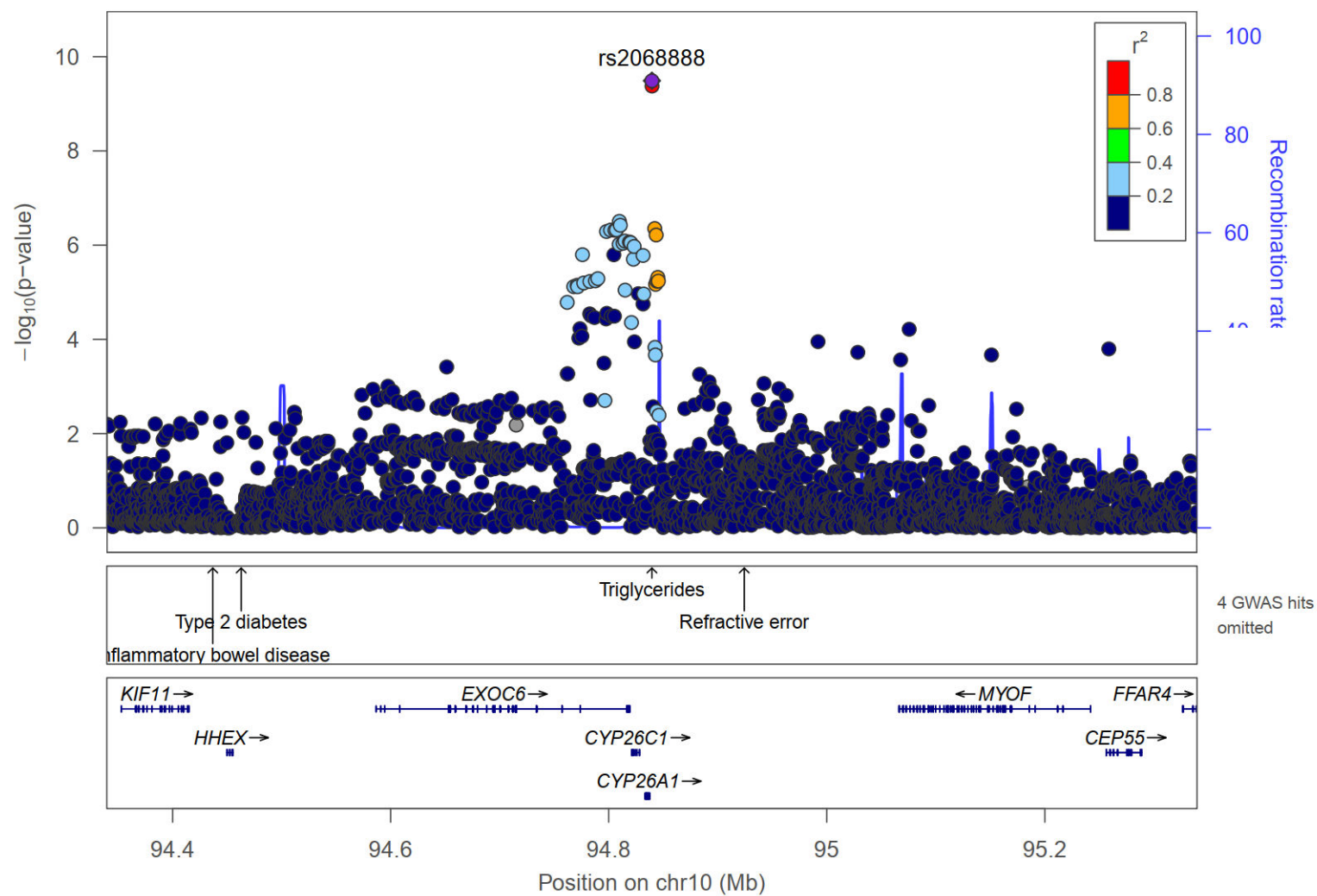


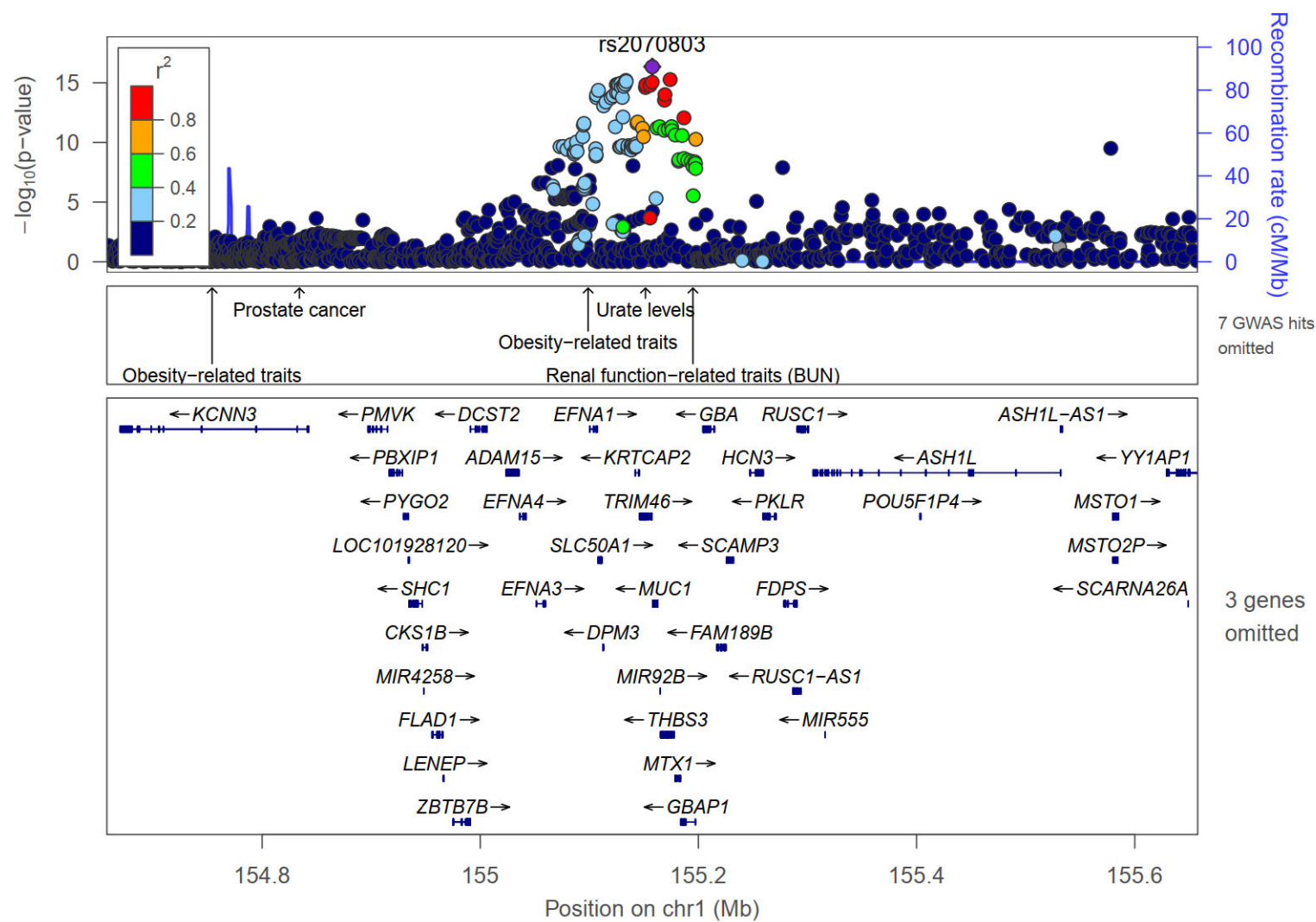


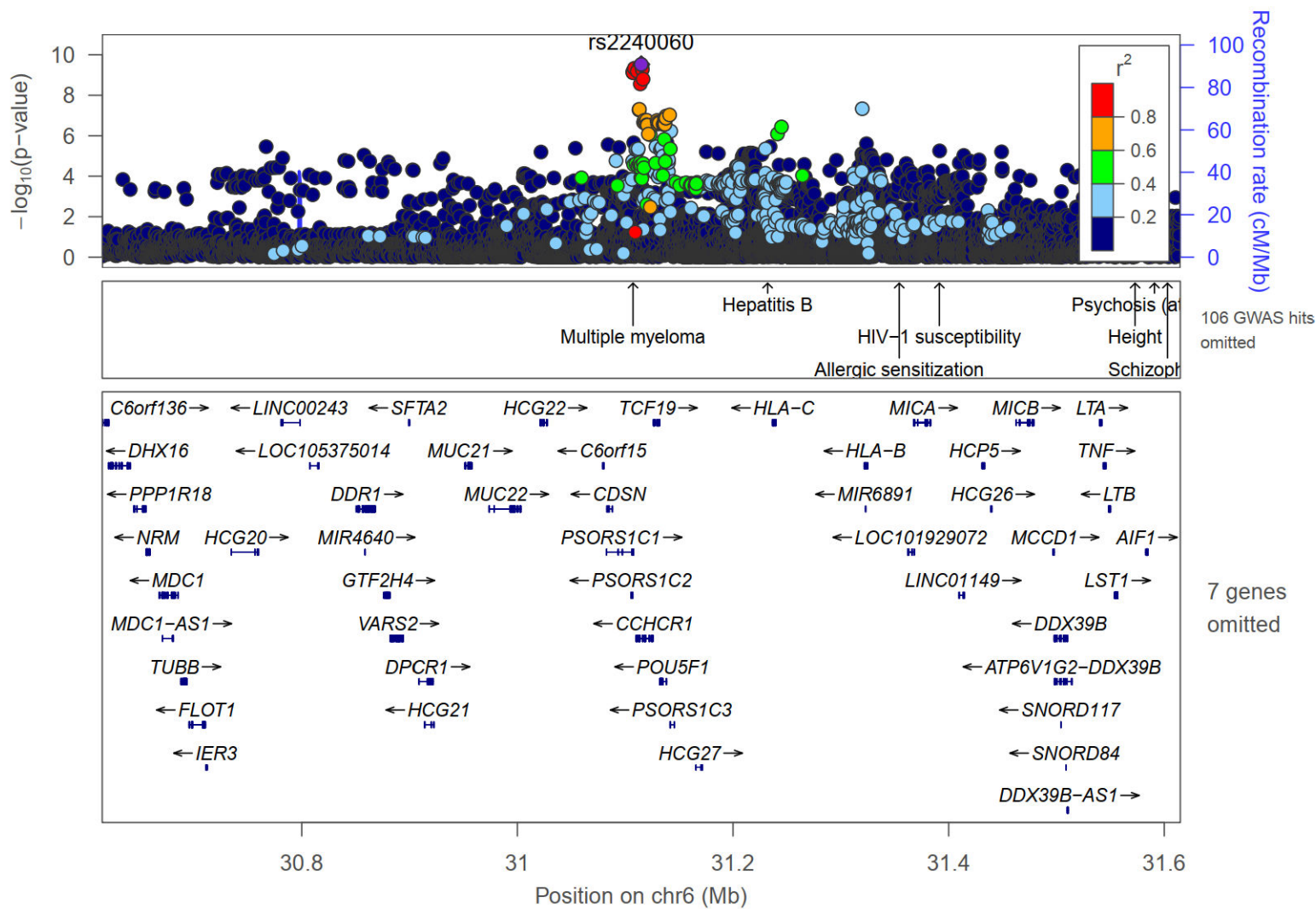


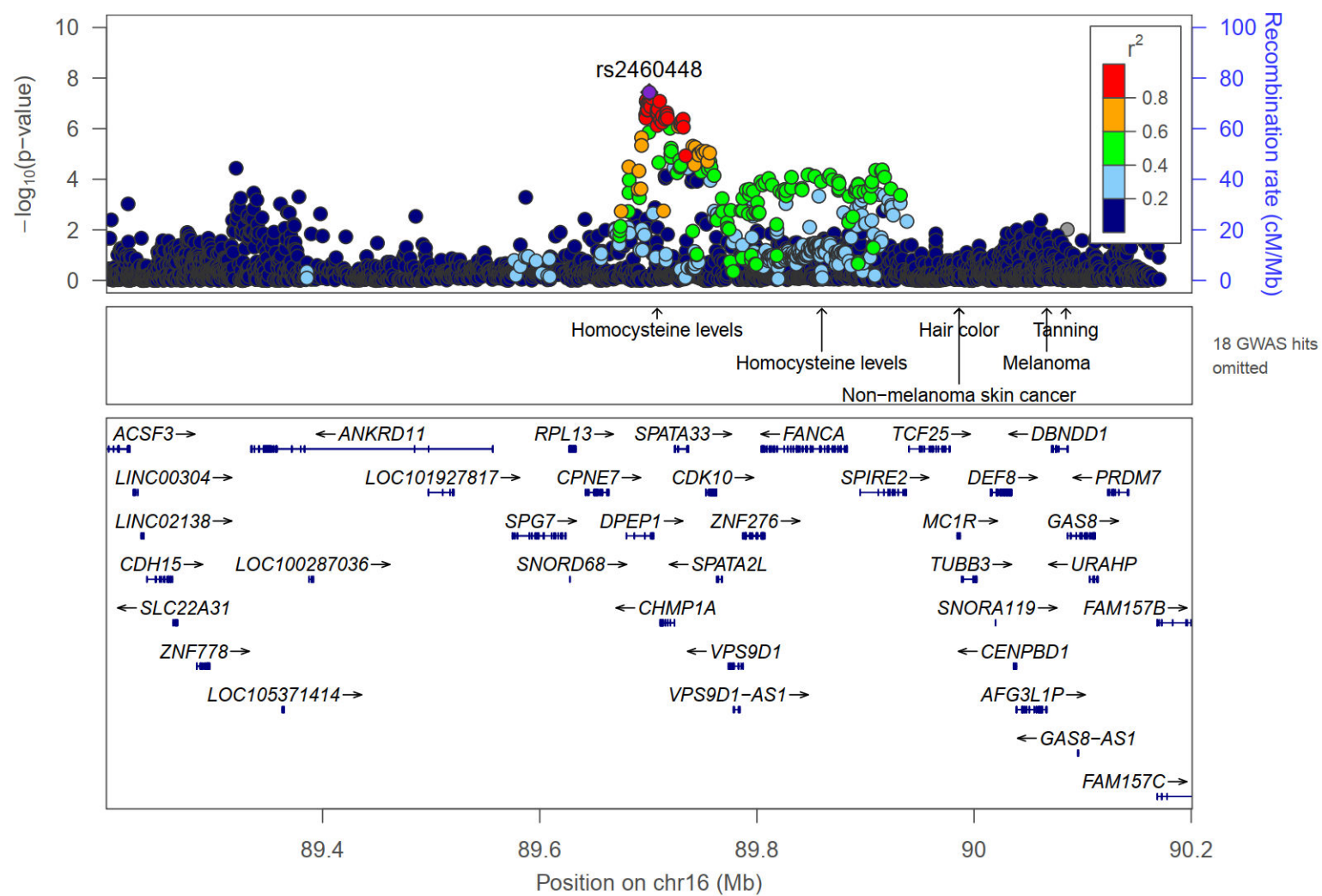


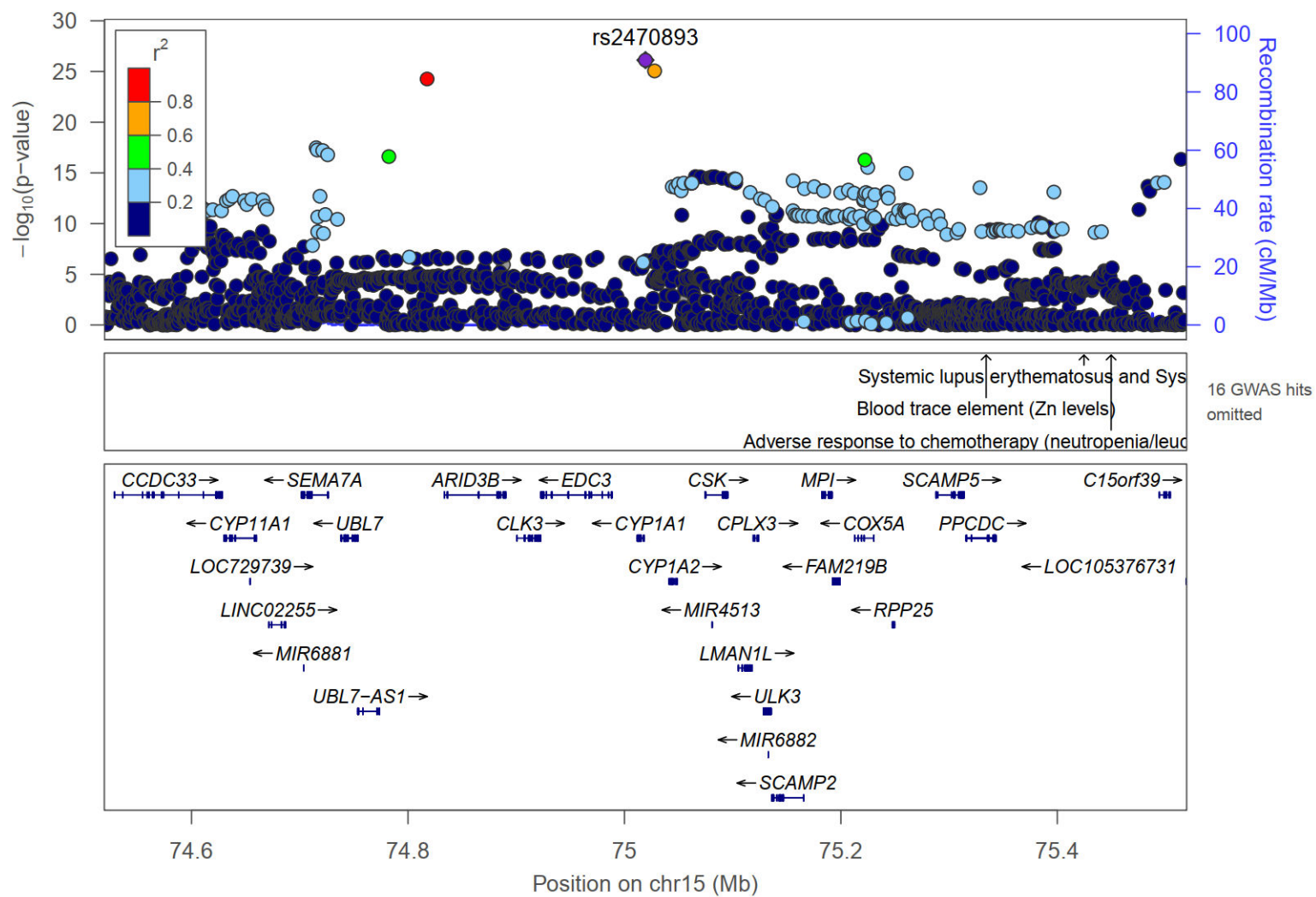


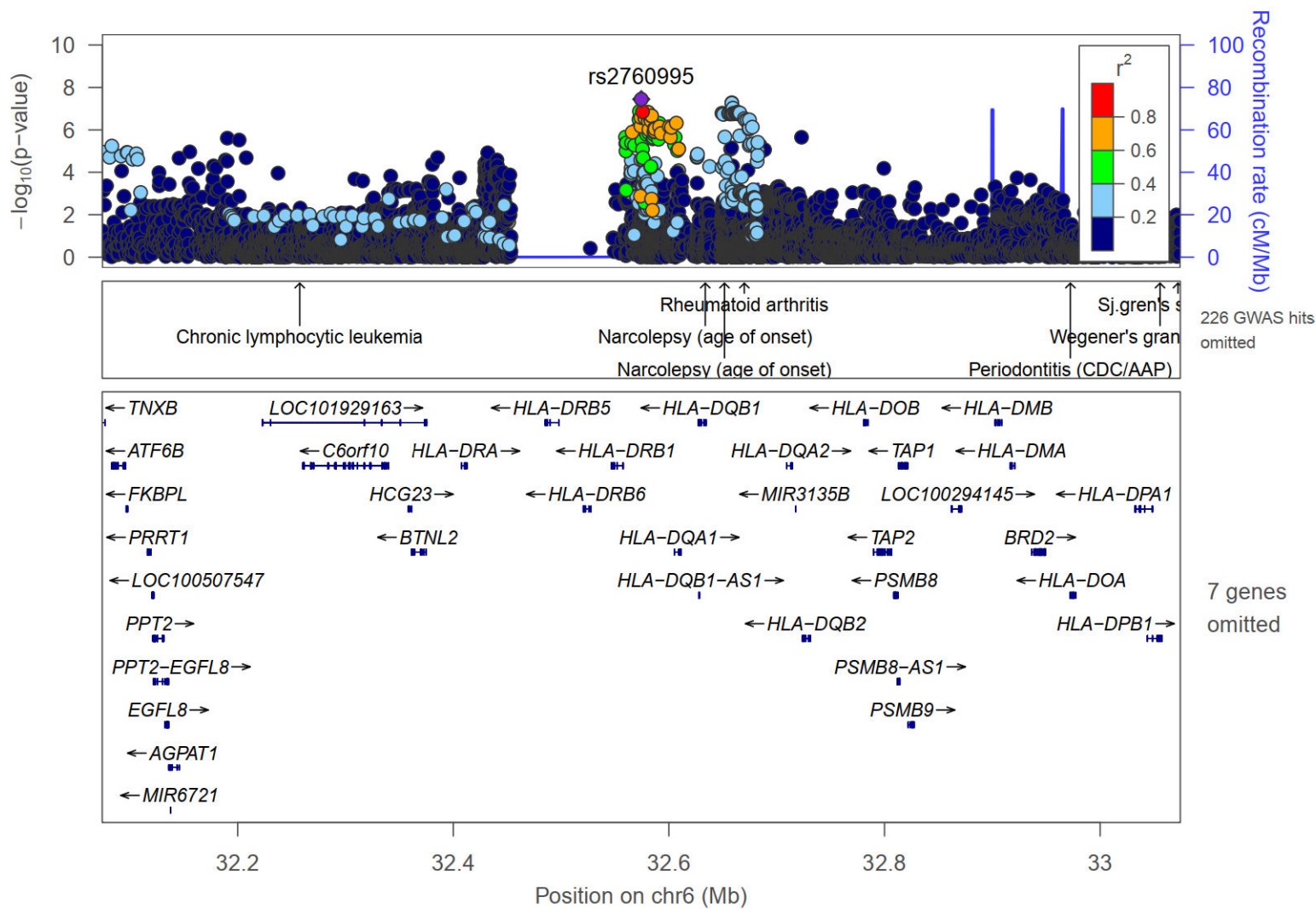


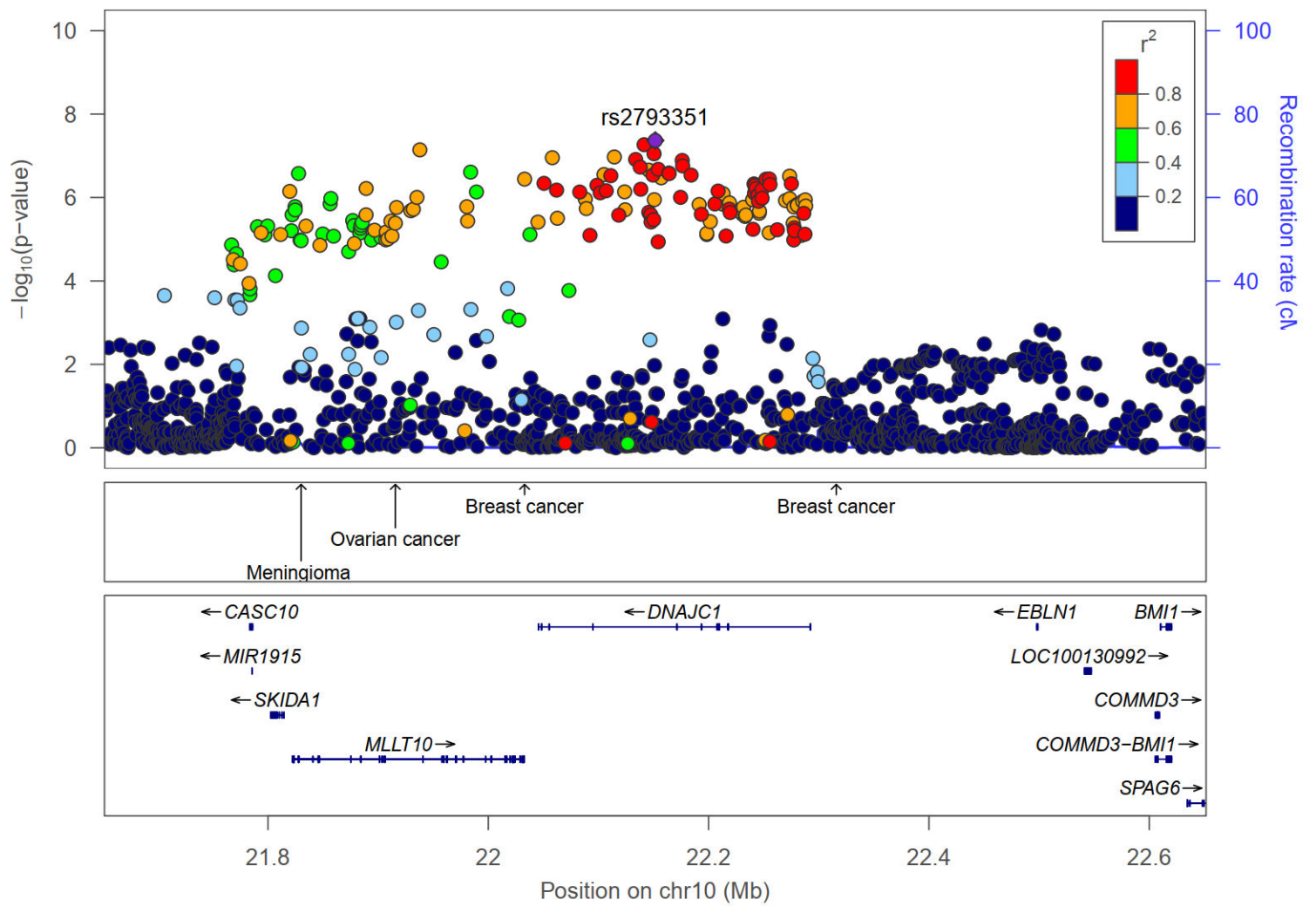


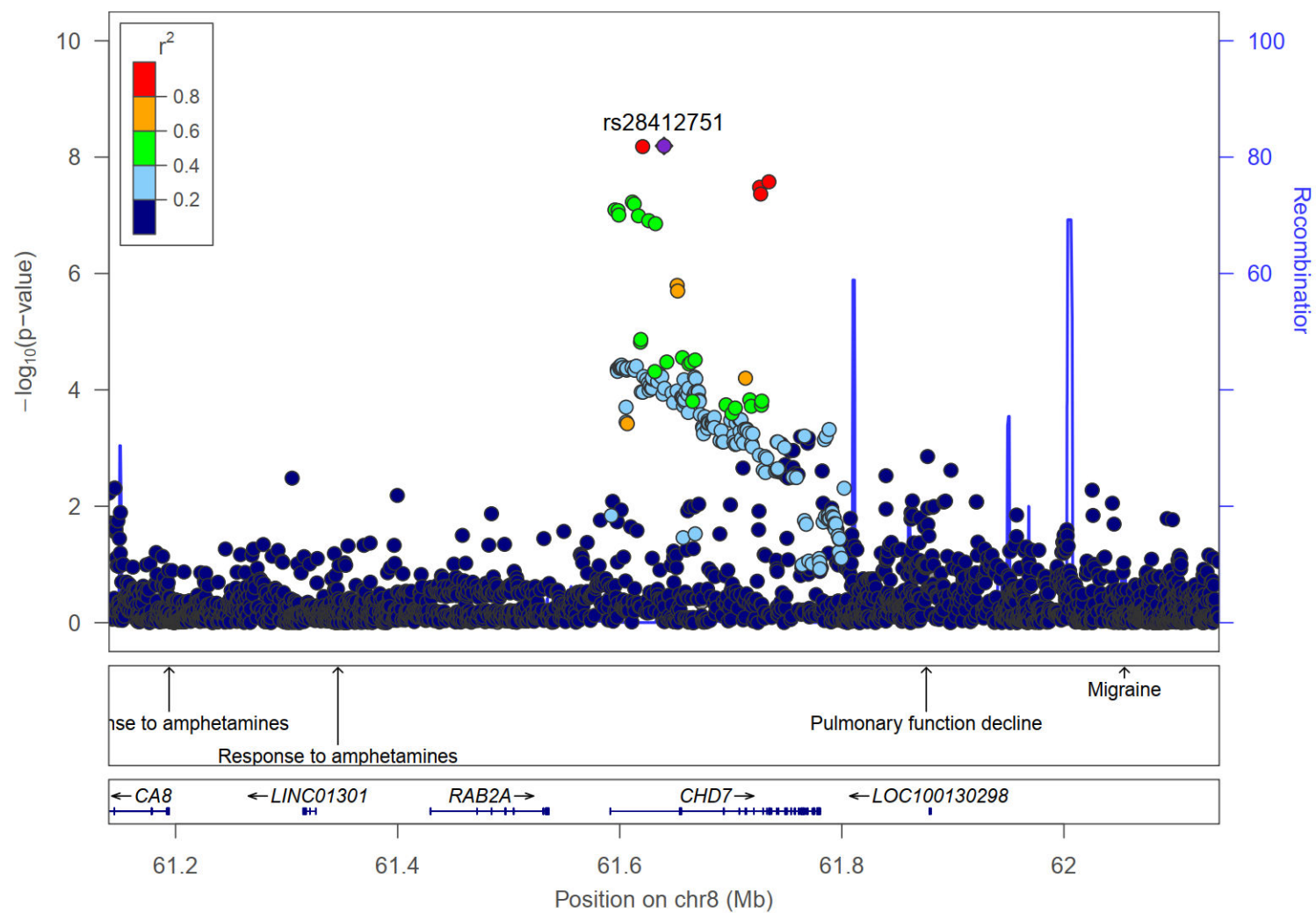


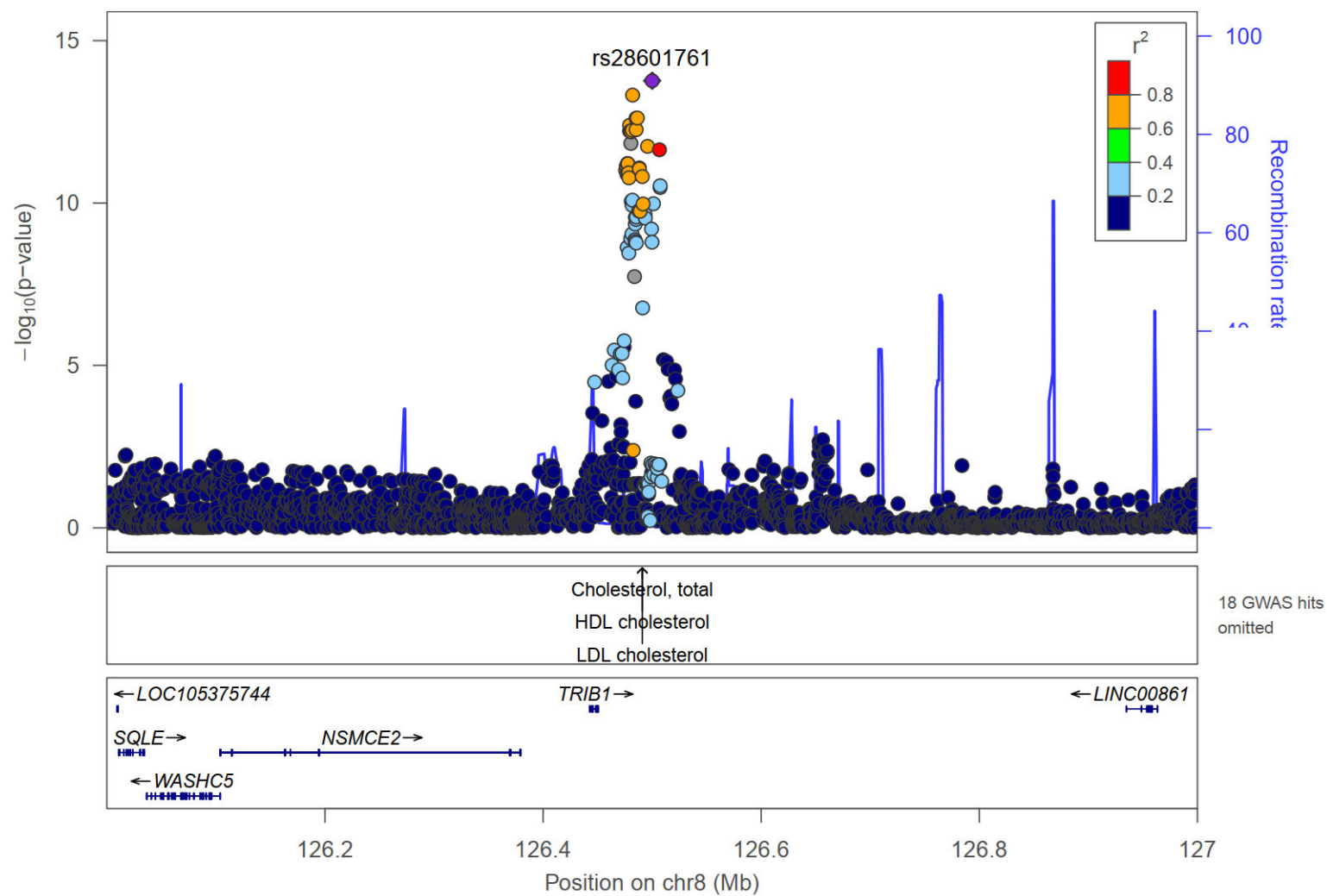


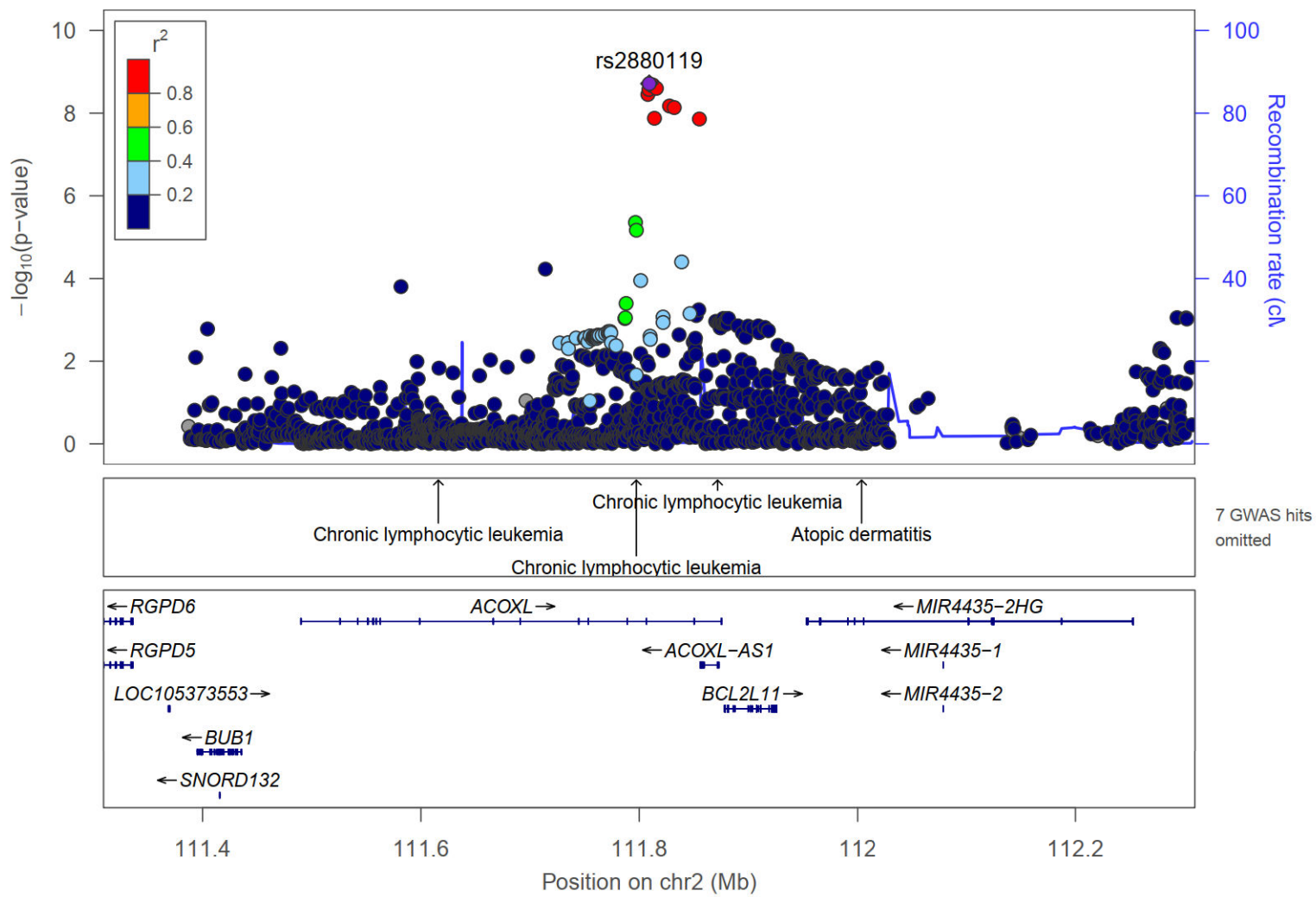


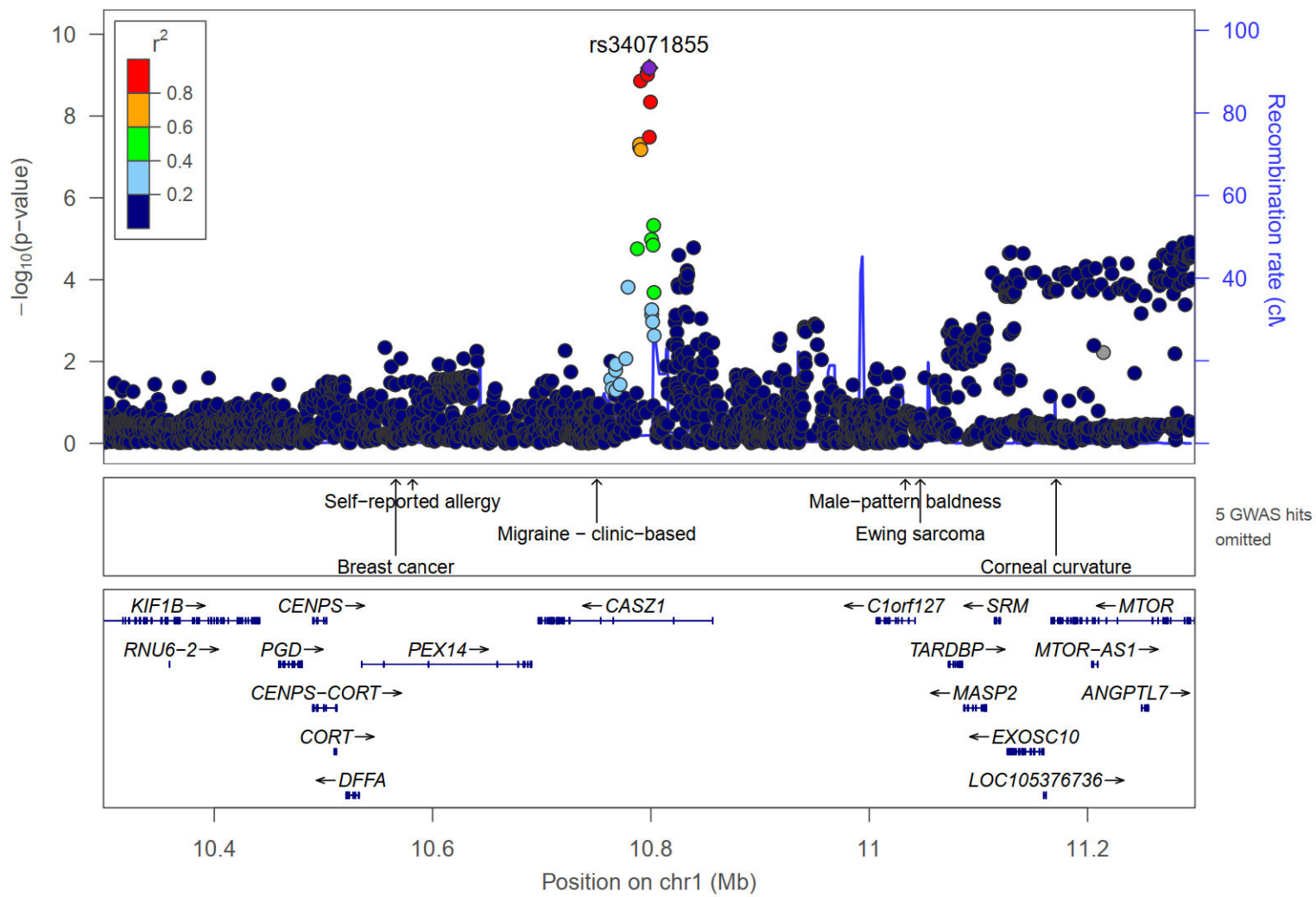


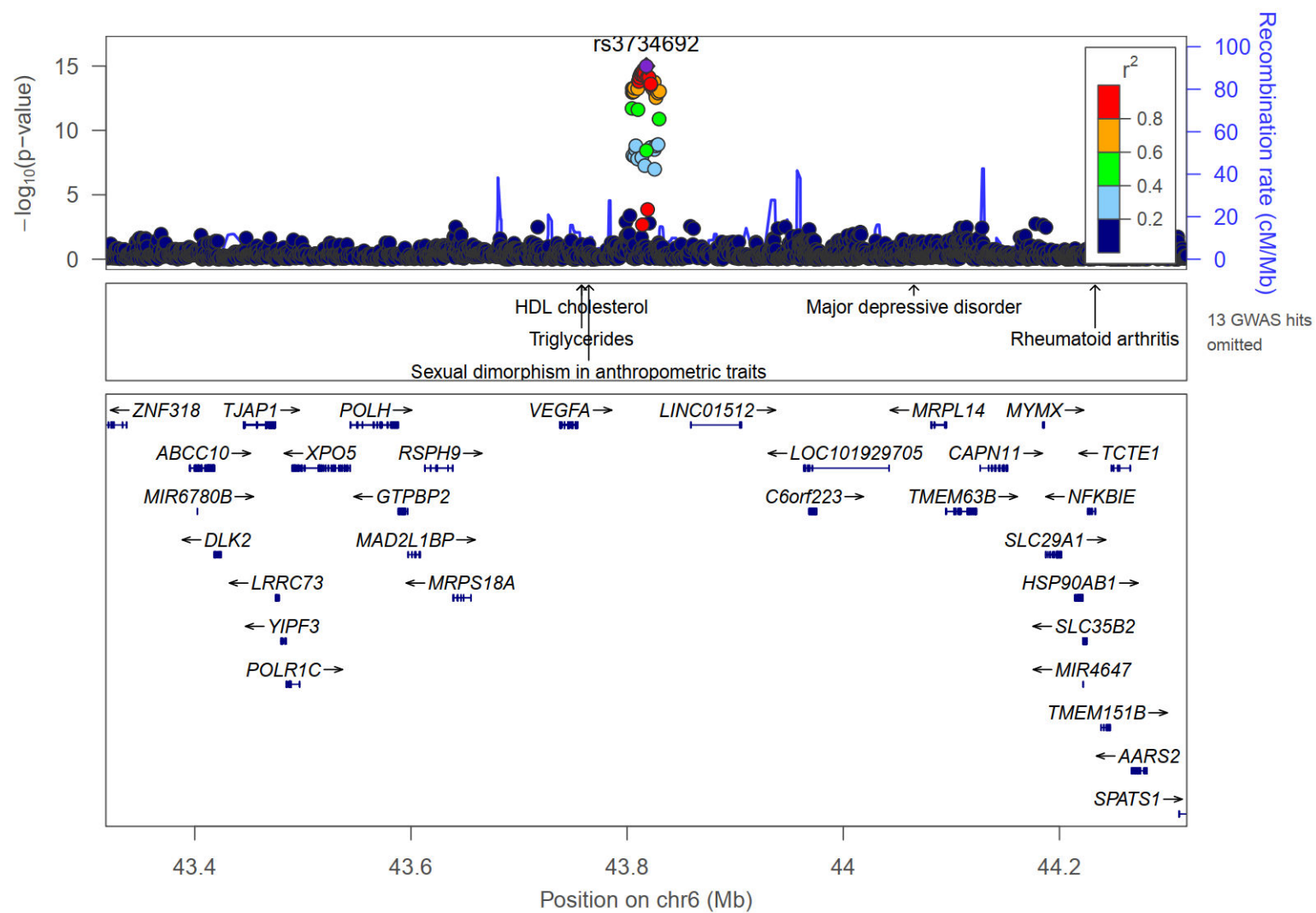


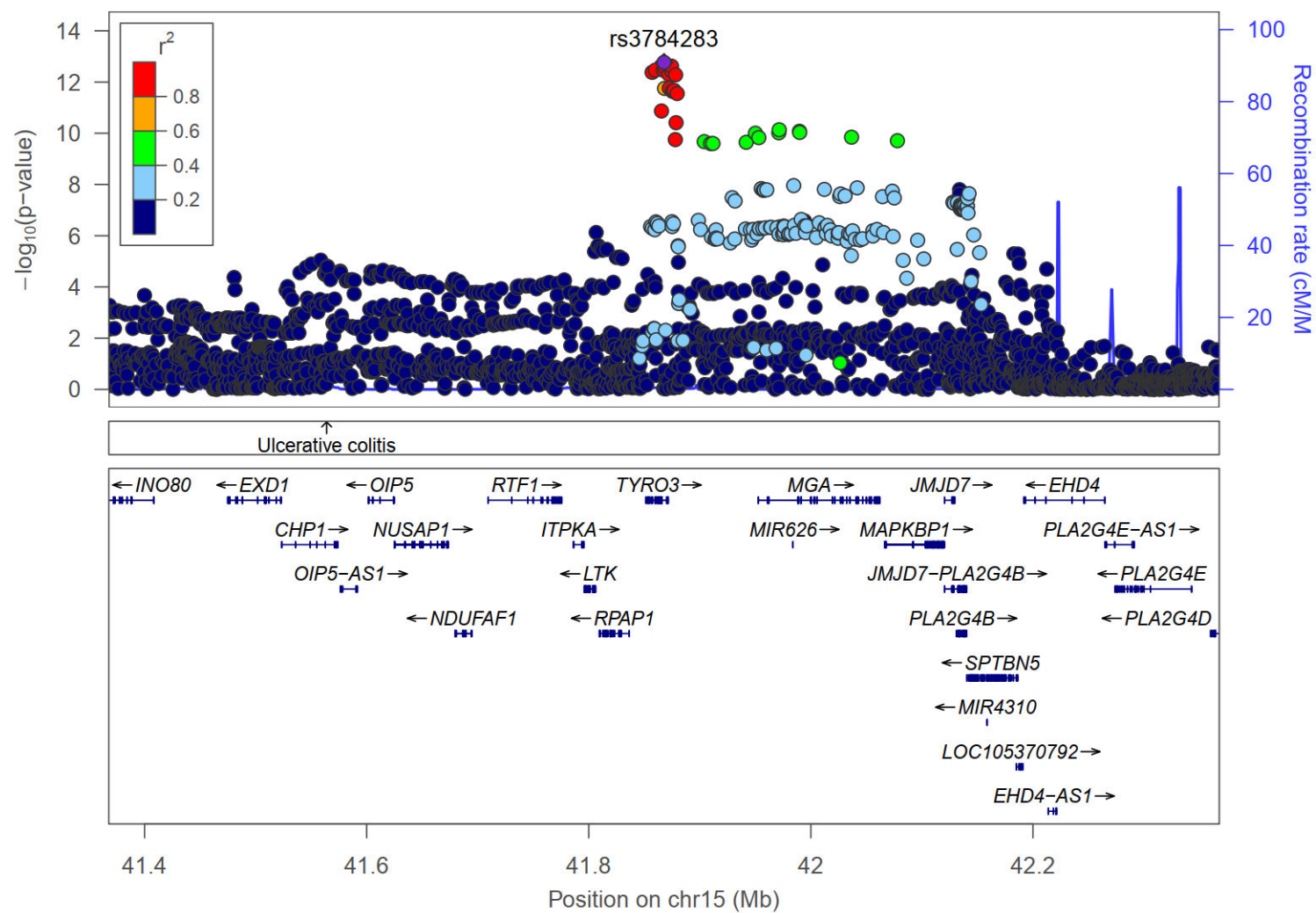


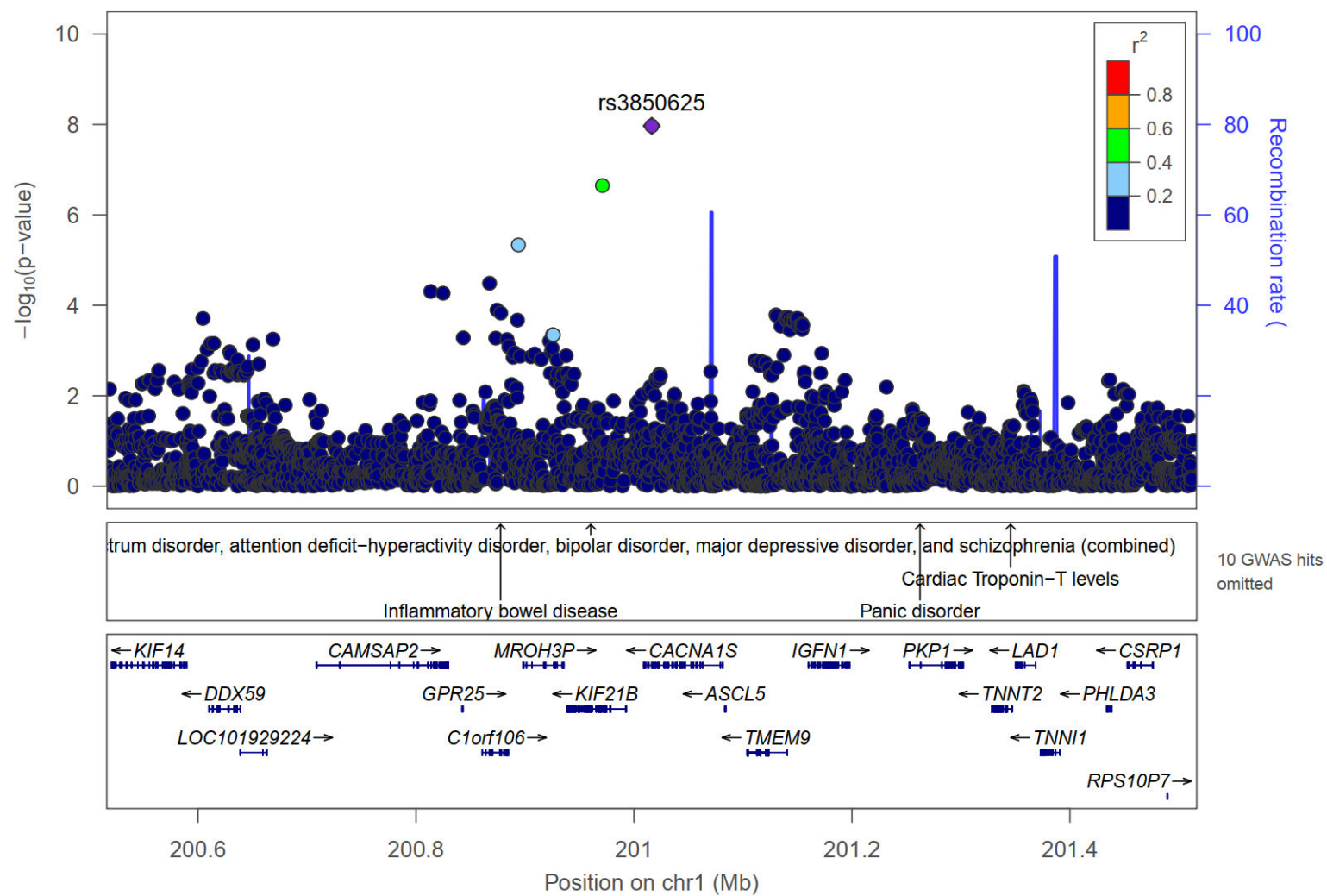


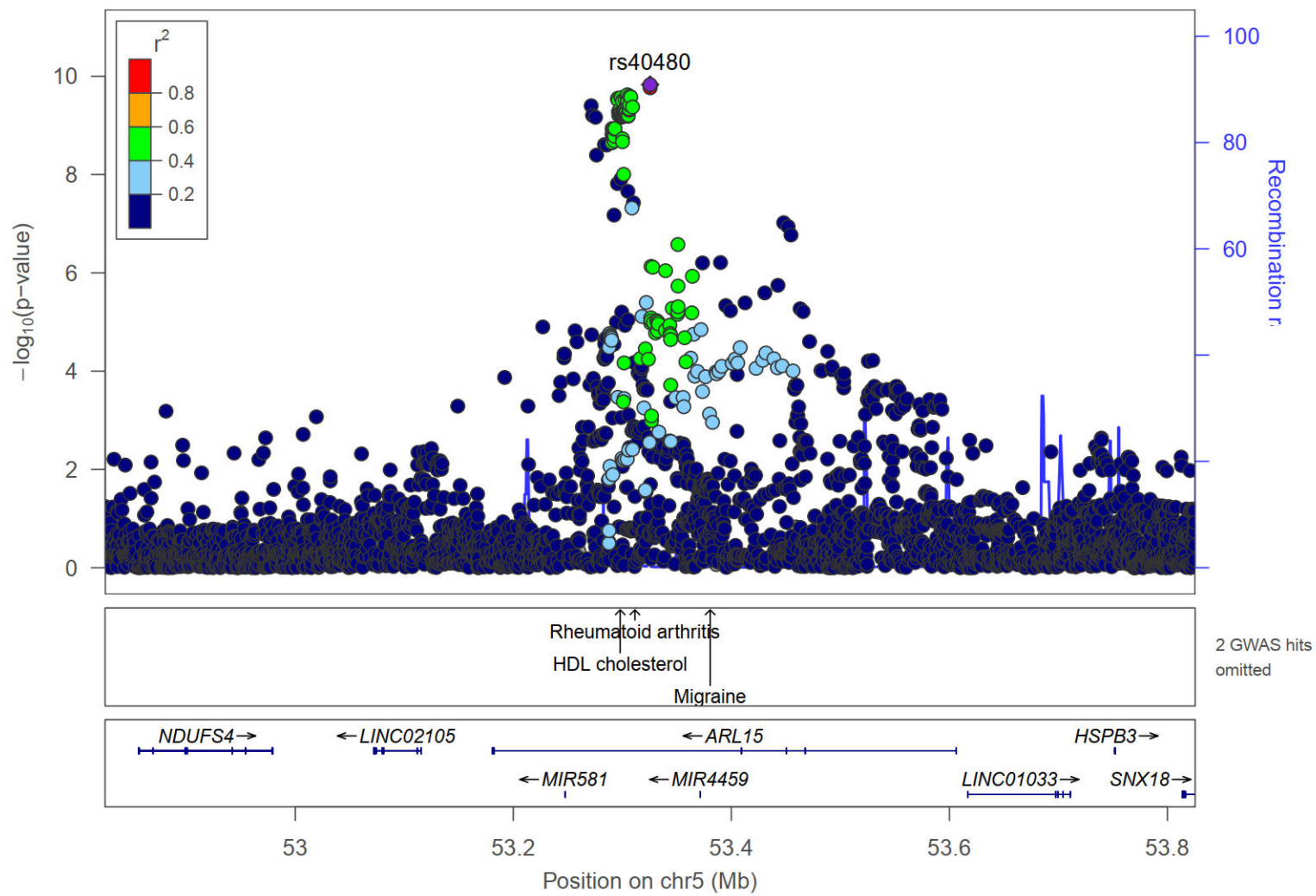


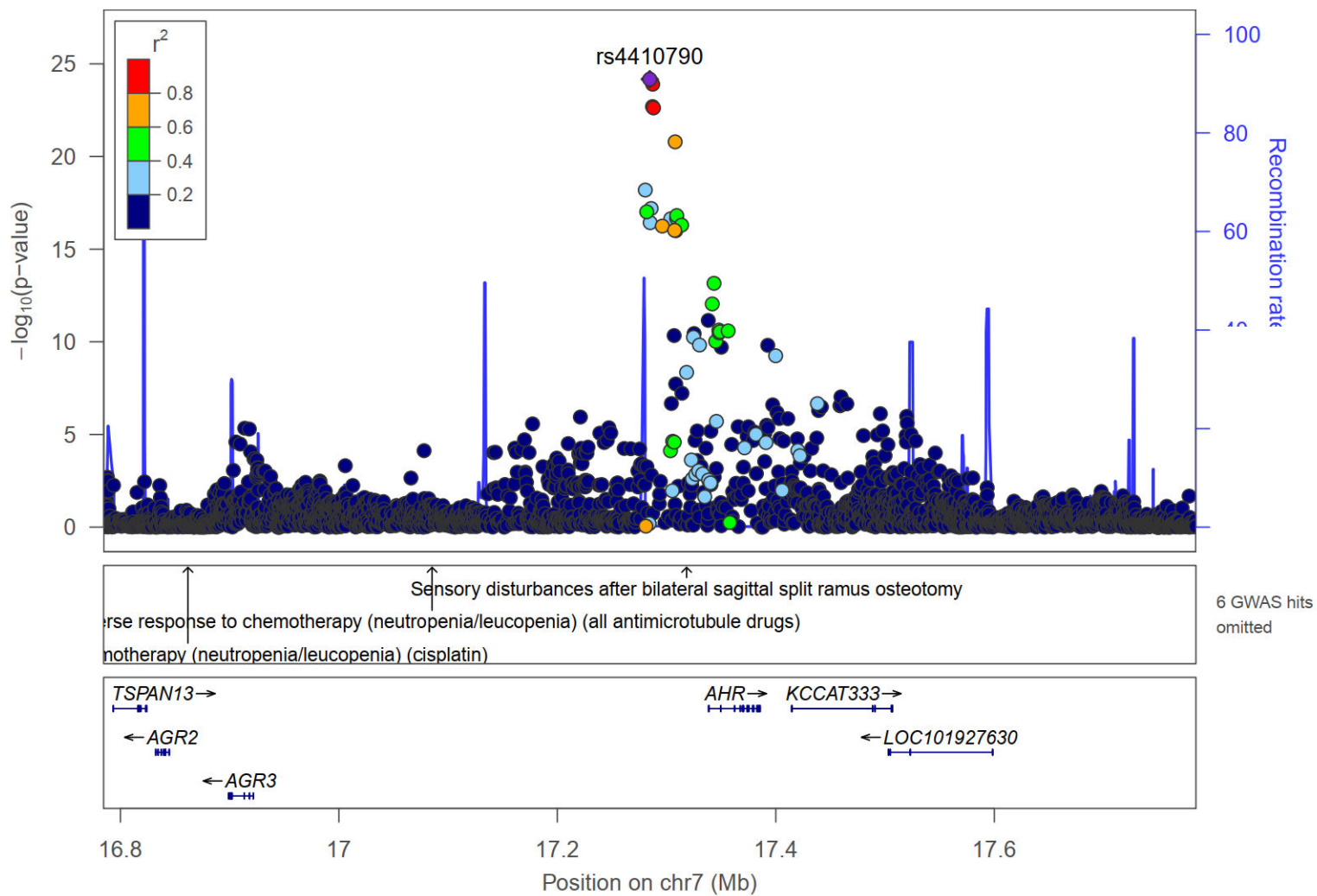


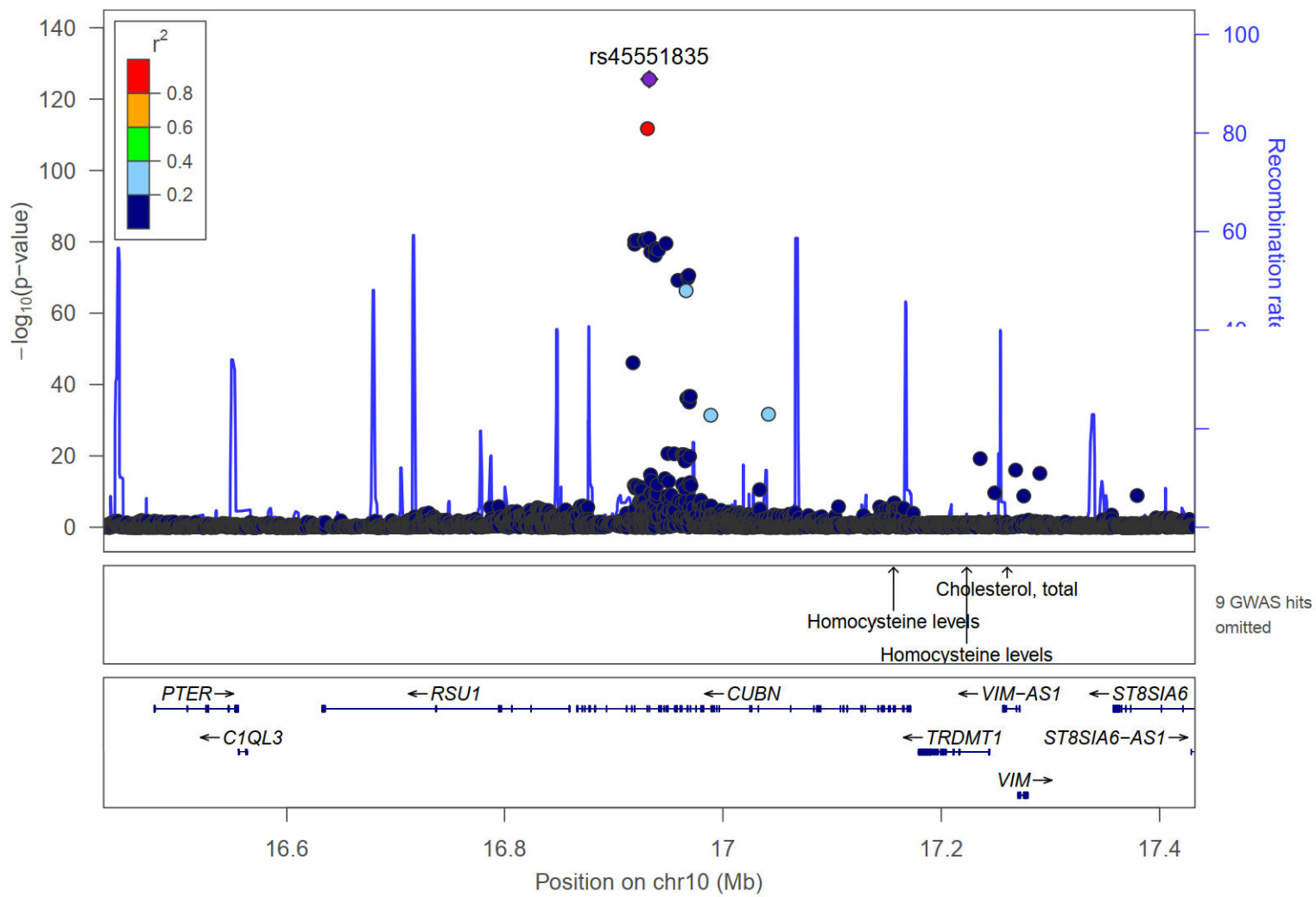


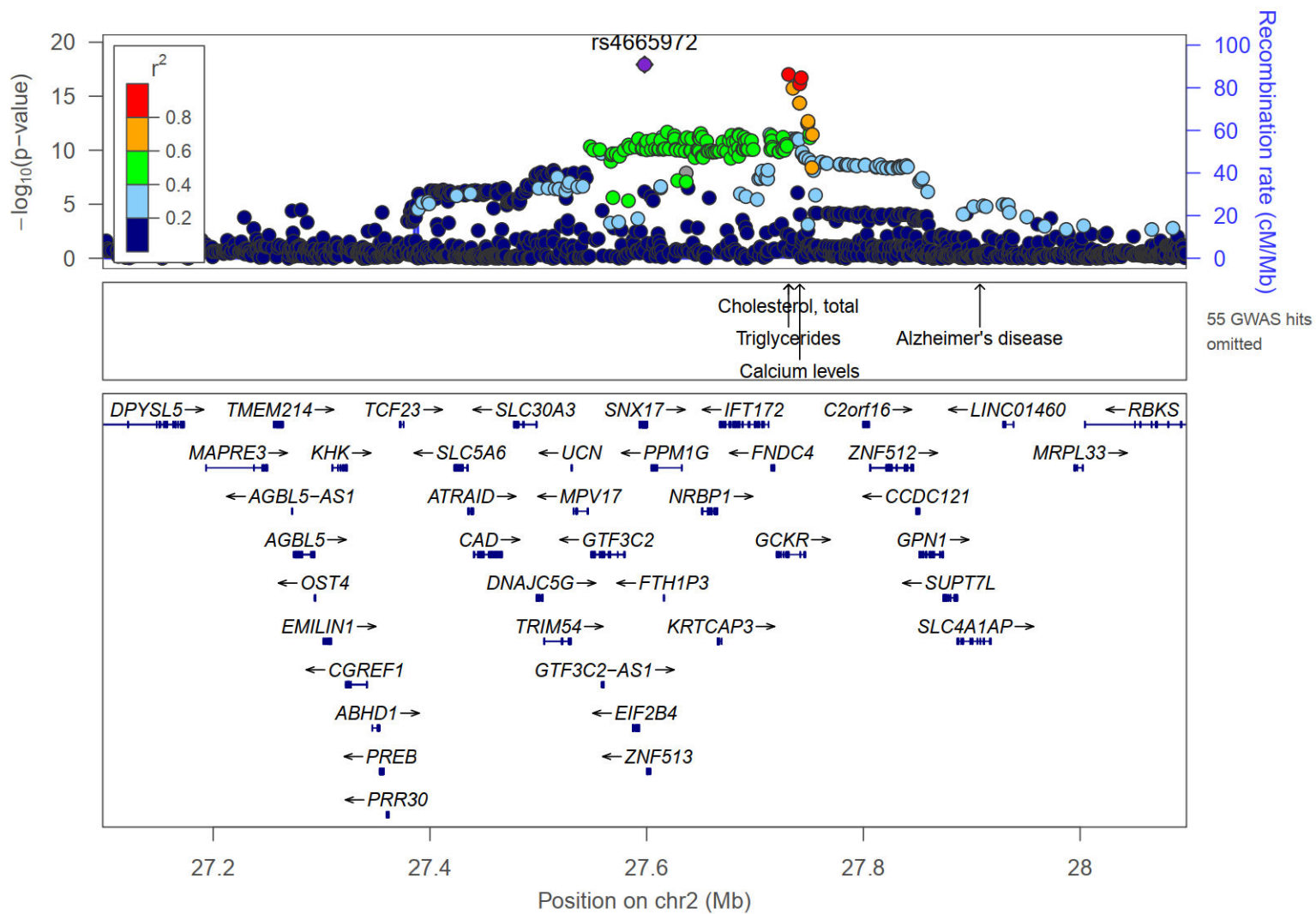


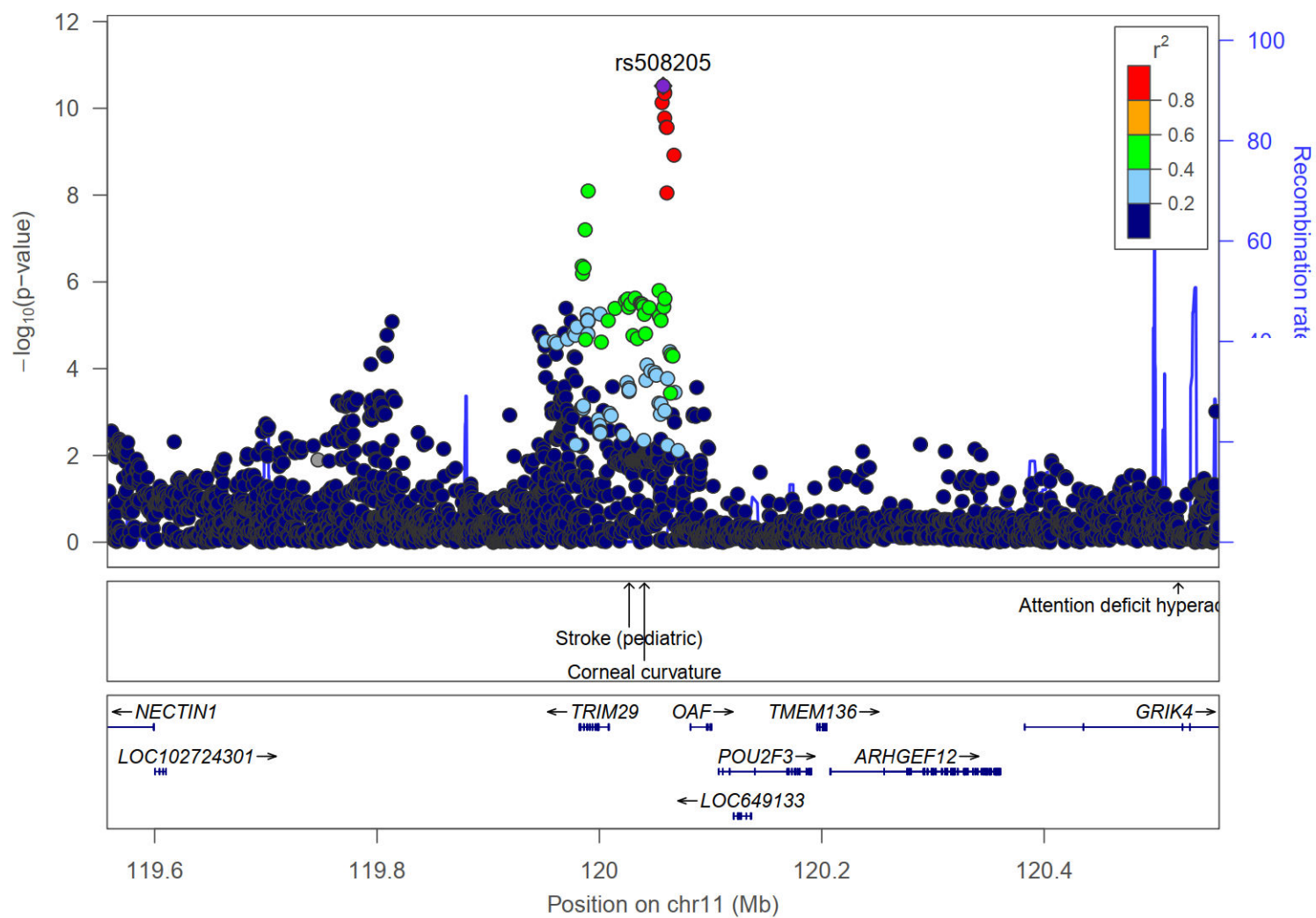


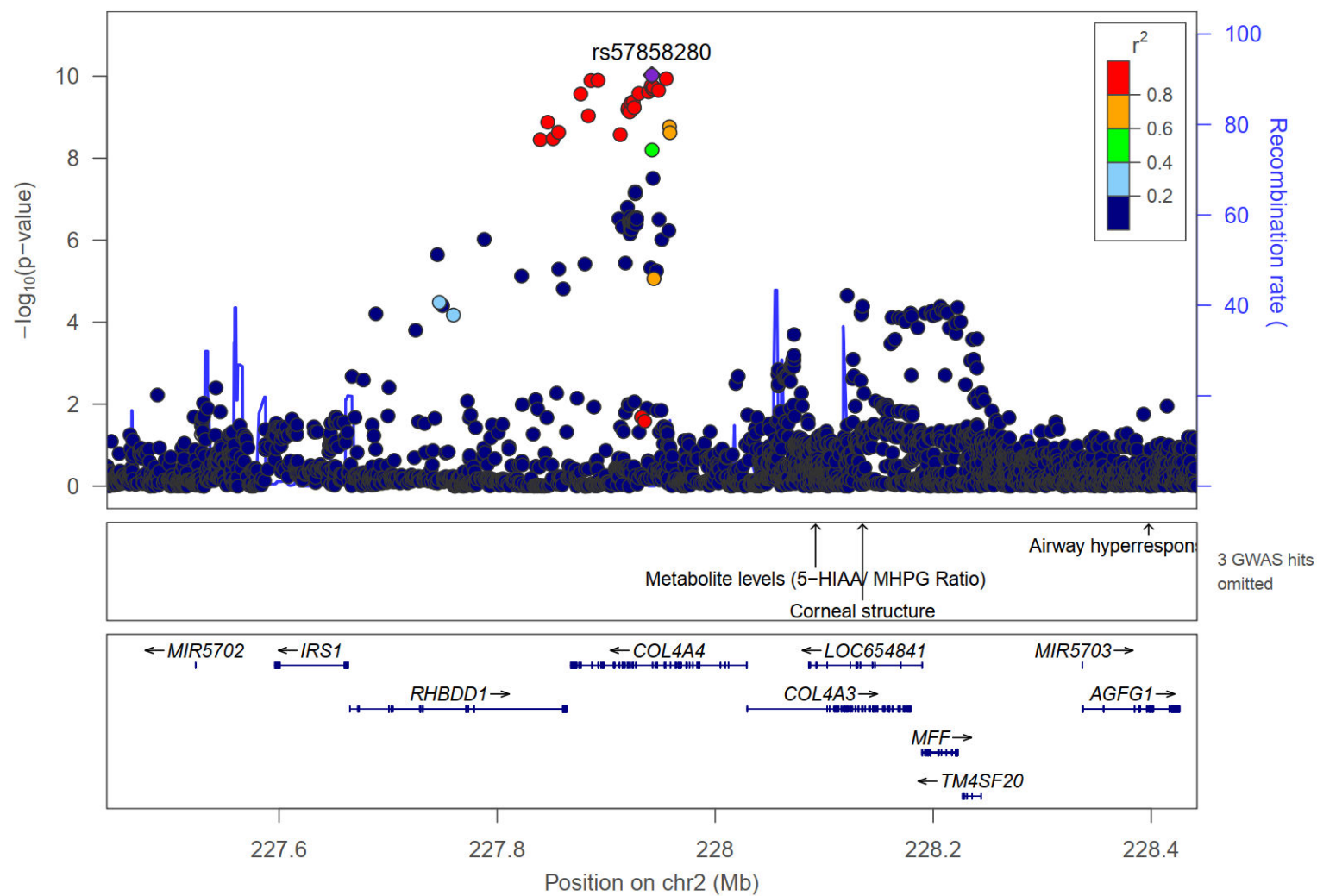


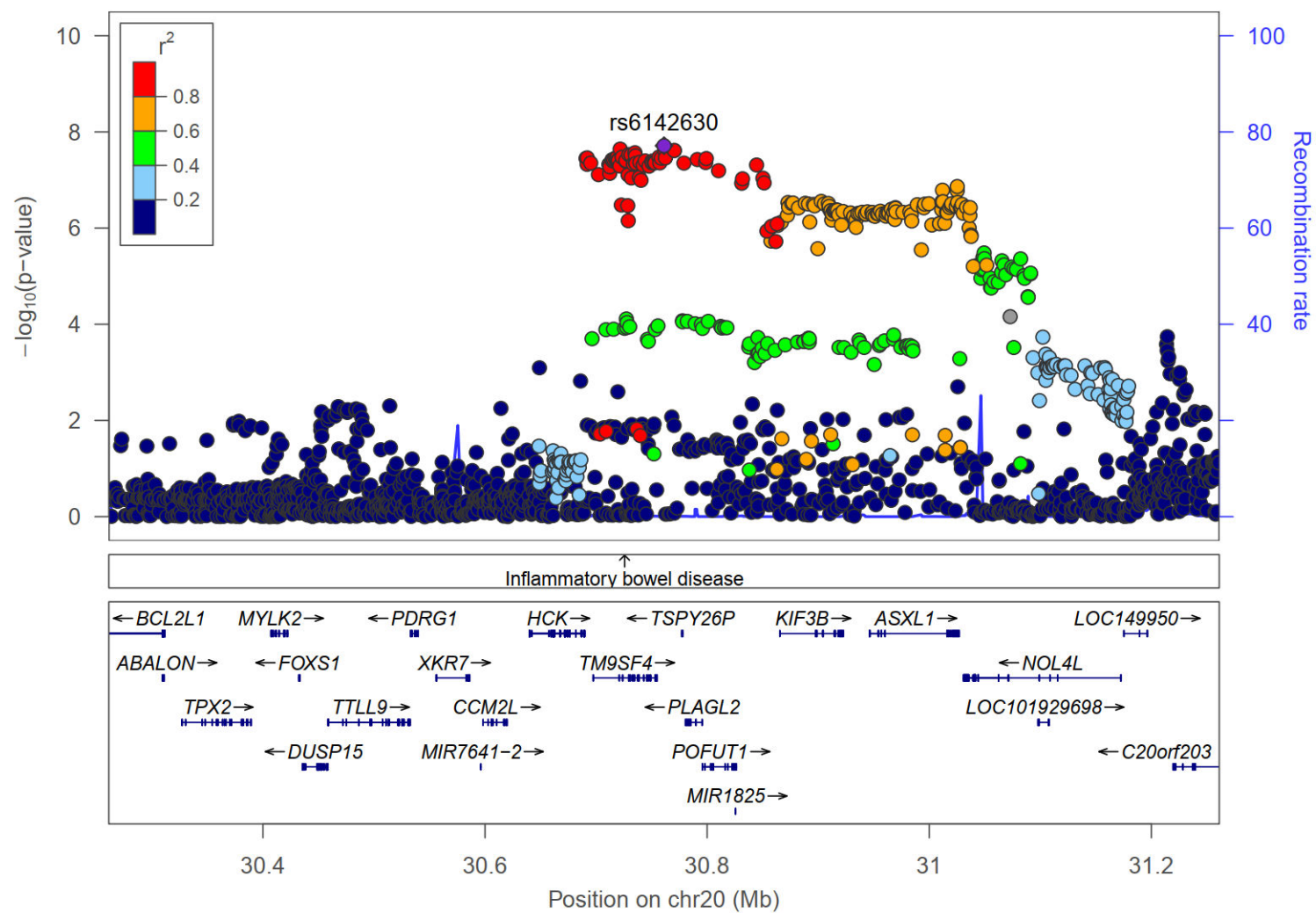


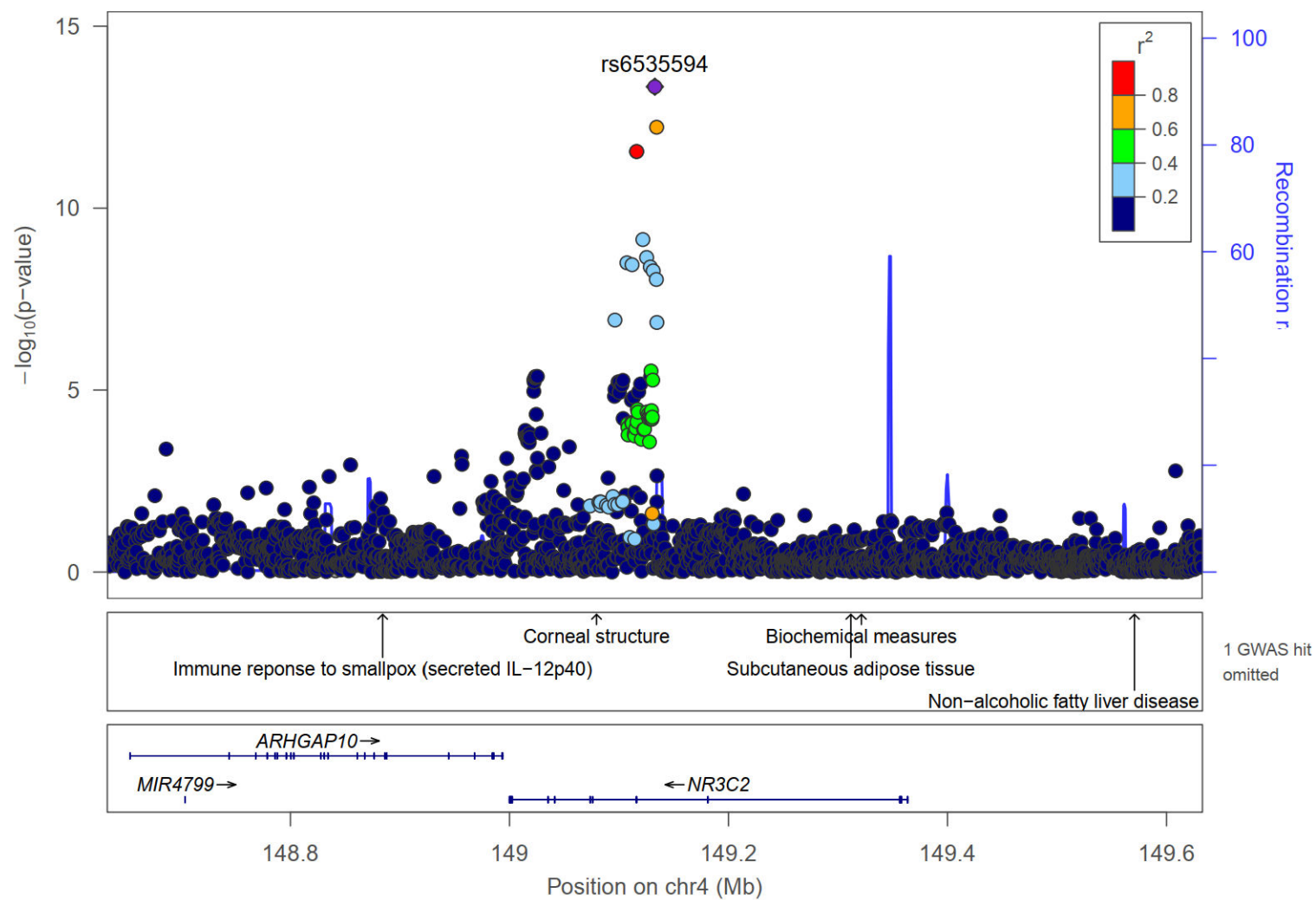


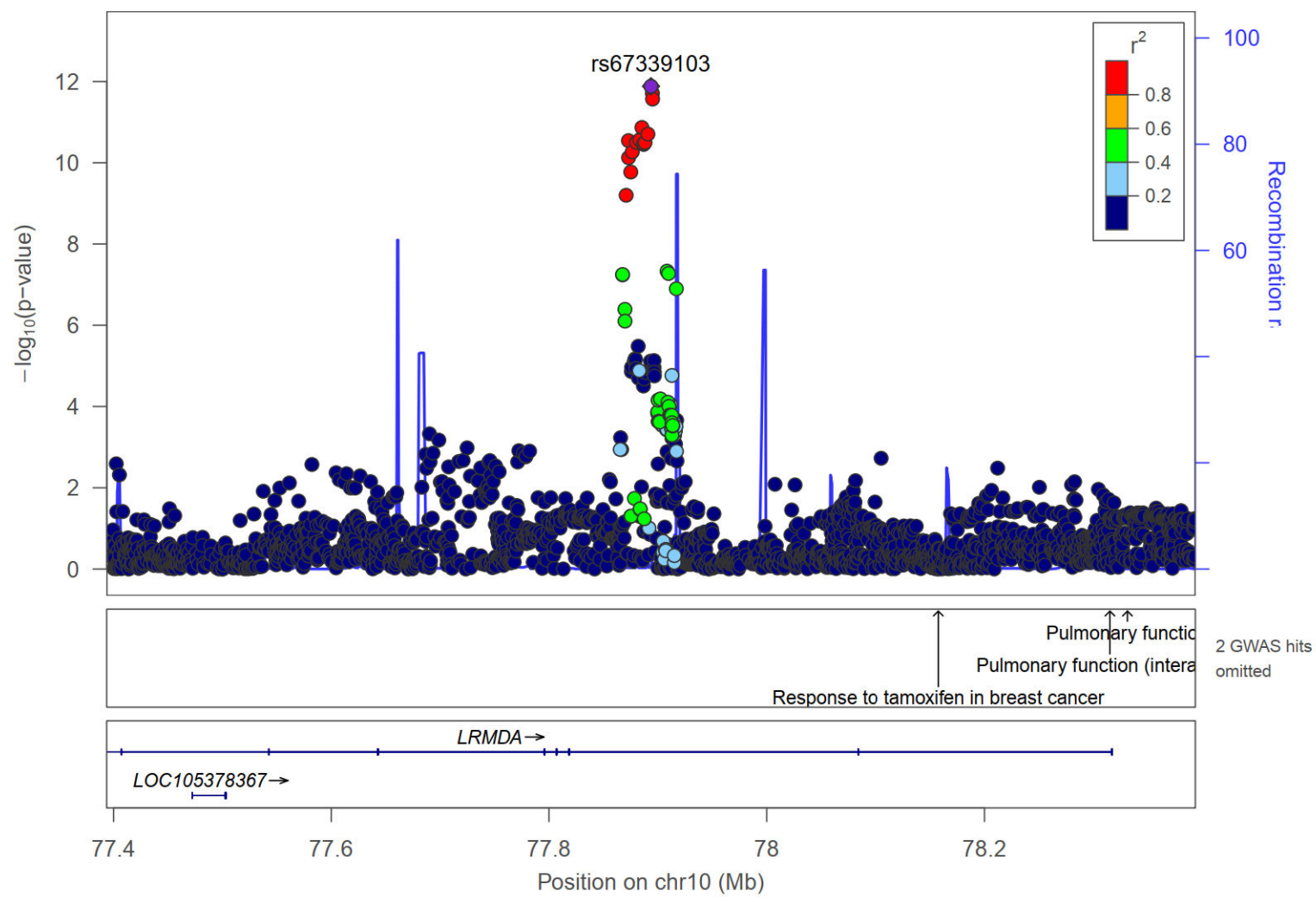


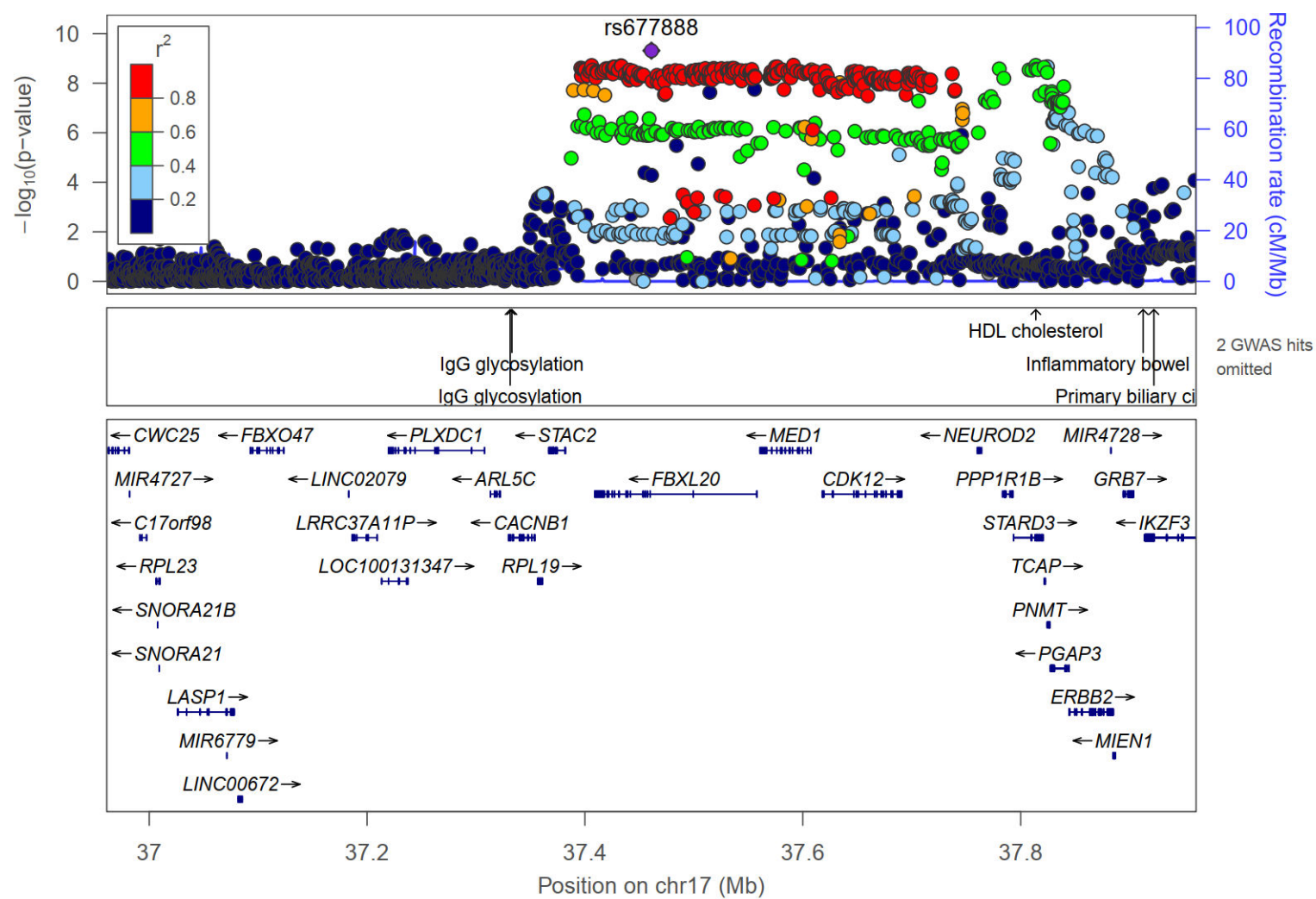


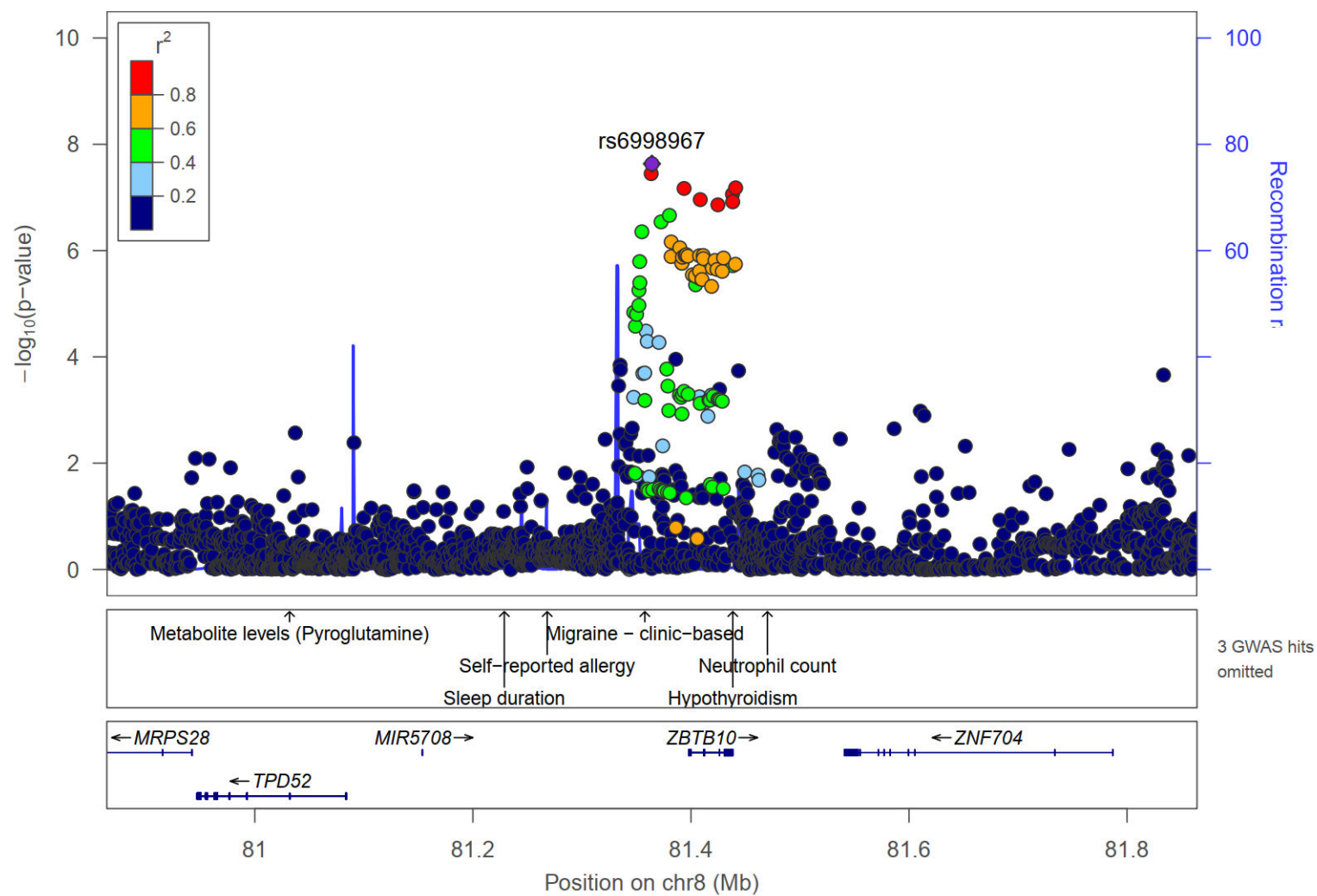


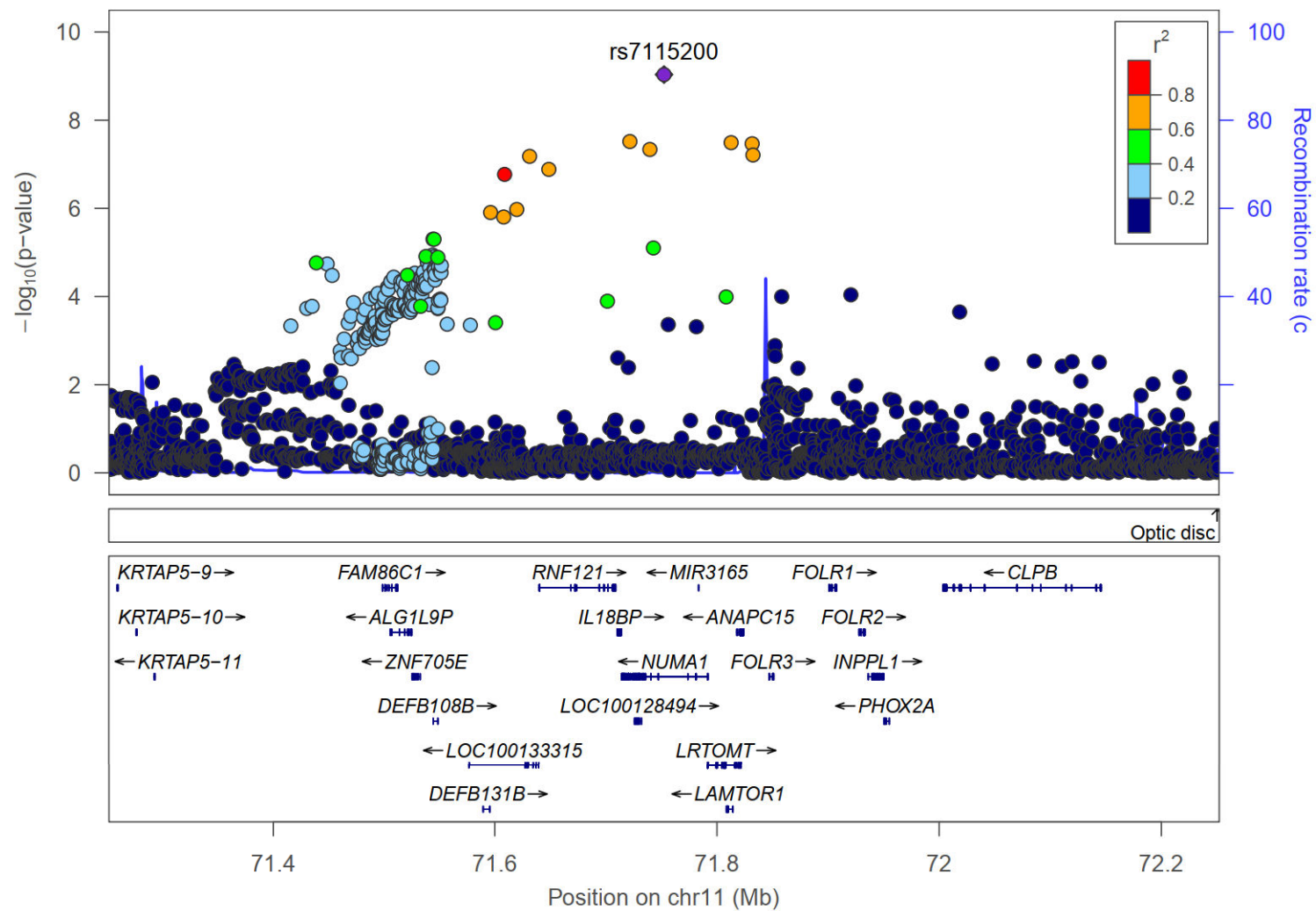


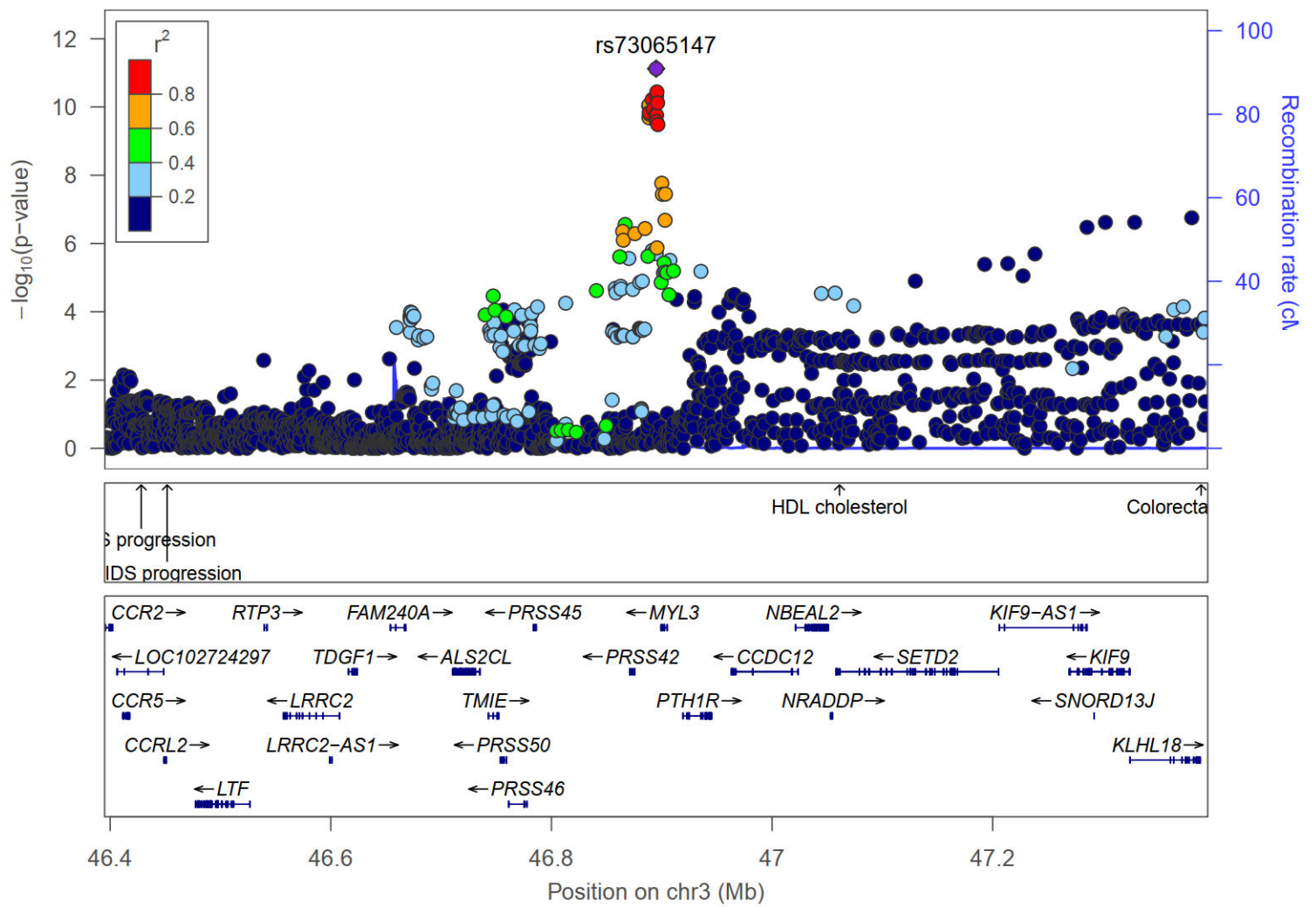


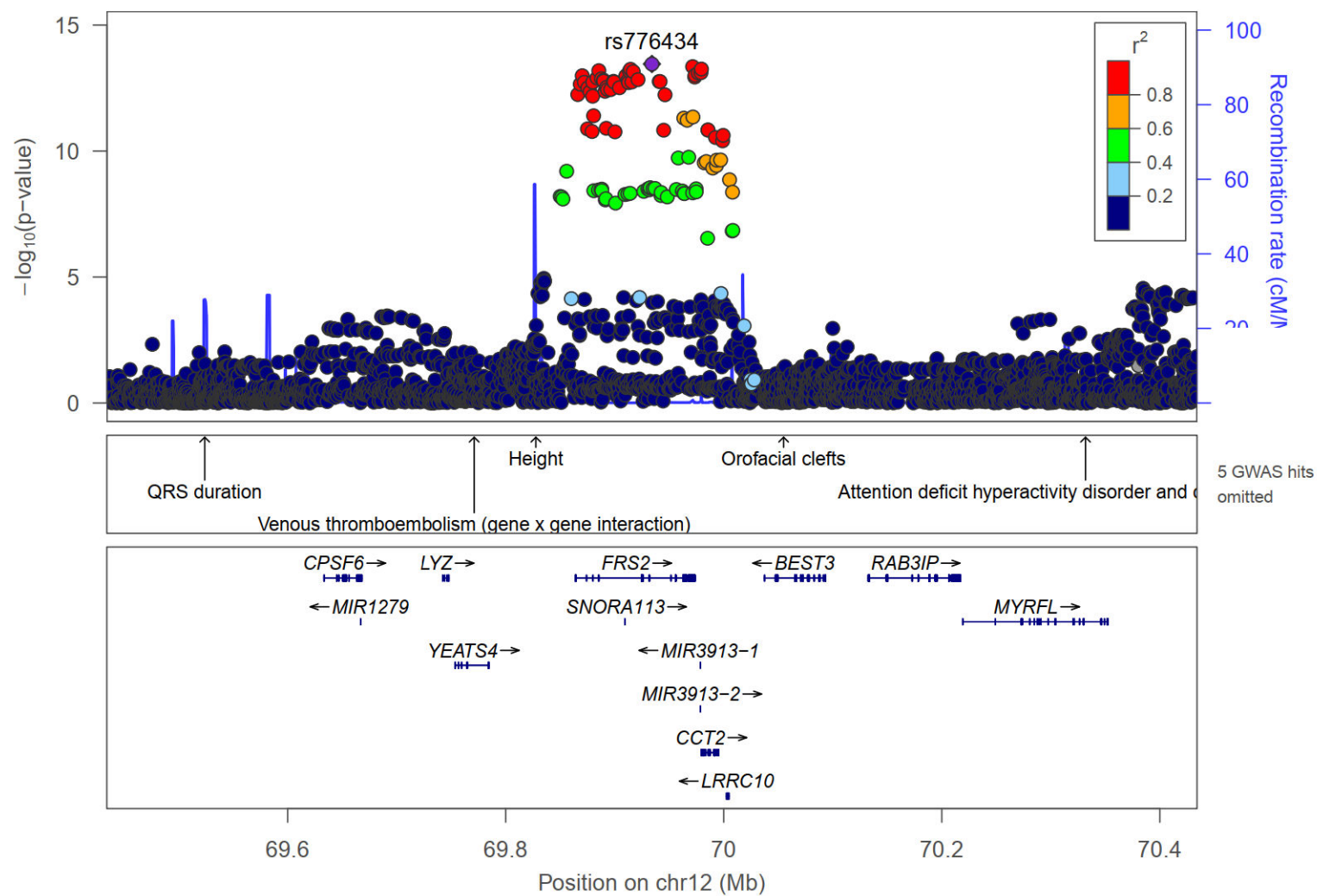


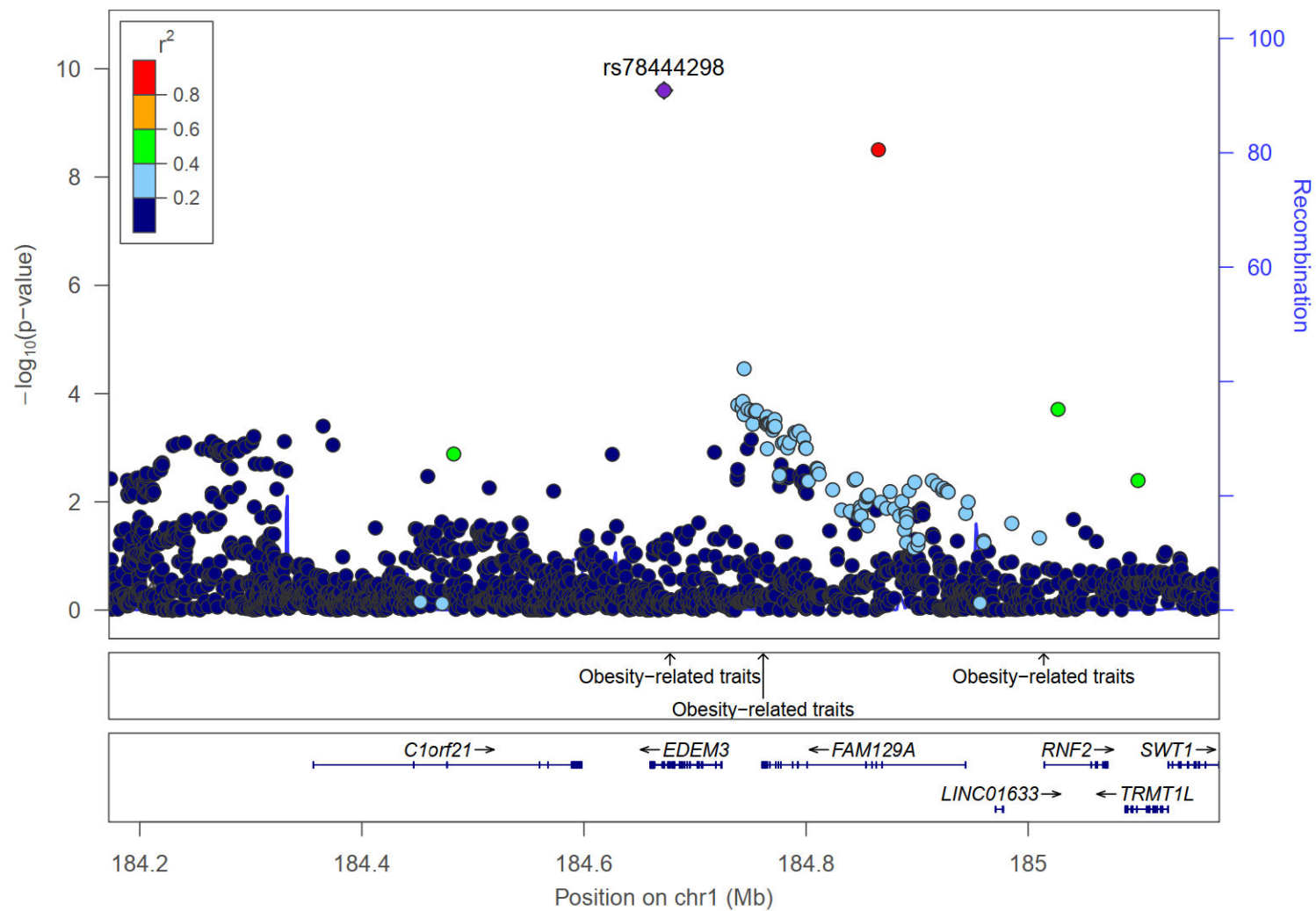


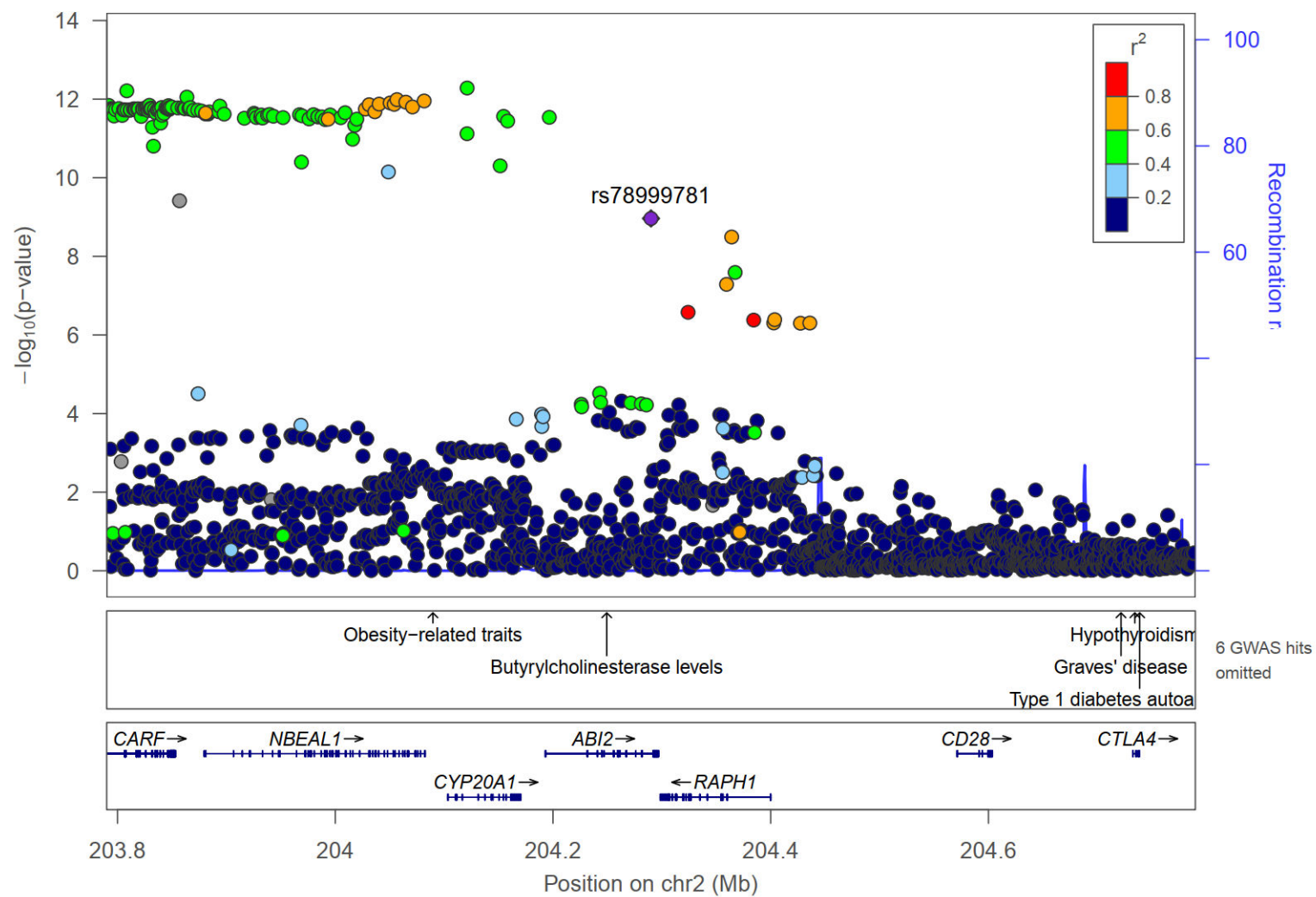


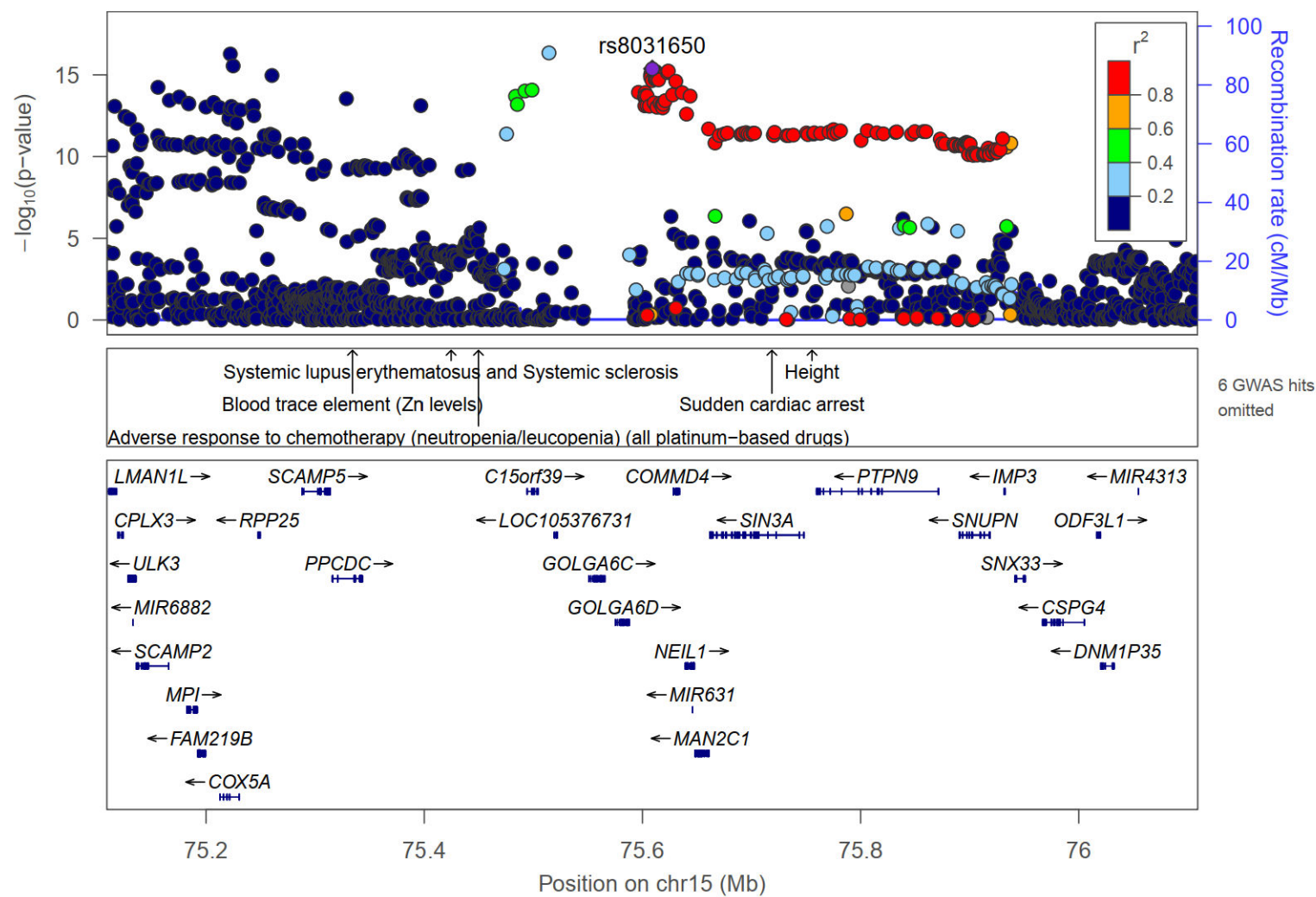


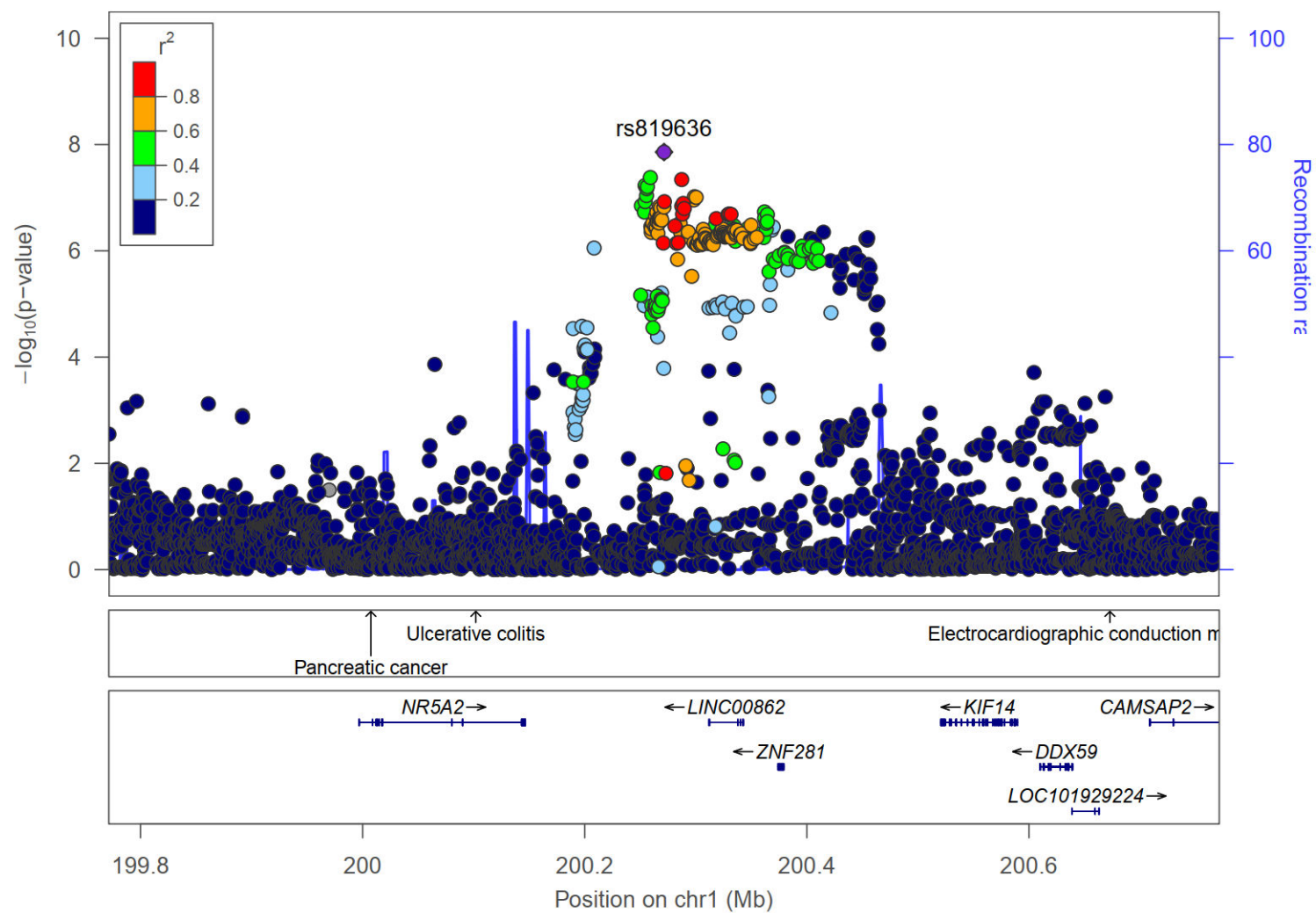






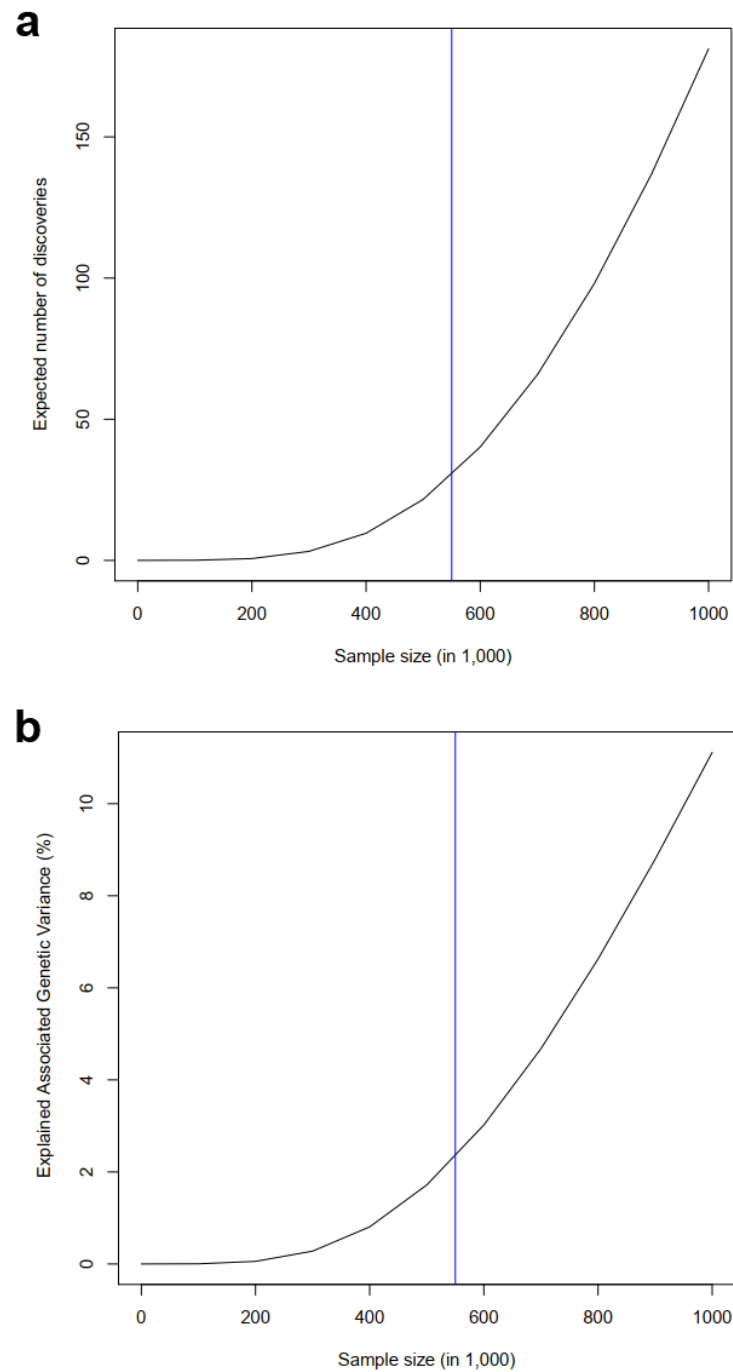






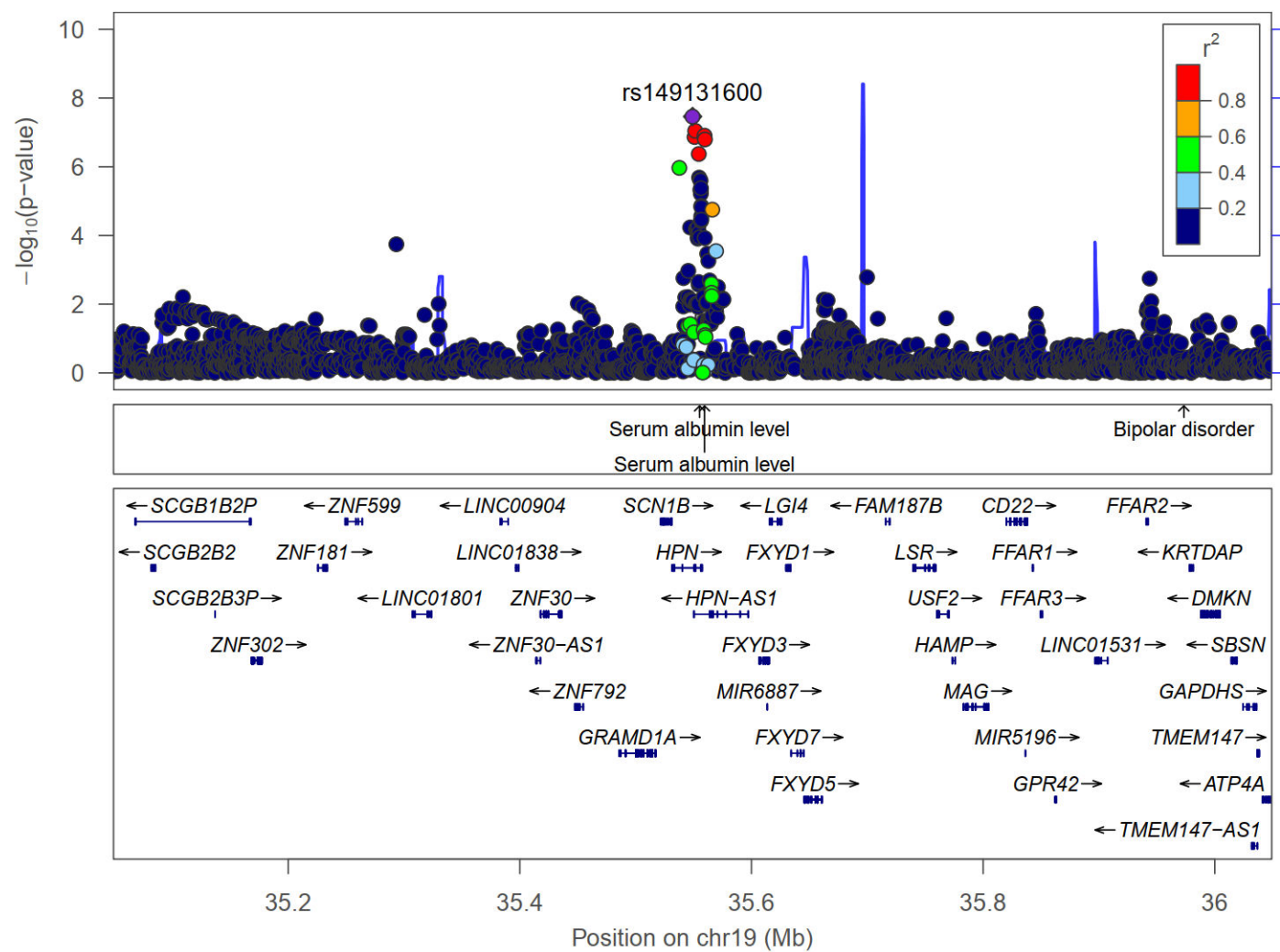
Regional association plots are shown for all genome-wide significant index SNPs. The dots are plotted on the y-axis according to their meta-analysis association p-value, and colored according to their correlation r^2 with the index SNP estimated based on the 1000 Genomes EUR reference samples (gray for missing data). Plots were generated using the stand-alone version 1.3 of LocusZoom². Genetic positions refer to GRCh37/hg19 coordinates.

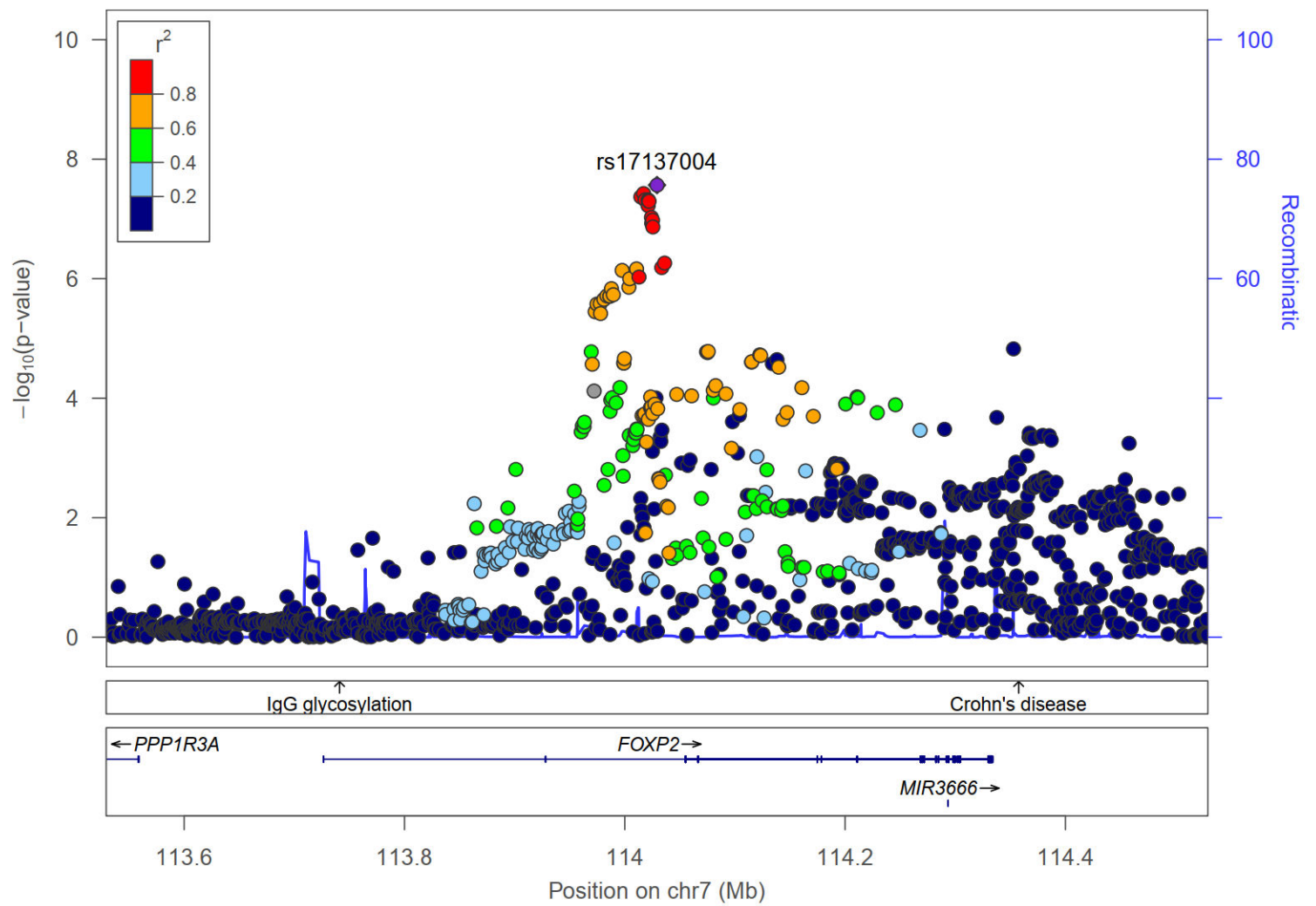
Supplementary Figure 3: Expected number of discoveries at increasing GWAS discovery sample sizes.

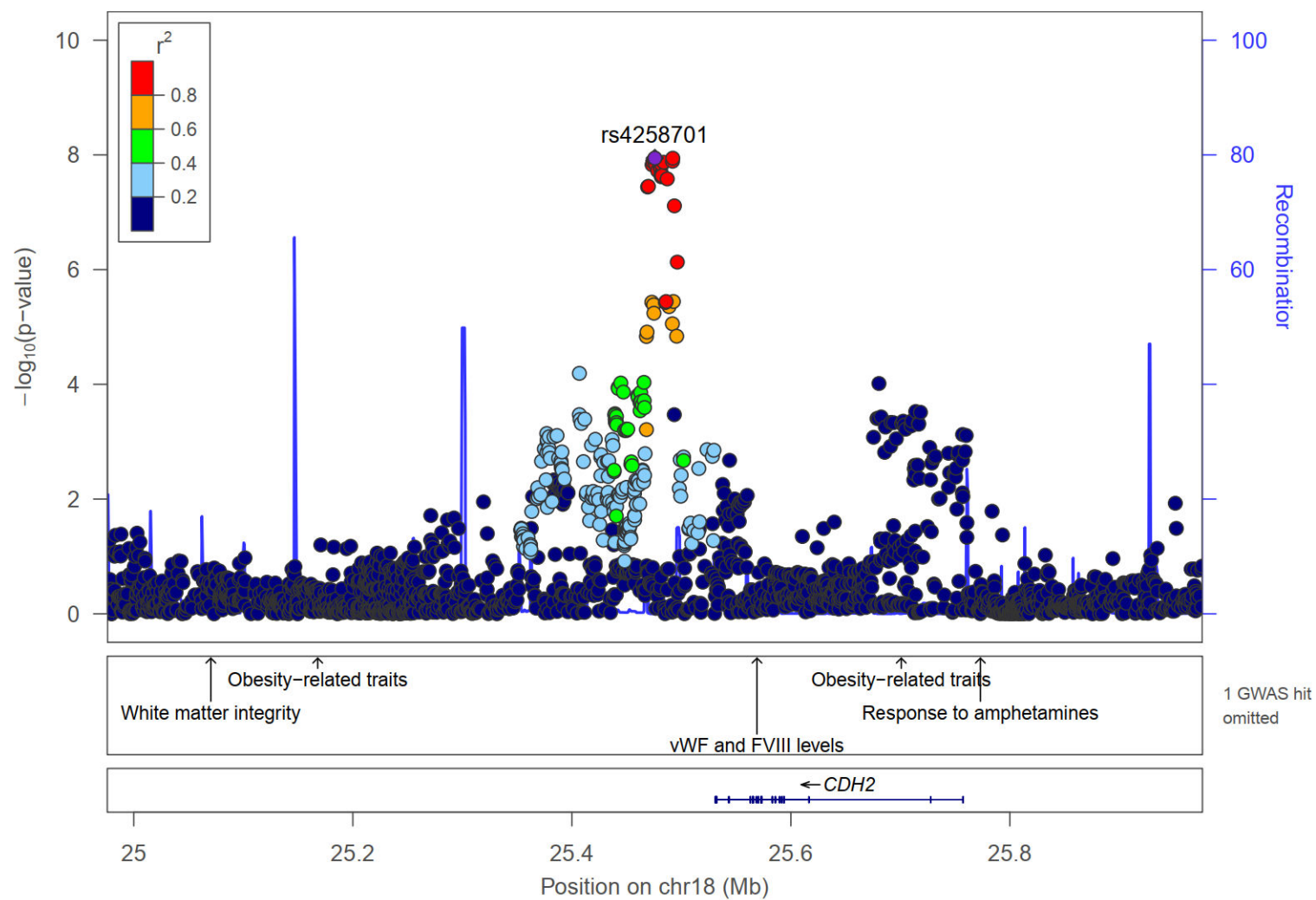


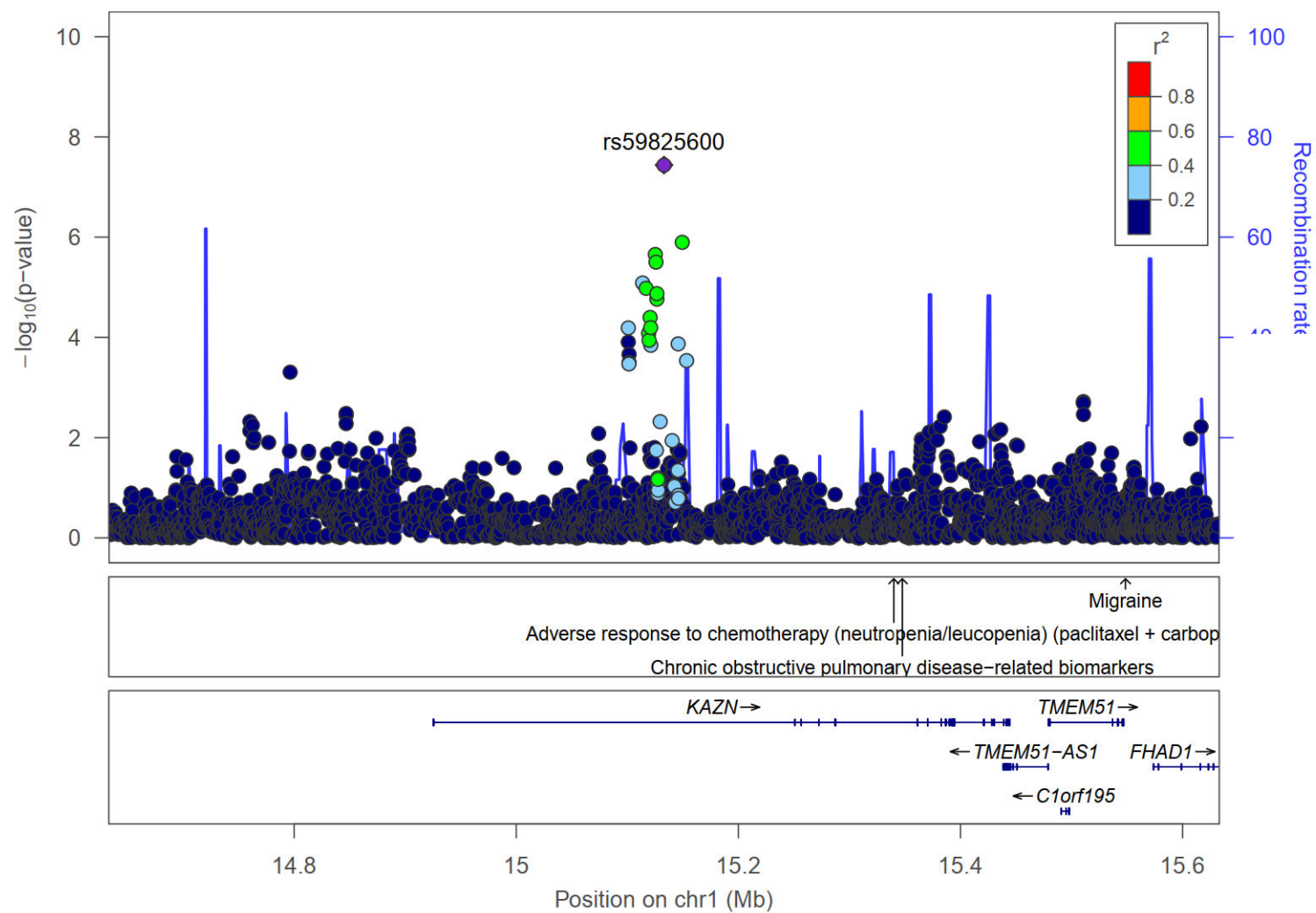
The panels show the estimate the number of expected discoveries (a) and the corresponding percentage of GWAS heritability explained (b) with increases in sample size using the summary statistics of our UACR trans-ethnic meta-analysis as input. The vertical blue line marks the number of predicted discoveries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

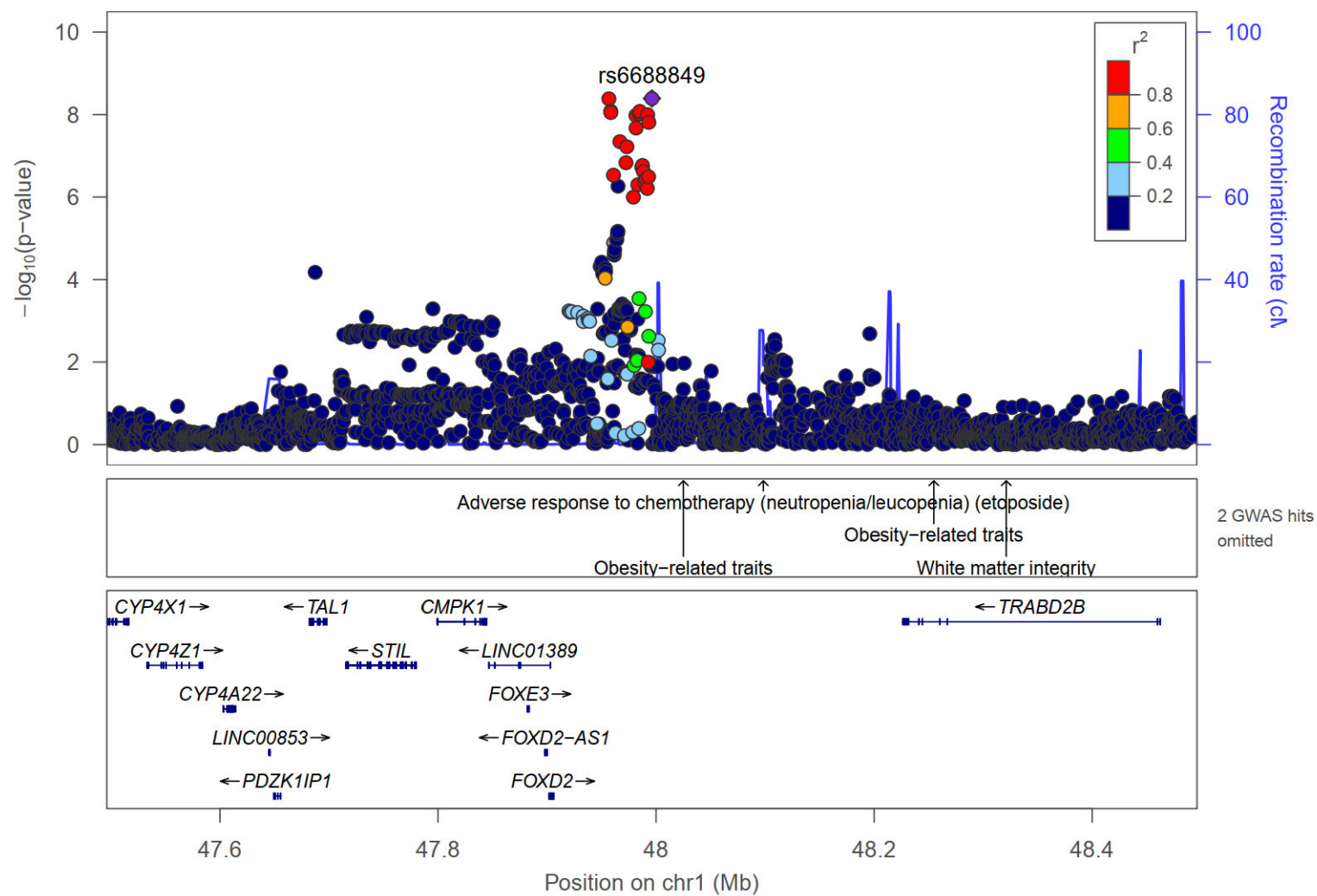
Supplementary Figure 4: Regional association plots for loci identified in trans-ethnic GWAS meta-analysis of UACR among individuals with diabetes

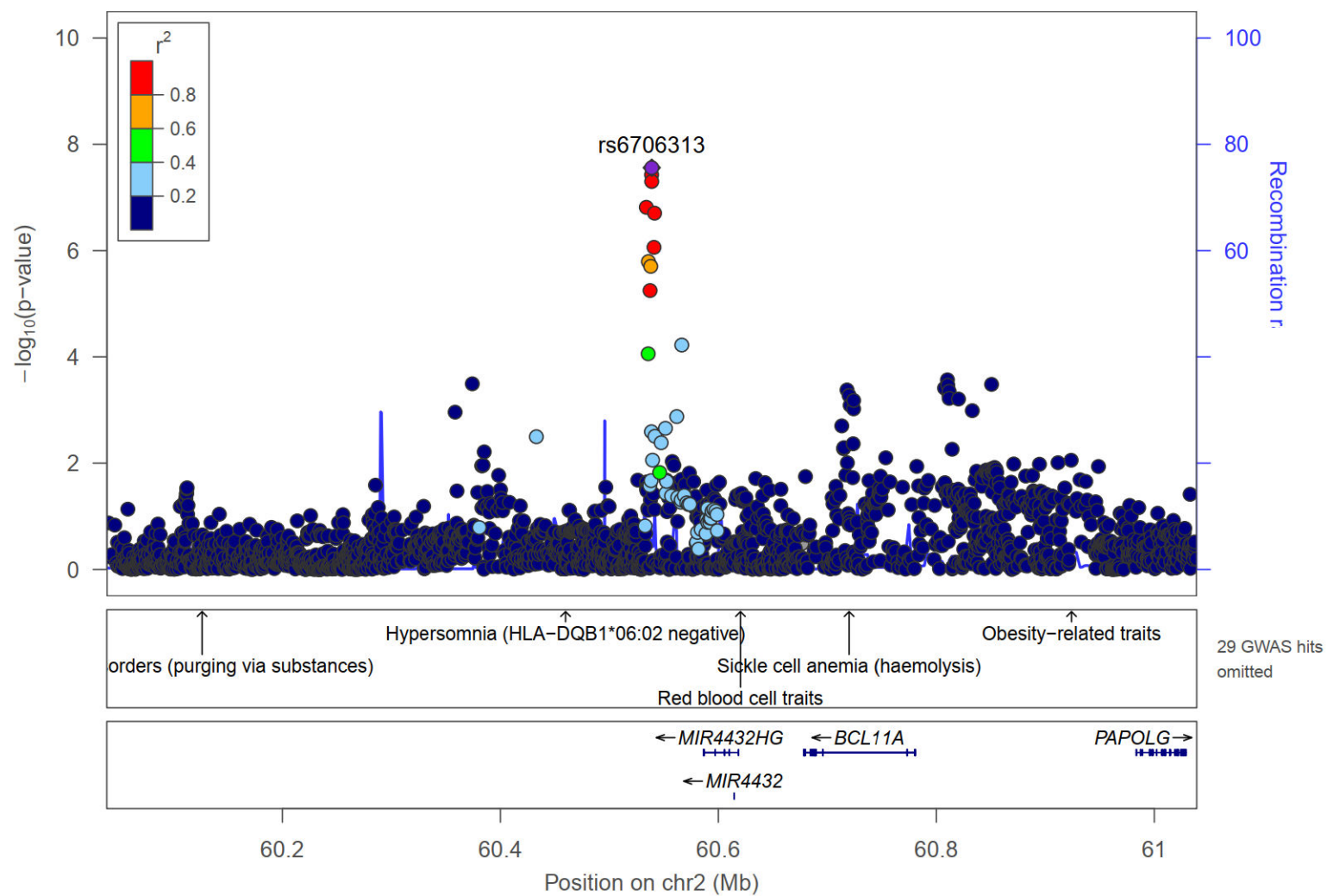


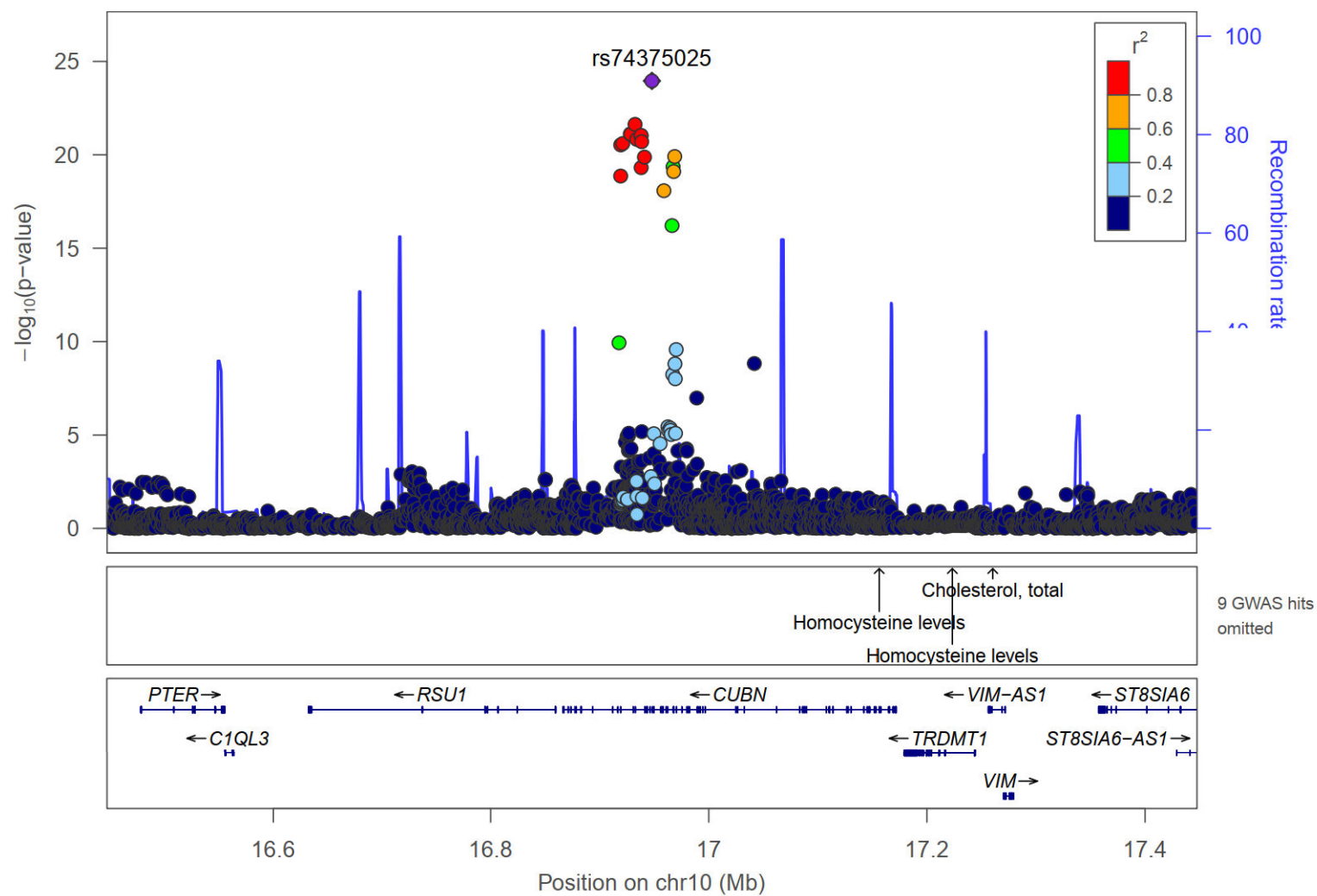


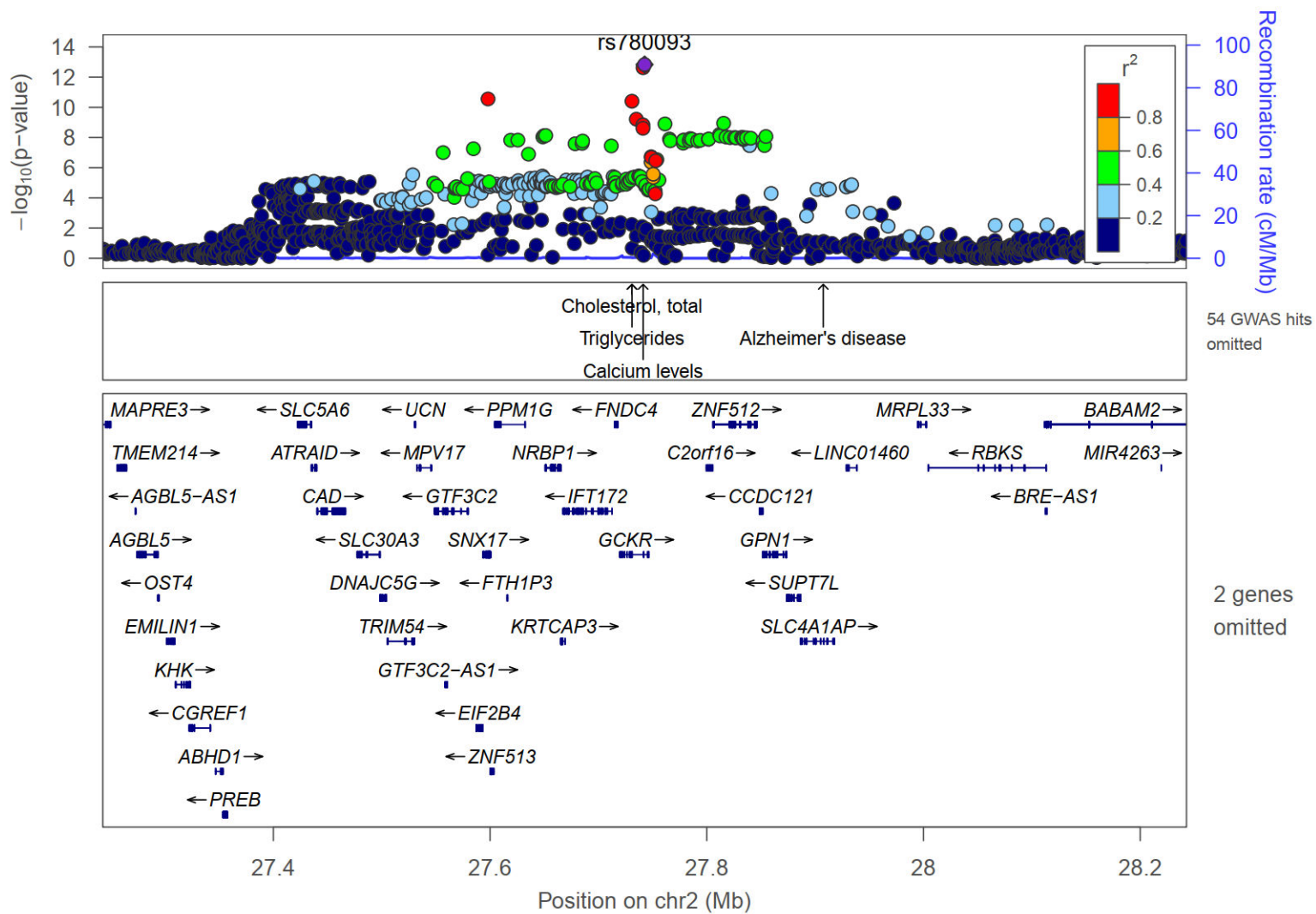






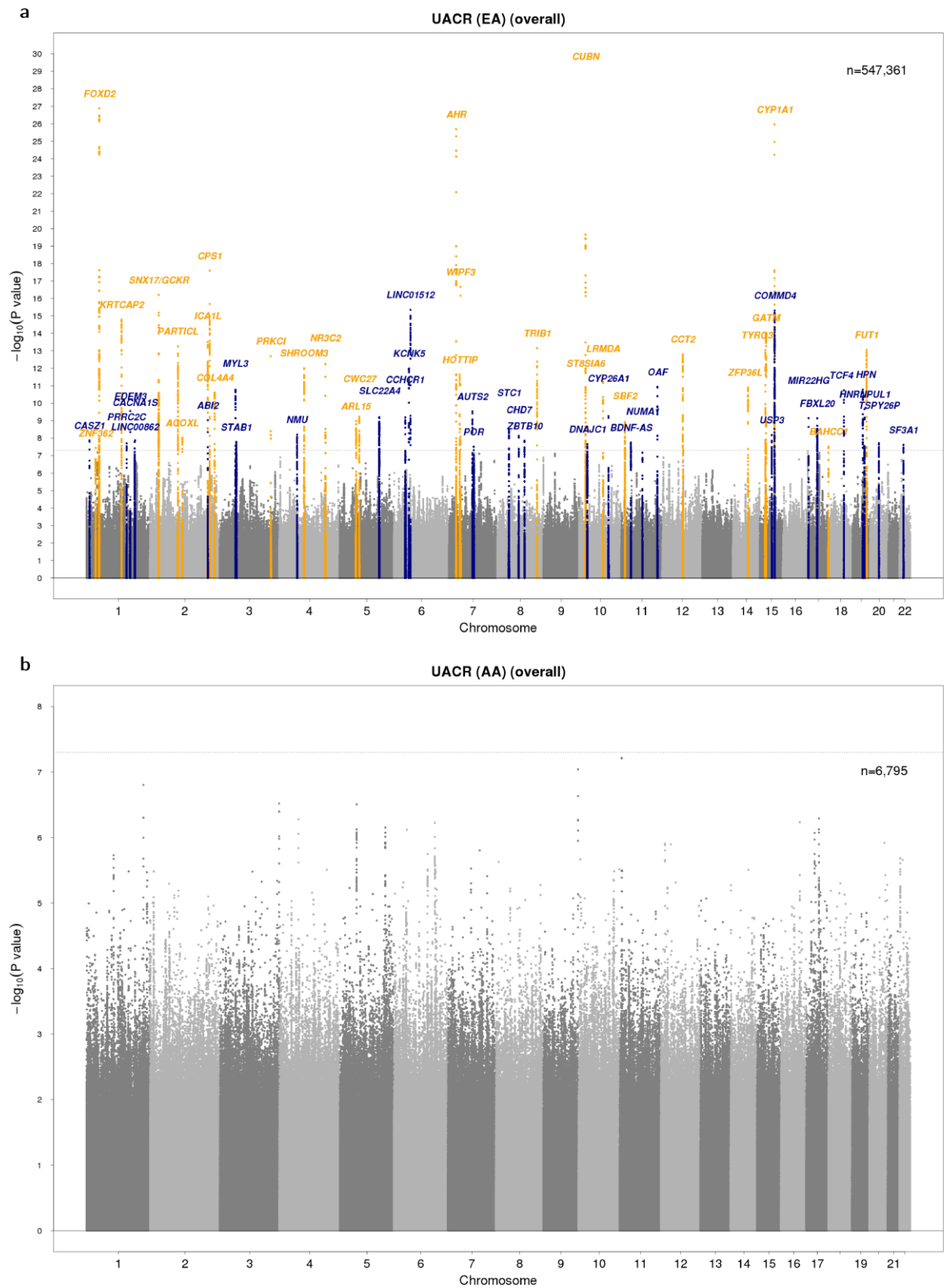


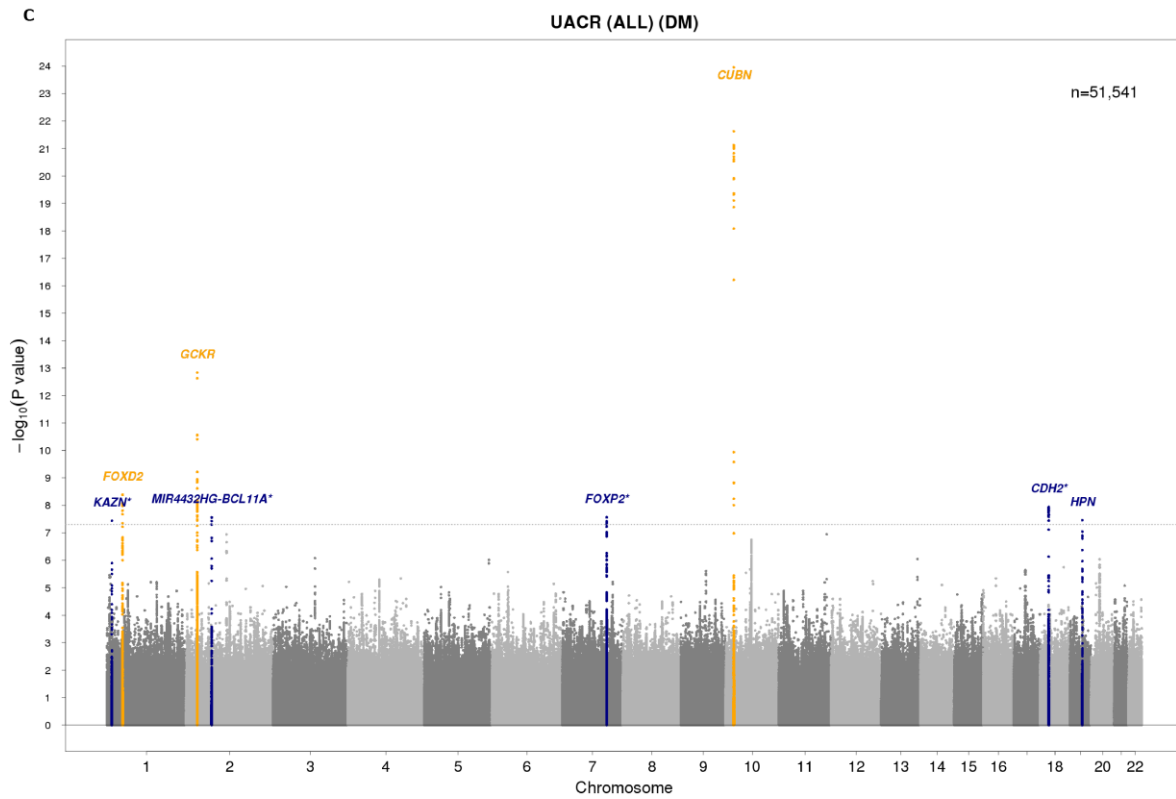




Regional association plots are shown for all genome-wide significant index SNPs. The dots are plotted on the y-axis according to their meta-analysis association p-value, and colored according to their correlation r^2 with the index SNP estimated based on the 1000 Genomes EUR reference samples (gray for missing data). Plots were generated using the stand-alone version 1.3 of LocusZoom². Genetic positions refer to GRCh37/hg19 coordinates.

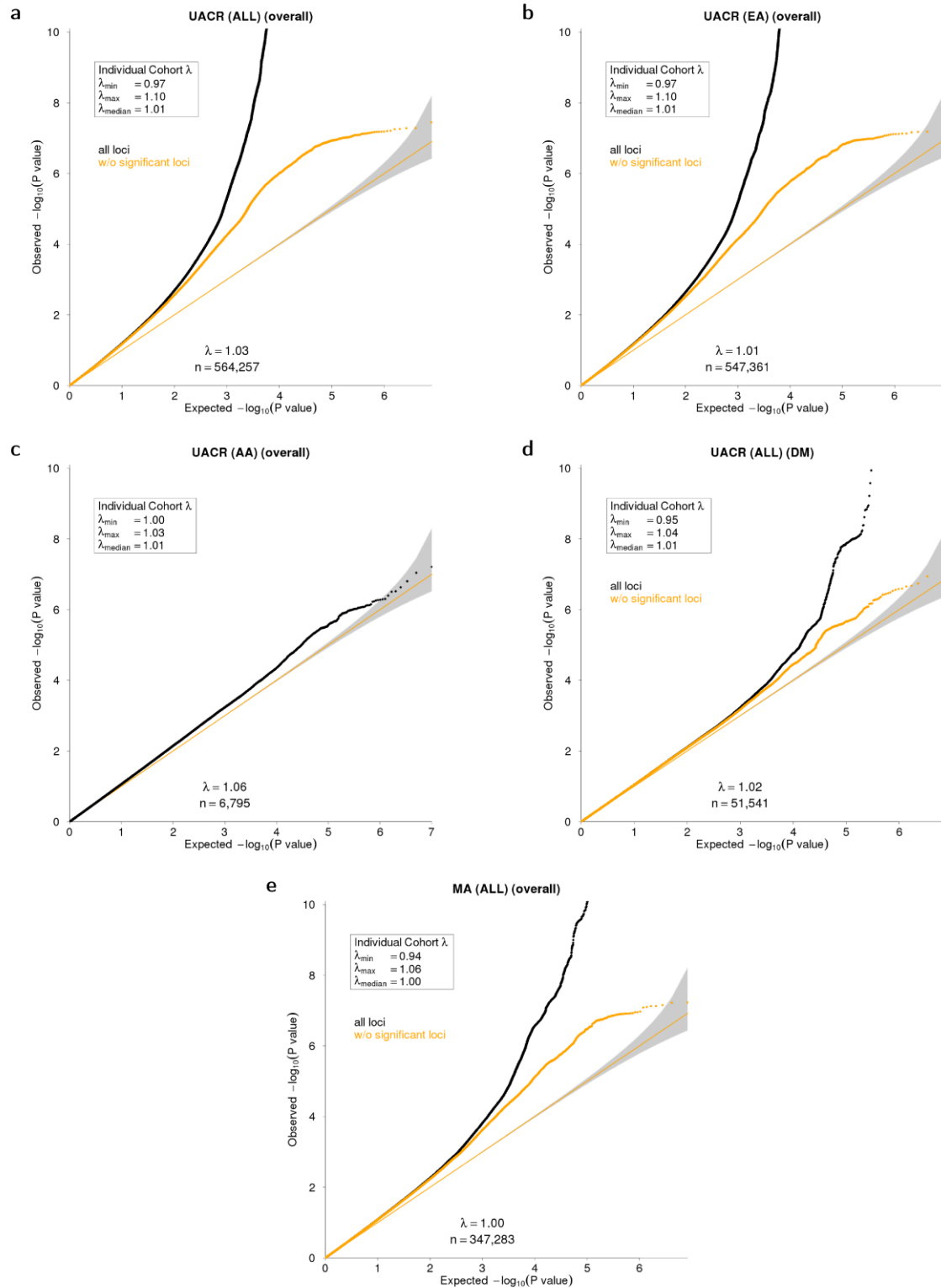
Supplementary Figure 5: Manhattan plots for all secondary GWAS meta-analyses





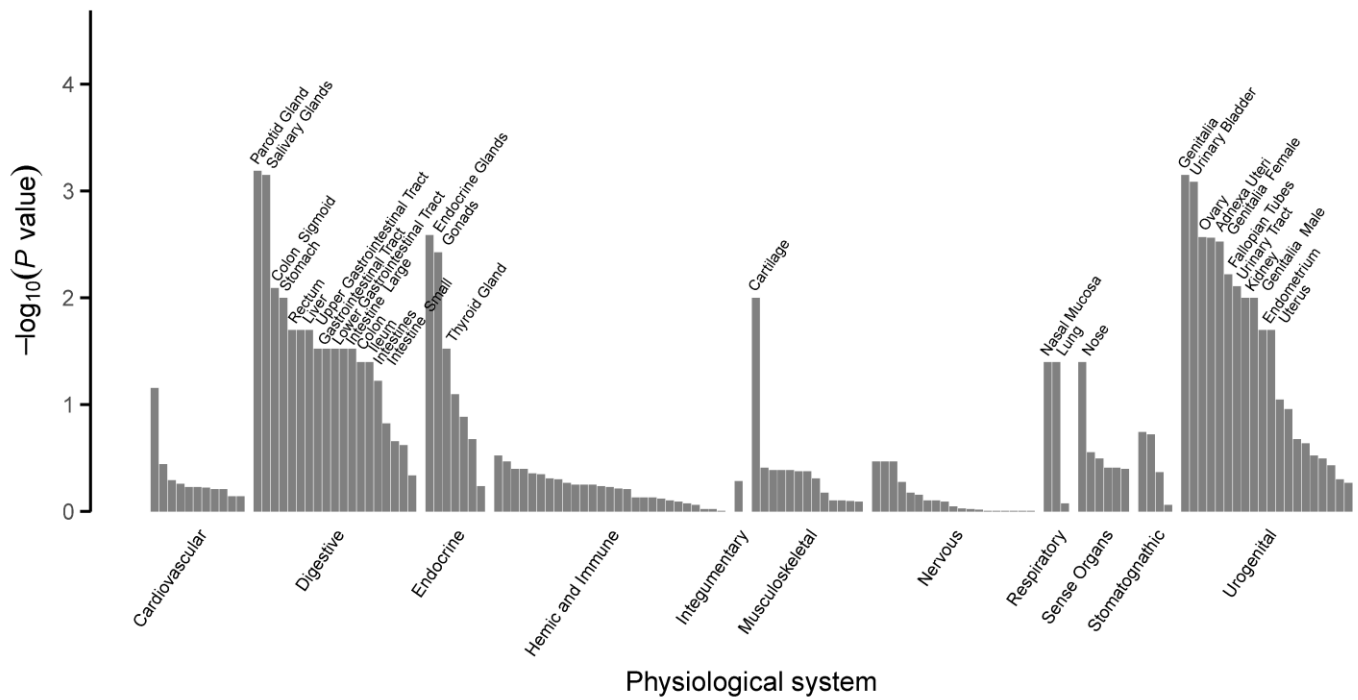
Manhattan plots of the GWAS meta-analysis results for UACR in individuals of European ancestry (a), in individuals of African ancestry (b), and among trans-ethnic individuals with diabetes (c). SNPs are plotted on the x-axis according to their position on each chromosome with the $-\log_{10}(\text{p-value})$ of the meta-analysis association test on the y-axis. The solid horizontal line indicates the threshold for genome-wide significance, 5×10^{-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 for all GWAS meta-analyses



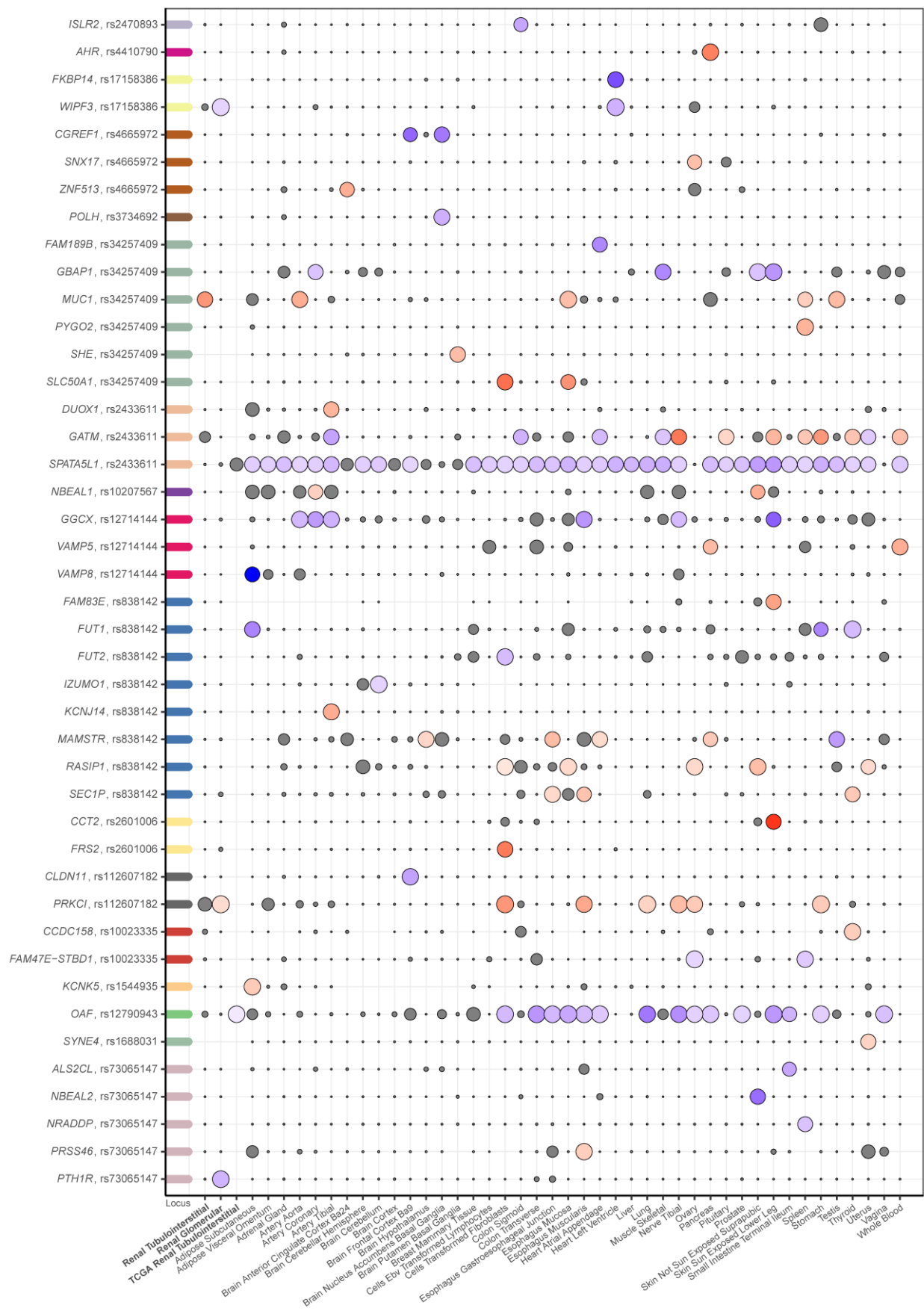
Quantile-quantile (QQ) plots of the GWAS meta-analysis results for UACR in the trans-ethnic sample (a), in individuals of European ancestry (b), in individuals of African ancestry (c), among trans-ethnic individuals with diabetes (d), and for trans-ethnic microalbuminuria meta-analysis (e). The observed 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 ($\pm 500\text{kb}$ of index SNP) genome-wide significantly ($p < 5 \times 10^{-8}$) 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.

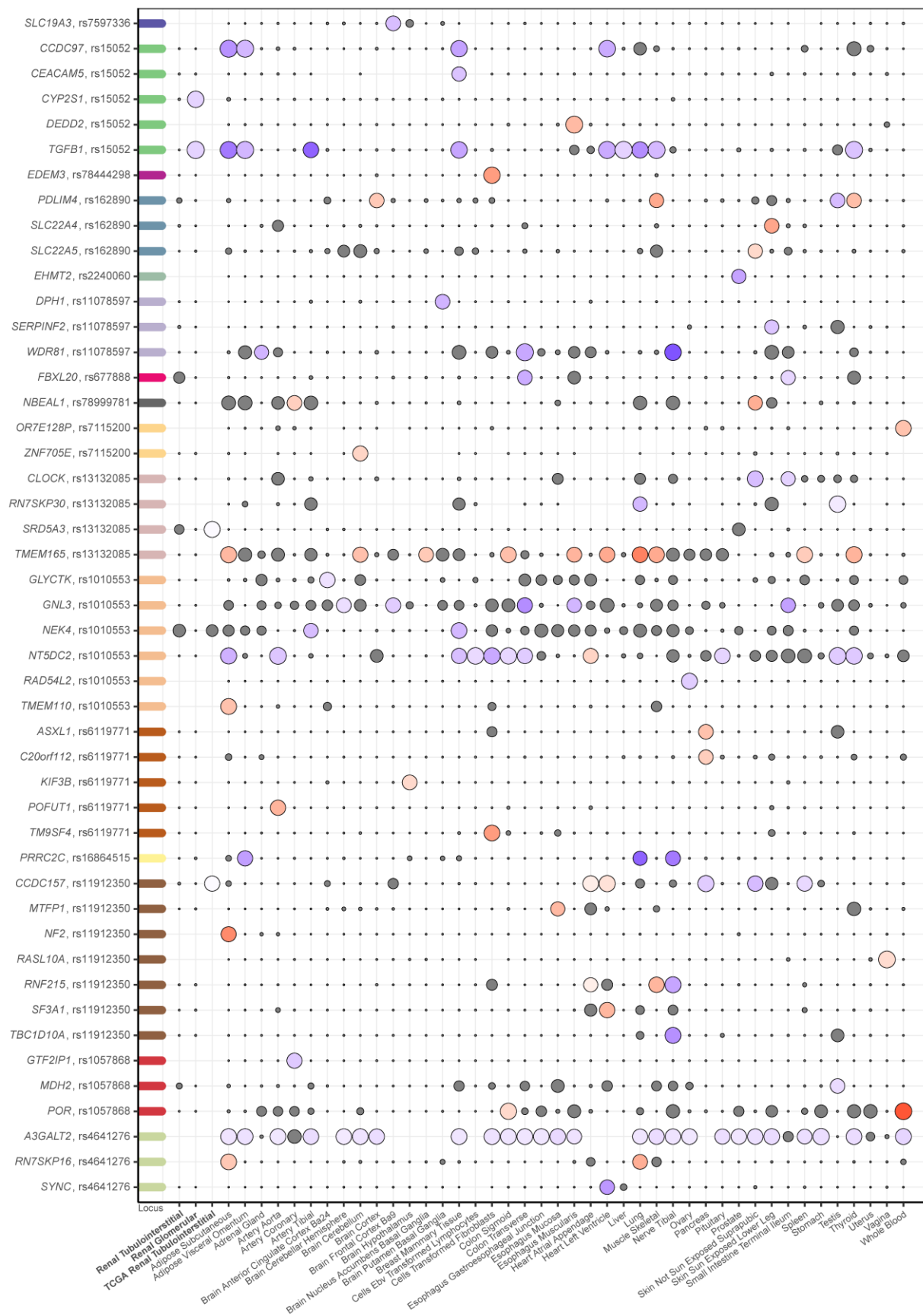
Supplementary Figure 7: Enrichment analysis results for physiological system where UACR-associated genes are highly expressed

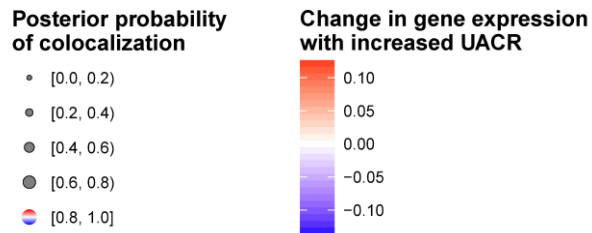


Results for enrichment of physiological systems based on the trans-ethnic UACR GWAS meta-analysis obtained by DEPICT software are shown. The x-axis is labeled by MeSH first level terms. Nominally significant associations ($p < 0.05$) are labeled in the figure. The y-axis represents the $-\log_{10}(p\text{-value})$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

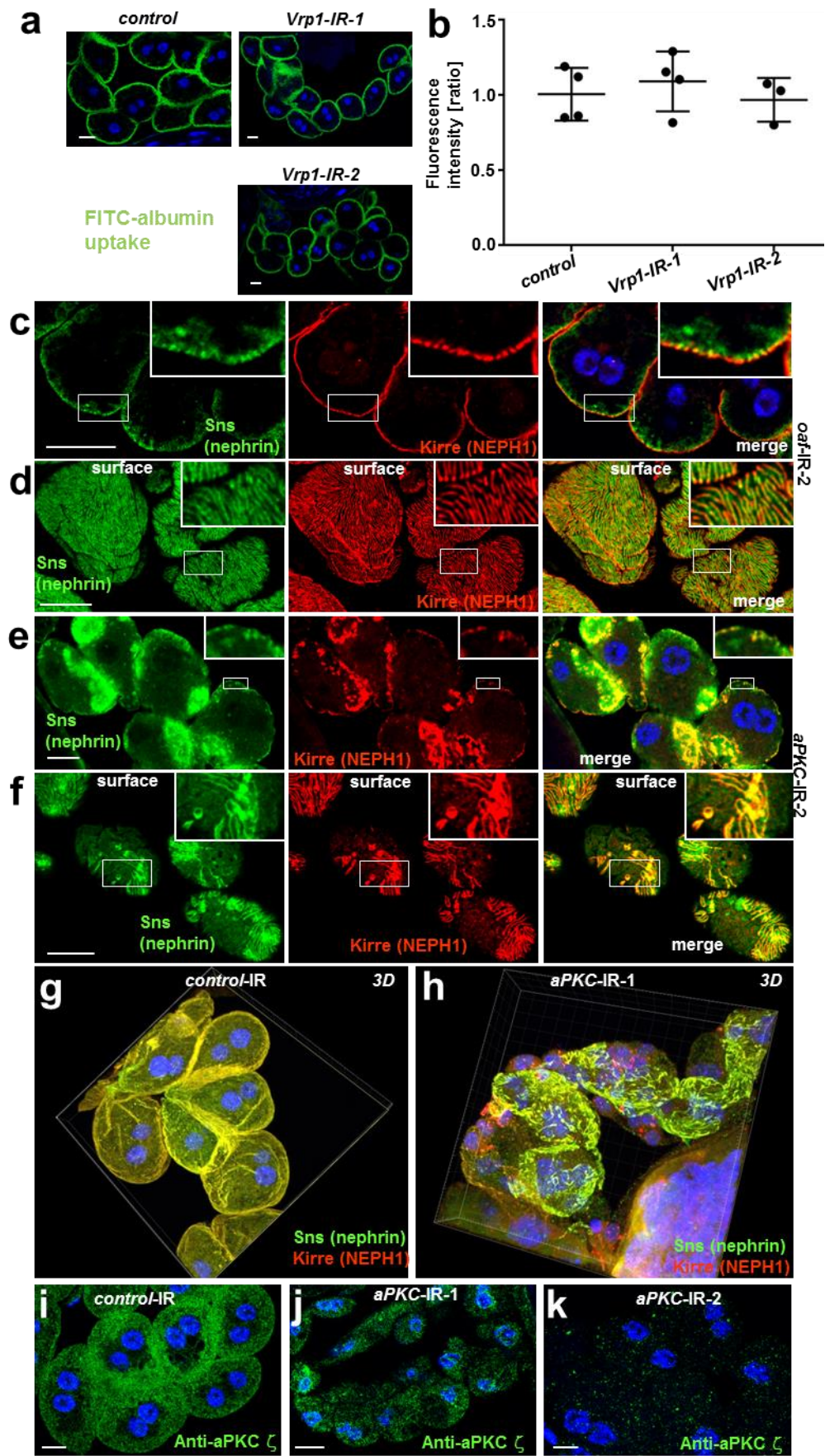






The plot shows genes whose expression levels in any tested tissues co-localized with the UACR association signal with a posterior probability of $\geq 80\%$. Genes and their respective index SNP are shown on the y-axis. Co-localization across tissues (x-axis) is illustrated as dots, where the size of 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 disease³

HF: heart failure (assessed in the UK BioBank)

HTN: hypertention (assessed in the UK BioBank)

Stroke: any stroke⁴

DBP, SBP: diastolic and systolic blood pressure⁵

T2DM: type 2 diabetes⁶

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
<i>EDEM3</i>	rs78444298	2	0.92	p.Pro746Ser (NP_079467.3)	24.6	-	The protein encoded by the ER Degradation Enhancing Alpha-Mannosidase Like Protein 3 (<i>EDEM3</i>) 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).
<i>CUBN</i>	rs45551835	1	1.00	p.Ala2914Val (NP_001072.2)	34.0	-	The cubilin gene (<i>CUBN</i>) 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. <i>CUBN</i> 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).
<i>CPS1</i>	rs1047891	15	0.96	p.Thr1412Asn (NP_001116105.1)	22.1	-	Carbamoyl-Phosphate Synthase 1 (<i>CPS1</i>) 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).
<i>GCKR</i>	rs1260326	5	0.09	p.Leu446Pro (NP_001477.2)	0.1	1*	The Glucokinase Regulator (<i>GCKR</i>) 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-chromosomal trans-eQTL
rs12714144	2:85754578	5.5E-14	0.194	0.97	chr2:85753464:D	2:85753464	<i>DPEP3</i>	16	*1	1.29E-14	yes
rs12714144	2:85754578	5.5E-14	0.194	0.97	2:85753464:TTTG_	2:85753464	<i>DPEP3</i>	16	*2	5.51E-11	yes
rs2240060	6:31114900	6.4E-10	0.183	1	rs115017941	6:31115604	<i>BTN3A2</i>	6	*1	3.08E-08	no
rs2240060	6:31114900	6.4E-10	0.183	1	6:31108485	6:31108485	<i>BTN3A2</i>	6	*2	2.70E-11	no
rs2240060	6:31114900	6.4E-10	0.183	1	rs115017941	6:31115604	<i>HLA-DRB1</i>	6	*1	3.21E-126	no
rs2240060	6:31114900	6.4E-10	0.183	1	6:31108485	6:31108485	<i>HLA-DRB1</i>	6	*2	1.82E-63	no

*1: PBMC and Whole Blood, LIFE A1&B3 study⁷⁻⁹

*2: Whole Blood, Framingham Heart Study¹⁰

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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