

Supplementary Information for

Item-level Analyses Reveal Genetic Heterogeneity in Neuroticism

Nagel et al.

Supplementary Note 1. Additional information on genetic overlap tests for top associated SNPs

Before conducting the sign concordance tests to establish whether signs of top associated SNPs were in the same direction across the 13 phenotypes, we used clumping ($r^2 = 0.1$ with window size 500 kb) based on the association P values to ensure that the most strongly associated variants were not lost. As clumping results in different SNP sets for different phenotypes, sign tests results are not symmetrical for pairs of phenotypes. To explicate the followed procedure:

- 1) Select two items I1 & I2
- 2) Retain only SNPs that survived clumping for item I1
- 3) Filter out all variants with $P >$ threshold for phenotype I1
- 4) Of the selected SNPs, compute the number of SNPs that have the same sign (i.e., concordant) for both I1 and I2
- 5) The proportion we report is: $prop = \frac{N_{concordant}}{N_{total}}$ (both numbers in this equation only contain SNPs below the specified P threshold for item I1, mentioned in step 3)
- 6) Repeat for all combinations of items and sum-score

In addition, we repeat the procedure with the difference that clumping and P value filtering is based on item I2 instead of item I1. This results in heatmaps (visualizing the proportion of concordant sign SNPs) that are not symmetric, which can be seen from the number of SNPs reported in each cell.

Prior to performing Fisher's exact tests to examine the overlap in the top associated SNPs across the 13 neuroticism phenotypes, we applied LD-based pruning on the summary statistics from all items to ensure that SNPs were independent (a subset of 10,000 individuals from the UK biobank, the UK10K set, was used as a reference set; $r^2 = 0.8$). Using the SNPs that survived pruning, we then created (for each combination of items, and for each P value

threshold) a table like the one depicted below. The categories in the table below are exclusive, meaning that a SNP in cell **A** is not included in the count of cells **B** and **C**.

A Number of SNPs < $P_{\text{threshold}}$ for both items	B Number of SNPs < $P_{\text{threshold}}$ for item 2 & > $P_{\text{threshold}}$ for item 1
C Number of SNPs < $P_{\text{threshold}}$ for item 1 & > $P_{\text{threshold}}$ for item 2	D Number of SNPs > $P_{\text{threshold}}$ for both items

Supplementary Note 2. Diagnostic criteria major depressive disorder

Below we list the symptoms used in the diagnosis of major depressive disorder, as described more extensively in the Diagnostic and Statistical Manual (DSM-5⁸).

1. Depressed mood
2. Diminished interest or pleasure
3. Weight loss or weight gain, or decrease or increase in appetite
4. Insomnia or hypersomnia
5. Psychomotor agitation or retardation
6. Fatigue or loss of energy
7. Feelings of worthlessness or excessive or inappropriate
8. Diminished ability to think or concentrate, or indecisiveness
9. Recurrent thoughts of death, recurrent suicidal ideation

Supplementary Table 1. Content, corresponding abbreviations, *N*, and endorsement rates of the 12 EPQ-RS¹ neuroticism items and the sum-score in sample 1

Abbreviation	Item (UKB field code)	Female		Male		Total	
		N	% yes	N	% yes	N	% yes
IRR	Are you an irritable person? (1940) “Feeling irritable” (IDS)	55,729	0.27	50,628	0.31	106,357	0.29
LONE	Do you often feel lonely? (2020) “I feel lonely” (YASR)	57,295	0.21	51,867	0.15	109,162	0.18
MIS	Do you ever feel ‘just miserable’ for no reason? (1930) Depressed mood (HDRS)	57,301	0.49	51,746	0.36	109,047	0.43
MOOD	Does your mood often go up and down? (1920)	56,935	0.48	51,416	0.43	108,351	0.45
FED-UP	Do you often feel ‘fed-up’? (1960)	57,086	0.43	51,677	0.38	108,763	0.41
NERV-FEEL	Would you call yourself a nervous person? (1970) “I am nervous or tense” (YASR)	56,639	0.27	51,624	0.19	108,263	0.23
WORRY	Are you a worrier? (1980) “I worry a lot” (YASR)	56,852	0.64	51,371	0.47	108,223	0.56
TENSE	Would you call yourself tense or ‘highly strung’? (1990) Feeling anxious or tense (IDS)	56,398	0.20	51,285	0.15	107,683	0.18
SUF-NERV	Do you suffer from ‘nerves’? (2010)	56,057	0.21	51,121	0.21	107,178	0.21
HURT	Are your feelings easily hurt? (1950) Interpersonal sensitivity (IDS)	56,713	0.64	51,190	0.45	107,903	0.55
WORR-EMB	Do you worry too long after an embarrassing experience? (2000)	55,793	0.54	50,838	0.40	106,631	0.47
GUILT	Are you often troubled by feelings of guilt? (2030) “I feel too guilty” (YASR); Feelings of guilt/worthlessness (BDI); Feelings of guilt (HDRS)	56,764	0.34	51,477	0.22	108,241	0.28
		Female		Male		Total	
	Phenotype	N	M (SD)	N	M (SD)	N	M (SD)
SUM-SCORE	Neuroticism sum-score	57,958	4.62 (3.20)	52,370	3.64 (3.16)	110,328	4.16 (3.22)

Descriptive statistics for the 12 neuroticism items and the sum-score in sample 1 (UKB data: first release). Below the neuroticism items (black font), highly similar items (content and source; grey font) from renowned depression/anxiety questionnaires are displayed. The neuroticism sum-score ranges from 0 to 12.

BDI = Beck Depression Inventory²; IDS = Inventory of Depressive Symptomatology³; HDRS = Hamilton Depression Rating Scale⁴; YASR = Young Adult Self Report scale⁵.

Supplementary Table 2. Content, corresponding abbreviations, *N*, and endorsement rates of the 12 EPQ-RS¹ neuroticism items and the sum-score in sample 2

Abbreviation	Item (UKB field code)	Female		Male		Total	
		N	% yes	N	% yes	N	% yes
IRR	Are you an irritable person? (1940)	141,978	0.26	118,391	0.31	260,369	0.28
LONE	Do you often feel lonely? (2020)	145,829	0.20	121,361	0.15	267,190	0.18
MIS	Do you ever feel 'just miserable' for no reason? (1930)	145,908	0.49	121,142	0.35	267,050	0.43
MOOD	Does your mood often go up and down? (1920)	145,029	0.47	120,353	0.42	265,382	0.45
FED-UP	Do you often feel 'fed-up'? (1960)	145,371	0.42	120,837	0.38	266,208	0.4
NERV-FEEL	Would you call yourself a nervous person? (1970)	144,117	0.27	120,741	0.20	264,858	0.24
WORRY	Are you a worrier? (1980)	144,680	0.64	119,966	0.48	264,646	0.57
TENSE	Would you call yourself tense or 'highly strung'? (1990)	143,631	0.20	120,004	0.15	263,635	0.18
SUF-NERV	Do you suffer from 'nerves'? (2010)	142,635	0.21	119,686	0.22	262,321	0.21
HURT	Are your feelings easily hurt? (1950)	144,356	0.64	119,788	0.45	264,144	0.56
WORR-EMB	Do you worry too long after an embarrassing experience? (2000)	142,172	0.54	118,922	0.40	261,094	0.48
GUILT	Are you often troubled by feelings of guilt? (2030)	144,580	0.34	120,559	0.22	265,139	0.29
		Female		Male		Total	
	Phenotype	N	M (SD)	N	M (SD)	N	M (SD)
SUM-SCORE	Neuroticism sum-score	147,598	4.58 (3.18)	122,580	3.65 (3.16)	270,178	4.16 (3.21)

Descriptive statistics for the 12 neuroticism items and the sum-score in sample 2 (UKB data: first release). The neuroticism sum-score ranges from 0 to 12.

Supplementary Table 3. Overview of binary external variables used in phenotypic association analysis in sample 1

Item	<i>N</i>	Percentage yes	UKB field code
<i>Binary variables</i>			
Depressed mood (“Not at all” vs. other categories)	106,152	23.4%	2050
Unenthusiasm/disinterest (“Not at all” vs. other categories)	107,125	21.0%	2060
Tenseness/restlessness (“Not at all” vs. other categories)	106,825	26.5%	2070
Tiredness/lethargy (“Not at all” vs. other categories)	107,516	52.7%	2080
Visit psychiatrist for nerves/anxiety/tension/depression	109,965	11.8%	2100
Visit doctor (GP) for nerves/anxiety/tension/depression	109,729	34.5%	2090
Ever highly irritable/argumentative for 2 days	36,395	18.5%	4653
Ever depressed for a whole week	36,472	53.6%	4598
Ever manic/hyper for 2 days	36,255	6.0%	4642
Ever disinterested/unenthusiastic for a whole week	35,728	37.0%	4631
Bipolar disorder (both hypo- and hypermania)	110,328	0.3%	20122
Probable recurrent MDD (severe)	110,328	1.9%	20125
Probable recurrent MDD (moderate)	110,328	3.1%	20124
Insomnia/sleeplessness (“never/rarely”/“sometimes” vs. “usually”)	110,255	28.5%	1200
Single episode of probable MDD	110,328	2.0%	20123
Risk taking	106,831	26.8%	2040
Sex (being male)	110,328	47.5%	31

Content, sample size (*N*) and endorsement rate (percentage of positive “yes” versus “no” or *NA* responses) for the binary external variables used in phenotypic association analysis in subsample 1 (UKB data: first release) as depicted in **Supplementary Figure 2**.

Supplementary Table 4. Overview of continuous external variables used in phenotypic association analysis in sample 1

Item	N	M	SD	Range	UKB field code
<i>Continuous variables</i>					
No. of depression episodes (duration at least one week)	14,269	3.7	4.4	1 - 20	4620
No. of disinterested/unenthusiastic episodes (duration at least one week)	9,431	4.1	4.8	1 - 20	5386
Longest period of depression	15,898	16.2	41.9	1 - 999	4609
Longest period of disinterest/unenthusiasm	10,151	16.0	44.9	1 - 999	5375
Townsend deprivation index (TDI)	110,183	-1.4	3.0	-6.3 - 10.6	189
Height	110,122	168.8	9.2	122 - 205	50
Age	110,328	56.7	8.0	39 - 70	21003
Financial satisfaction	36,944	4.3	1.0	1 - 6	4581
Friendships satisfaction	36,693	4.8	0.7	1 - 6	4570
Family satisfaction	36,707	4.8	0.9	1 - 6	4559
Health satisfaction	36,981	4.2	0.9	1 - 6	4548
Work satisfaction	25,554	4.4	0.9	1 - 6	4537
Happiness	36,970	4.5	0.7	1 - 6	4526

Content, sample size (*N*), mean (*M*) and standard deviation (*SD*) and item response range for the continuously measured external variables used in phenotypic association analyses in subsample 1 (UKB data: first release) as depicted in **Supplementary Figure 3**.

Supplementary Table 5. Content, corresponding abbreviations, *N*, and endorsement rates of the 12 EPQ-RS¹ neuroticism items and the sum-score in the full (meta-analyzed) sample

Abbreviation	Item (UKB field code)	Female		Male		Total	
		N	% yes	N	% yes	N	% yes
IRR	Are you an irritable person? (1940)	197,707	0.26	169,019	0.31	366,726	0.28
LONE	Do you often feel lonely? (2020)	203,124	0.21	173,228	0.15	376,352	0.18
MIS	Do you ever feel 'just miserable' for no reason? (1930)	203,209	0.49	172,888	0.35	376,097	0.43
MOOD	Does your mood often go up and down? (1920)	201,964	0.47	171,769	0.43	373,733	0.45
FED-UP	Do you often feel 'fed-up'? (1960)	202,457	0.43	172,514	0.38	374,971	0.4
NERV-FEEL	Would you call yourself a nervous person? (1970)	200,756	0.27	172,365	0.20	373,121	0.24
WORRY	Are you a worrier? (1980)	201,532	0.64	171,337	0.48	372,869	0.57
TENSE	Would you call yourself tense or 'highly strung'? (1990)	200,029	0.20	171,289	0.15	371,318	0.18
SUF-NERV	Do you suffer from 'nerves'? (2010)	198,692	0.21	170,807	0.22	369,499	0.21
HURT	Are your feelings easily hurt? (1950)	201,069	0.64	170,978	0.45	372,047	0.55
WORR-EMB	Do you worry too long after an embarrassing experience? (2000)	197,965	0.54	169,760	0.40	367,725	0.48
GUILT	Are you often troubled by feelings of guilt? (2030)	201,344	0.34	172,036	0.22	373,380	0.29
		Female		Male		Total	
	Phenotype	N	M (SD)	N	M (SD)	N	M (SD)
SUM-SCORE	Neuroticism sum-score	205,556	4.59 (3.19)	174,950	3.65 (3.16)	380,506	4.16 (3.21)

Descriptive statistics for the 12 neuroticism items and the sum-score in the full sample (UKB data: sample 1 and 2 combined). The neuroticism sum-score ranges from 0 to 12.

Supplementary Table 6. Functional consequences on genes of all SNPs in LD with an independent significant SNP in item- vs. sum-score analysis

	Item-level*	Sum-score
3'-UTR	322	175
5'-UTR	110	74
Exonic	286	151
Intergenic	9,693	5,141
Intronic	13,023	7,265
Non-coding RNA exonic	299	142
Non-coding RNA intronic	2,821	1,887
Non-coding RNA splicing	-	-
Splicing	1	-
Downstream	324	131
Upstream	313	109

Note: SNPs in the MHC region were excluded from annotation. A small portion of the SNPs could not be annotated by ANNOVAR.

*SNPs that were in LD with an independent significant SNP for at least one of the 12 neuroticism items.

Supplementary Table 7. Minimum chromatin state of all SNPs in LD with an independent significant SNP in item- vs. sum-score analysis

	Item-level*	Sum-score
1: Active TSS	1,749	890
2: Flanking Active TSS	1,403	863
3: Transcr. at gene 5' & 3'	285	145
4: Strong transcription	5,230	3,080
5: Weak transcription	9,833	5,972
6: Genic enhancers	10	5
7: Enhancers	1,021	537
8: ZNF genes & repeats	787	201
9: Heterochromatin	5,085	2,596
12: Bivalent enhancer	8	3
13: Repressed PolyComb	368	157
14: Weak Repressed PolyComb	1,070	490
15: Quiescent/Low	364	221

Note: SNPs in the MHC region were excluded from annotation.

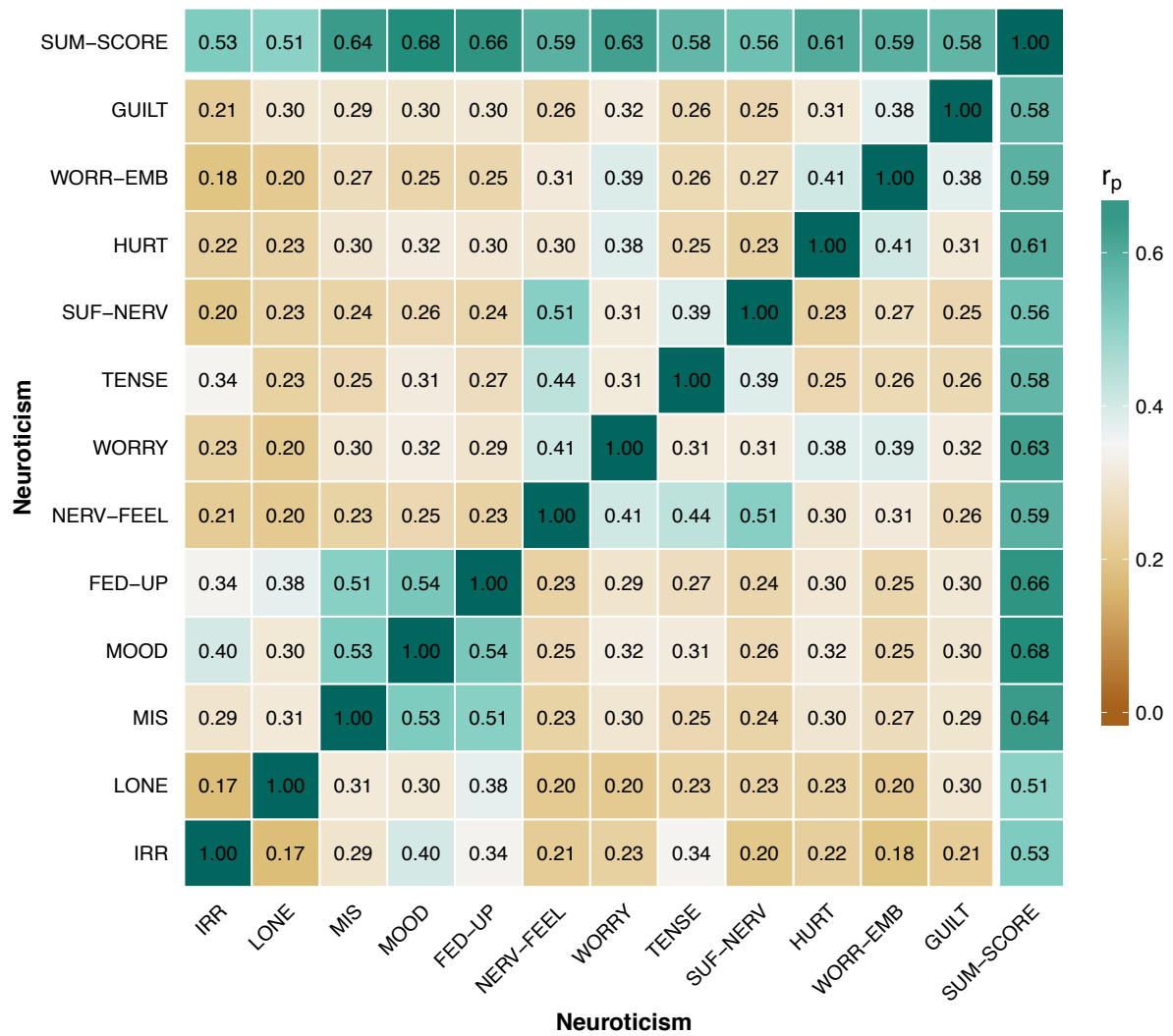
*SNPs that were in LD with an independent significant SNP for at least one of the 12 neuroticism items.

Supplementary Table 8. Regulome database score of all SNPs in LD with an independent significant SNP in item- vs. sum-score analysis

	Item-level*	Sum-score
1a: eQTL + TF binding + matched TF motif + matched DNase Footpr	9	4
1b: eQTL + TF binding + any motif + DNase Footpr + DNase peak	71	35
1c: eQTL + TF binding + matched TF motif + DNase peak	4	4
1d: eQTL + TF binding + any motif + DNase peak	73	42
1e: eQTL + TF binding + matched TF motif	2	-
1f: eQTL + TF binding / DNase peak	866	534
2a: TF binding + match TF motif + matchDNase Footpr + DNase peak	43	24
2b: TF binding + any motif + DNase Footpr + DNase peak	385	214
2c: TF binding + matched TF motif + DNase peak	23	12
3a: TF binding + any motif + DNase peak	464	258
3b: TF binding + matched TF motif	11	6
4: TF binding + DNase peak	1,349	744
5: TF binding or DNase peak	4,532	2,829
6: other	7,355	3,990
7: not regulatory	8,520	4,589

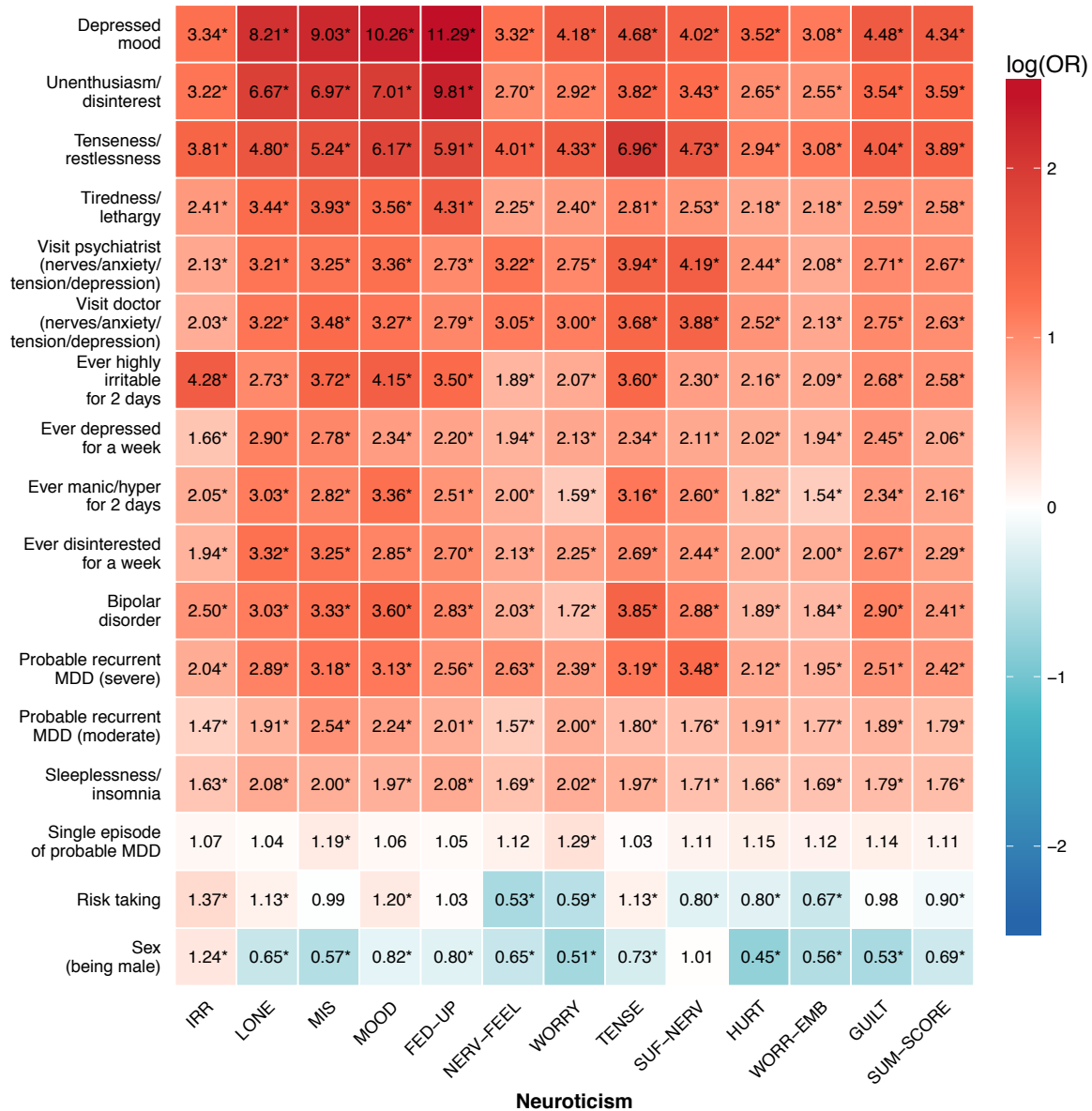
Note: SNPs in the MHC region were excluded from annotation.

*SNPs that were in LD with an independent significant SNP for at least one of the 12 neuroticism items.



Supplementary Figure 1. Phenotypic correlations between all 12 neuroticism items and the neuroticism sum-score in sample 1.

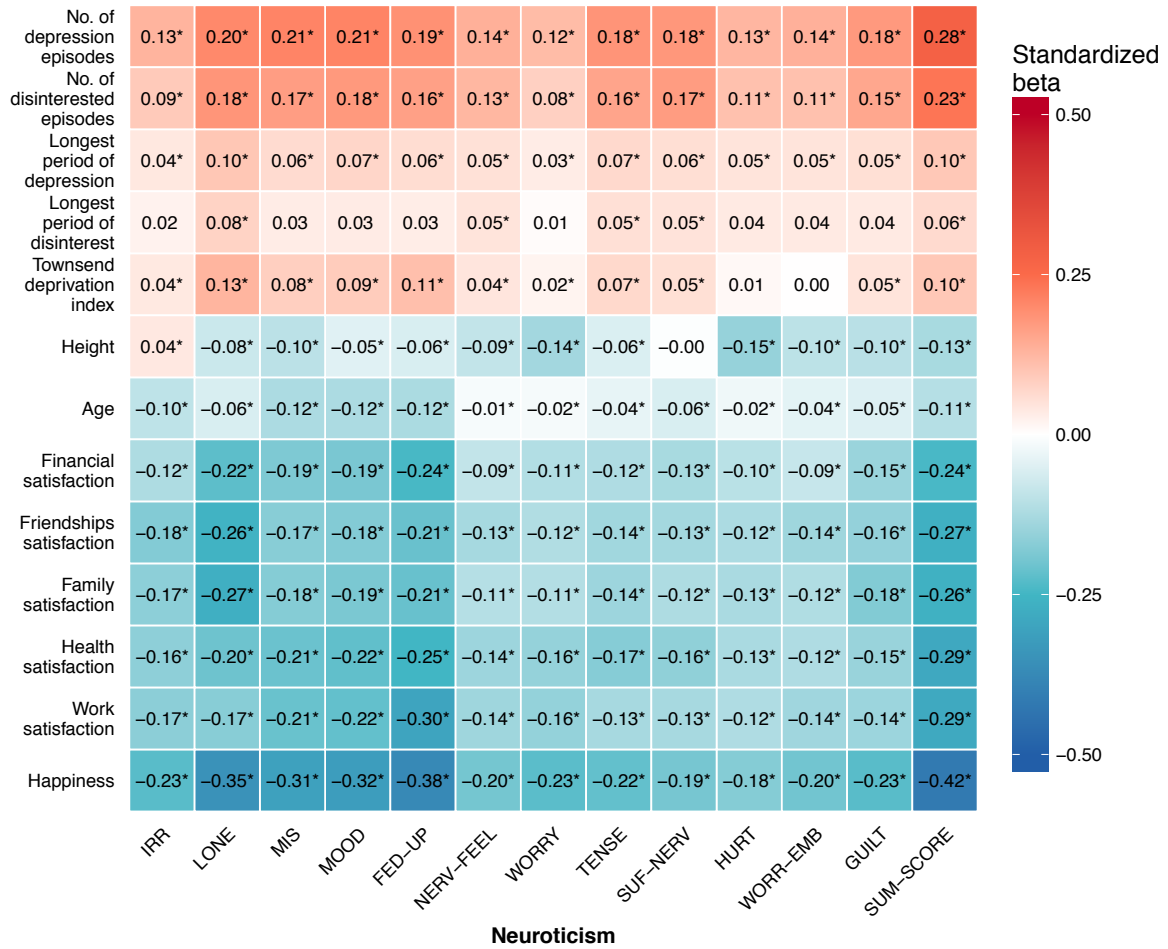
The correlation heatmap is symmetric. See **Supplementary Table 1** for an explanation of item labels.



Supplementary Figure 2. Phenotypic associations of the 12 neuroticism items and the neuroticism sum-score (x-axis) with 17 dichotomous external variables (y-axis) in sample 1.

The numbers in the heatmap represent effect sizes expressed as odds ratios (coloring is based on log odds). See **Supplementary Table 1** for an explanation of neuroticism item labels. See **Supplementary Table 3** for descriptives on the external variables displayed in this figure.

*Bonferroni corrected P value threshold: $P < 1.28 \times 10^{-4}$ ($0.05 / ((17+13) \times 13)$).

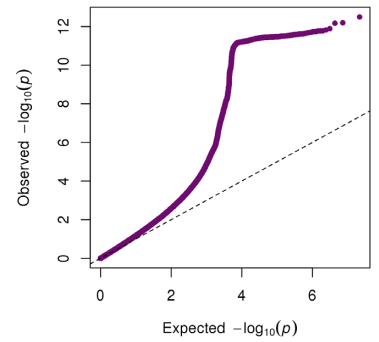
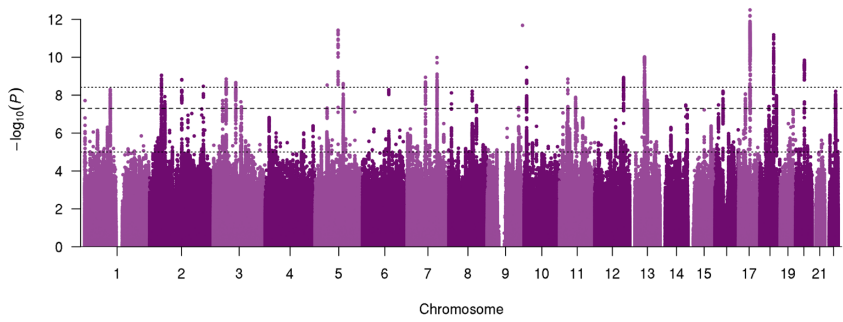
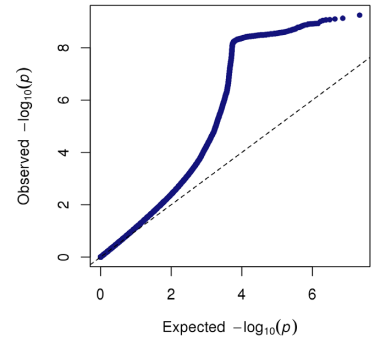
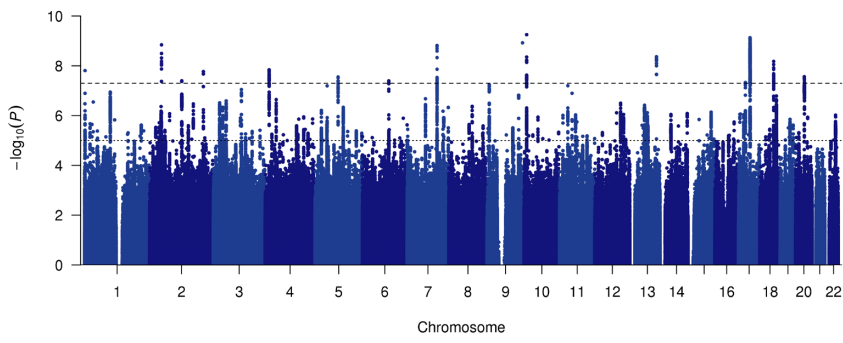
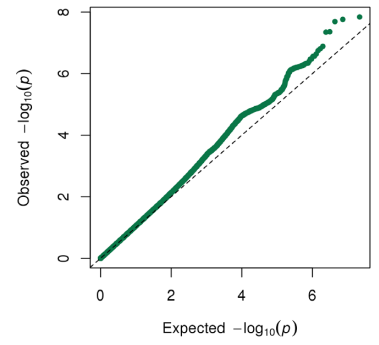
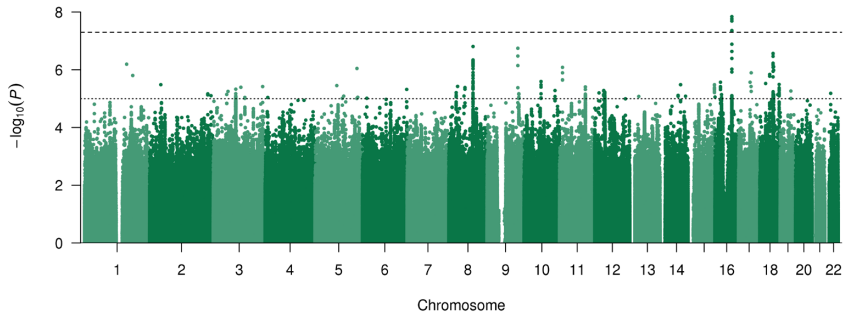


Supplementary Figure 3. Phenotypic associations of the 12 neuroticism items and the neuroticism sum-score (x-axis) with 13 continuous external variables (y-axis) in sample 1.

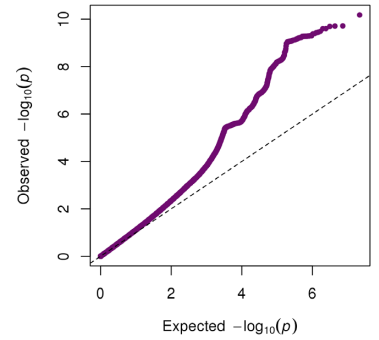
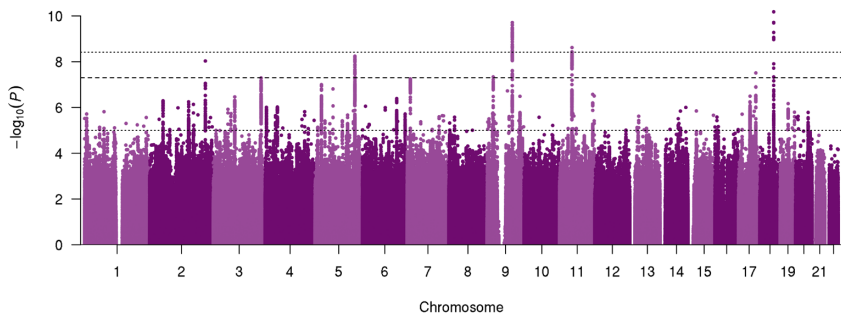
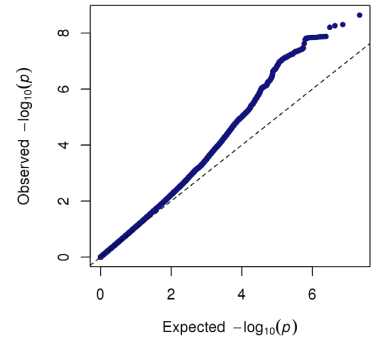
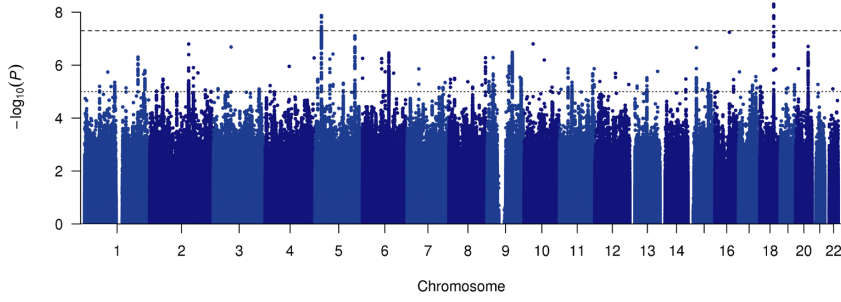
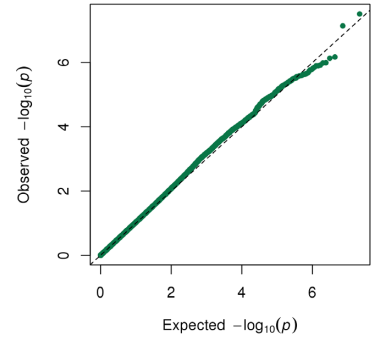
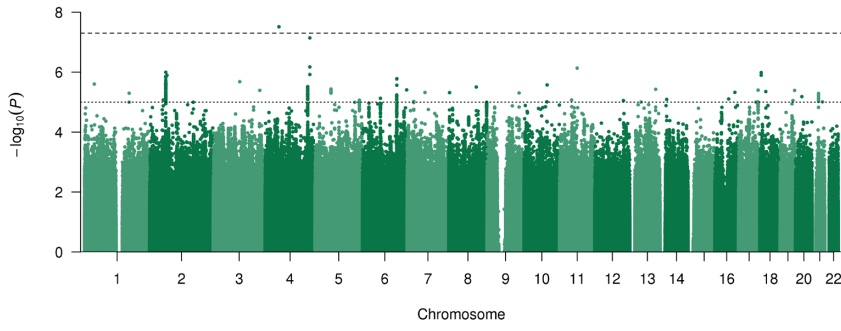
The numbers in the heatmap represent effect sizes expressed as standardized beta coefficients. See **Supplementary Table 1** for an explanation of neuroticism item labels. See **Supplementary Table 4** for descriptives on the external variables displayed in this figure.

*Bonferroni corrected P value threshold: $P < 1.28 \times 10^{-4}$ ($0.05 / ((17+13) \times 13)$).

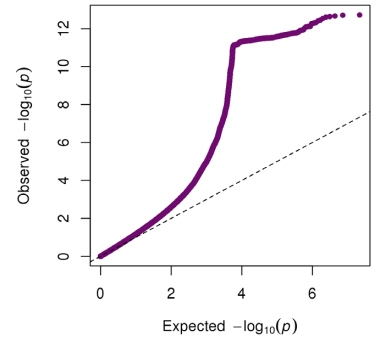
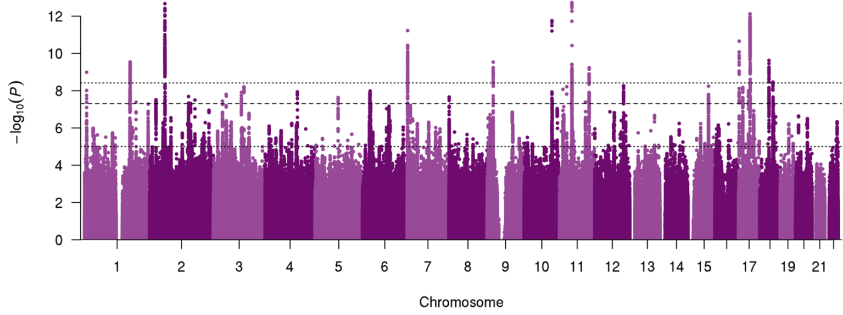
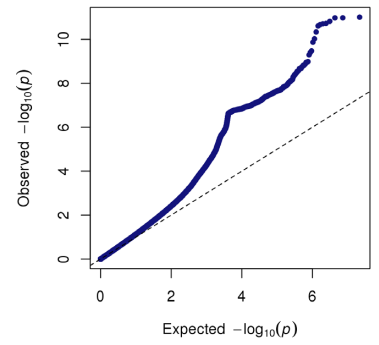
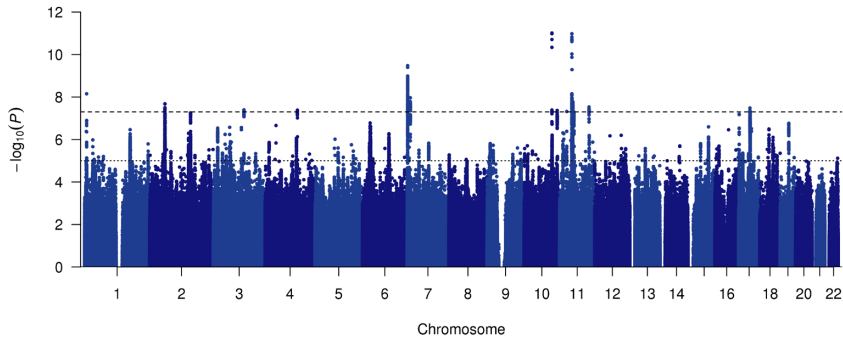
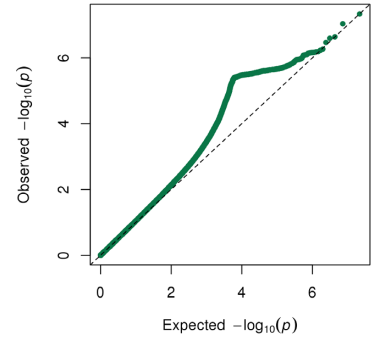
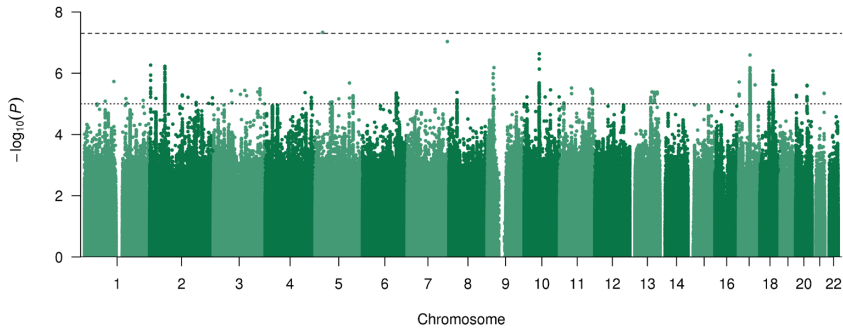
IRR - Are you an irritable person?



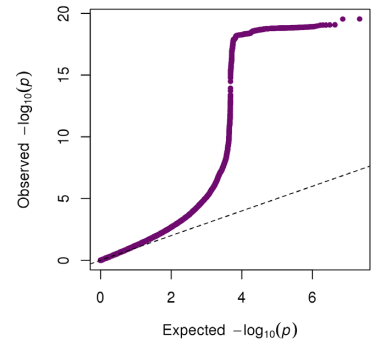
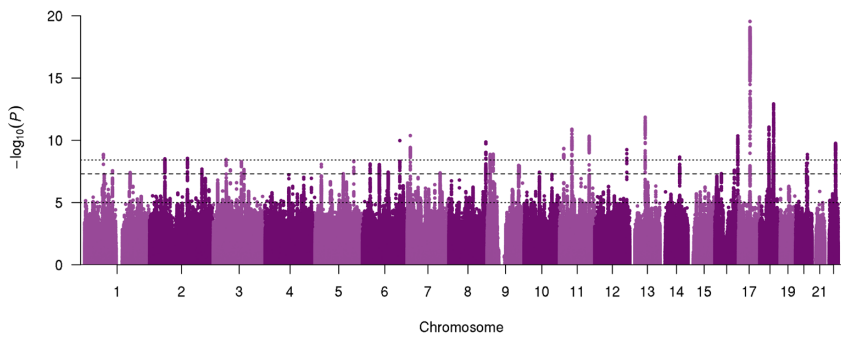
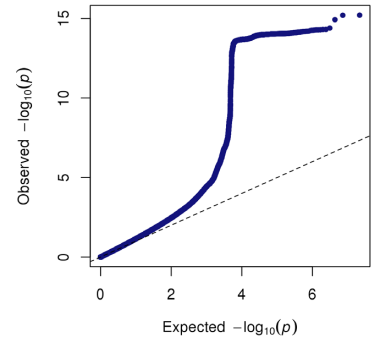
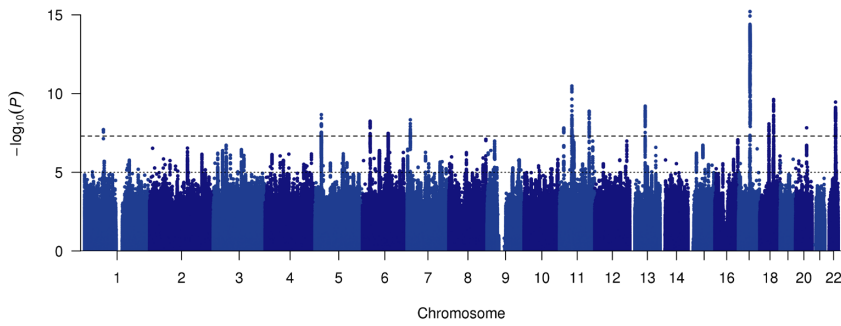
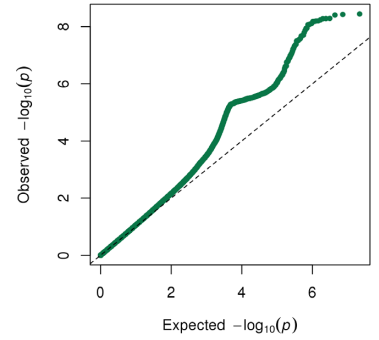
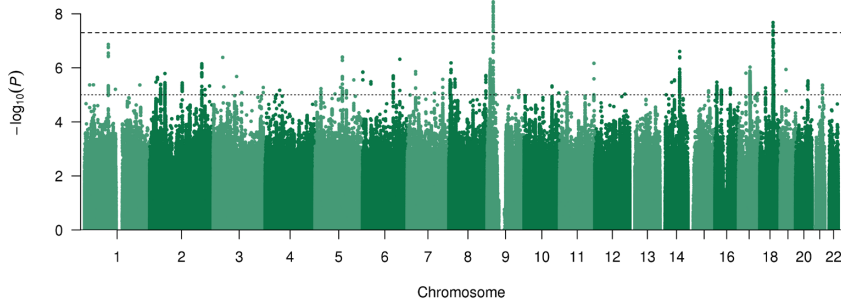
LONE - Do you often feel lonely?



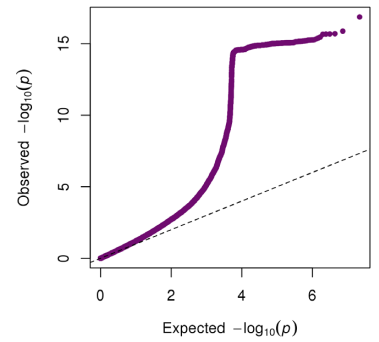
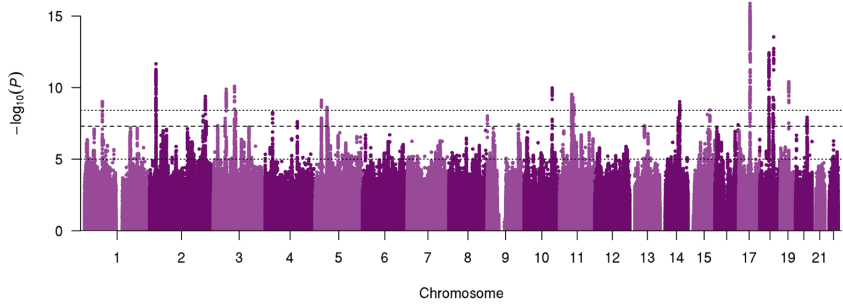
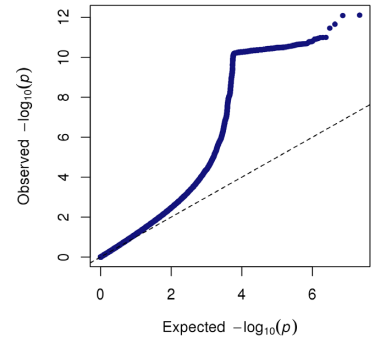
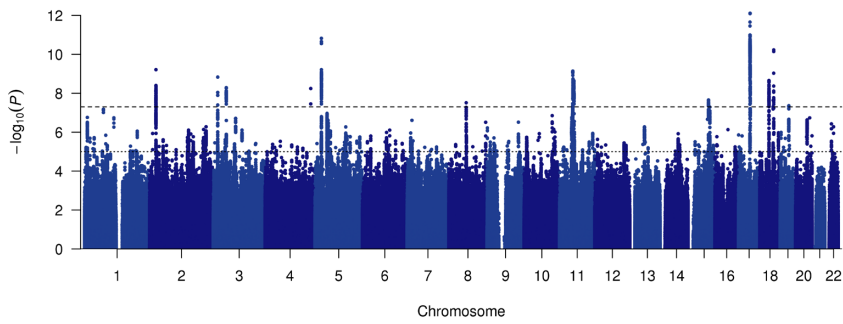
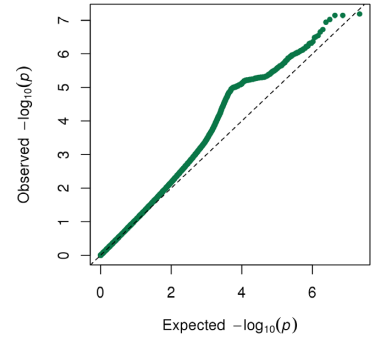
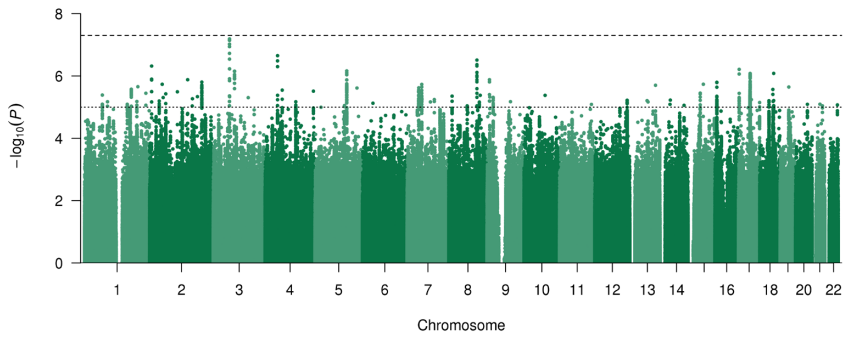
MIS - Do you ever feel 'just miserable' for no reason?



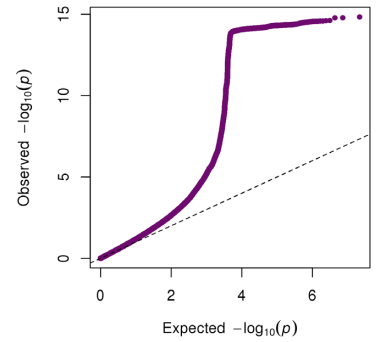
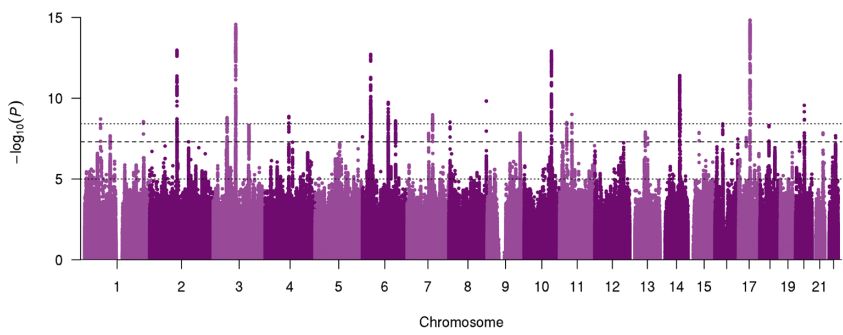
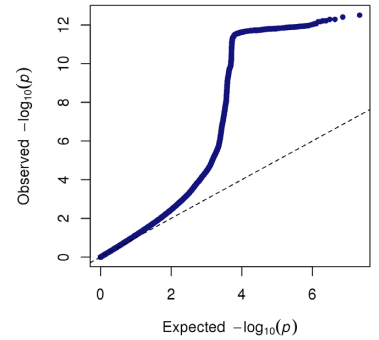
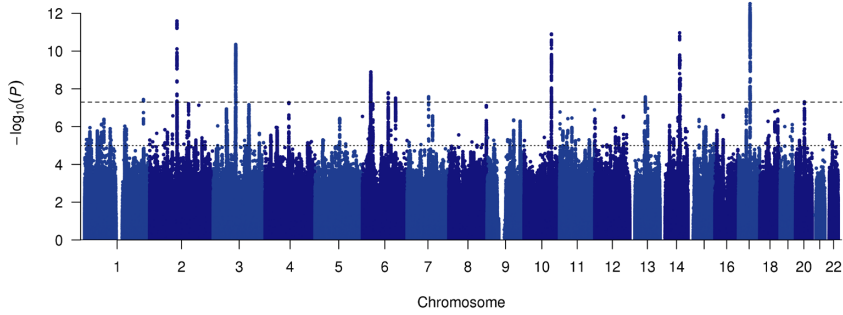
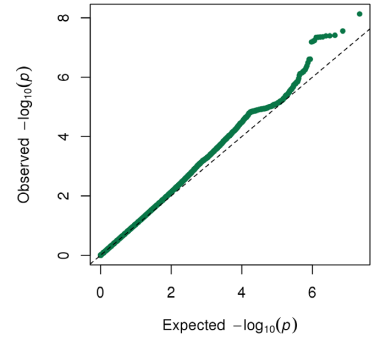
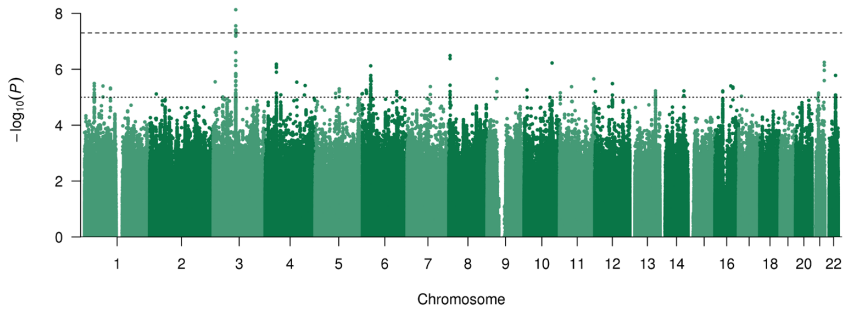
MOOD - Does your mood often go up and down?



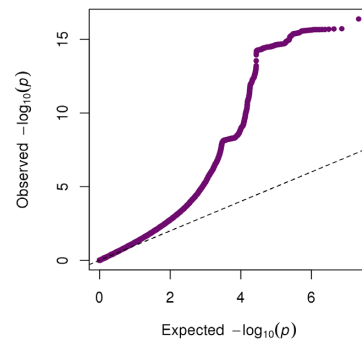
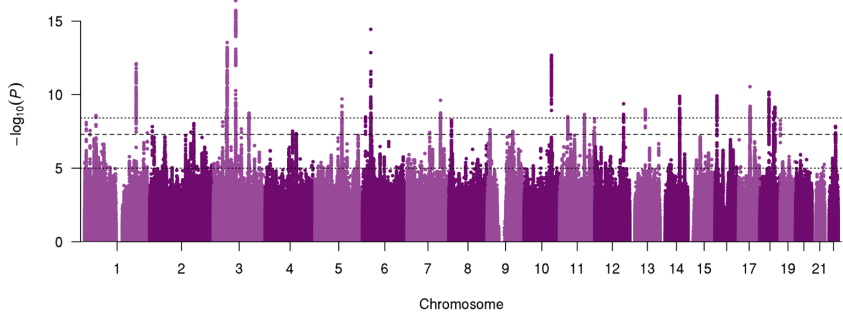
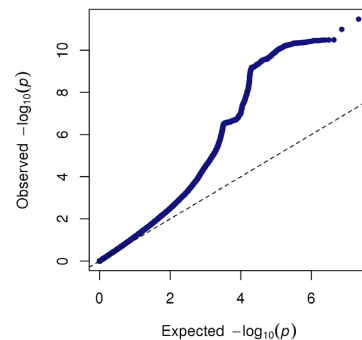
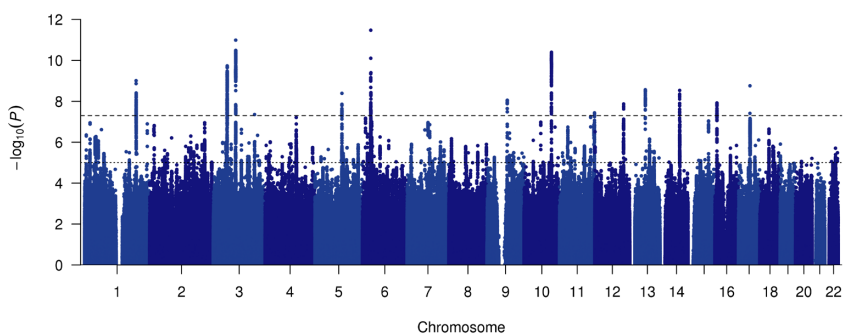
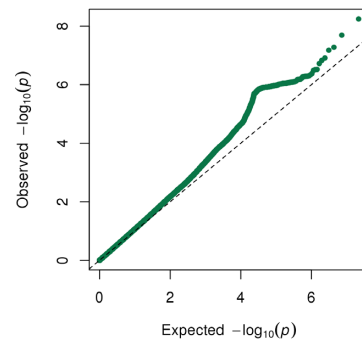
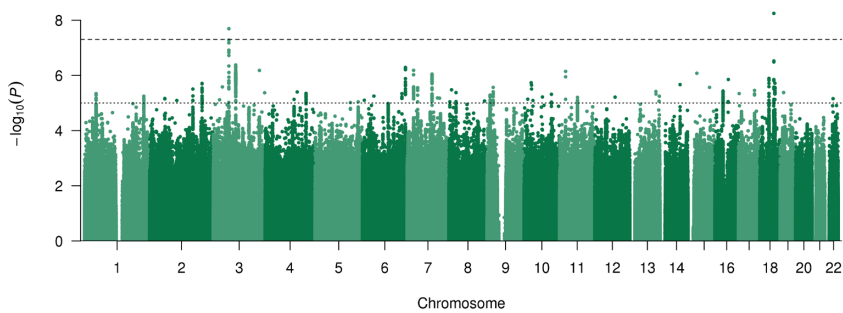
FED-UP - Do you often feel 'fed-up'?



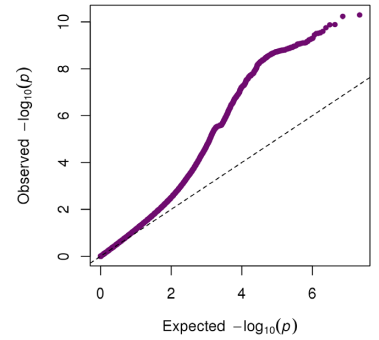
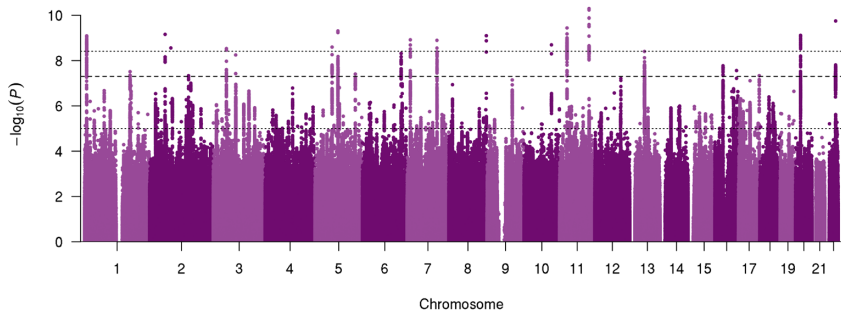
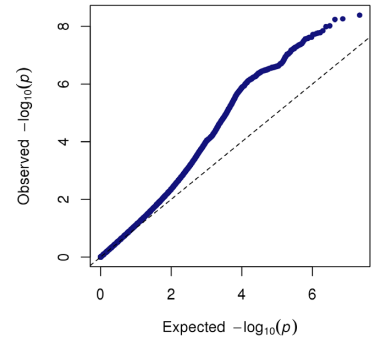
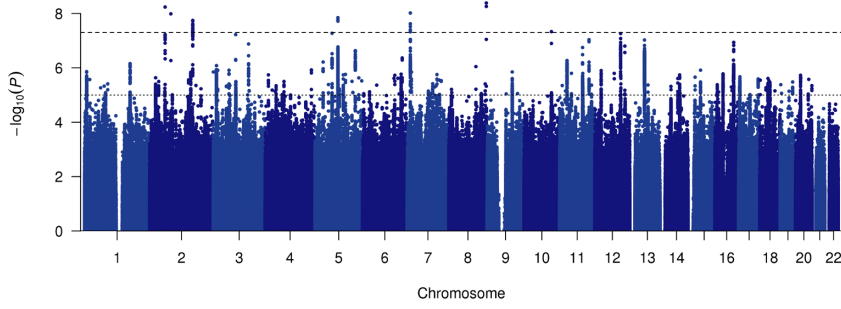
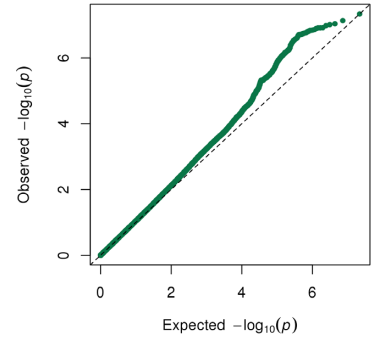
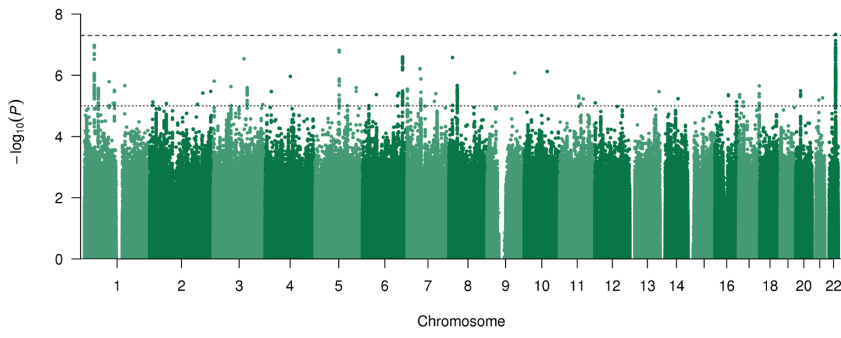
NERV-FEEL - Would you call yourself a nervous person?



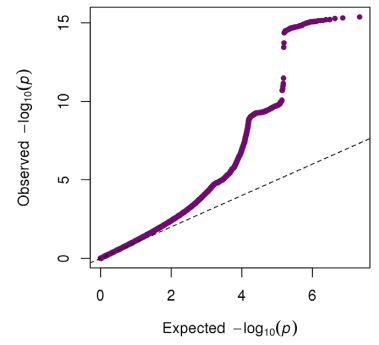
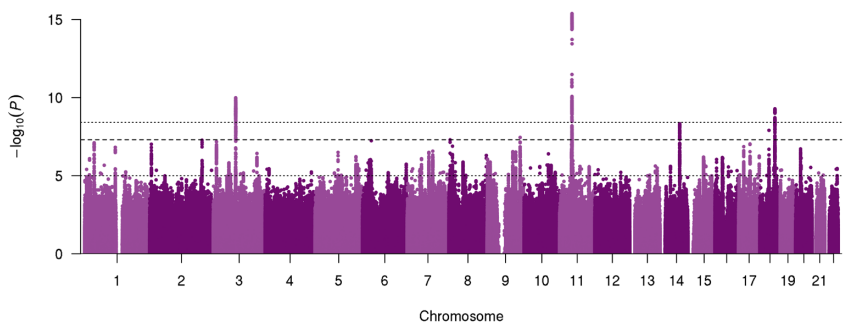
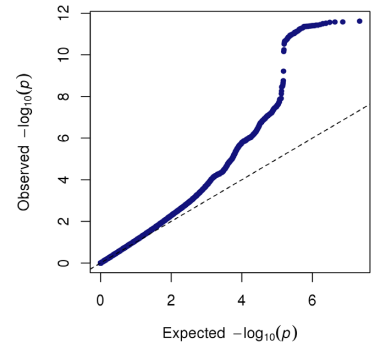
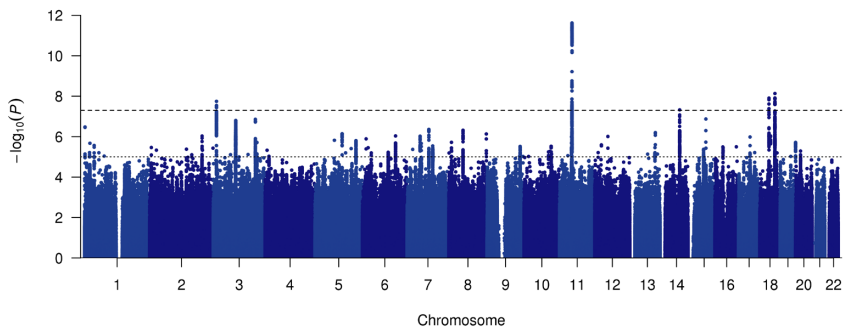
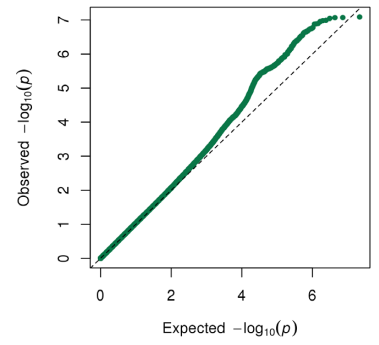
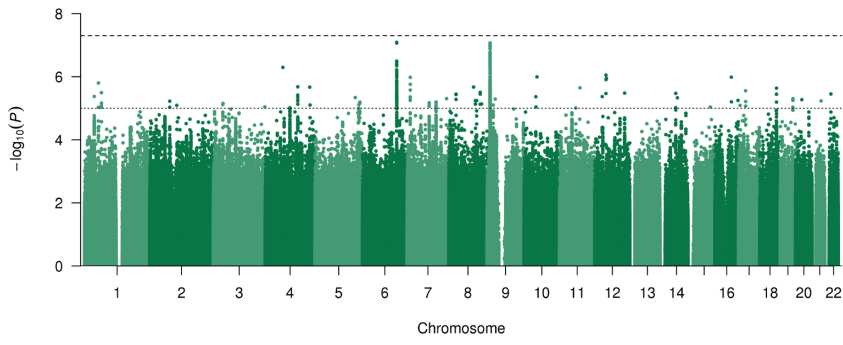
WORRY - Are you a worrier?



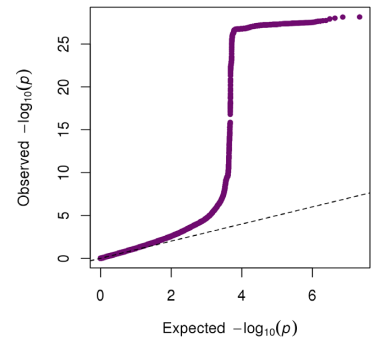
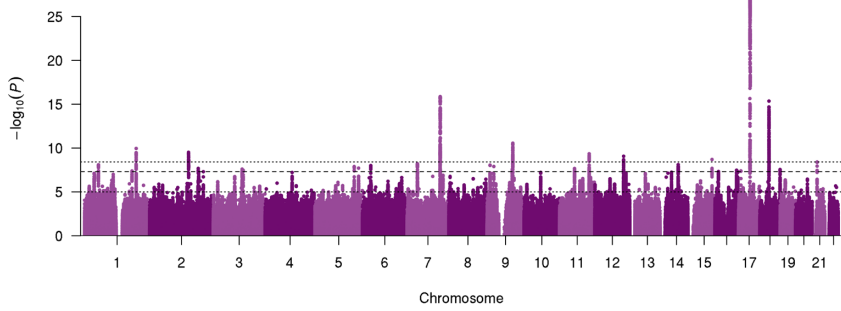
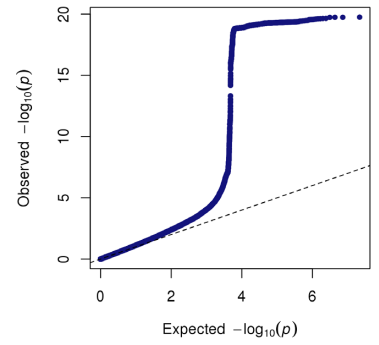
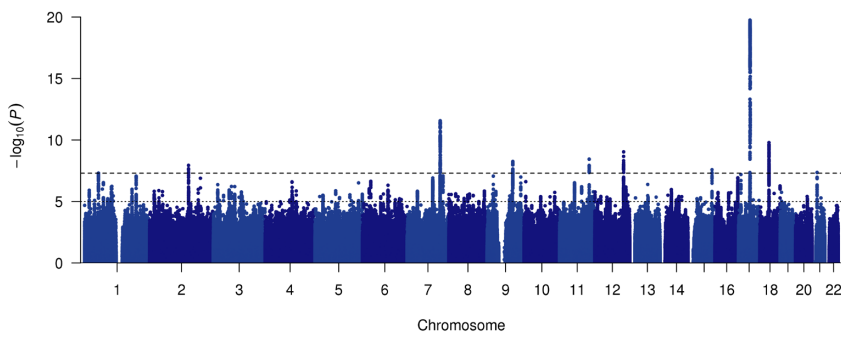
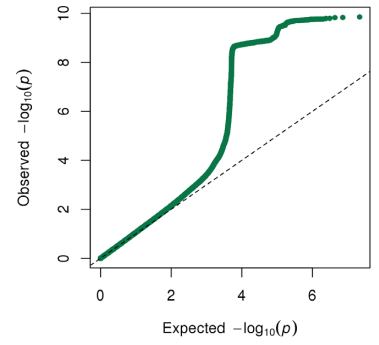
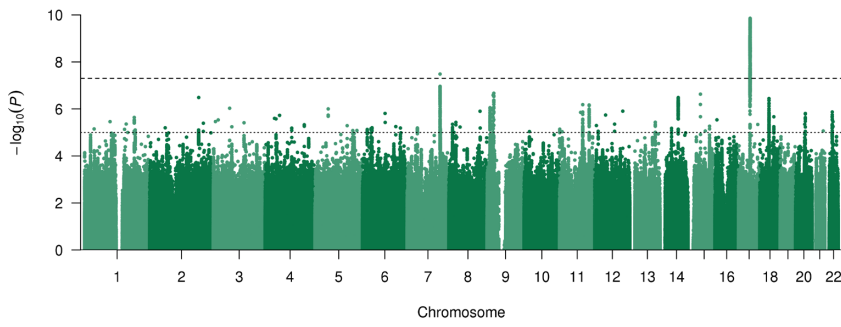
TENSE - Would you call yourself tense or 'highly strung'?



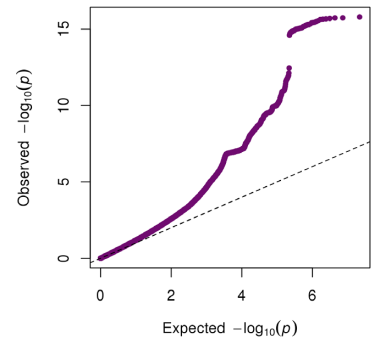
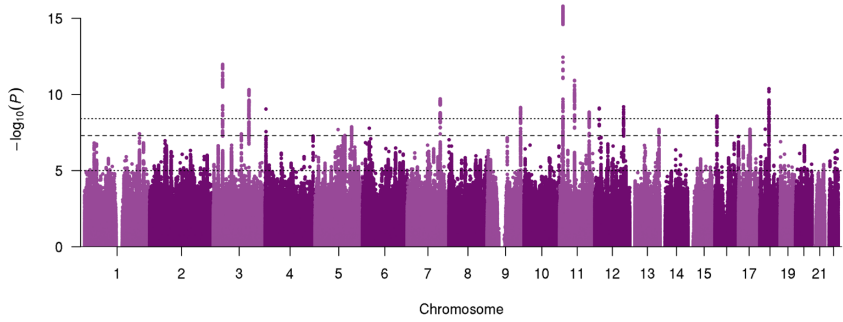
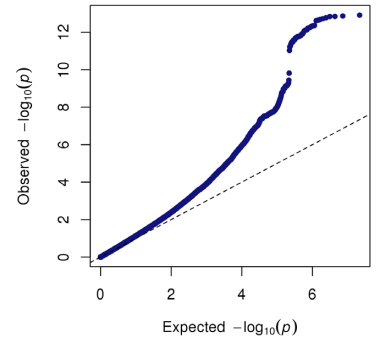
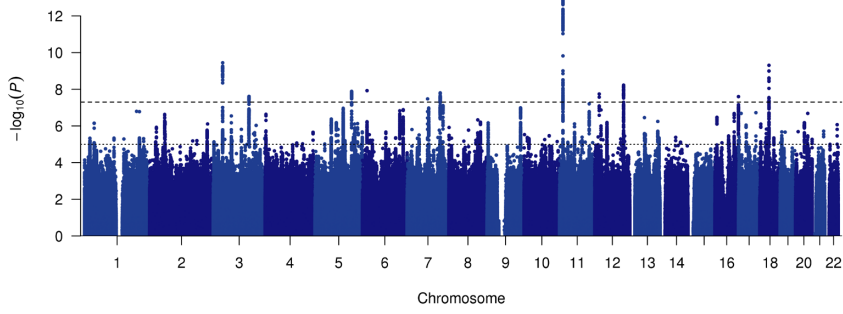
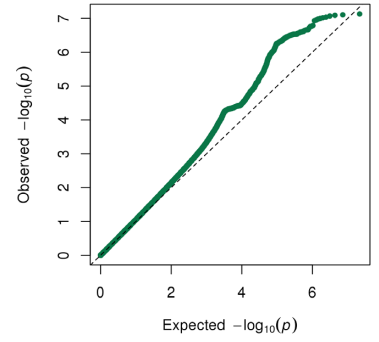
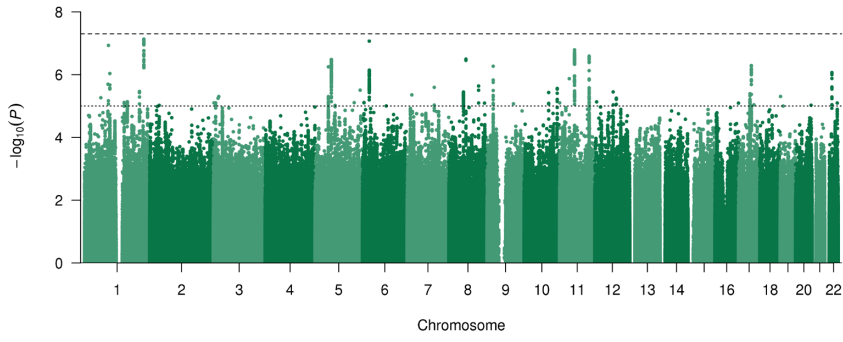
SUF-NERV - Do you suffer from 'nerves'?



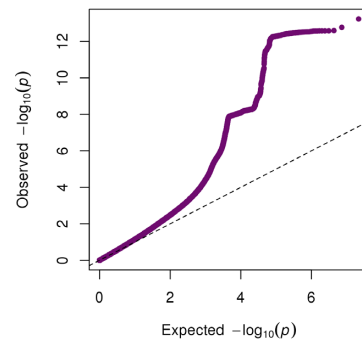
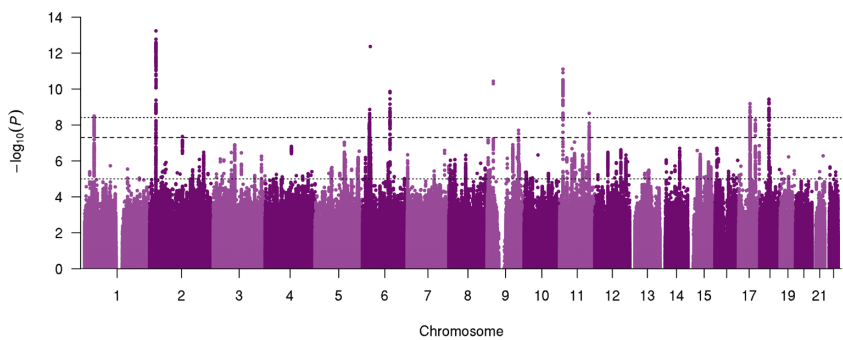
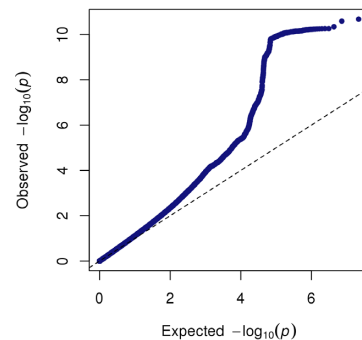
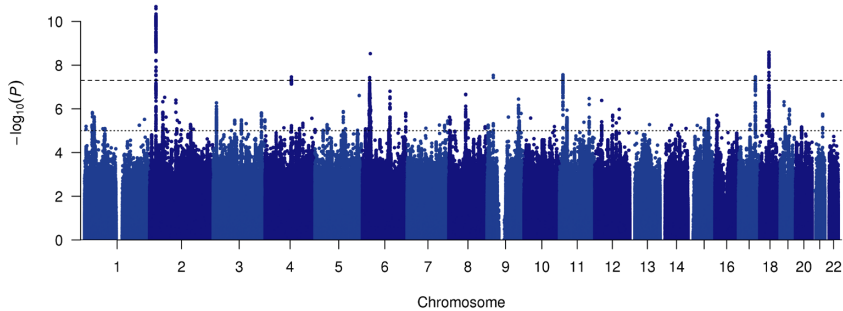
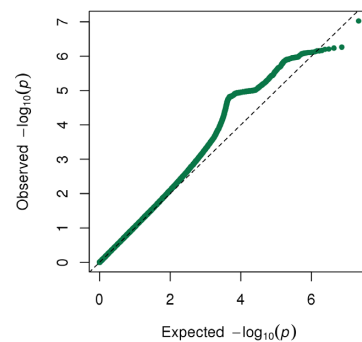
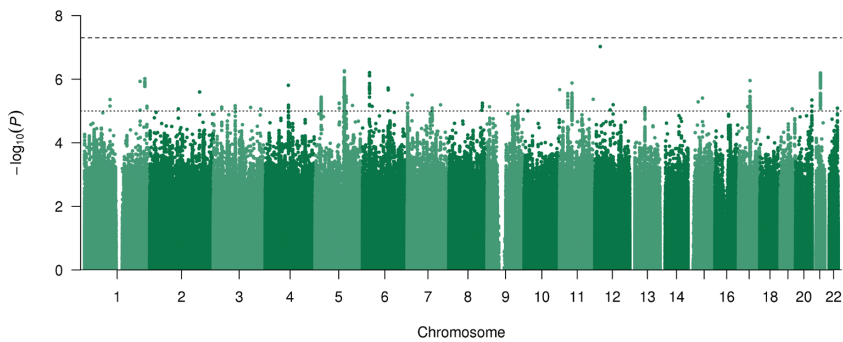
HURT - Are your feelings easily hurt?



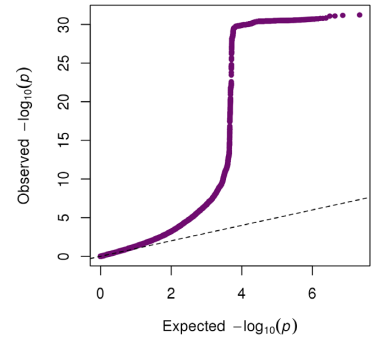
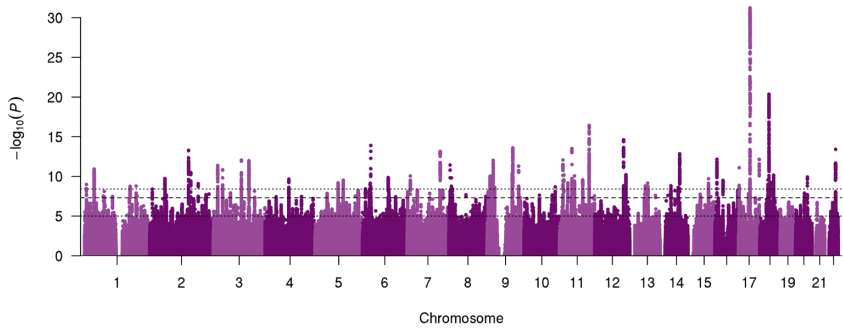
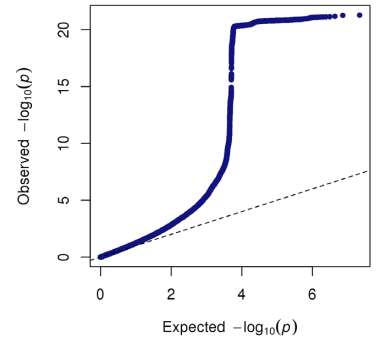
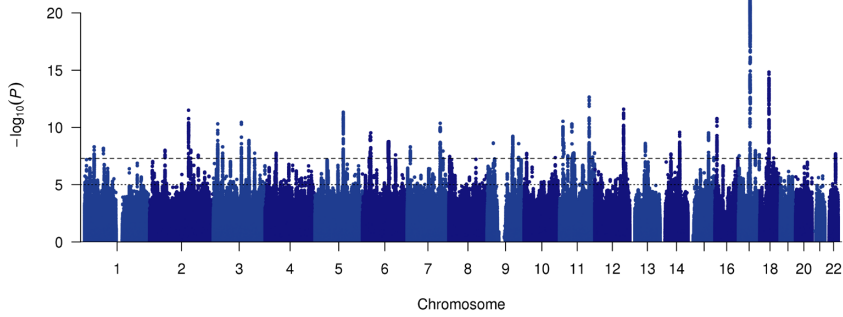
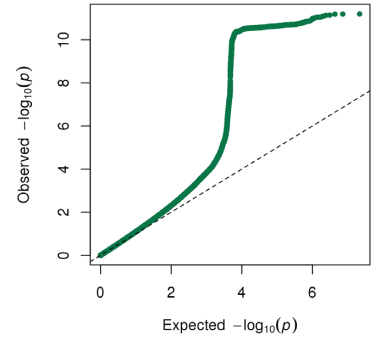
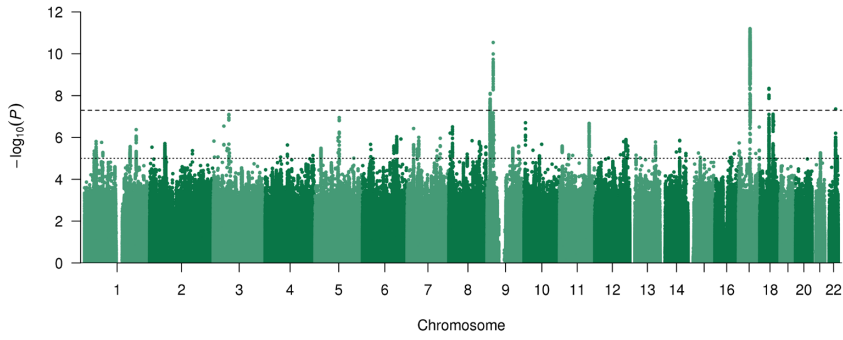
WORR-EMB - Do you worry too long after an embarrassing experience?



GUILT - Are you often troubled by feelings of guilt?



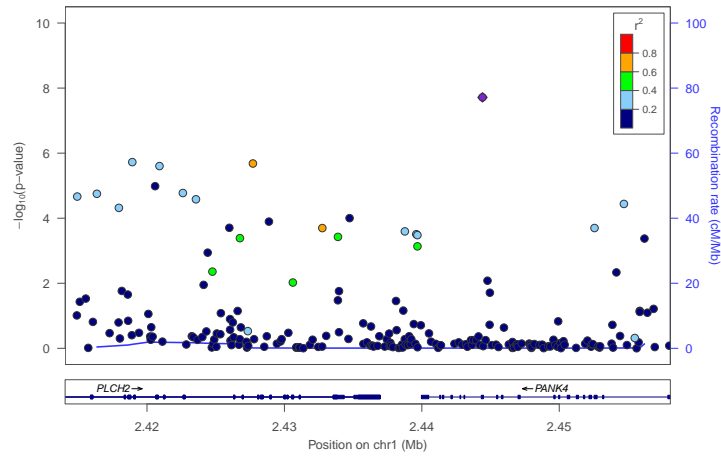
SUM-SCORE - Neuroticism sum-score



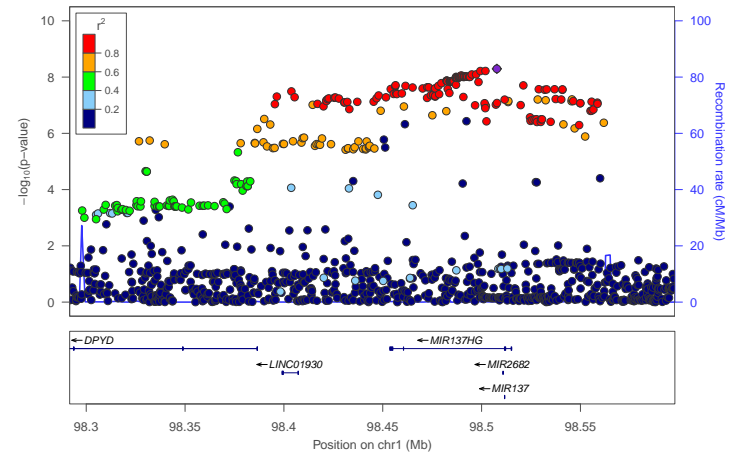
Supplementary Figure 4. Manhattan and quantile-quantile (Q-Q) plots of the SNP-based association results for the 12 individual items and the neuroticism sum-score.

SNP association results from the GWAS on the 12 neuroticism items and the sum-score in sample 1 (green), sample 2 (blue) and the meta-analysis (purple), respectively. Each dot represents a SNP. The y -axis shows the $-\log_{10} P$ values and the x -axis the chromosomal position of a given SNP. Dashed lines indicate genome-wide significance ($P < 5 \times 10^{-8}$) and dotted lines indicate the ‘suggestive’ significance threshold ($P < 1 \times 10^{-5}$). The upper dotted line in the Manhattan plots of the meta-analyses indicates a more stringent Bonferroni-corrected significance threshold, where we corrected for testing 13 phenotypes; $P < 5 \times 10^{-8}/13$ (3.85×10^{-9}). See **Supplementary Table 1** for an explanation of item labels.

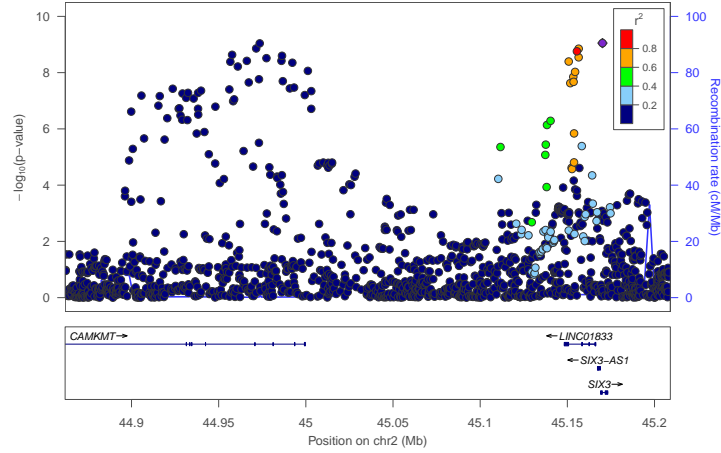
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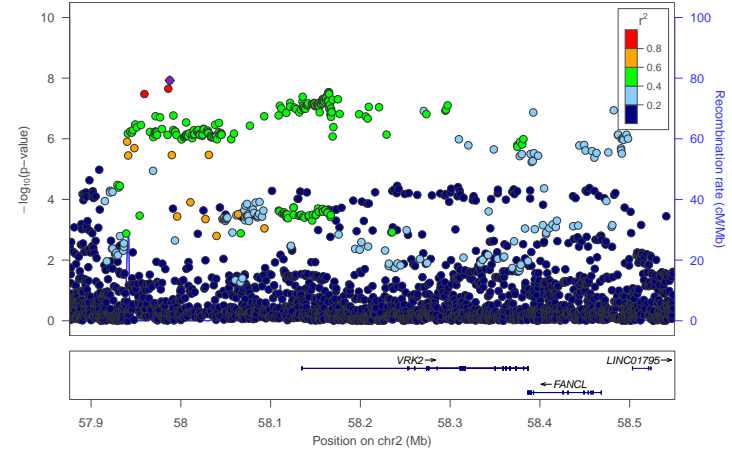
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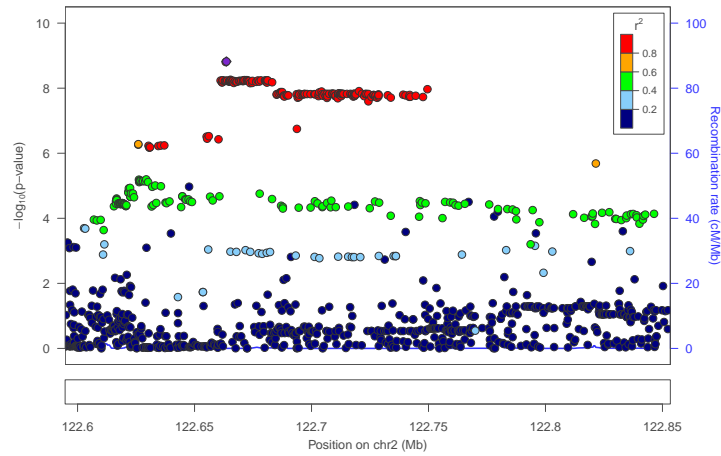
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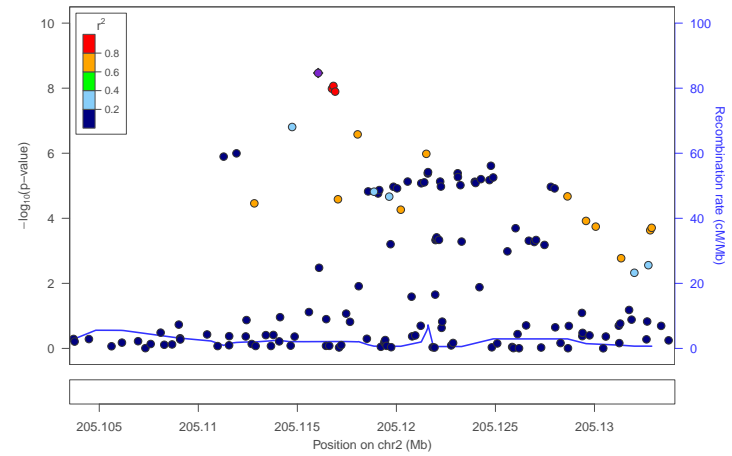
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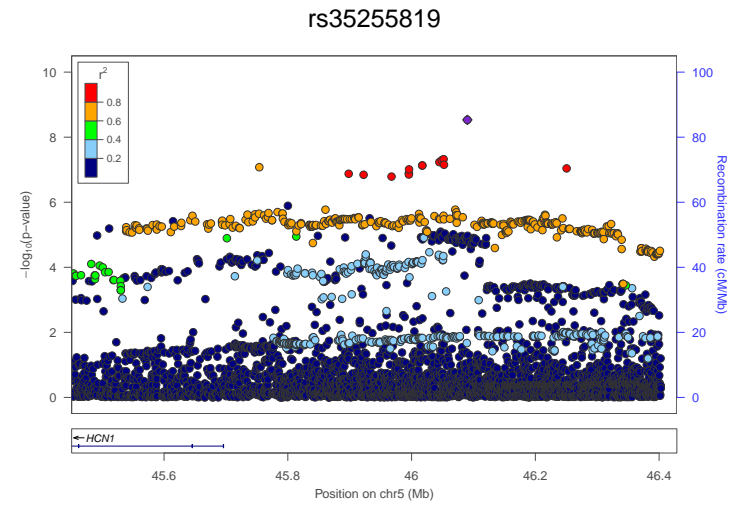
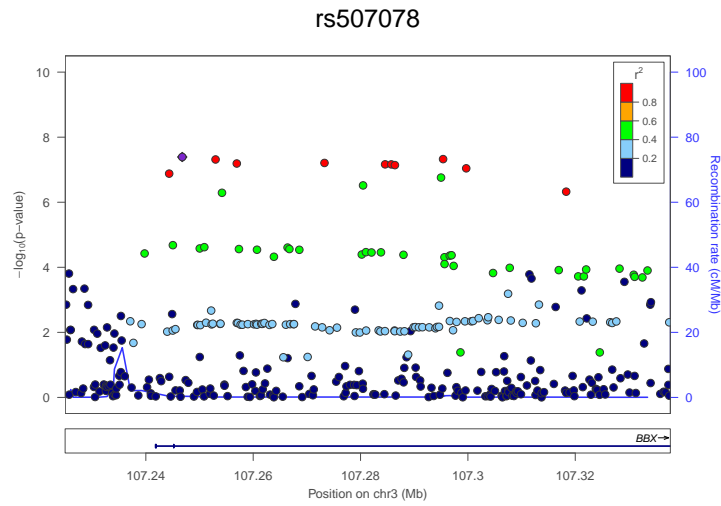
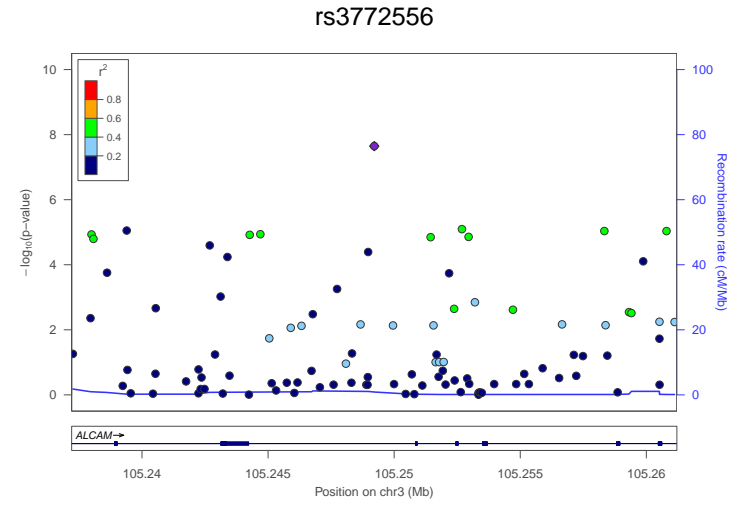
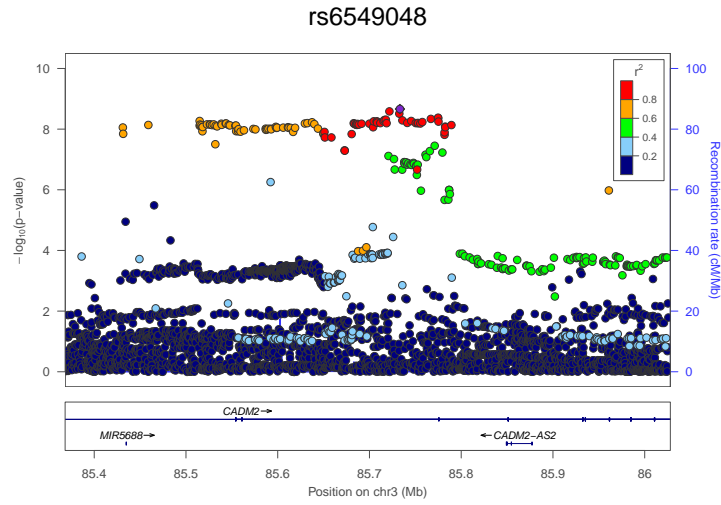
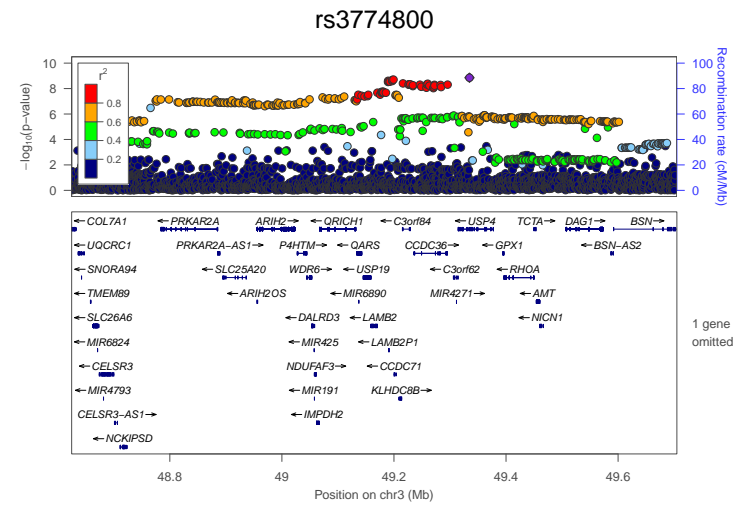
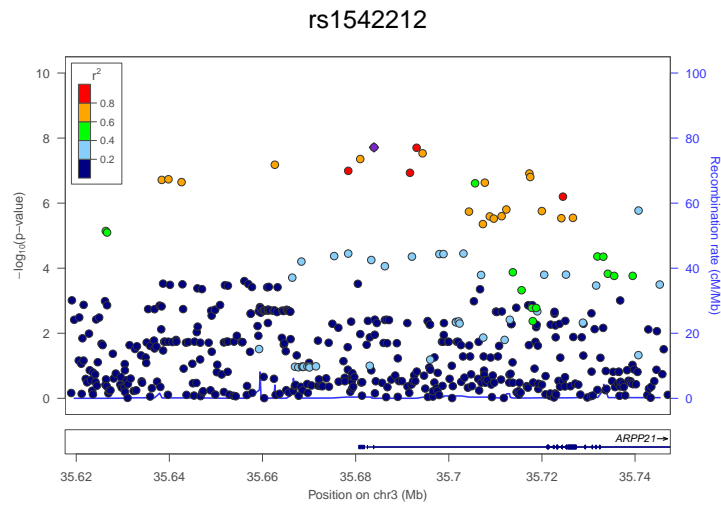


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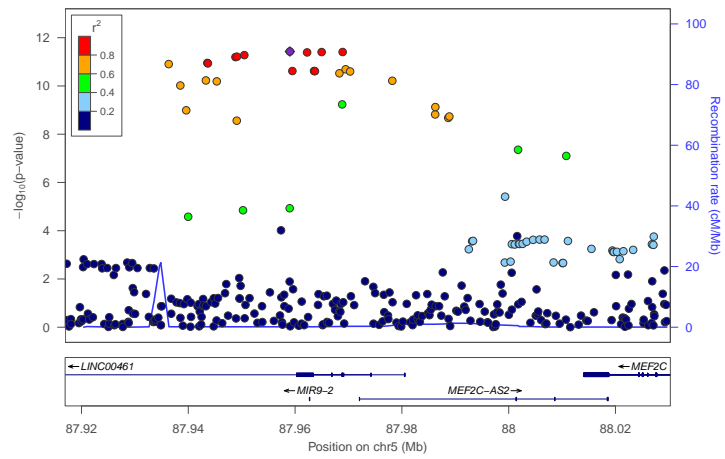


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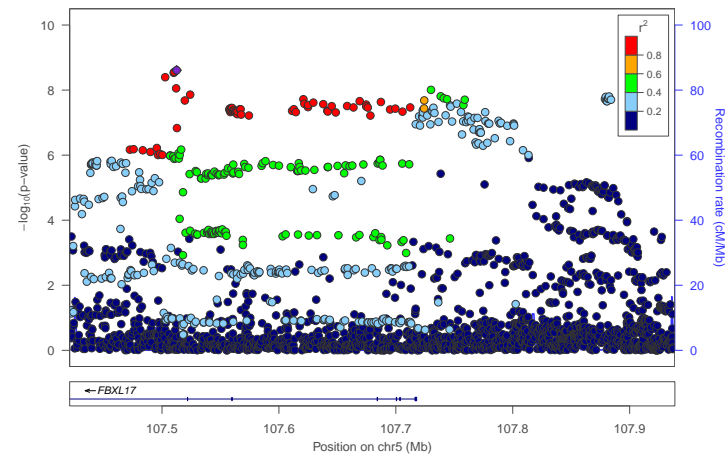




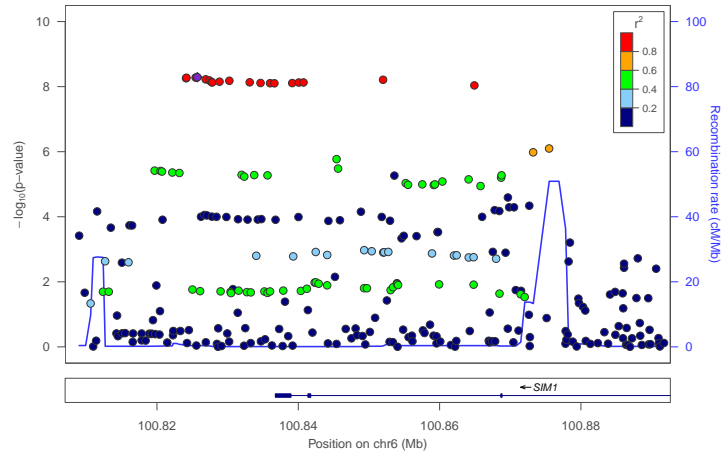
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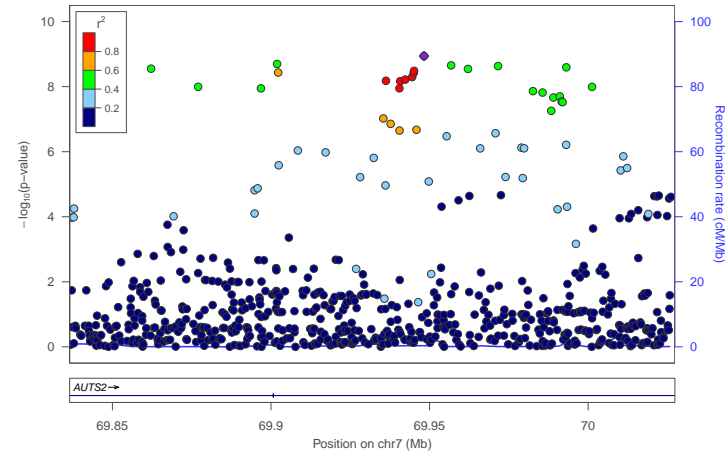
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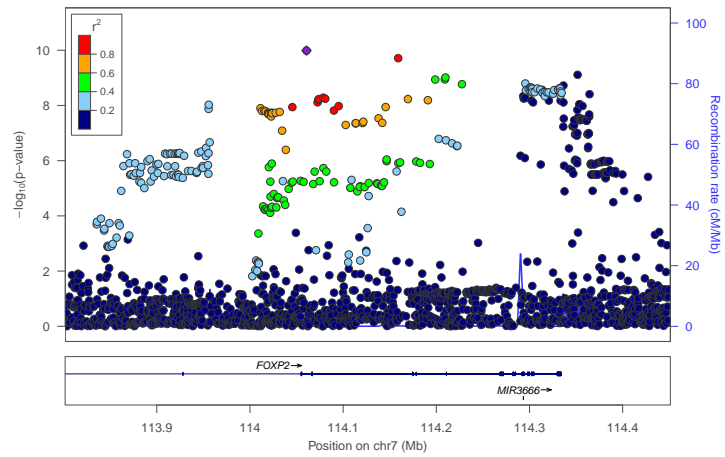
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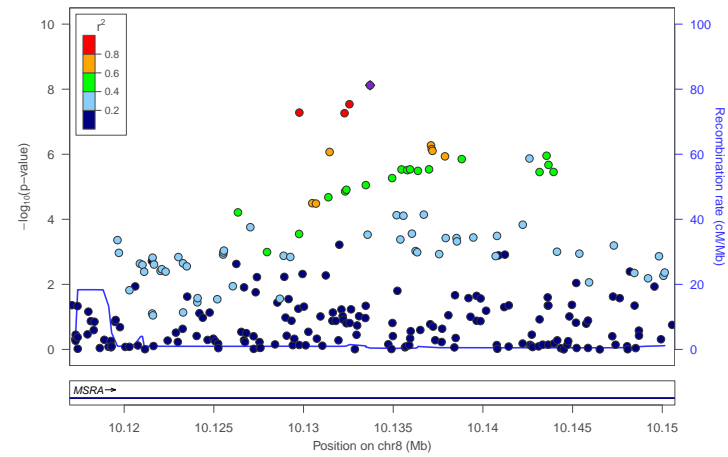
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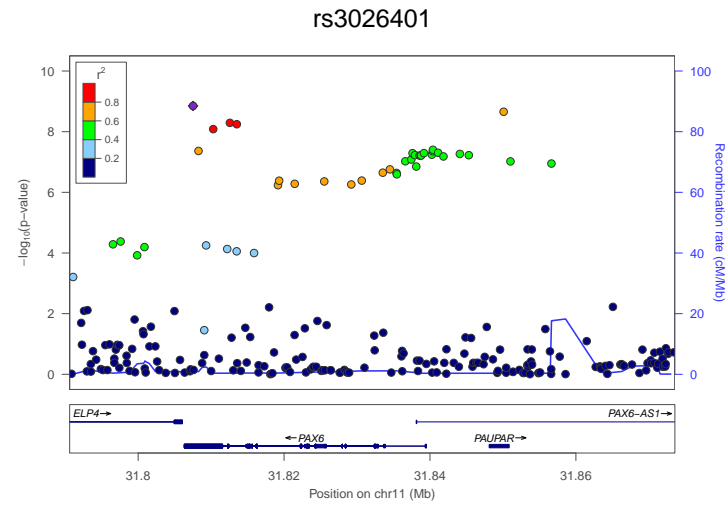
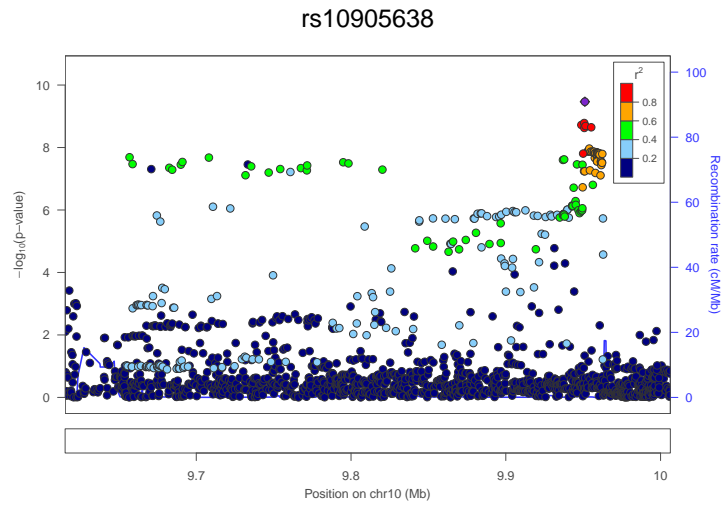
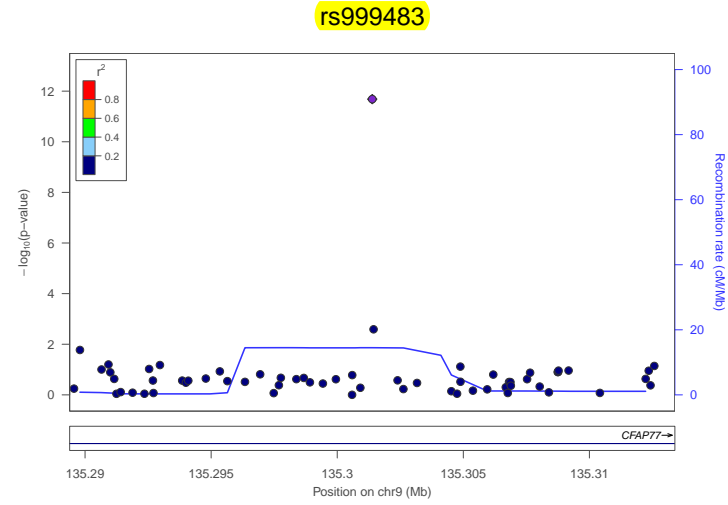
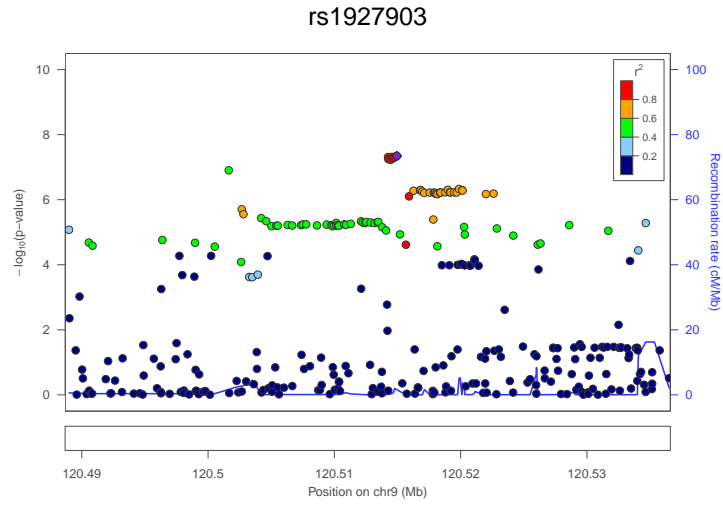
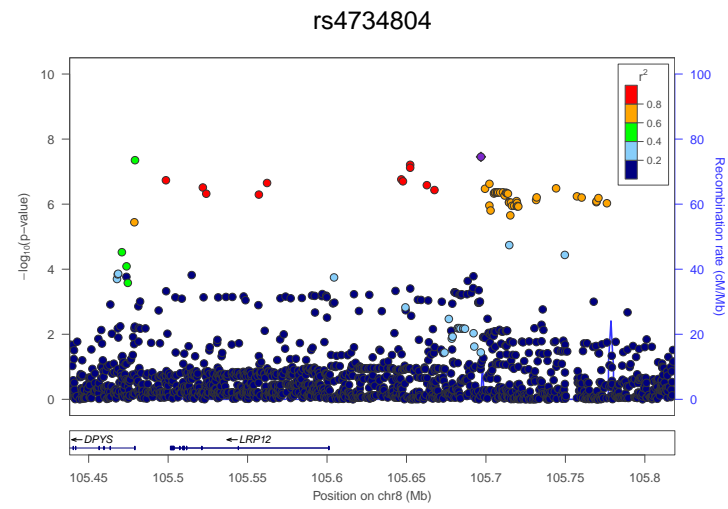
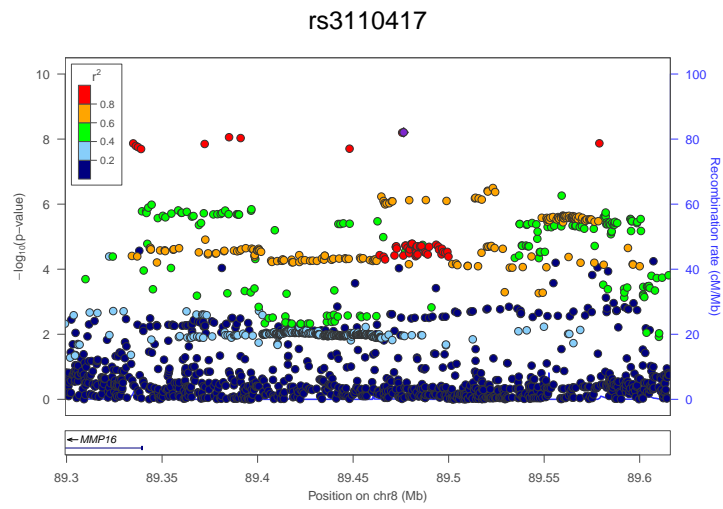


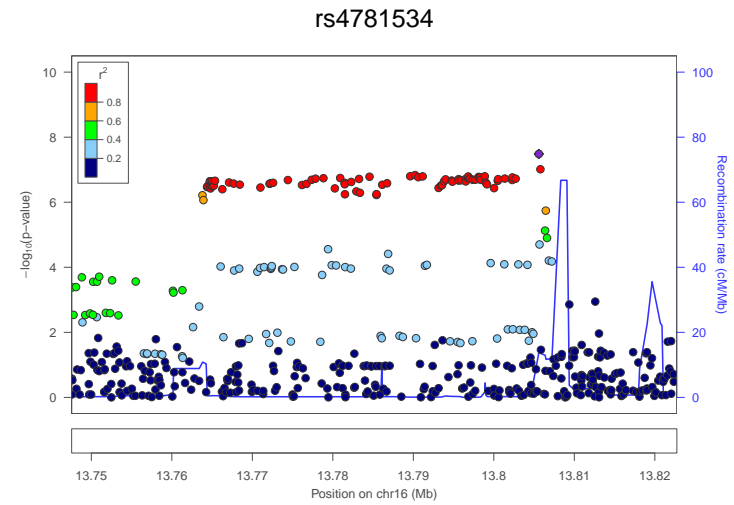
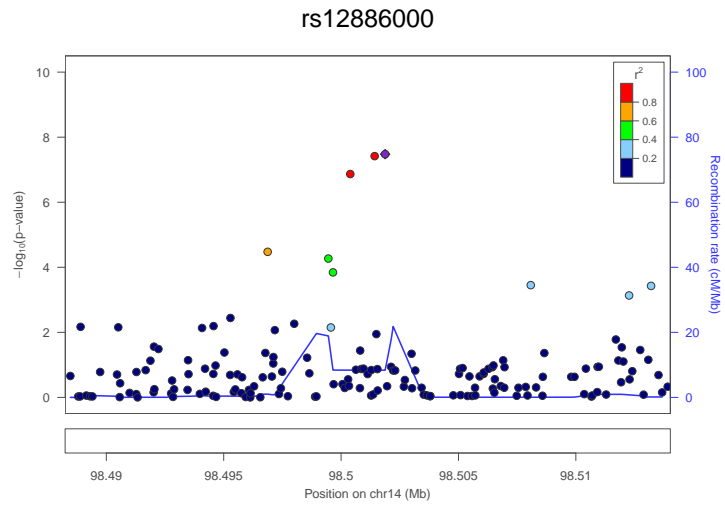
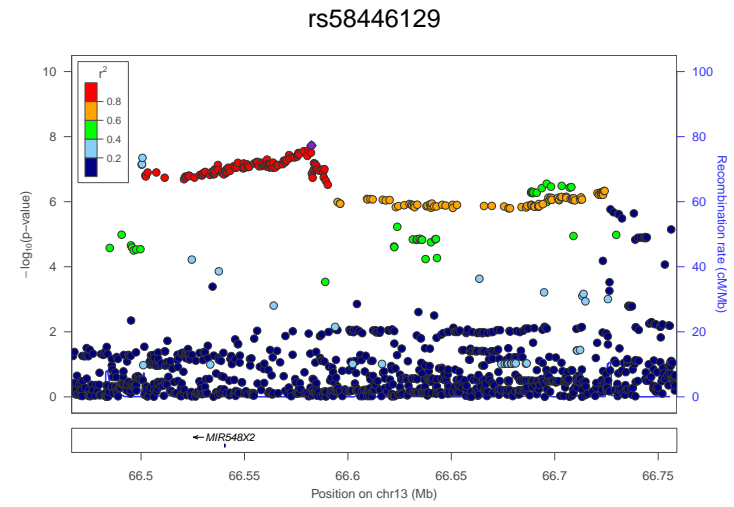
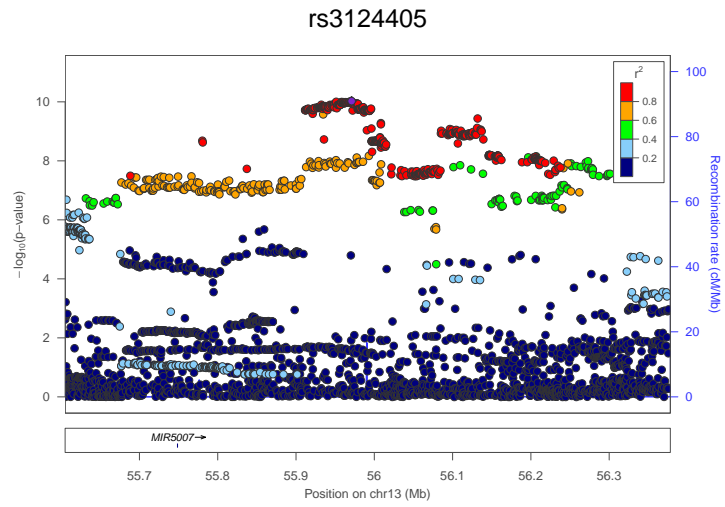
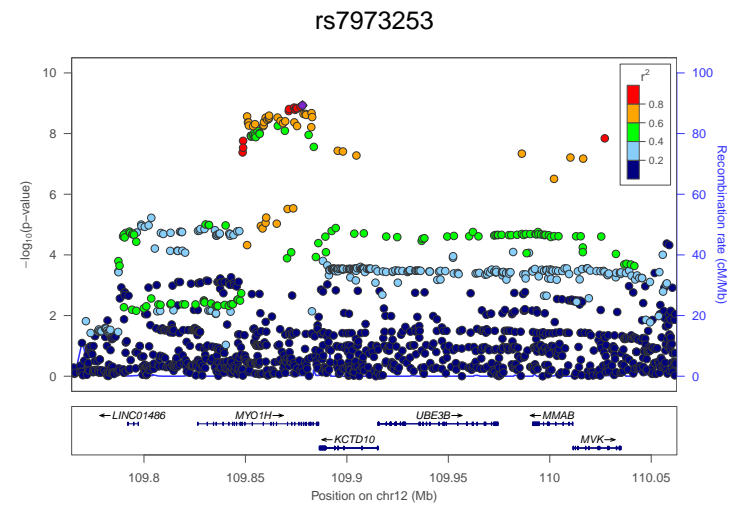
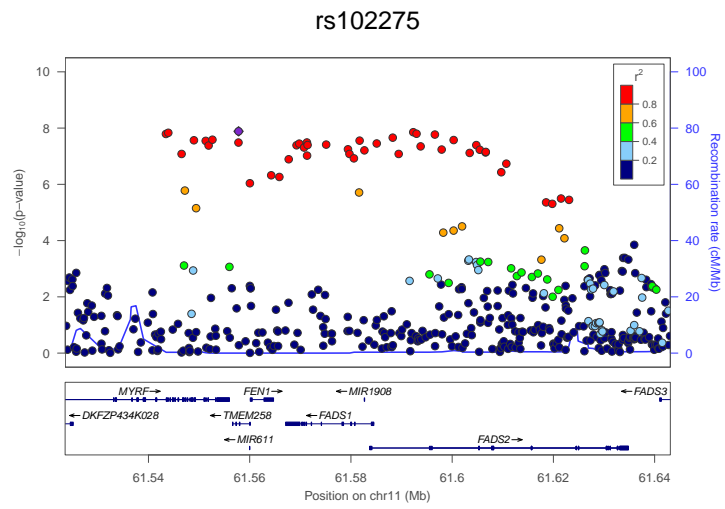
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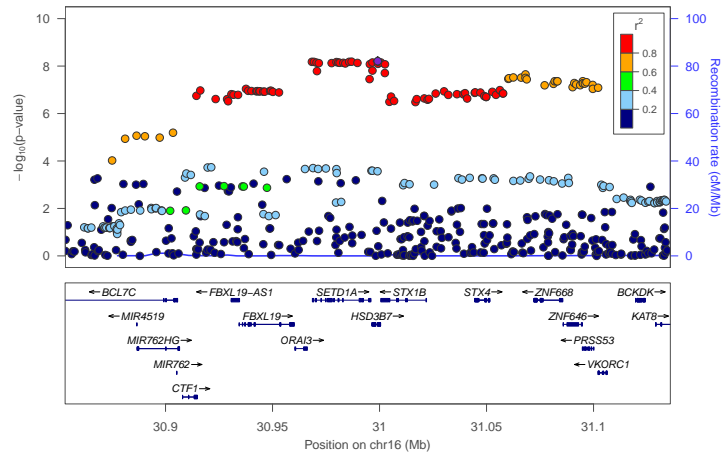
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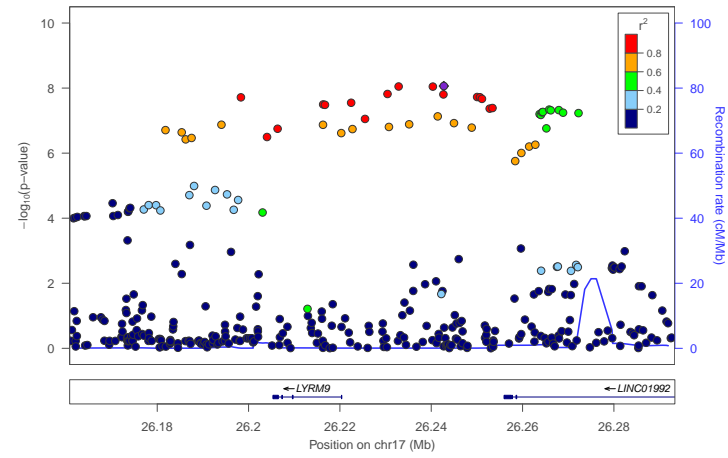




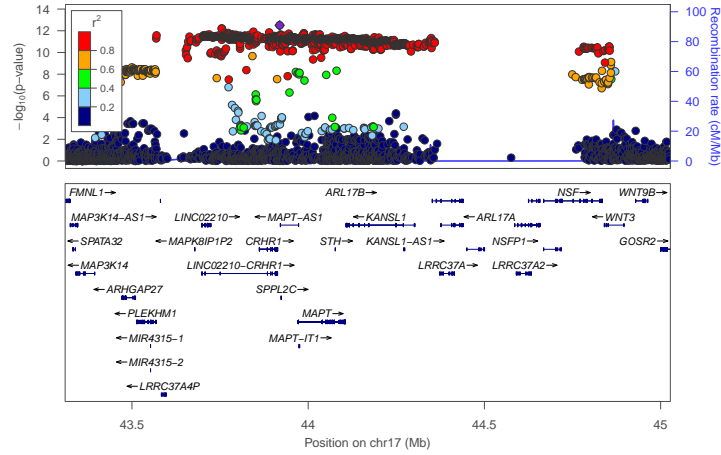
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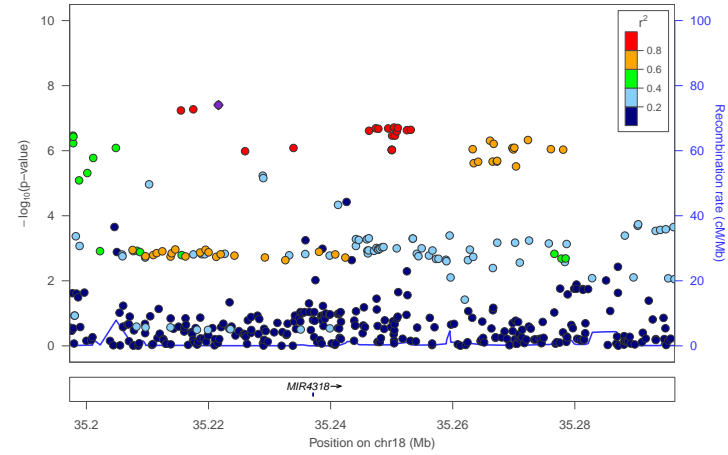
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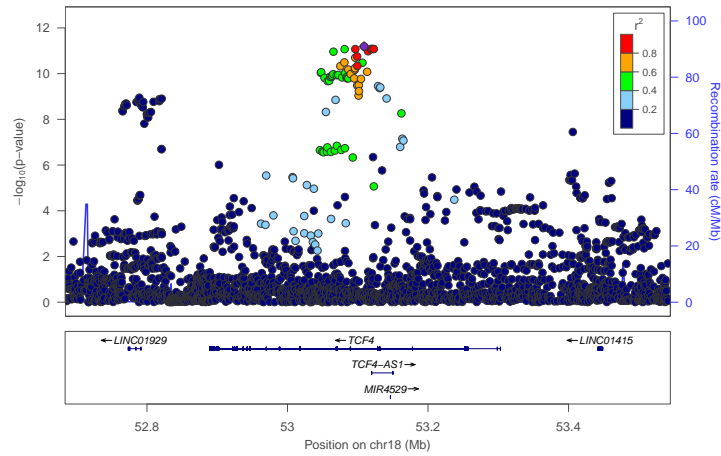
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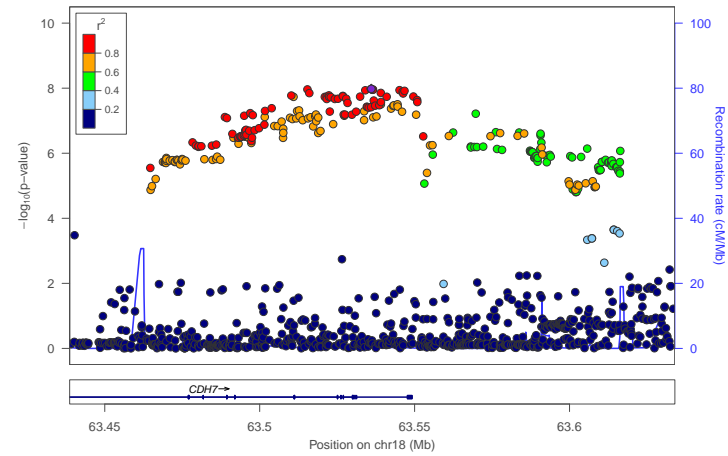
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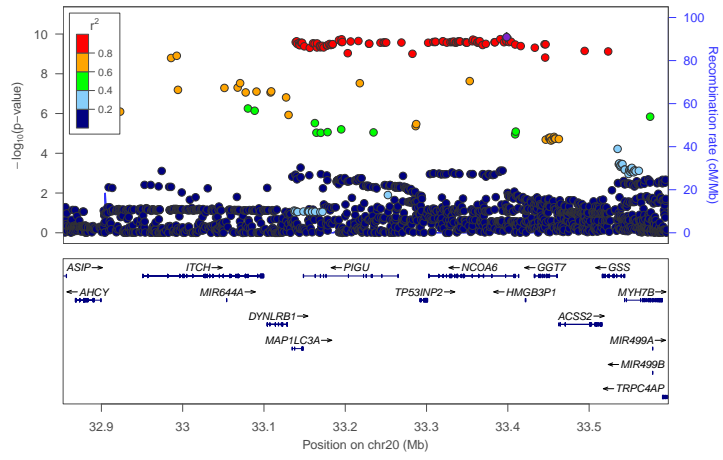
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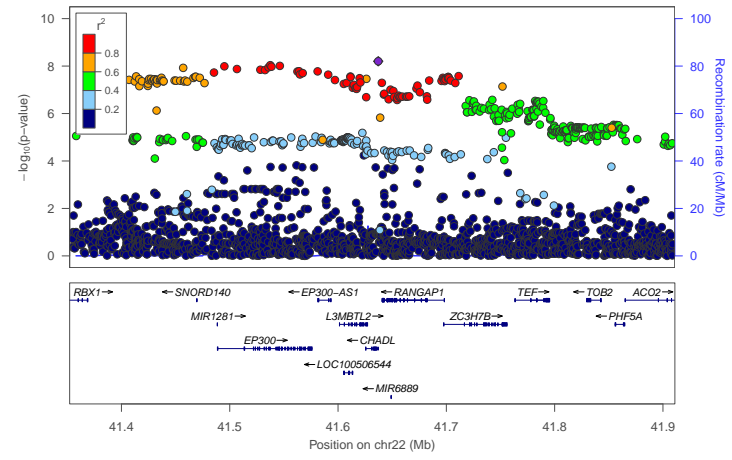
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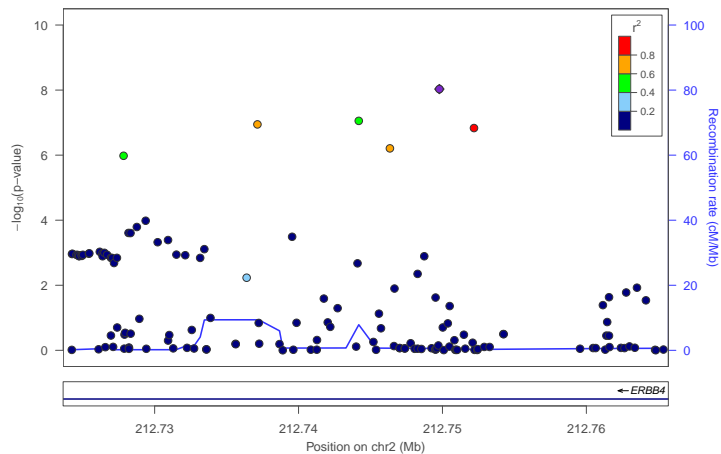
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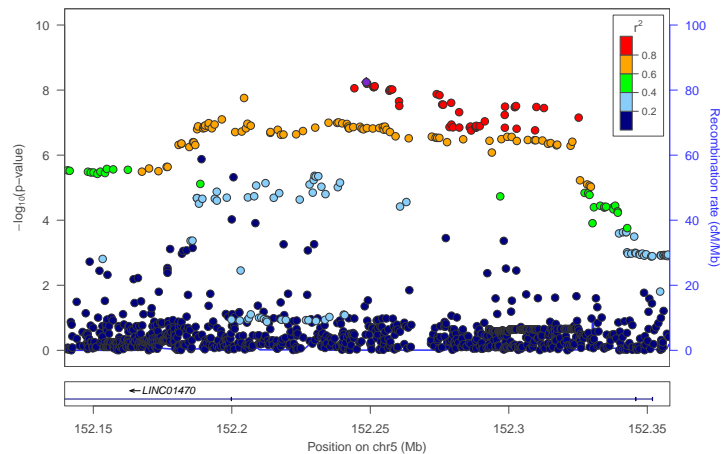
Supplementary Figure 5. Regional plots of GWA analyses of item IRR.

The y -axis represents the negative logarithm (base 10) of the SNP P value and the x -axis the position on the chromosome, with the name and location of genes in the UCSC Genome Browser in the bottom panel. The SNP with the lowest P value in the region is marked by a purple diamond. The colors of the other SNPs indicate the r^2 of these SNPs with the lead SNP, with grey color indicating SNPs below the user-defined r^2 . Plots are generated with LocusZoom. See **Supplementary Data 2** for an overview of all lead SNPs for which a regional plot is presented above. For excluded loci (see **Methods; Supplementary Data 3-4**) the rsID's are marked yellow.

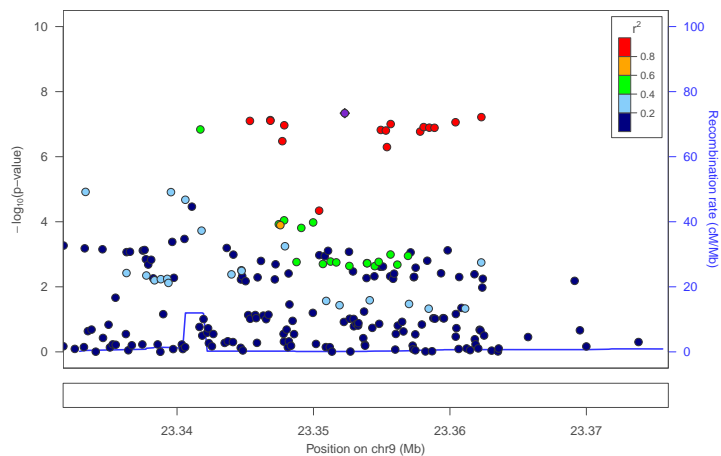
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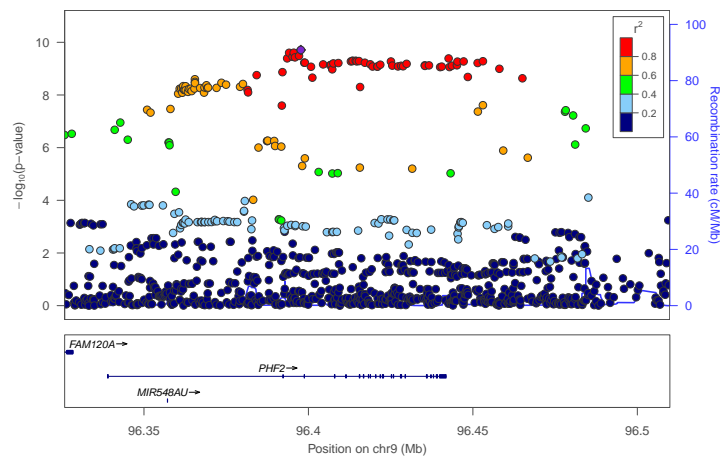
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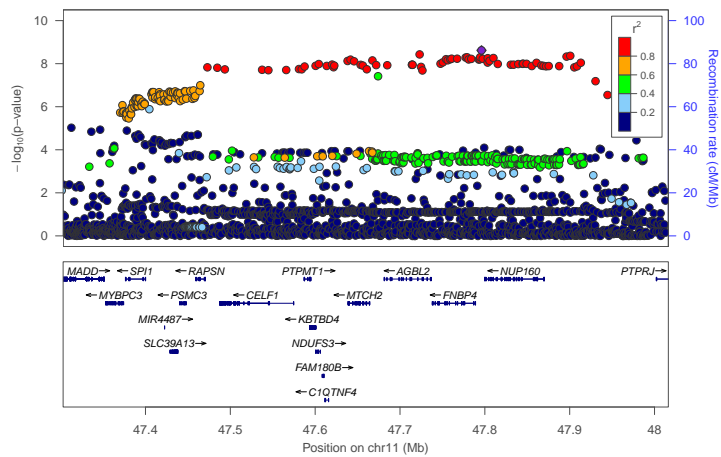
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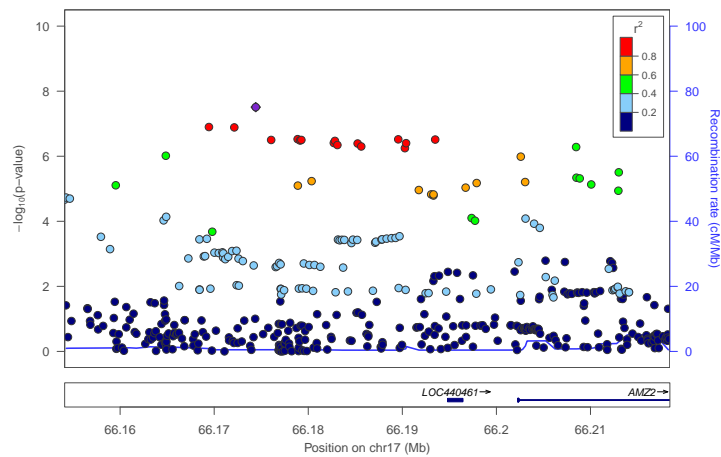
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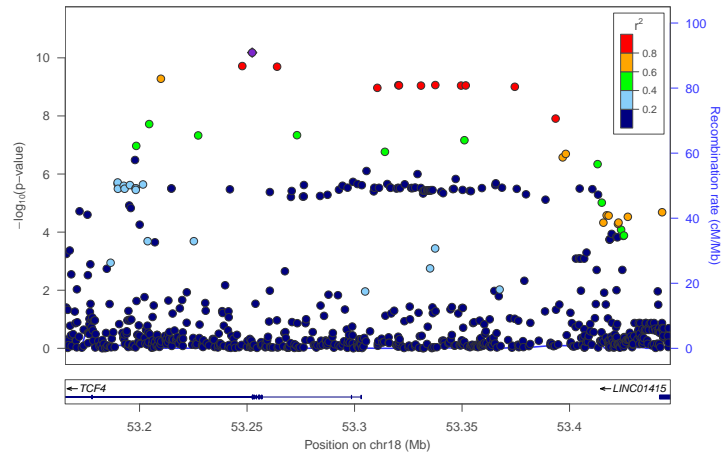
rs11039389



rs7209581

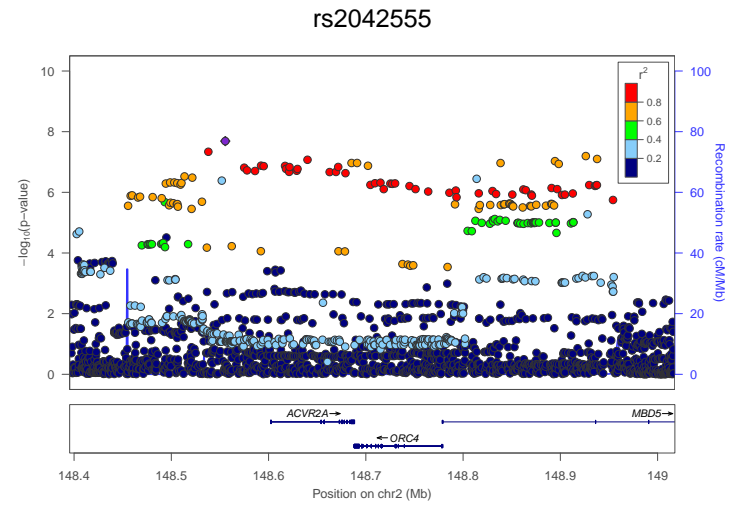
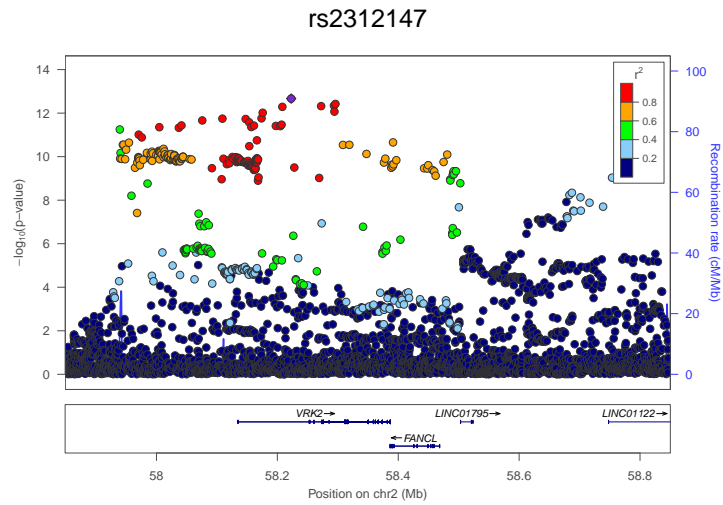
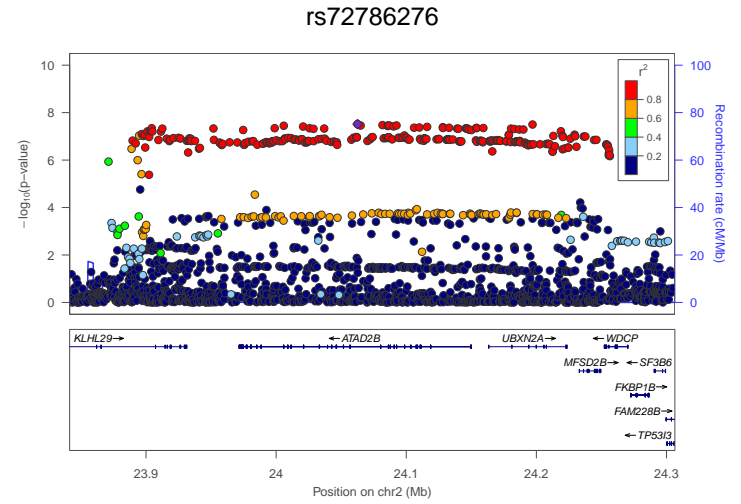
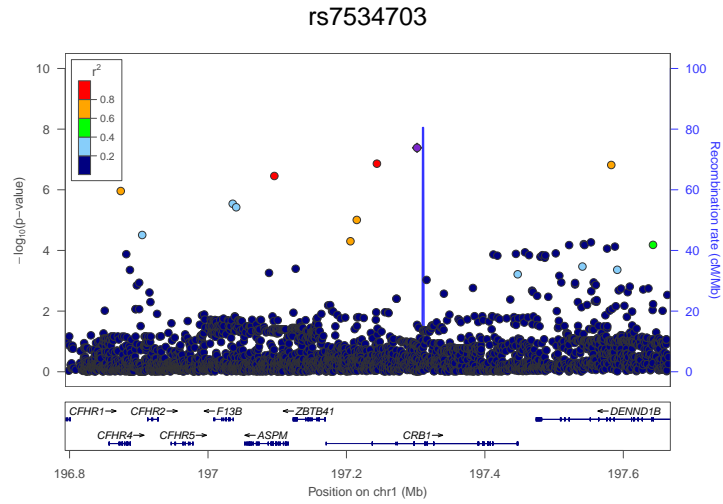
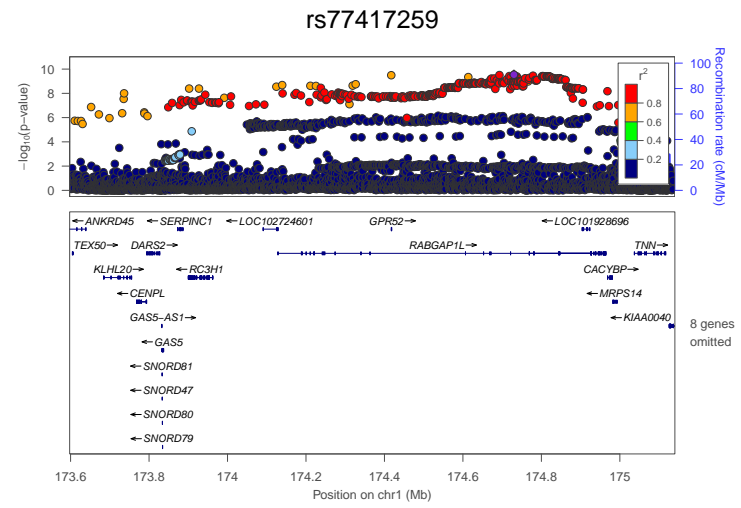
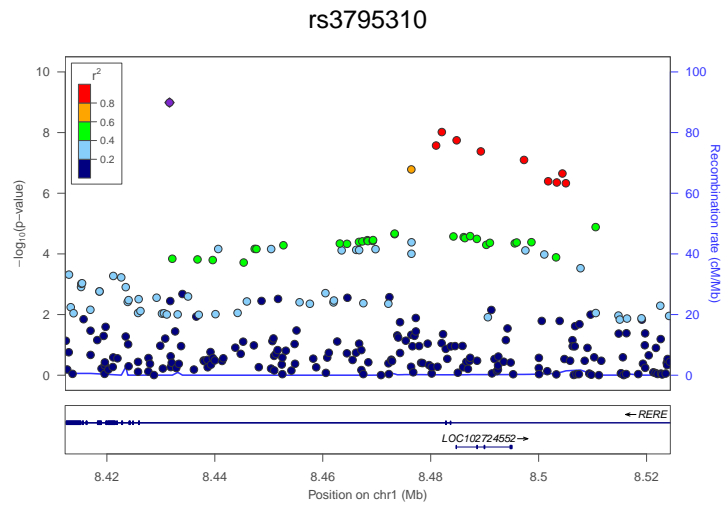


rs599550

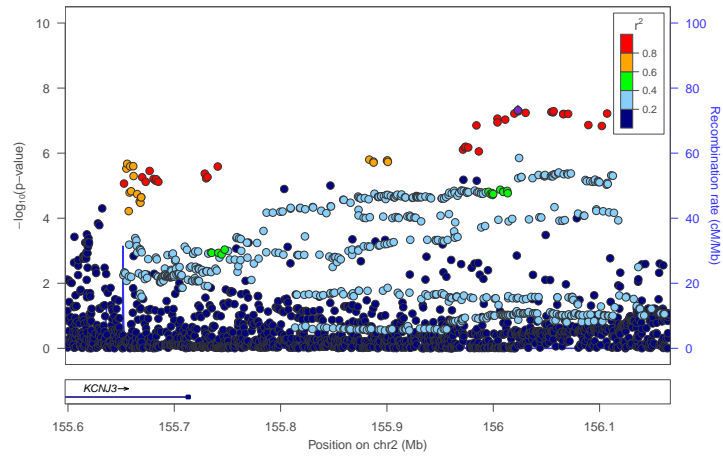


Supplementary Figure 6. Regional plots of GWA analyses of item LONE.

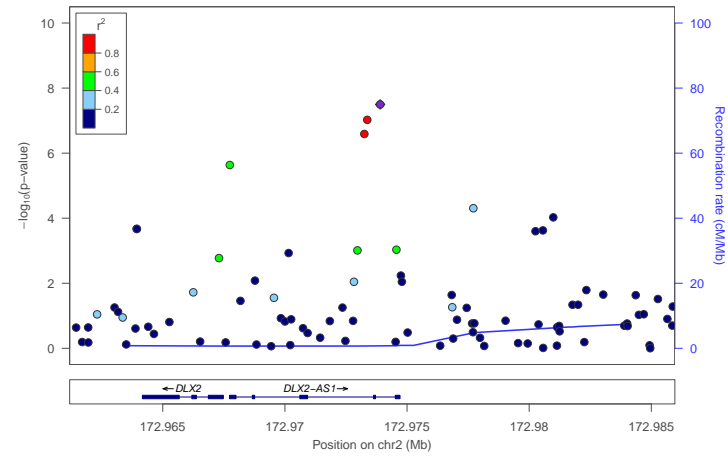
The y -axis represents the negative logarithm (base 10) of the SNP P value and the x -axis the position on the chromosome, with the name and location of genes in the UCSC Genome Browser in the bottom panel. The SNP with the lowest P value in the region is marked by a purple diamond. The colors of the other SNPs indicate the r^2 of these SNPs with the lead SNP, with grey color indicating SNPs below the user-defined r^2 . Plots are generated with LocusZoom. See **Supplementary Data 2** for an overview of all lead SNPs for which a regional plot is presented above.



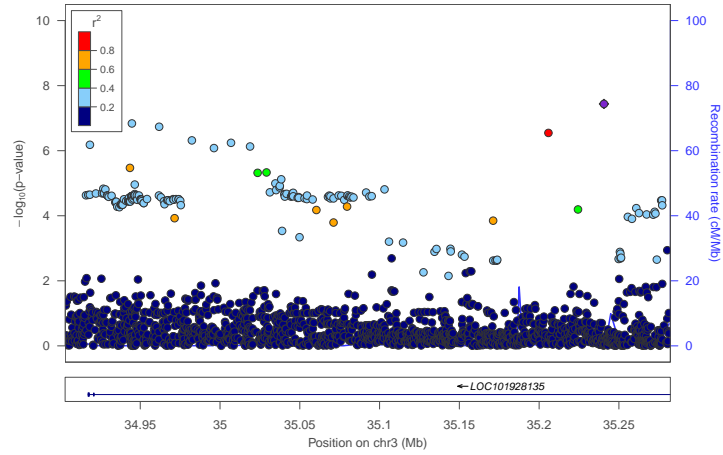
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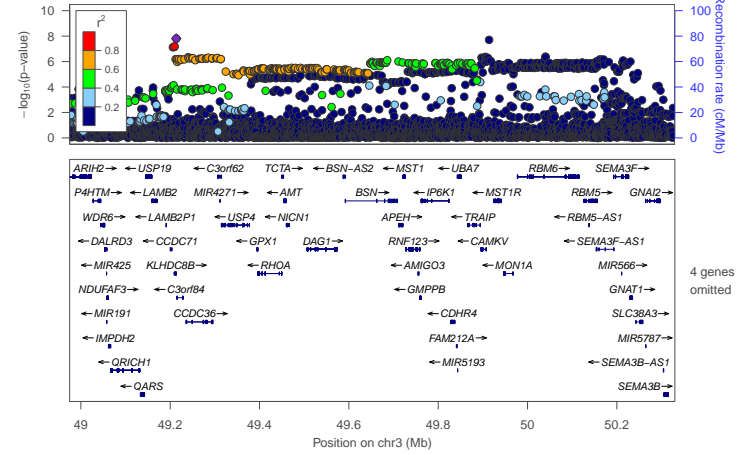
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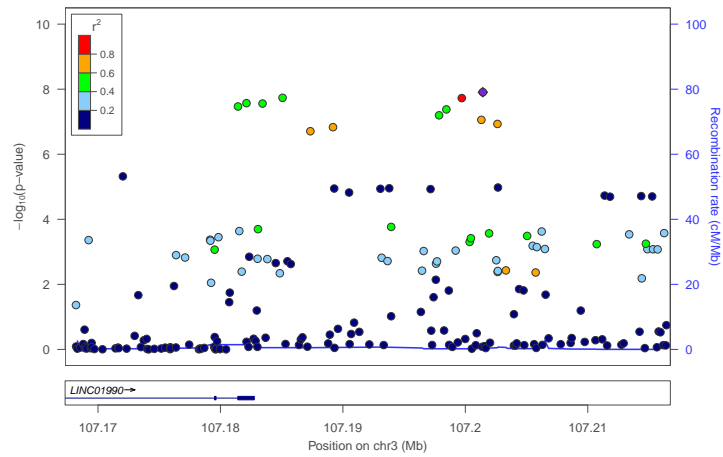
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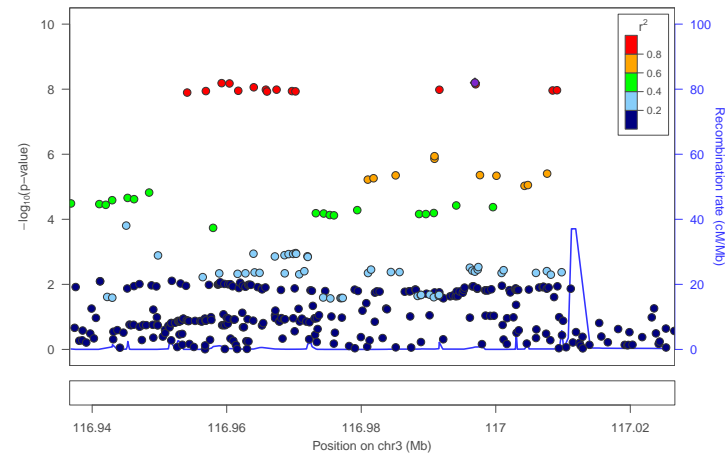
rs9586



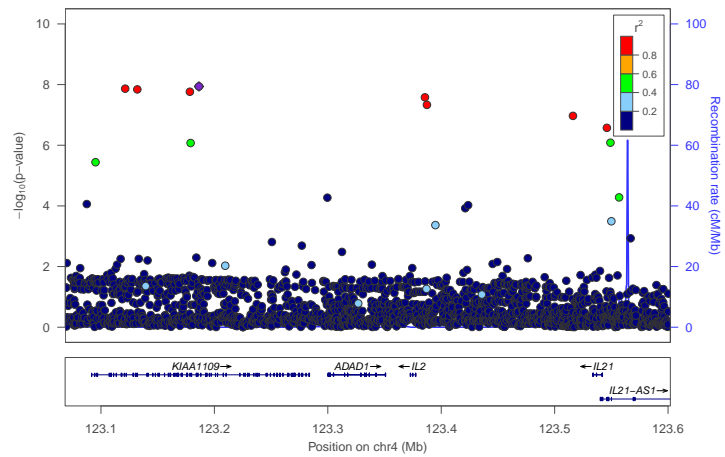
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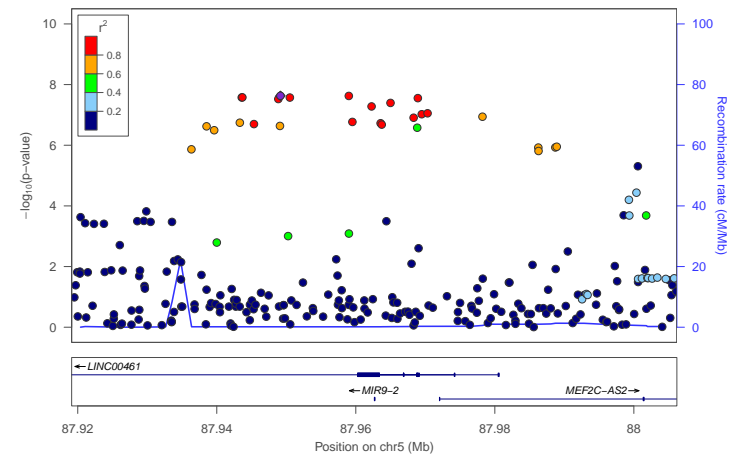
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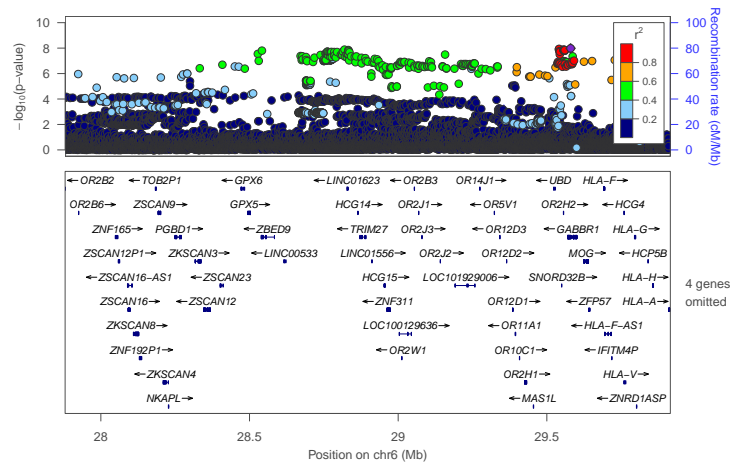
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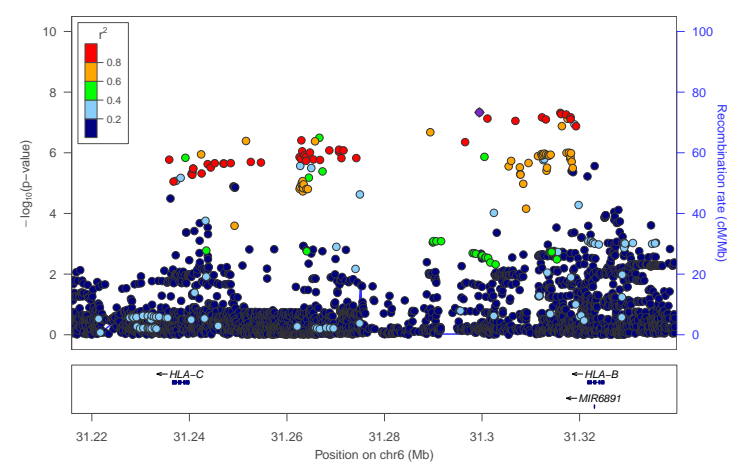
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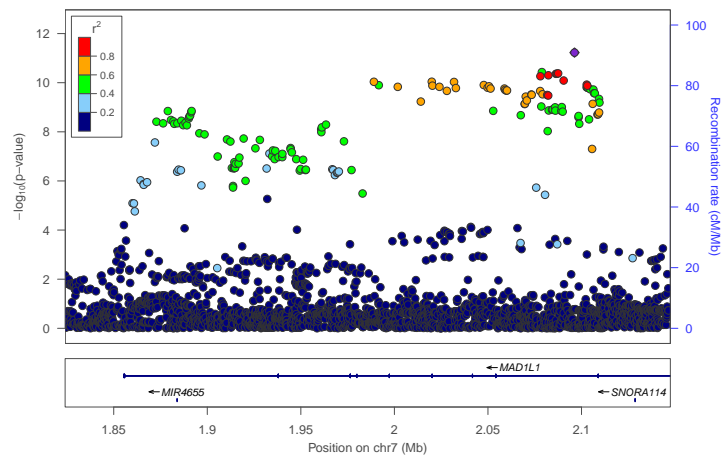
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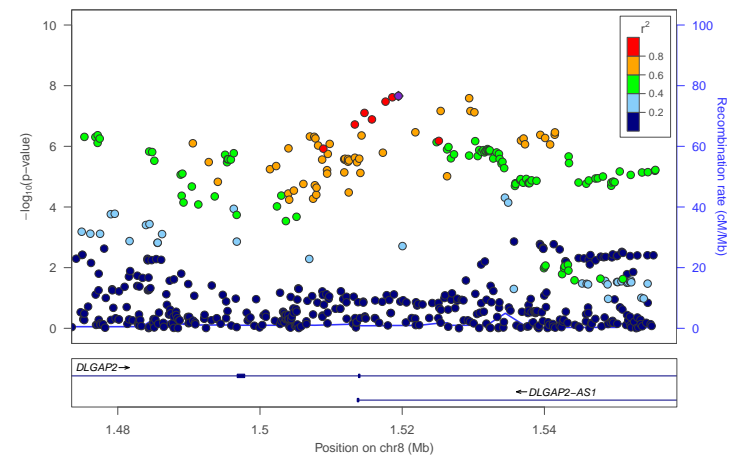
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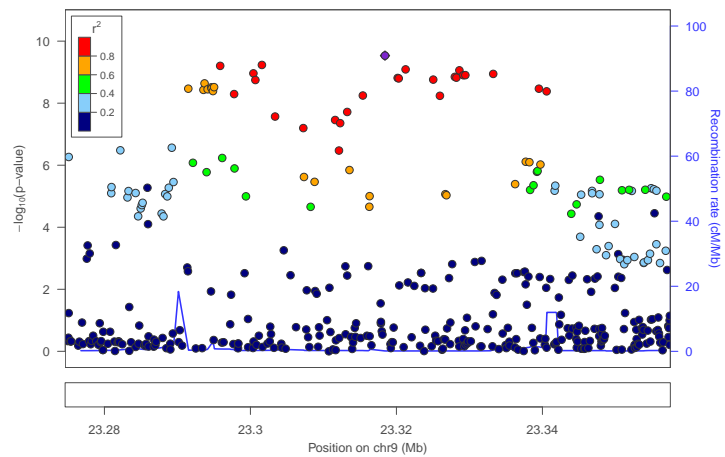
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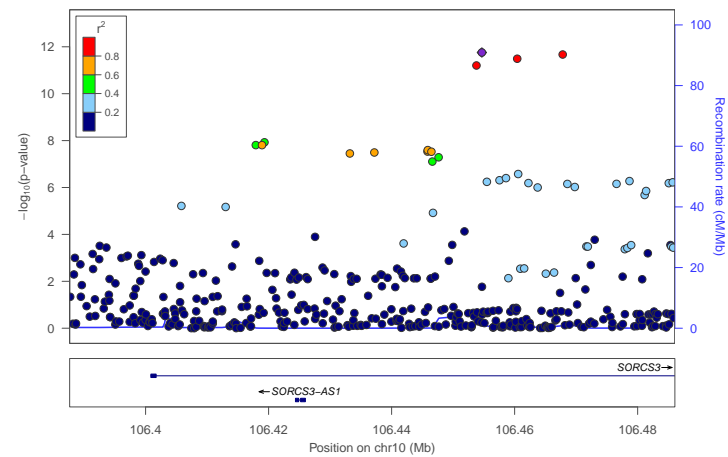
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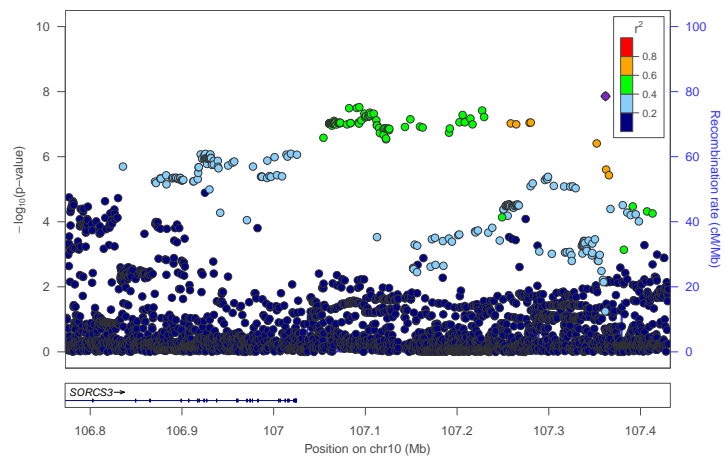
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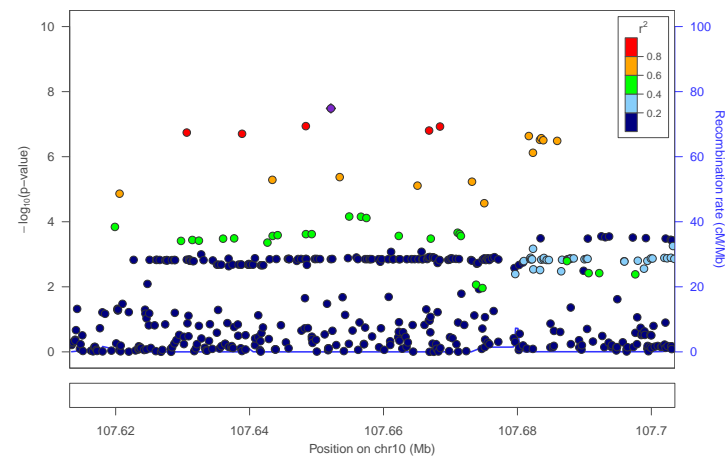
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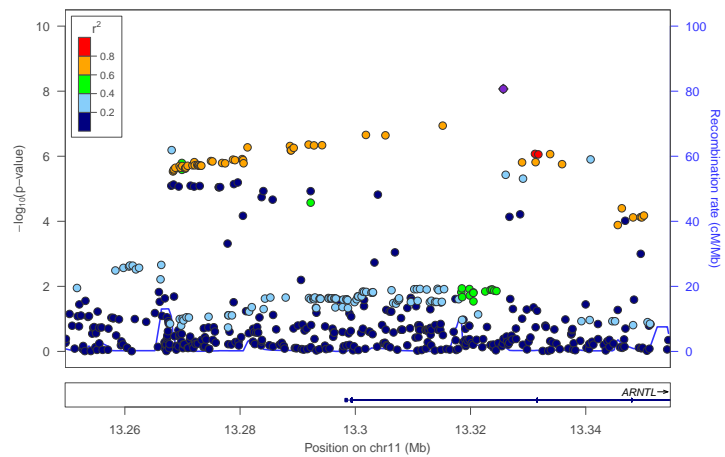
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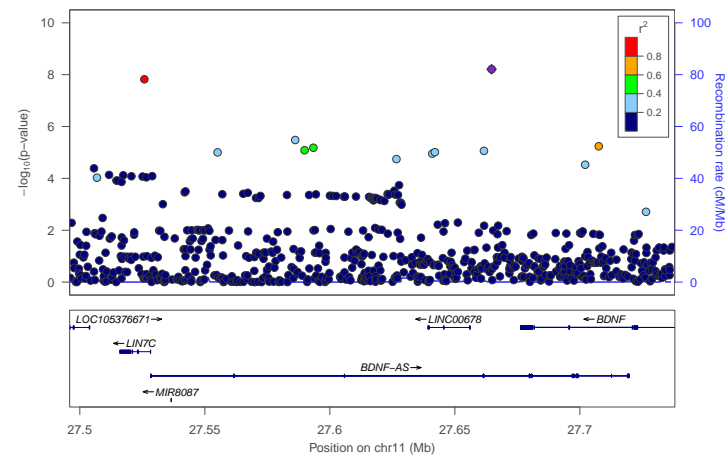
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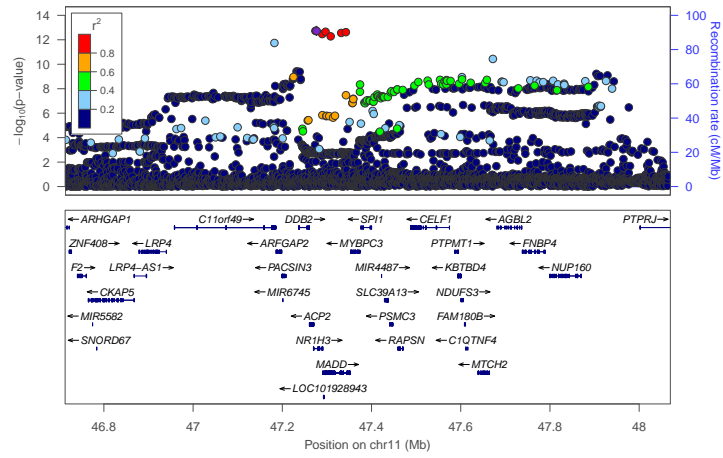
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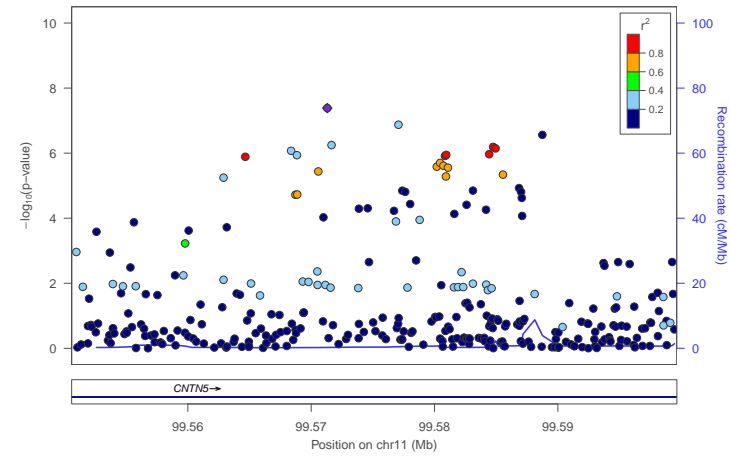
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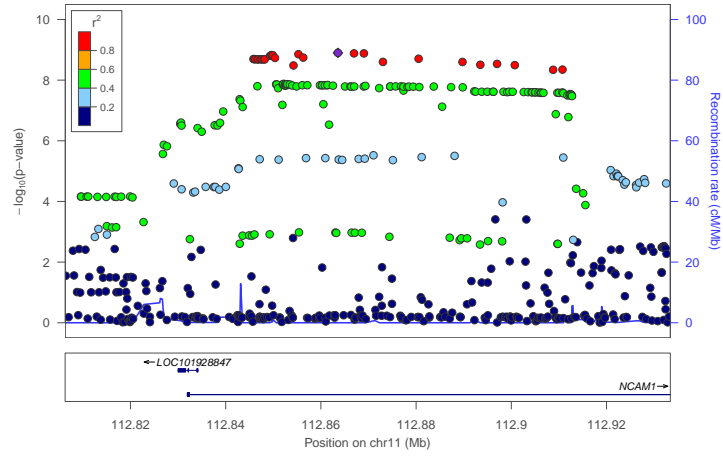
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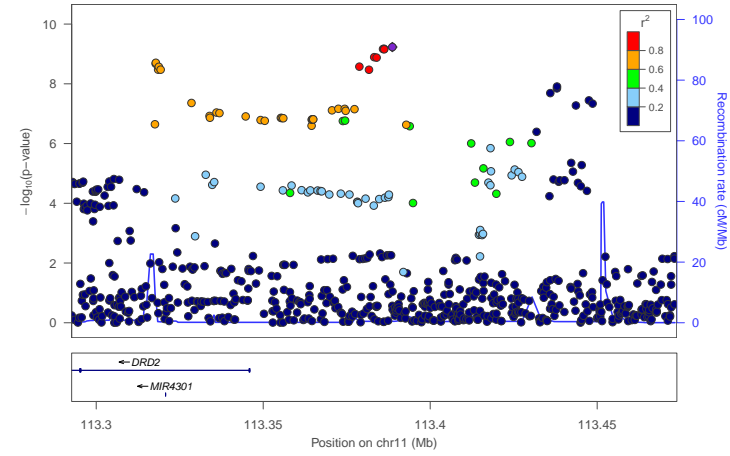
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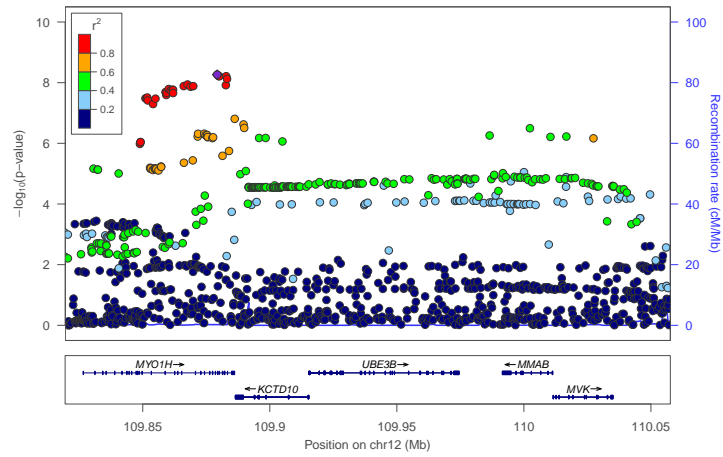
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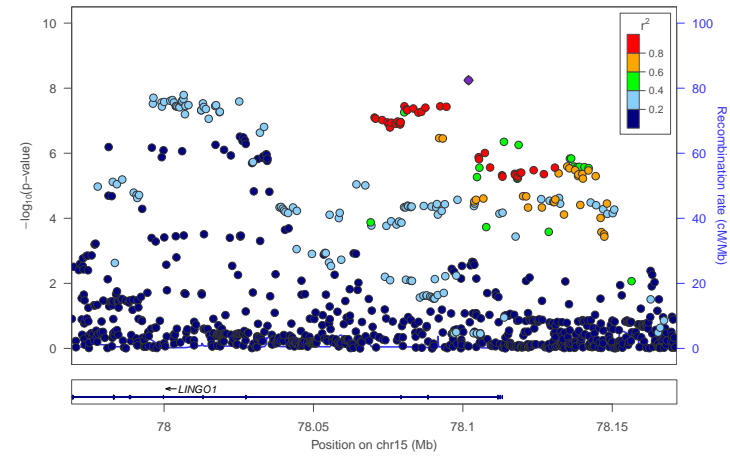
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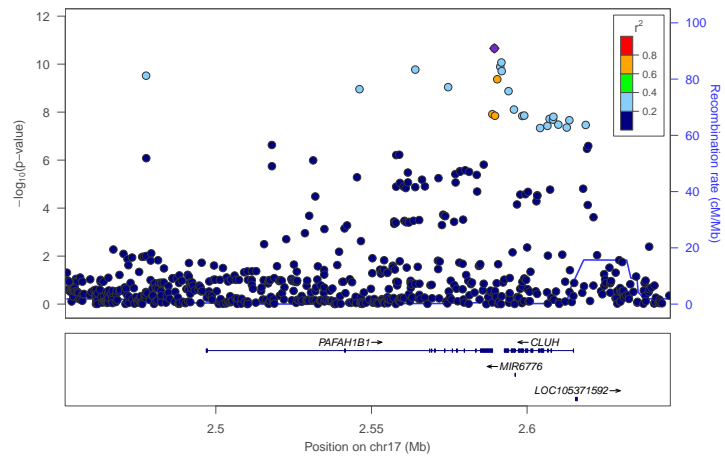
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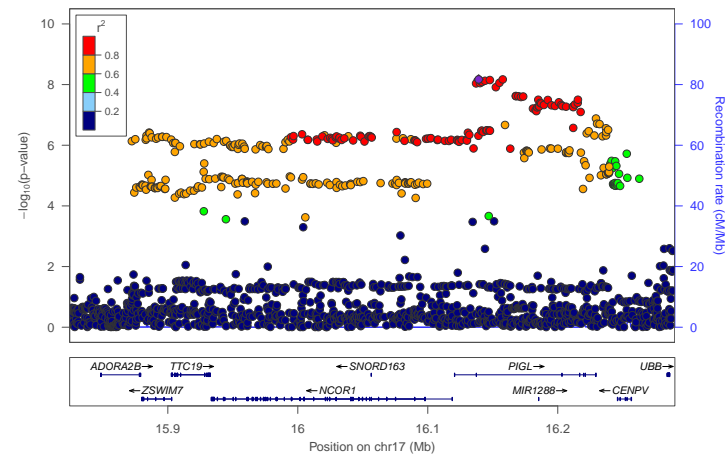
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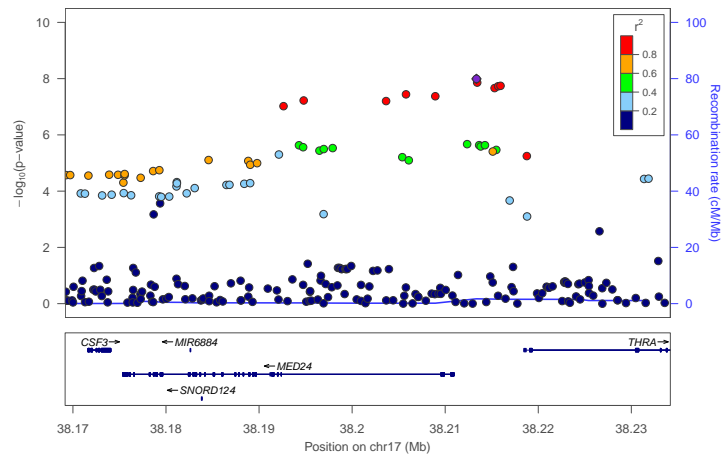
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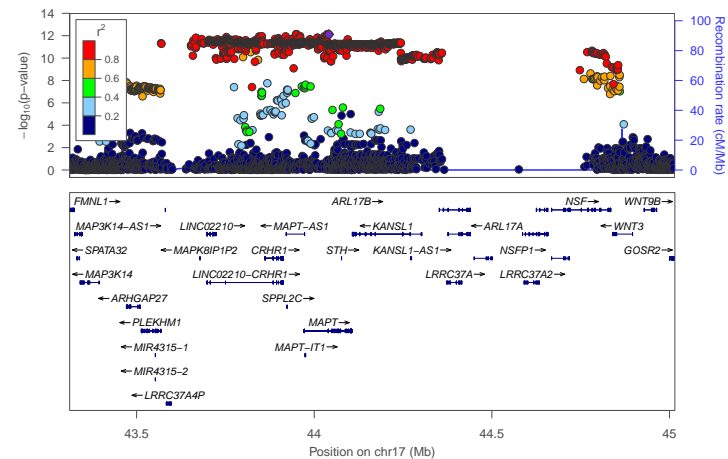
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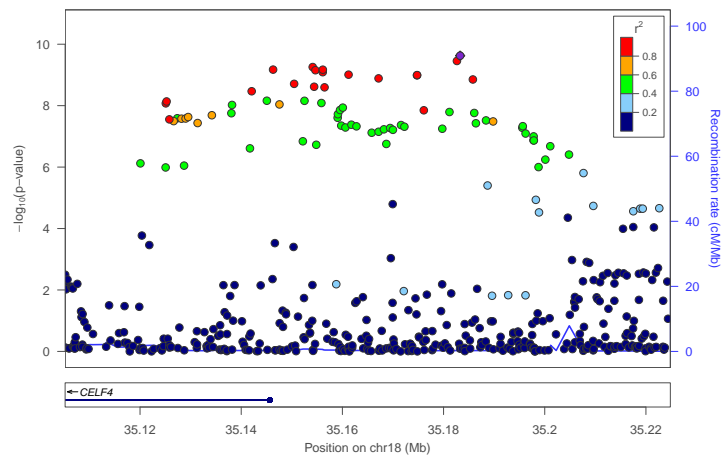
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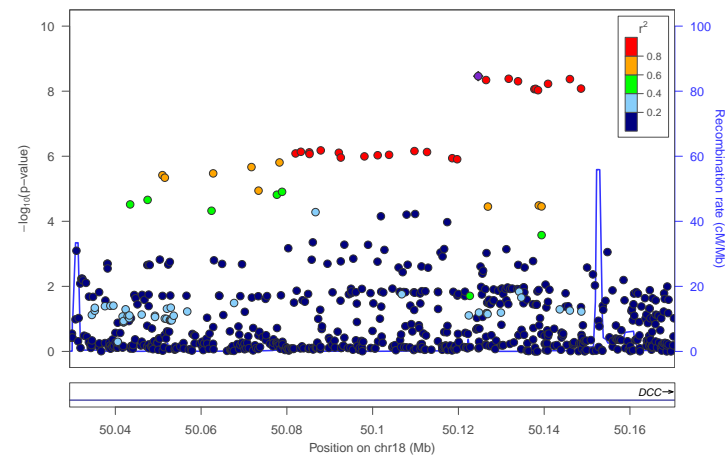
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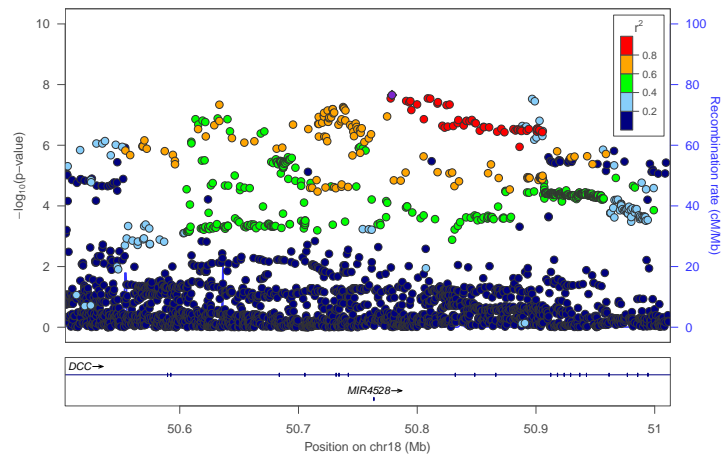
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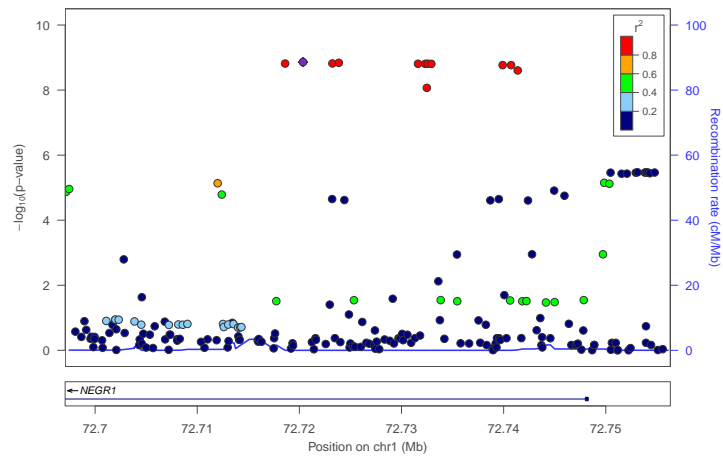
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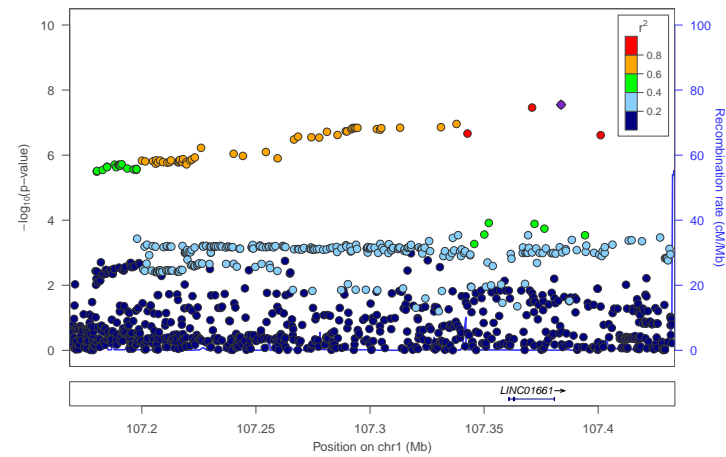
Supplementary Figure 7. Regional plots of GWA analyses of item MIS.

The y -axis represents the negative logarithm (base 10) of the SNP P value and the x -axis the position on the chromosome, with the name and location of genes in the UCSC Genome Browser in the bottom panel. The SNP with the lowest P value in the region is marked by a purple diamond. The colors of the other SNPs indicate the r^2 of these SNPs with the lead SNP, with grey color indicating SNPs below the user-defined r^2 . Plots are generated with LocusZoom. See **Supplementary Data 2** for an overview of all lead SNPs for which a regional plot is presented above.

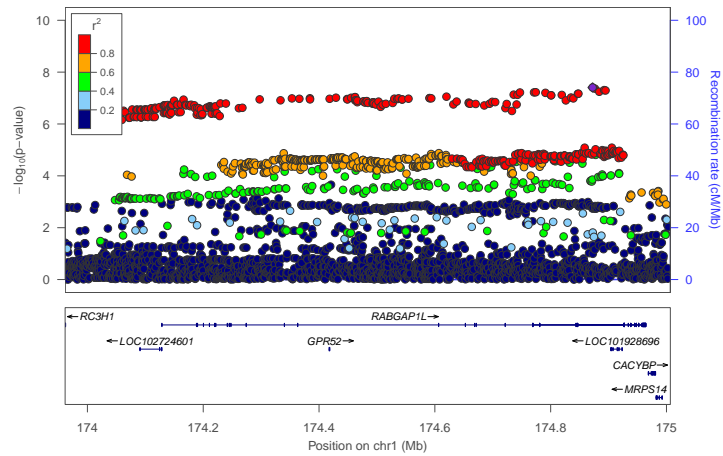
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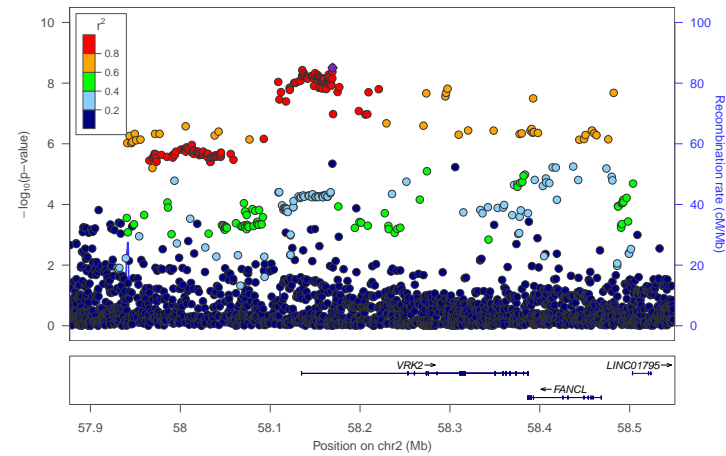
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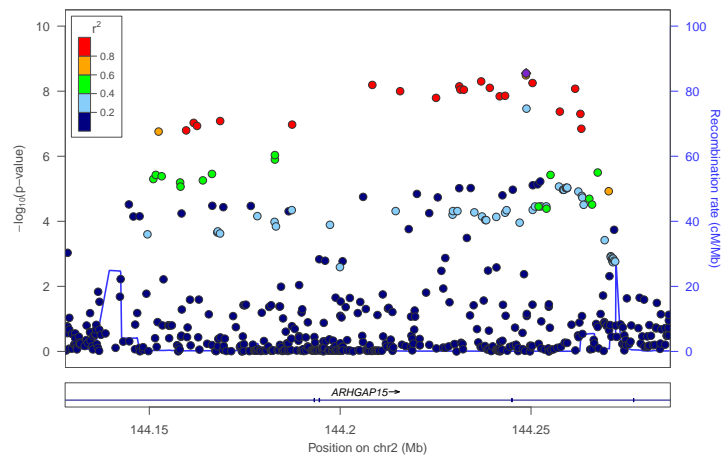
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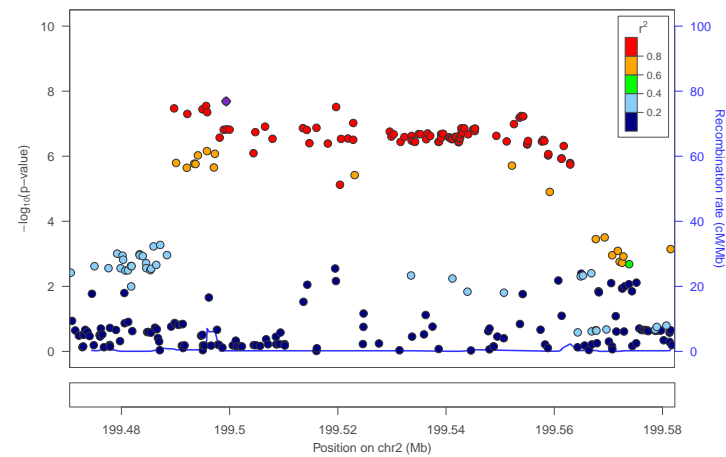
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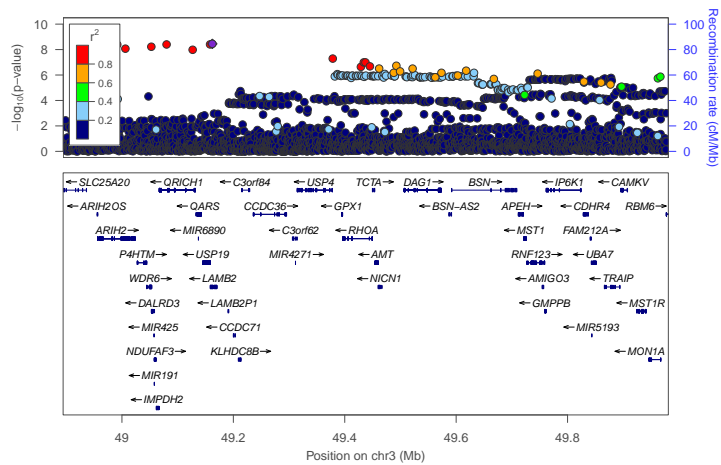
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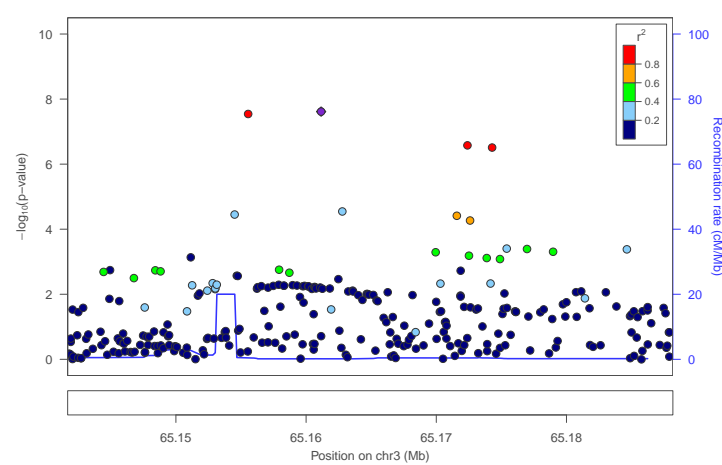
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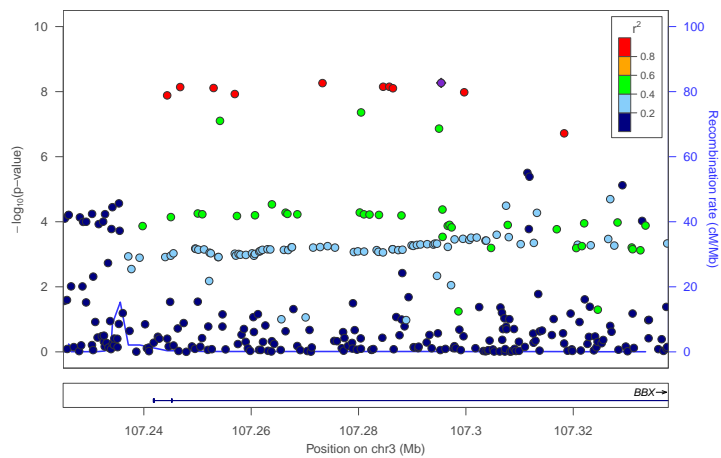
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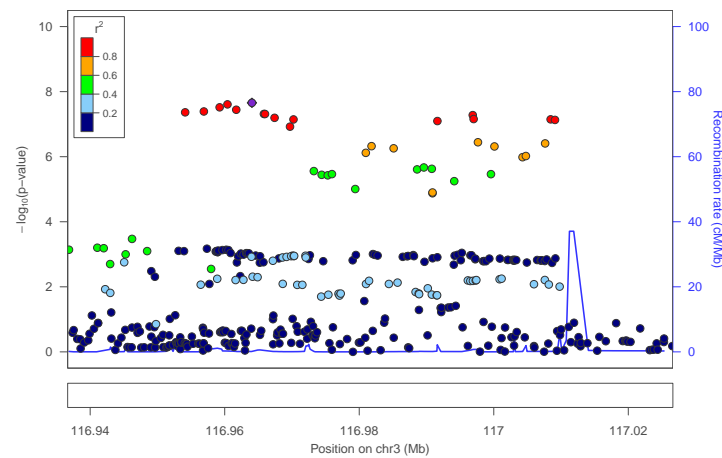
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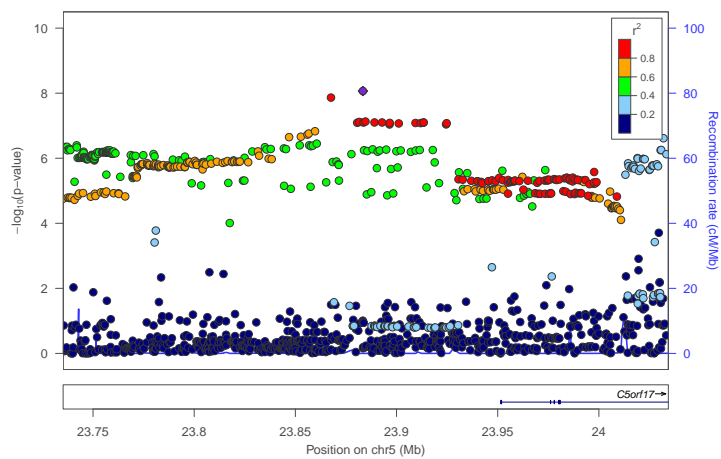
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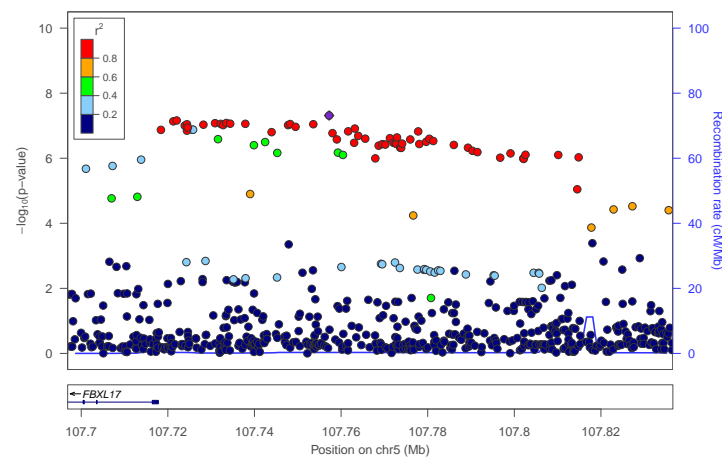
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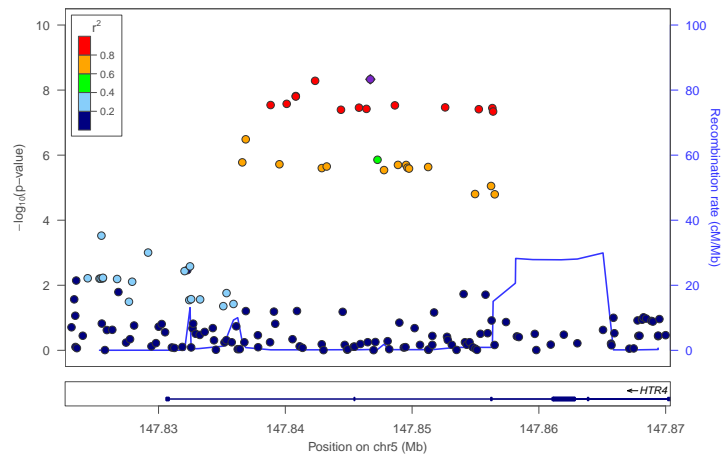
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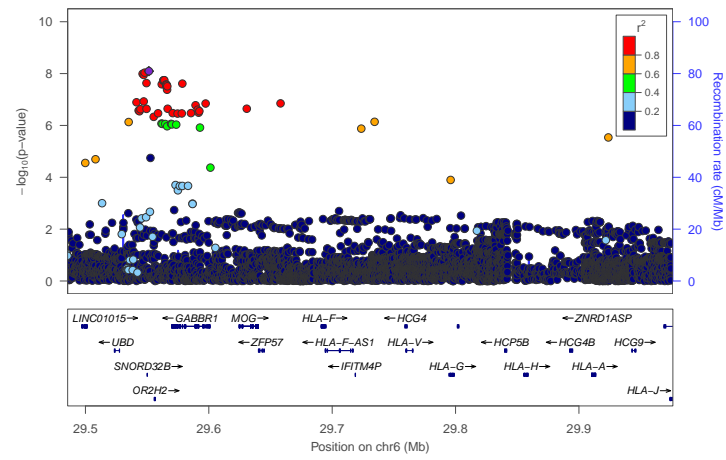
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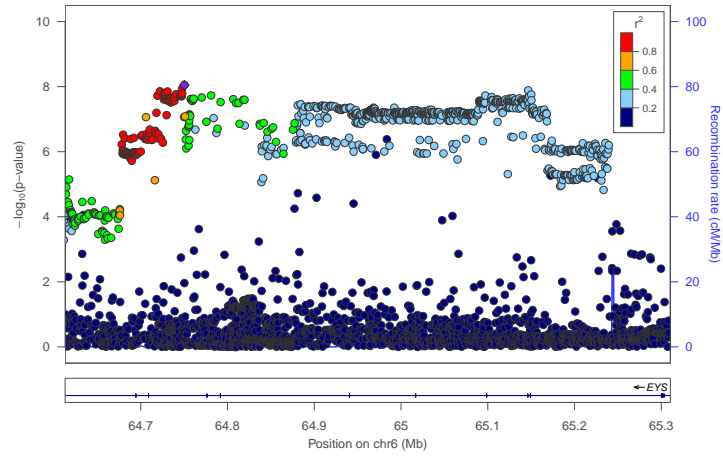
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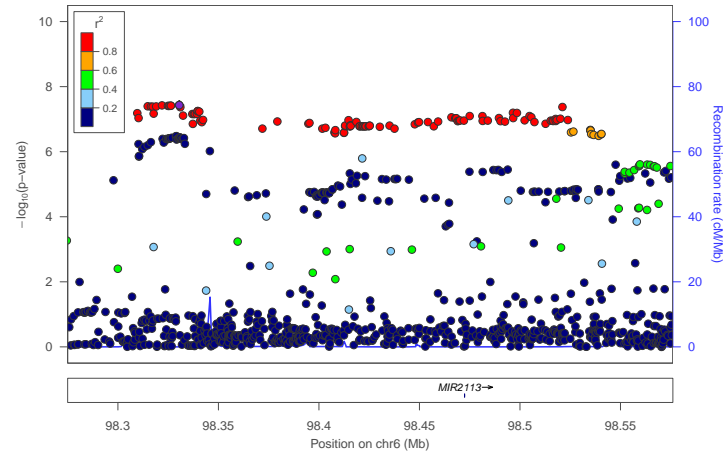
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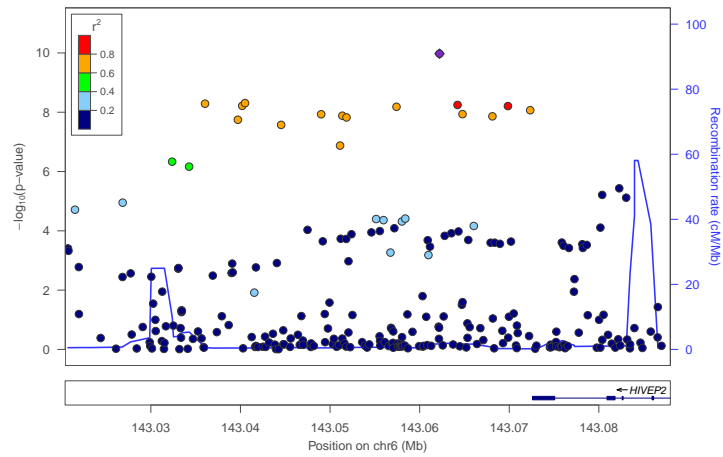
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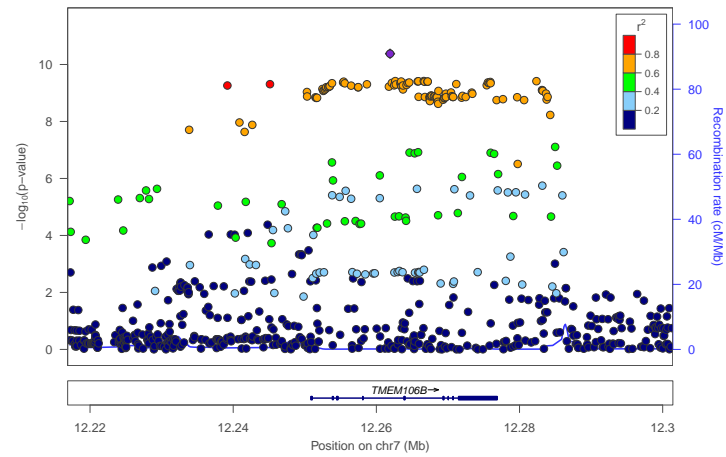
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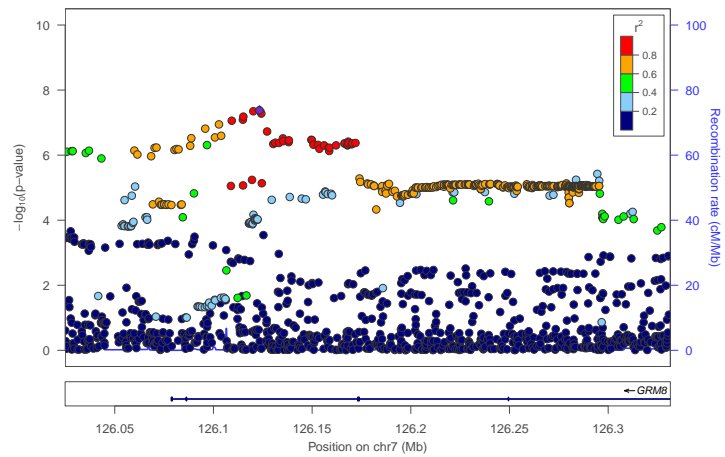
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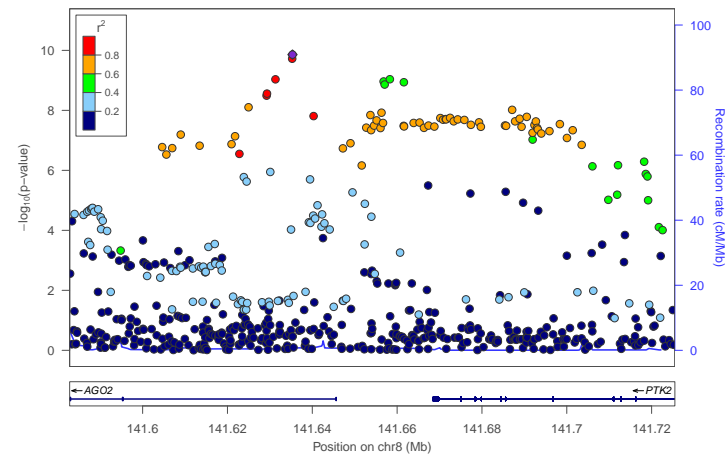
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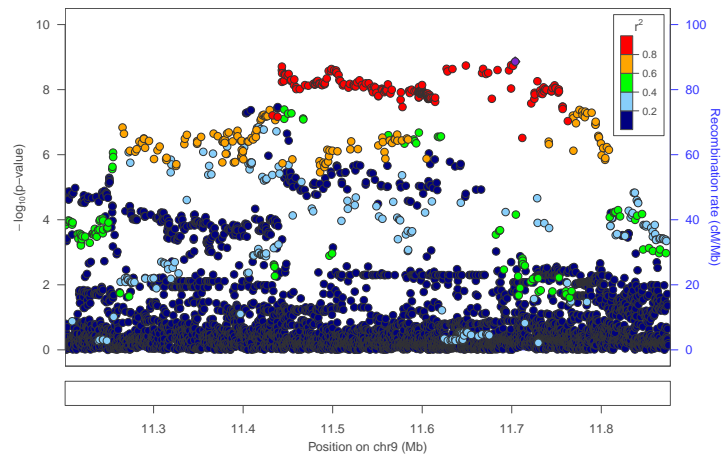
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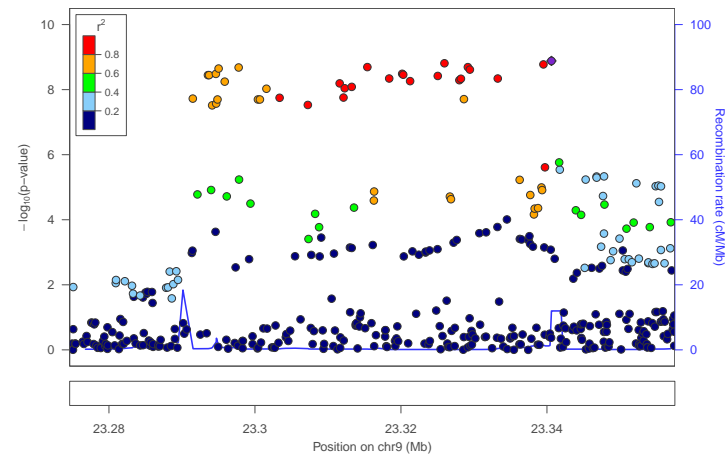
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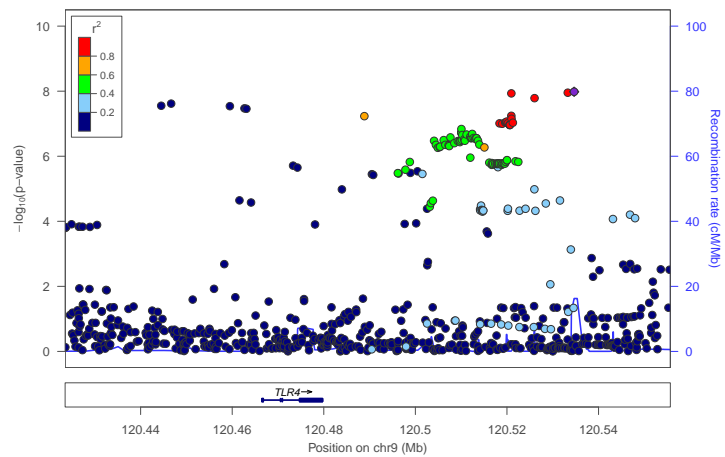
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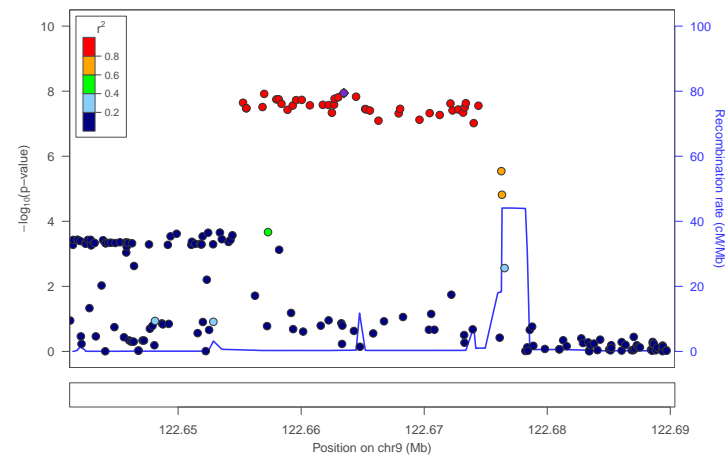
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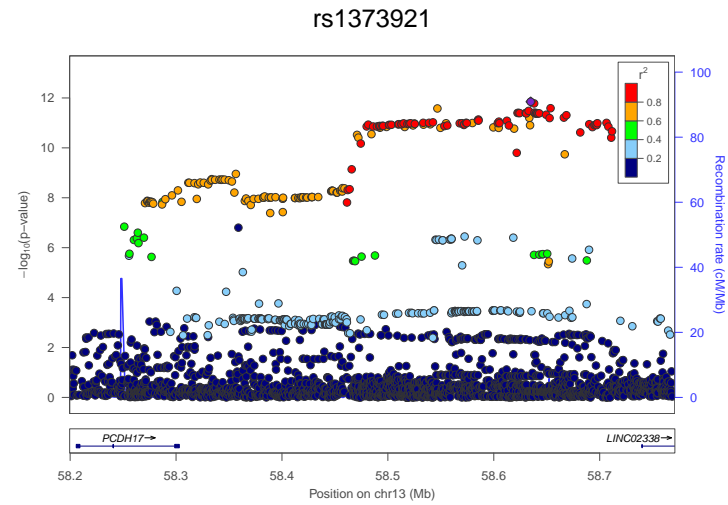
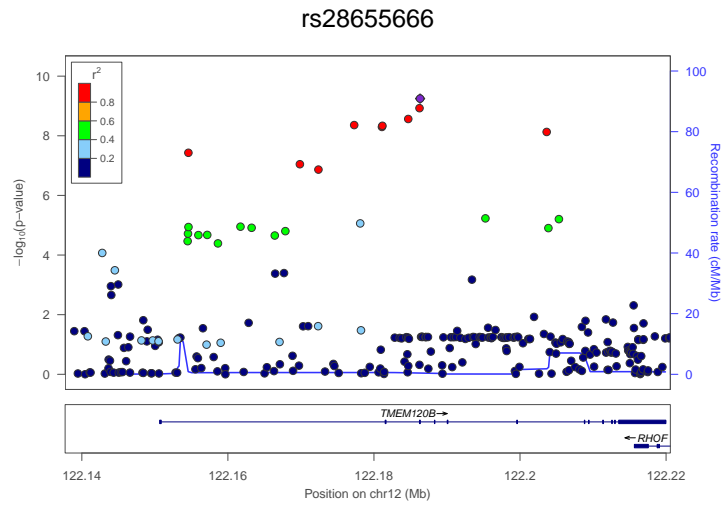
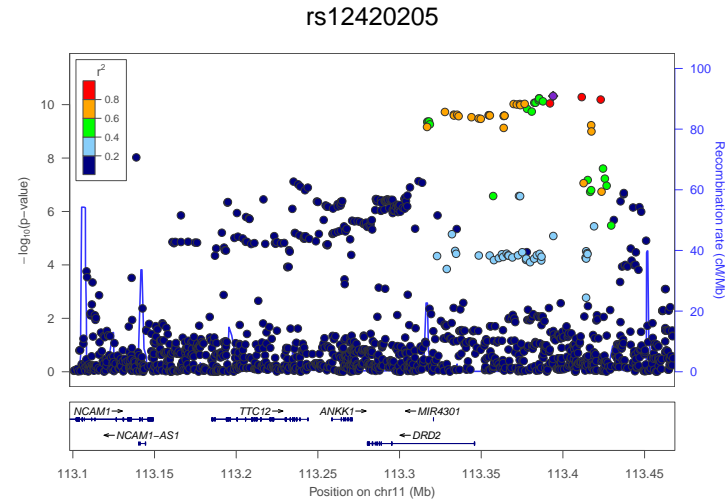
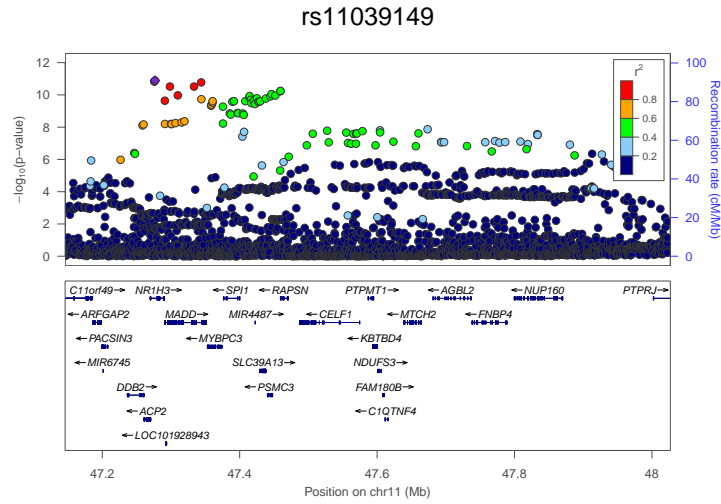
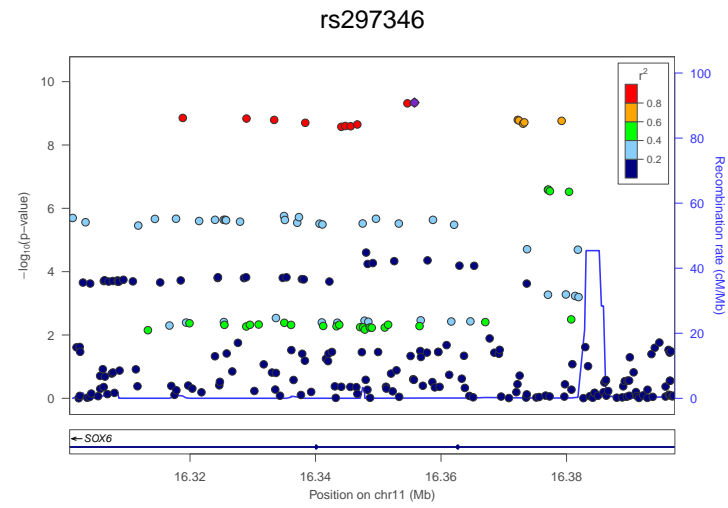
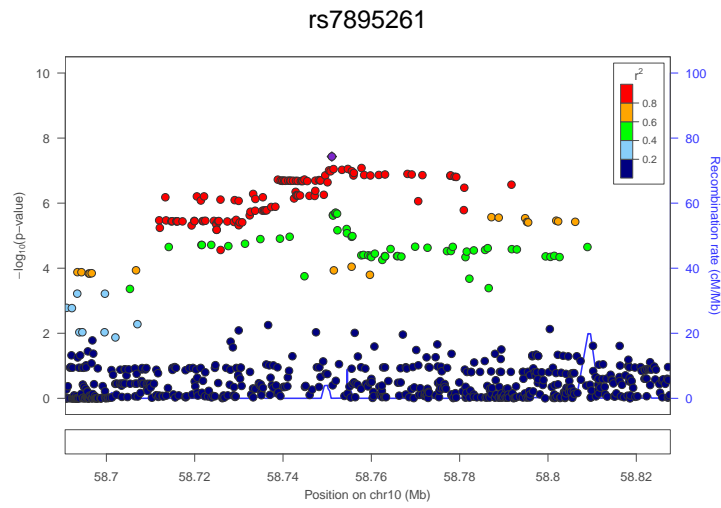


rs10983783

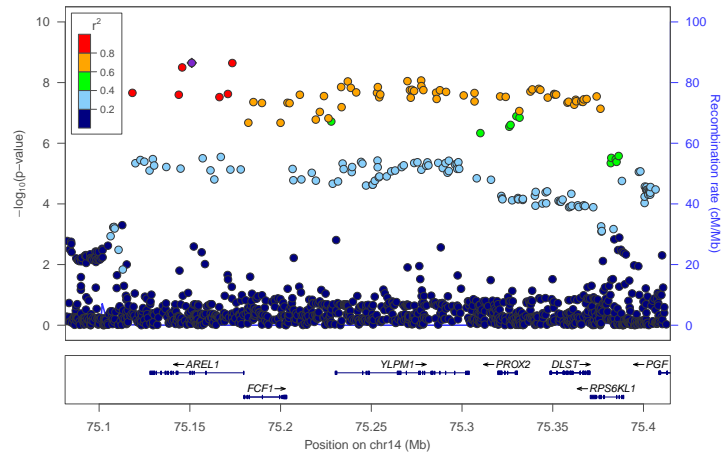


rs4836789

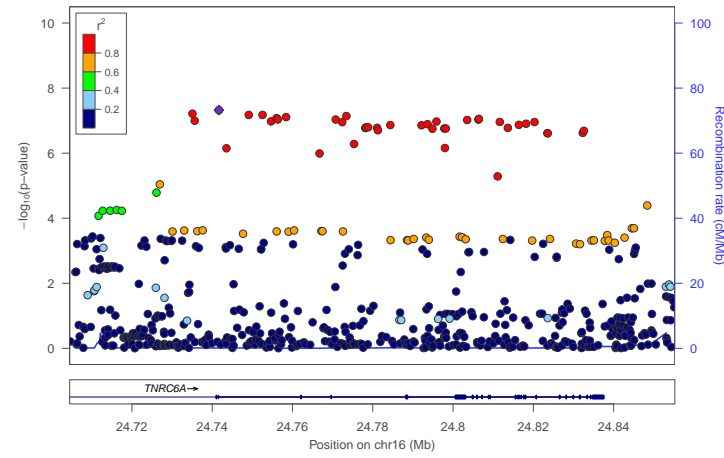




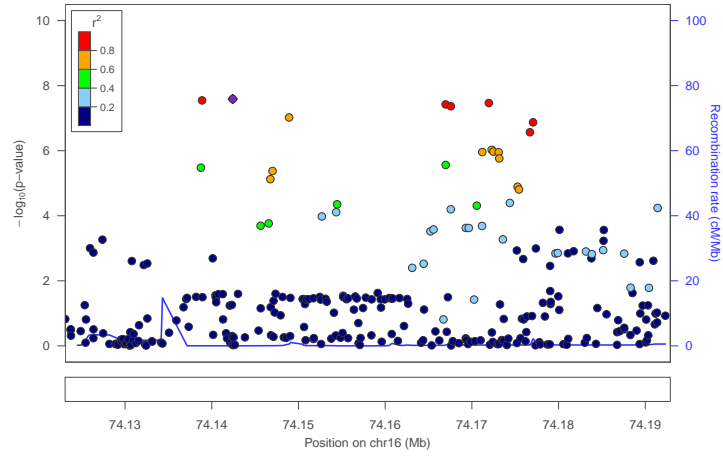
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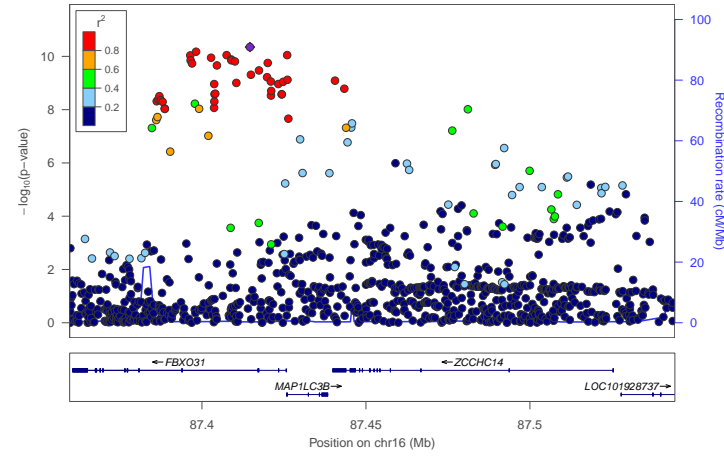
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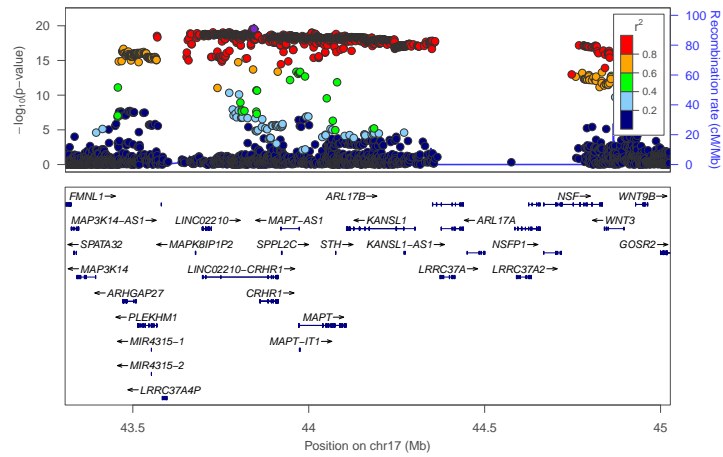
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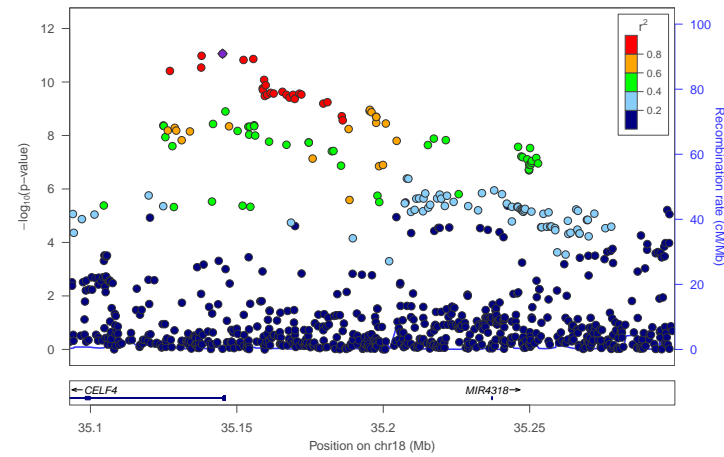
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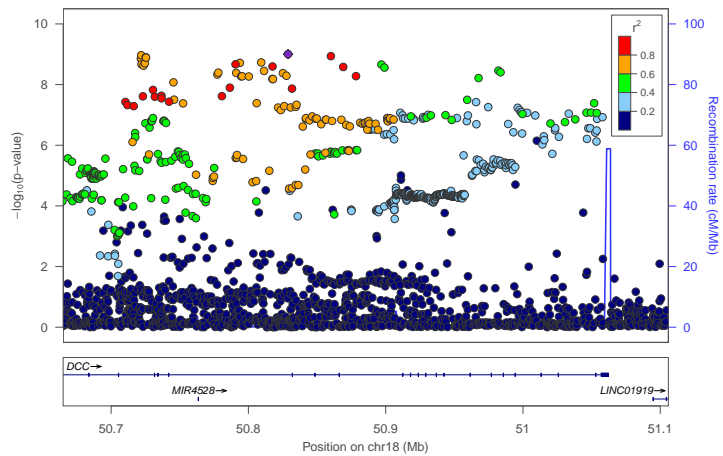
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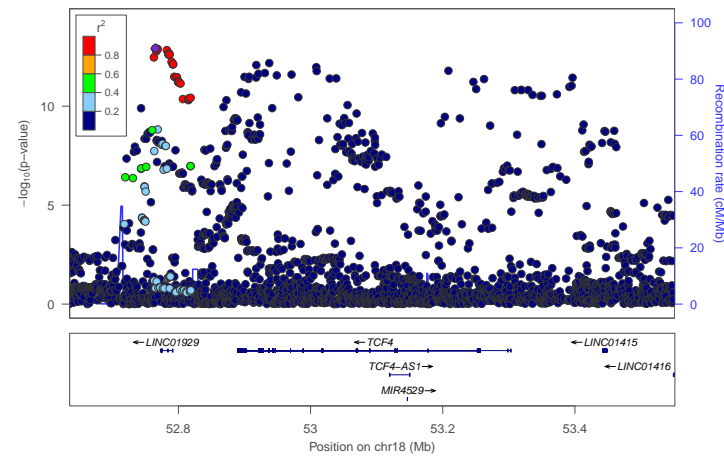
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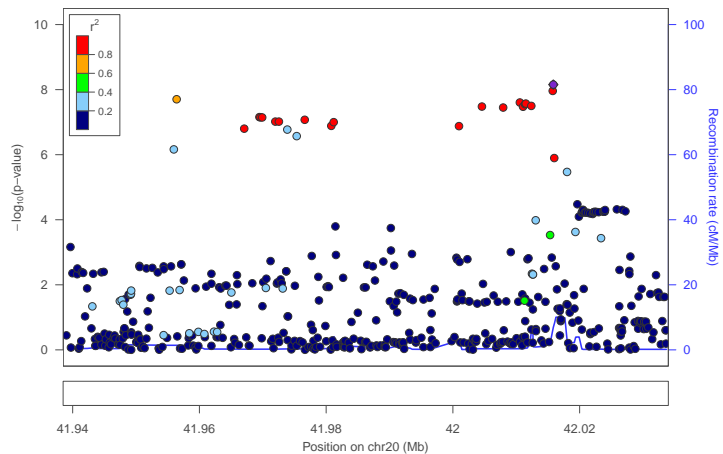
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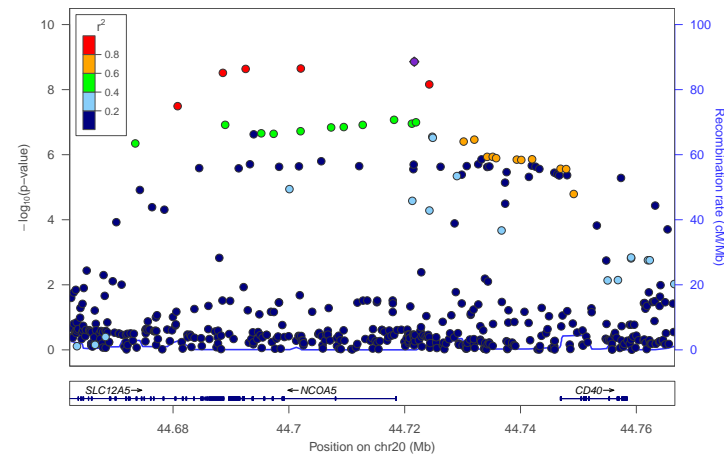
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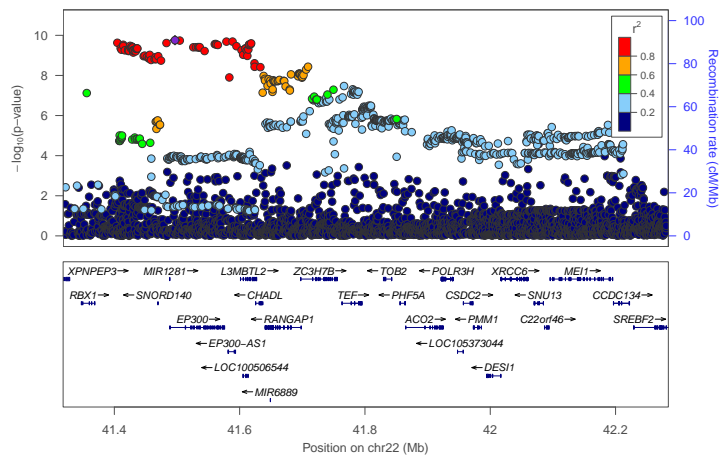
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rs4578918



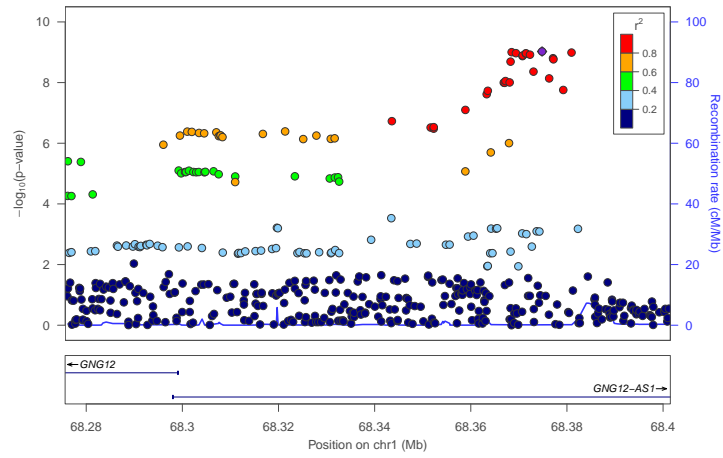
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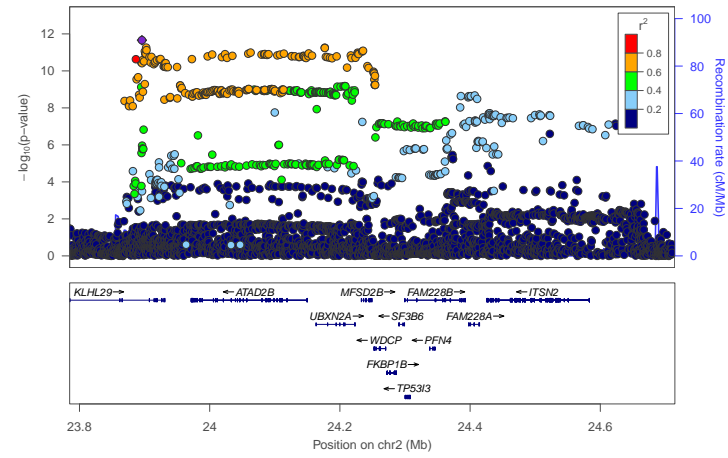
Supplementary Figure 8. Regional plots of GWA analyses of item MOOD.

The y -axis represents the negative logarithm (base 10) of the SNP P value and the x -axis the position on the chromosome, with the name and location of genes in the UCSC Genome Browser in the bottom panel. The SNP with the lowest P value in the region is marked by a purple diamond. The colors of the other SNPs indicate the r^2 of these SNPs with the lead SNP, with grey color indicating SNPs below the user-defined r^2 . Plots are generated with LocusZoom. See **Supplementary Data 2** for an overview of all lead SNPs for which a regional plot is presented above.

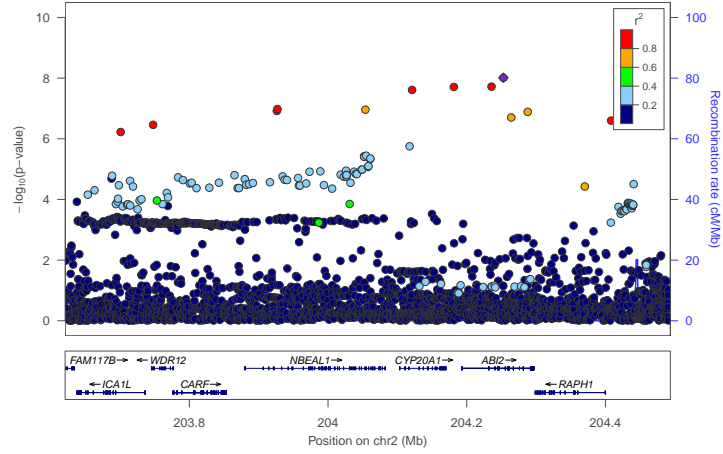
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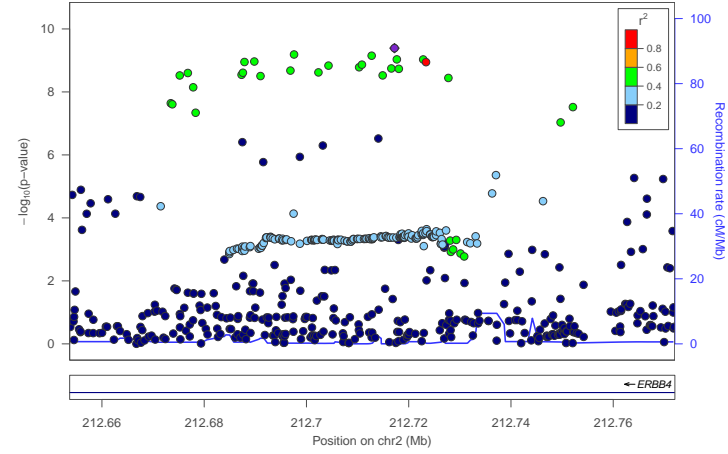
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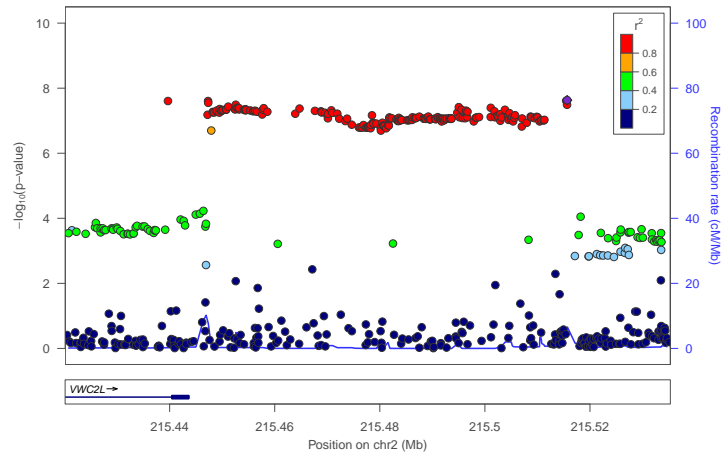
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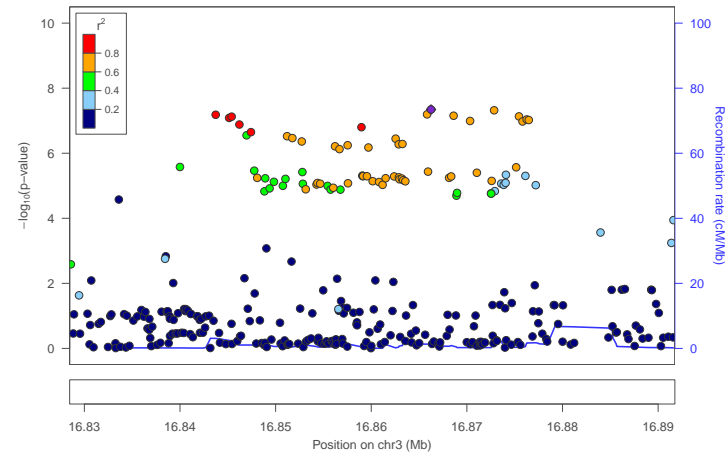
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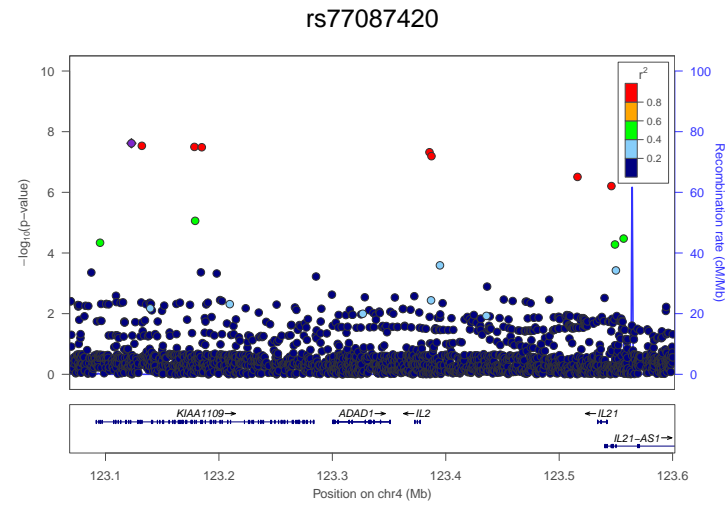
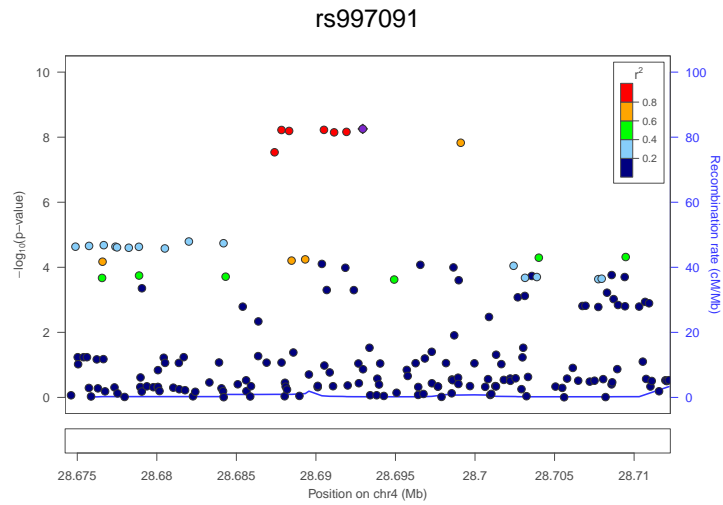
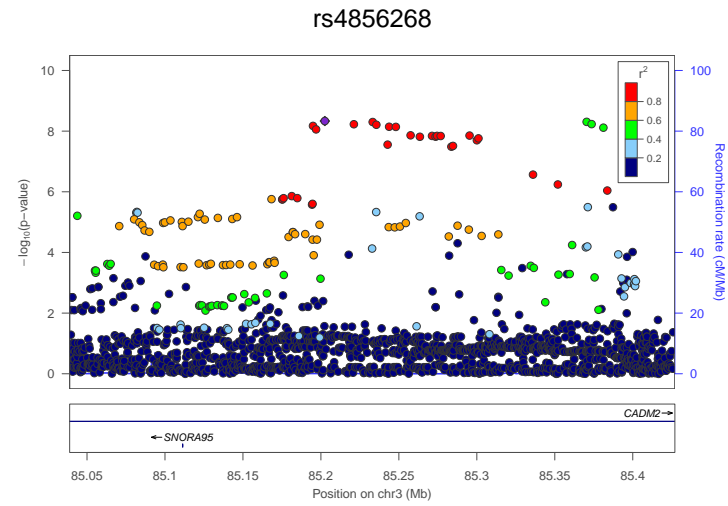
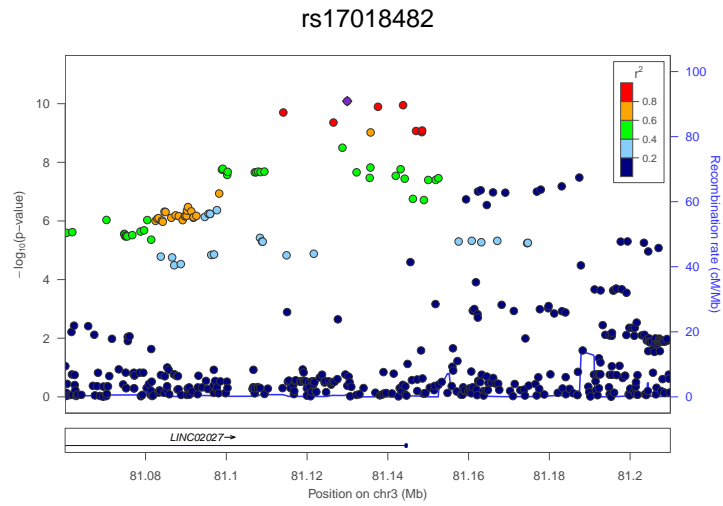
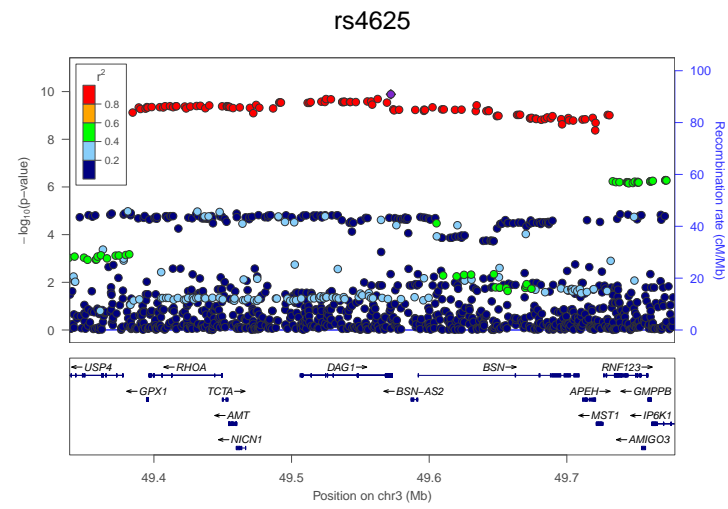
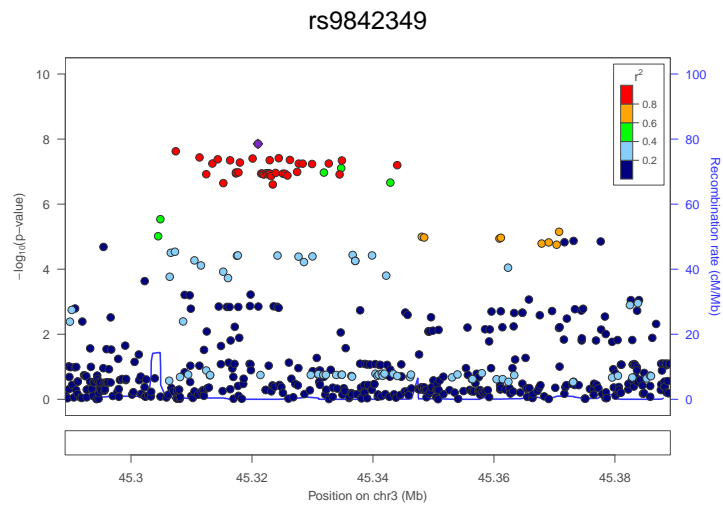


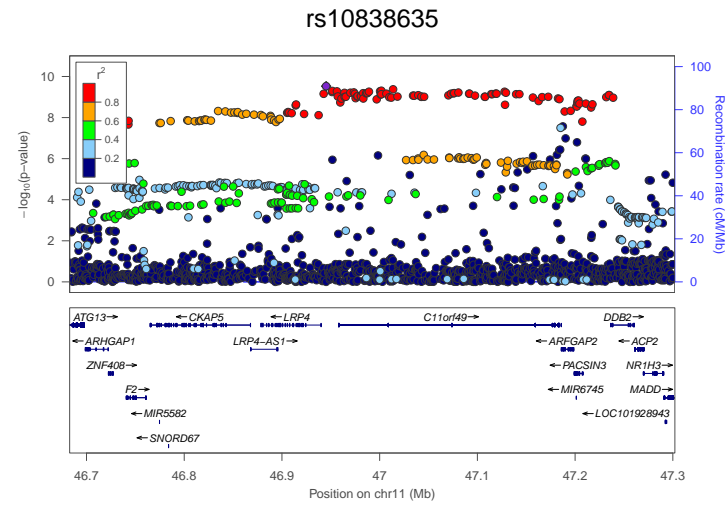
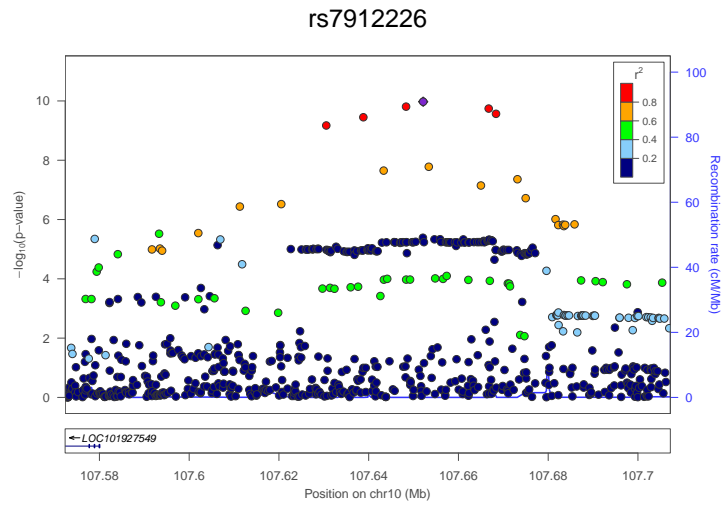
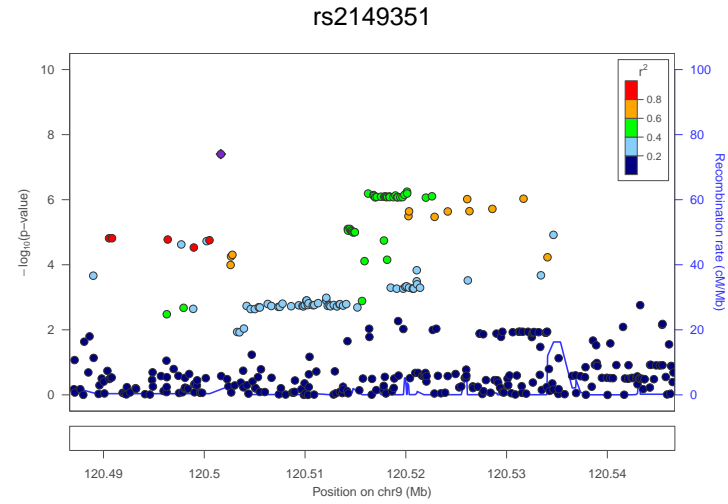
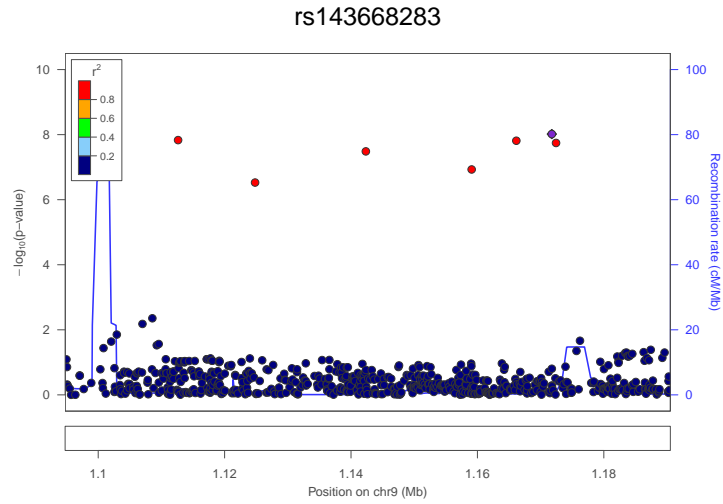
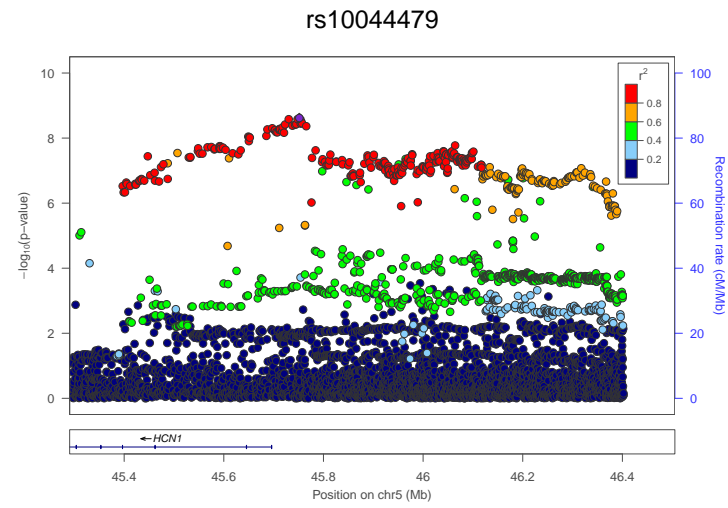
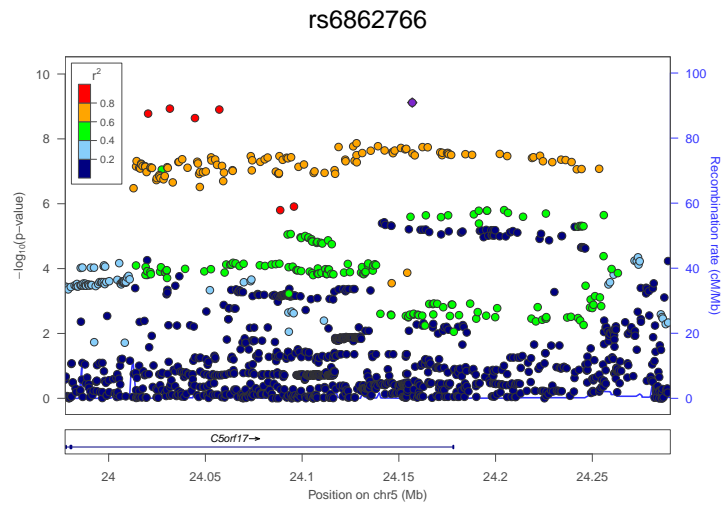
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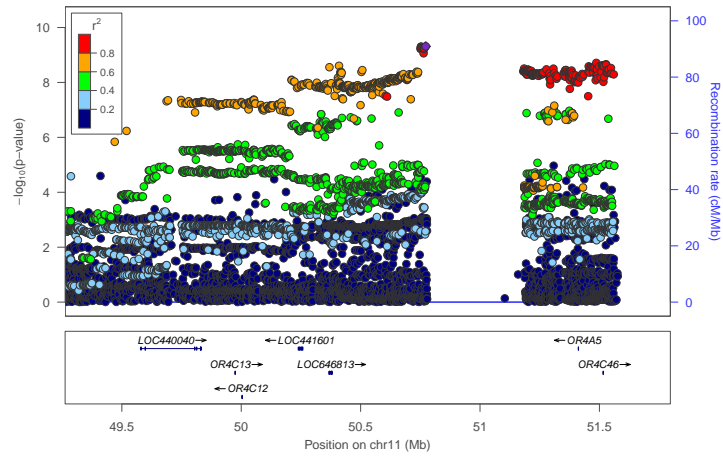
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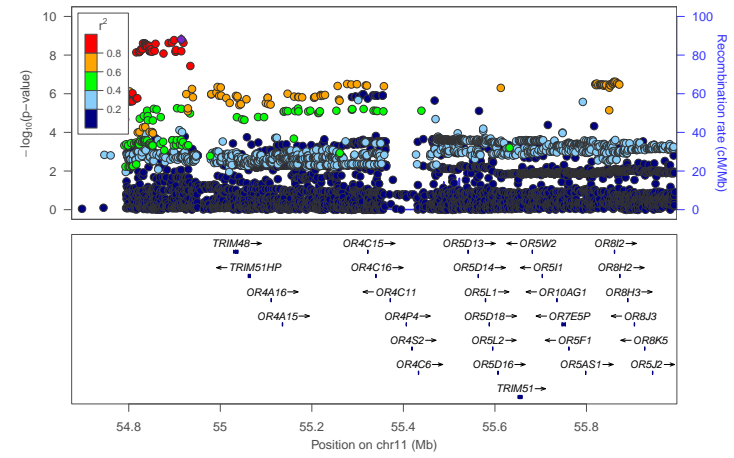




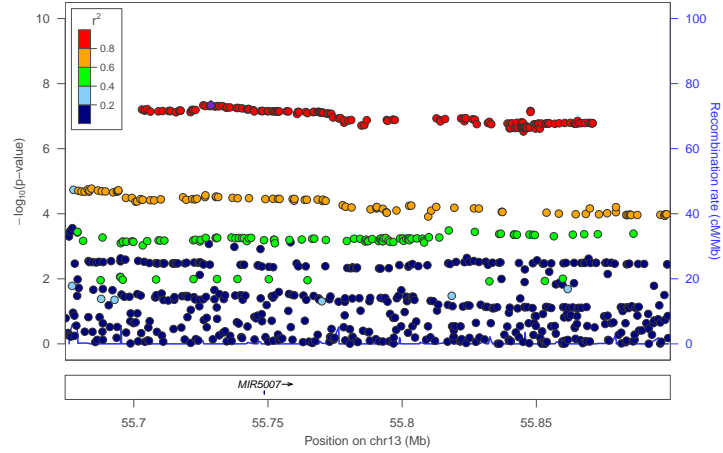
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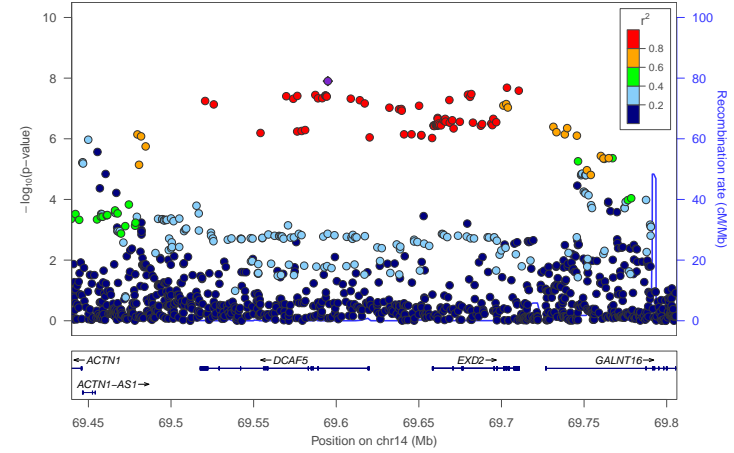
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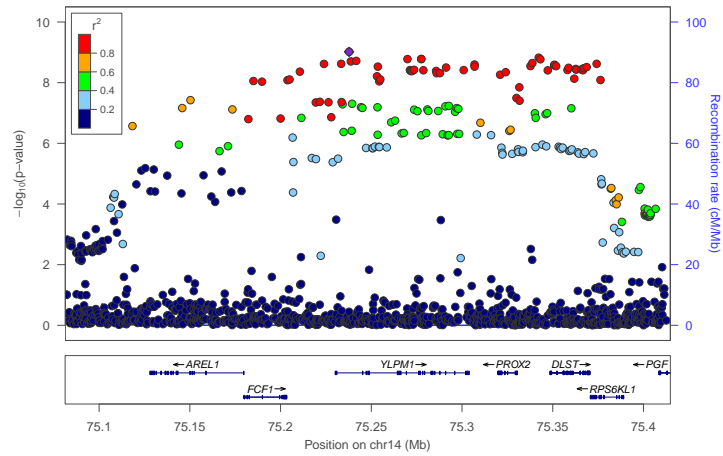
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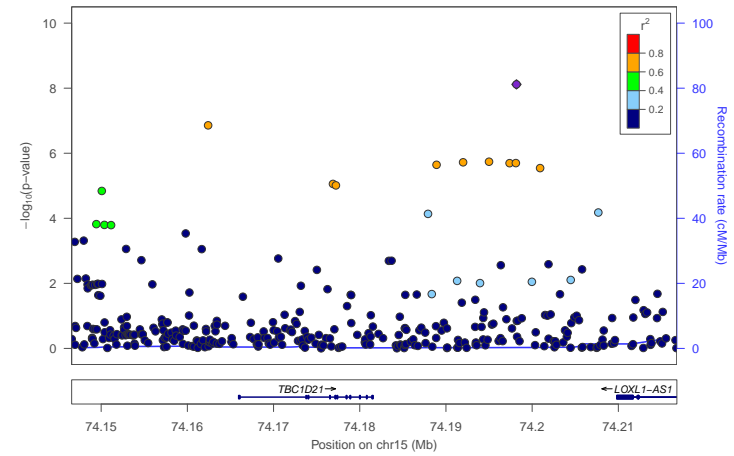
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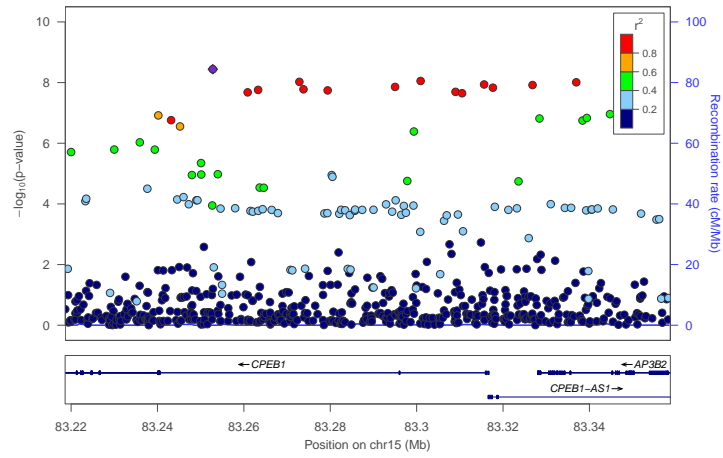
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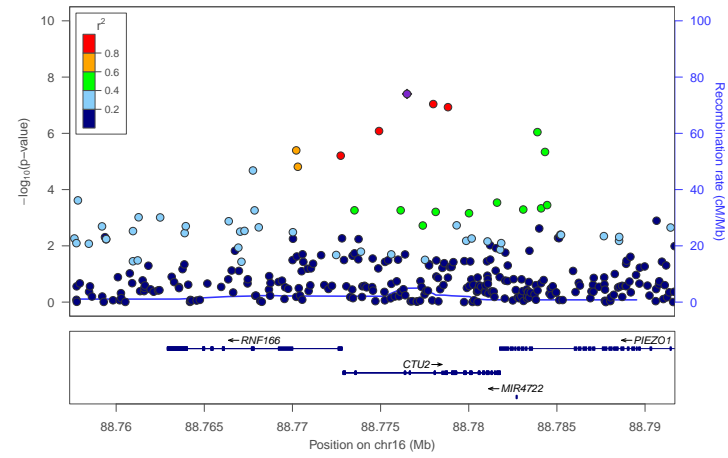
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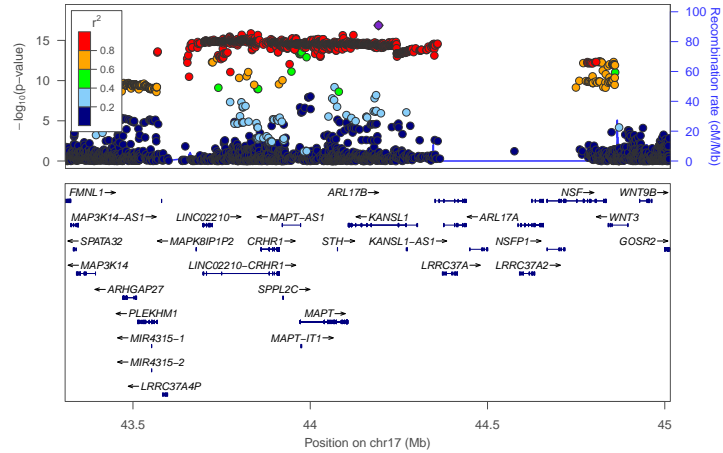
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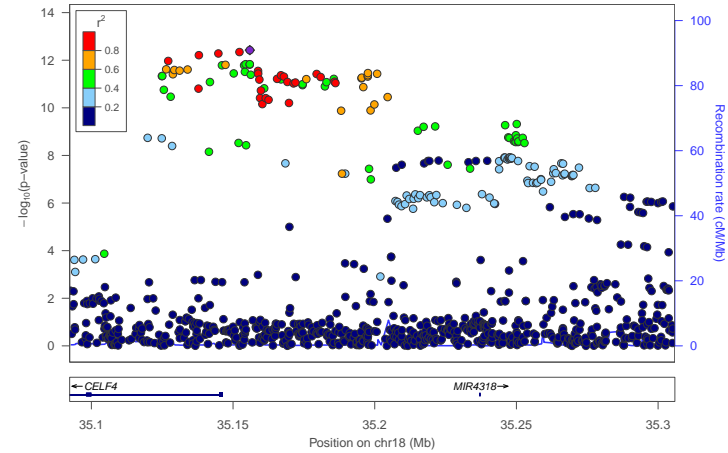
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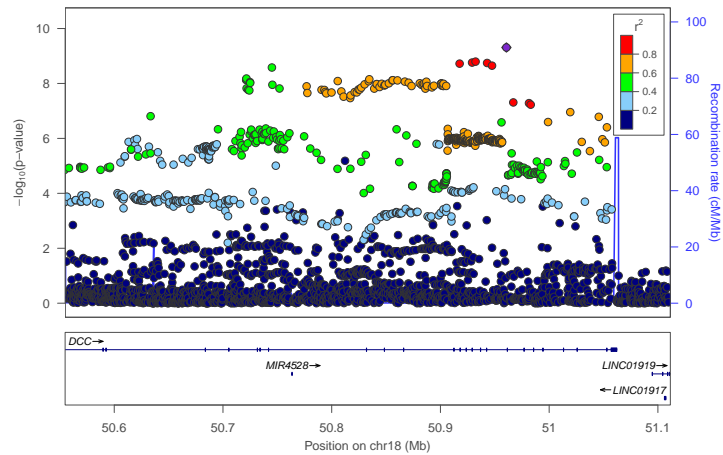
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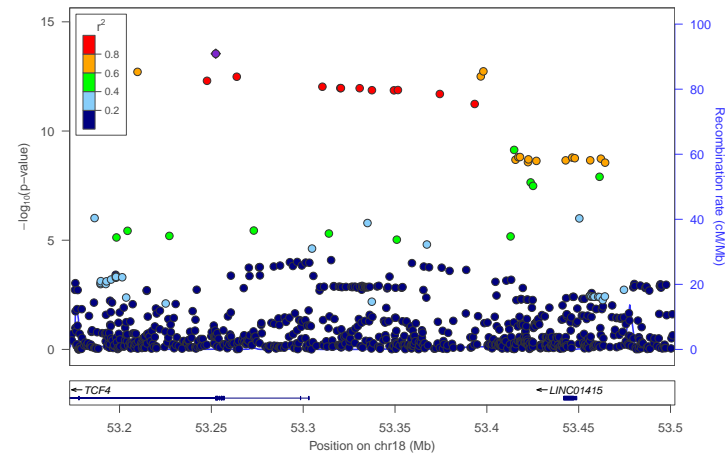
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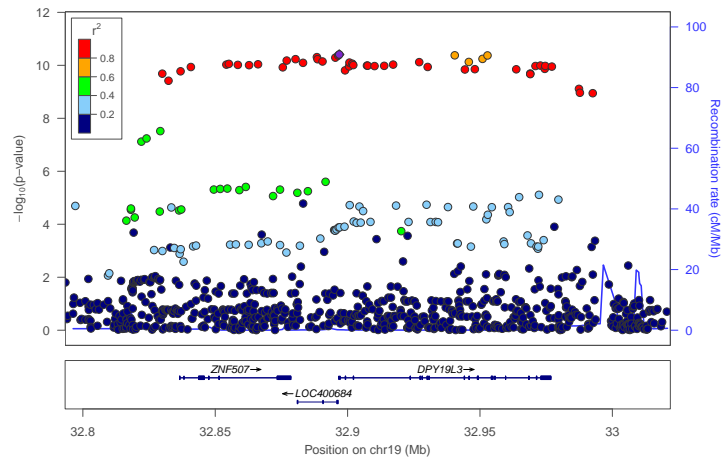
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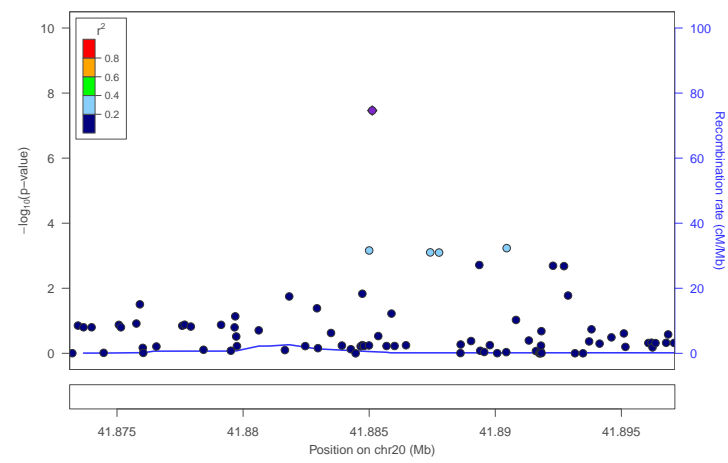
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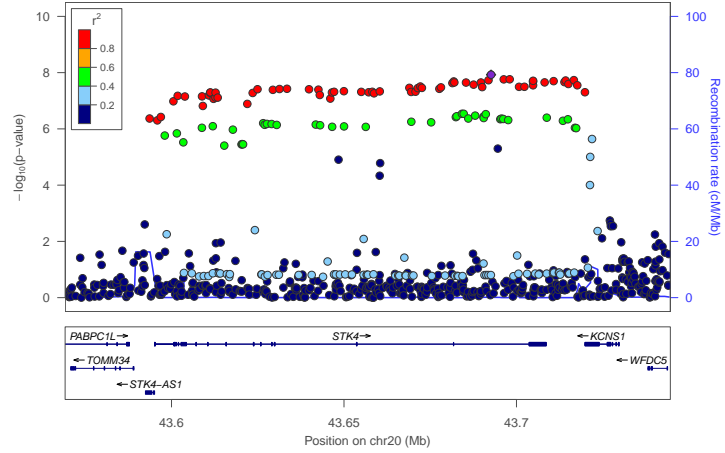
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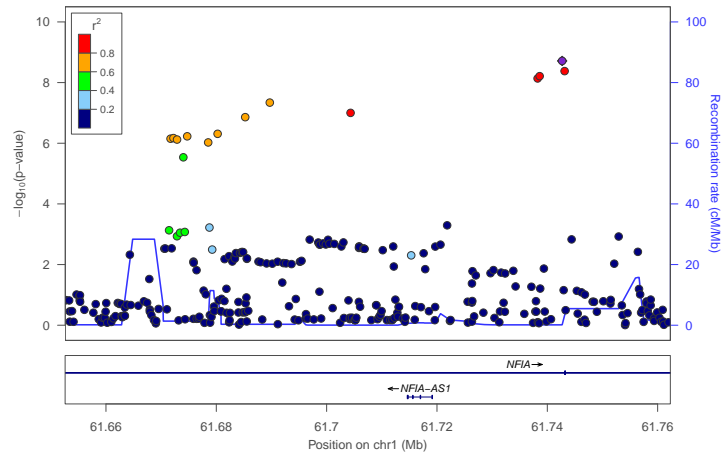
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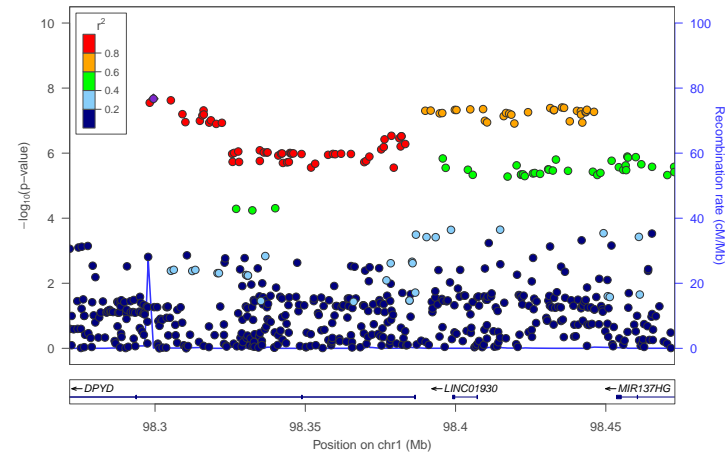
Supplementary Figure 9. Regional plots of GWA analyses of item FED-UP.

The y -axis represents the negative logarithm (base 10) of the SNP P value and the x -axis the position on the chromosome, with the name and location of genes in the UCSC Genome Browser in the bottom panel. The SNP with the lowest P value in the region is marked by a purple diamond. The colors of the other SNPs indicate the r^2 of these SNPs with the lead SNP, with grey color indicating SNPs below the user-defined r^2 . Plots are generated with LocusZoom. See **Supplementary Data 2** for an overview of all lead SNPs for which a regional plot is presented above. For excluded loci (see **Methods; Supplementary Data 3-4**) the rsID's are marked yellow.

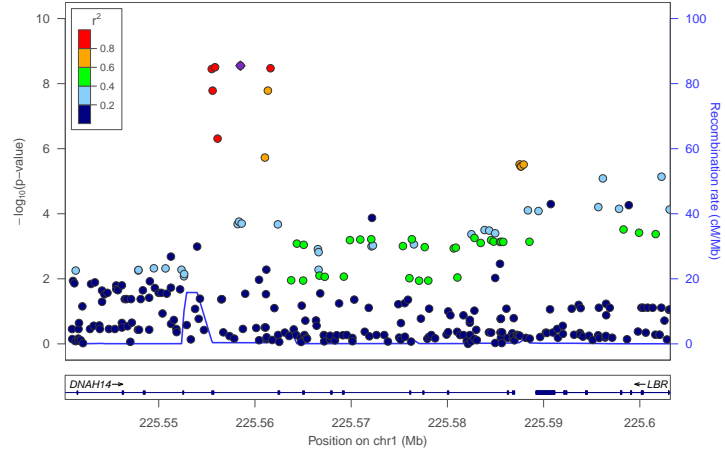
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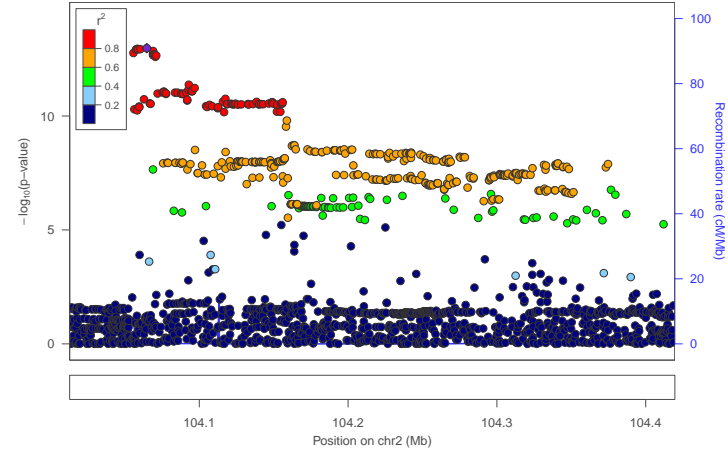
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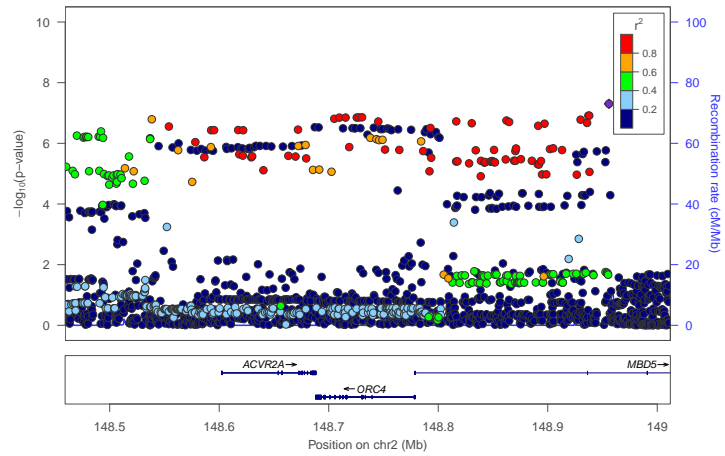
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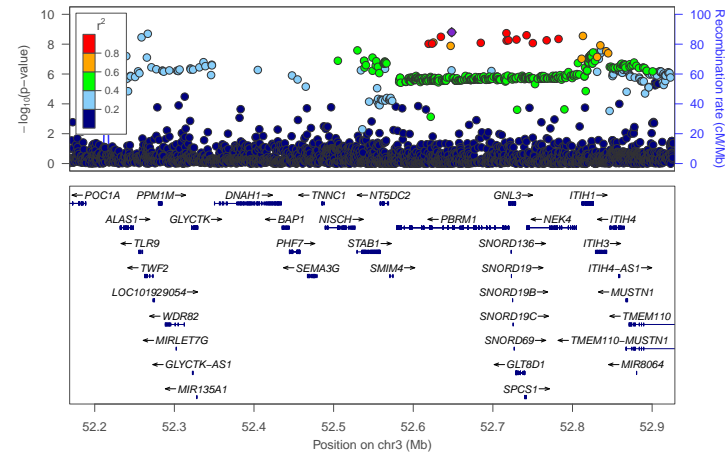
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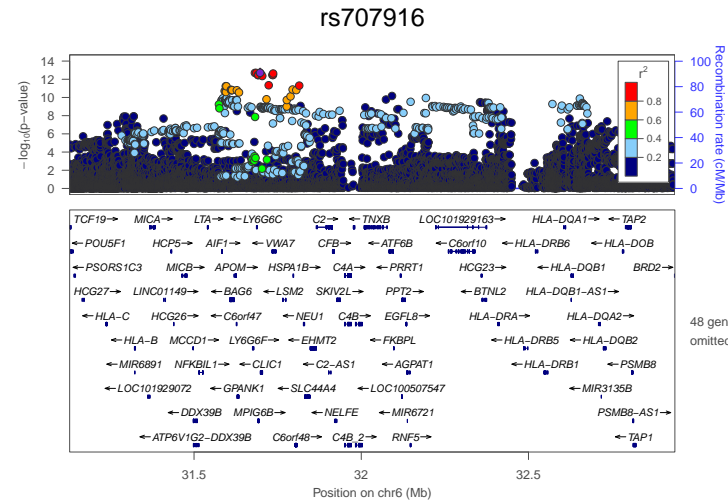
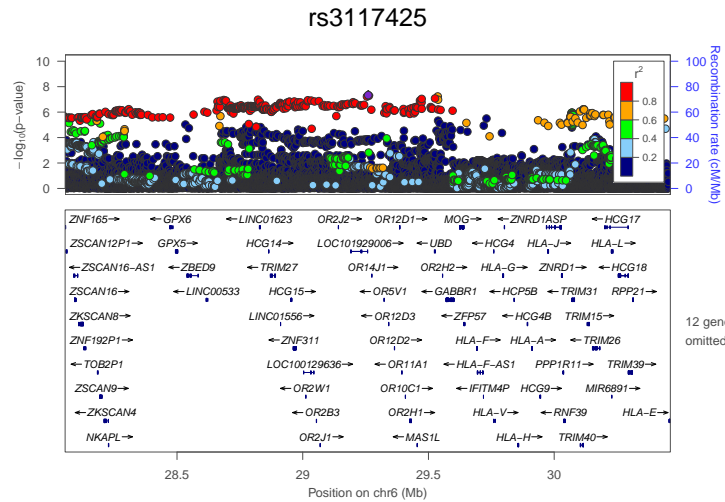
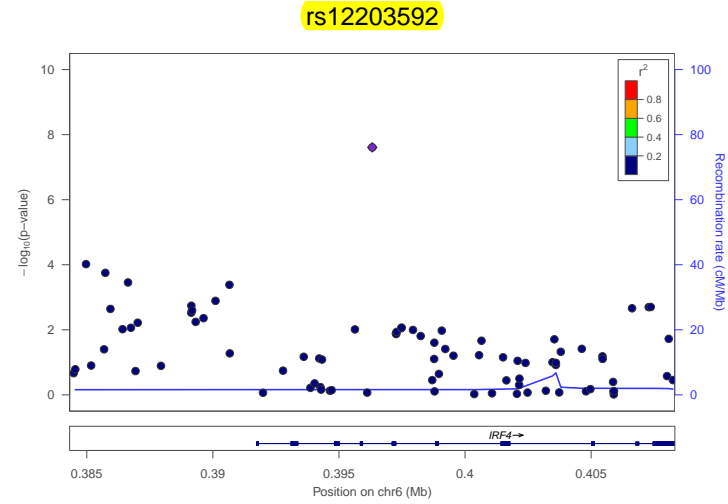
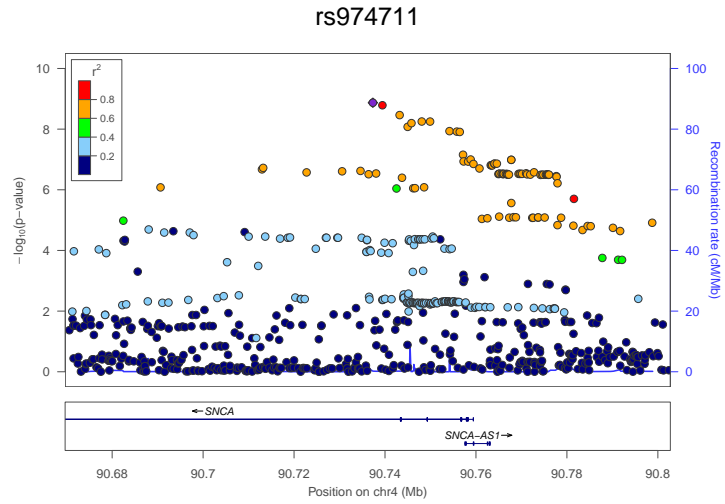
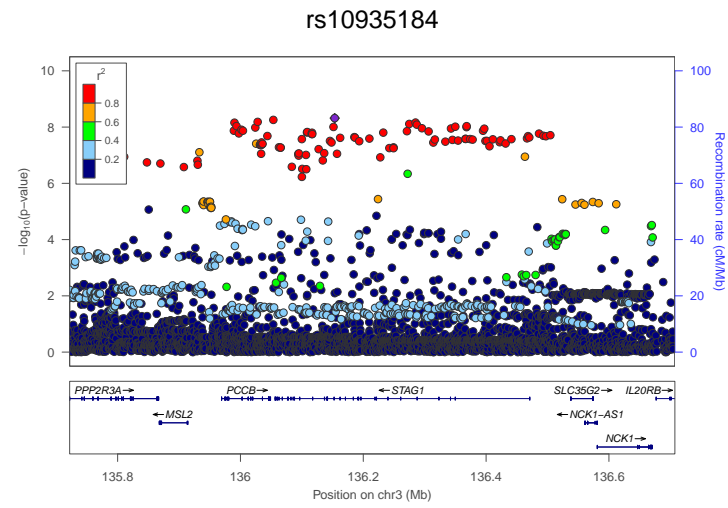
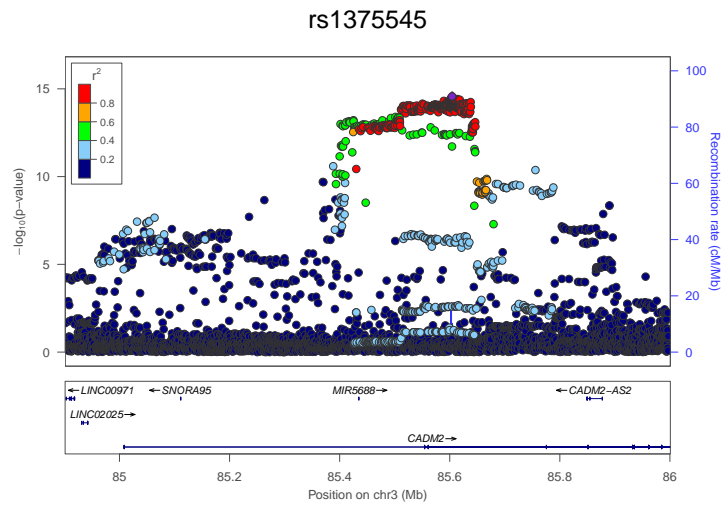


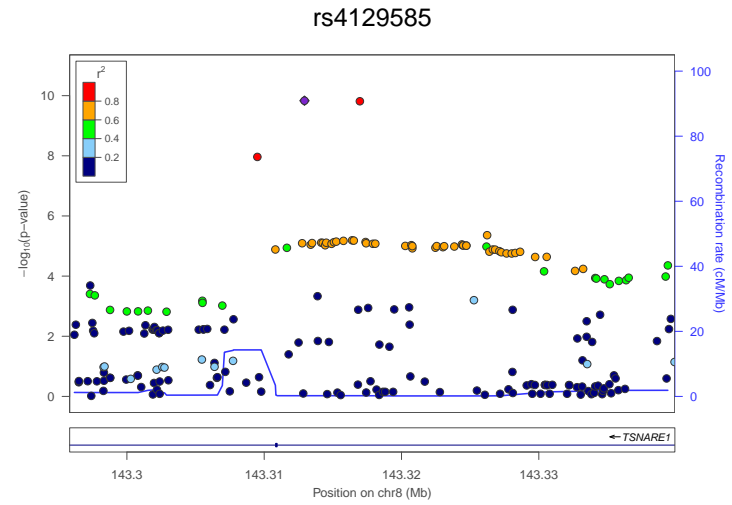
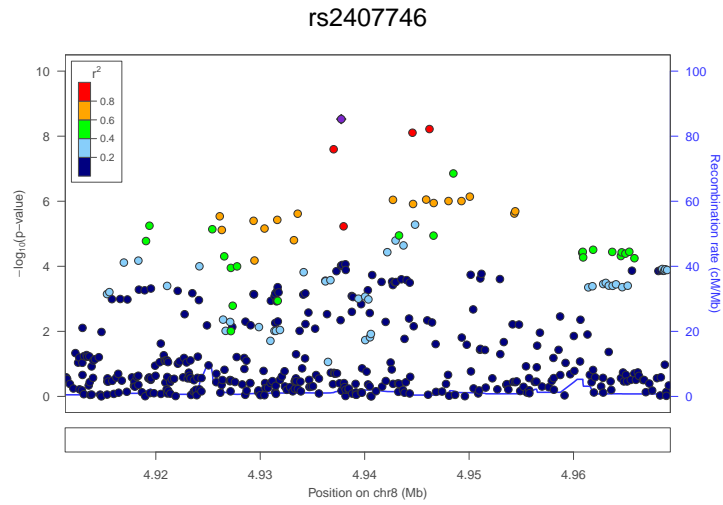
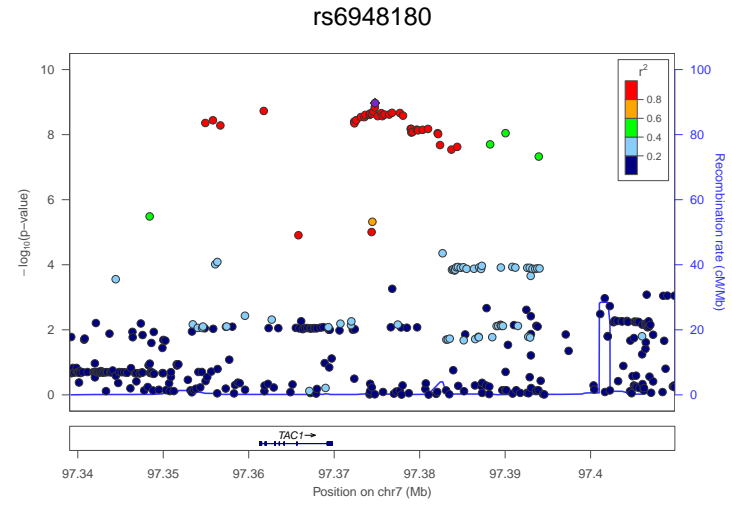
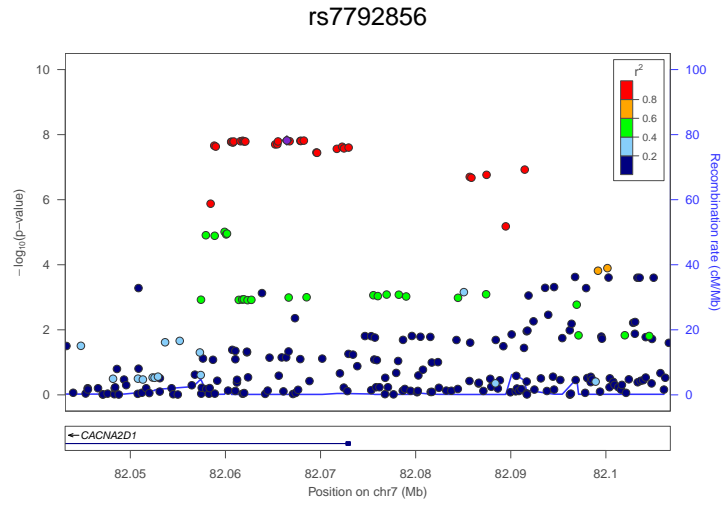
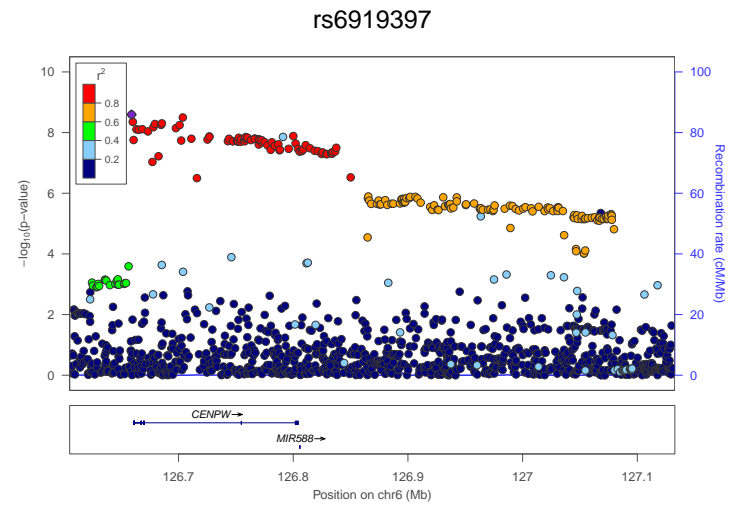
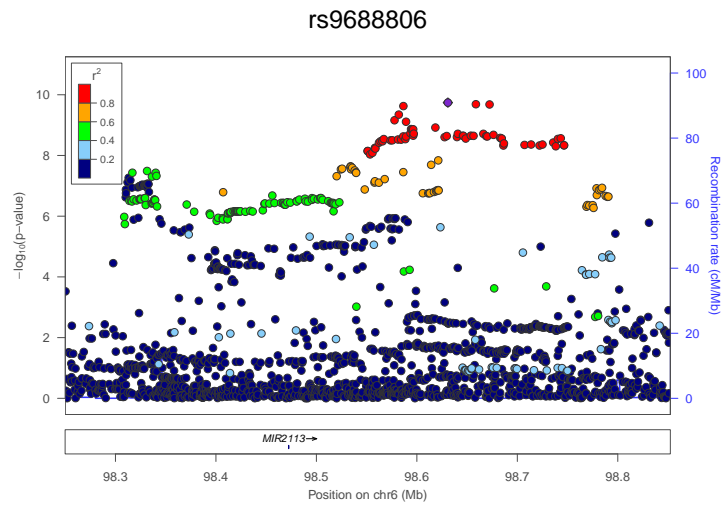
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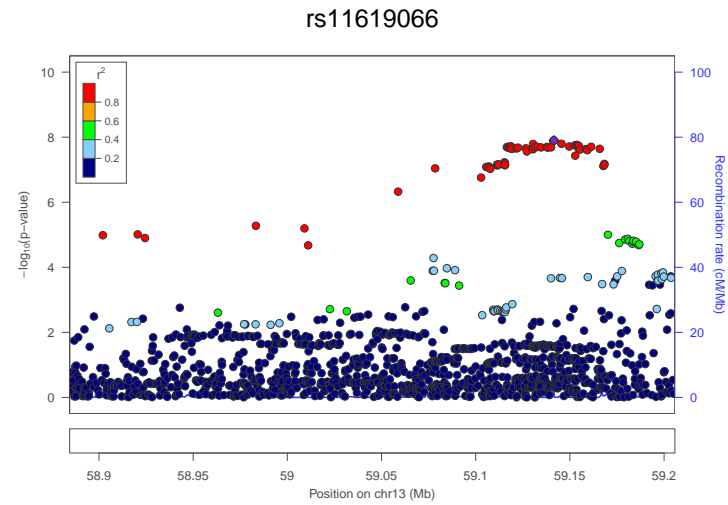
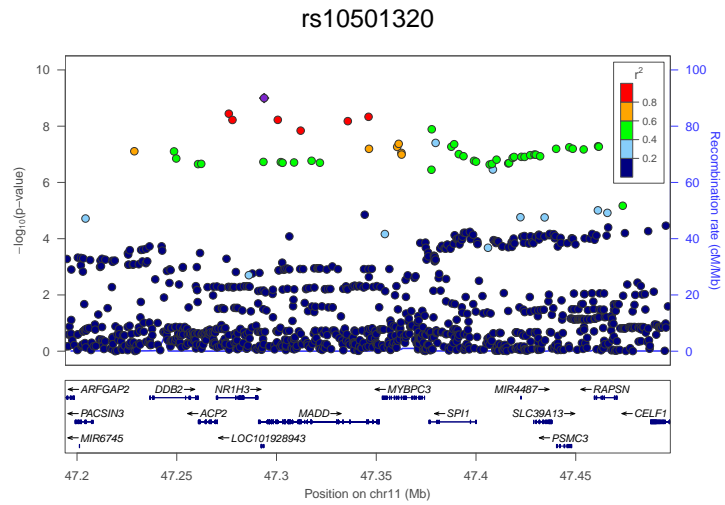
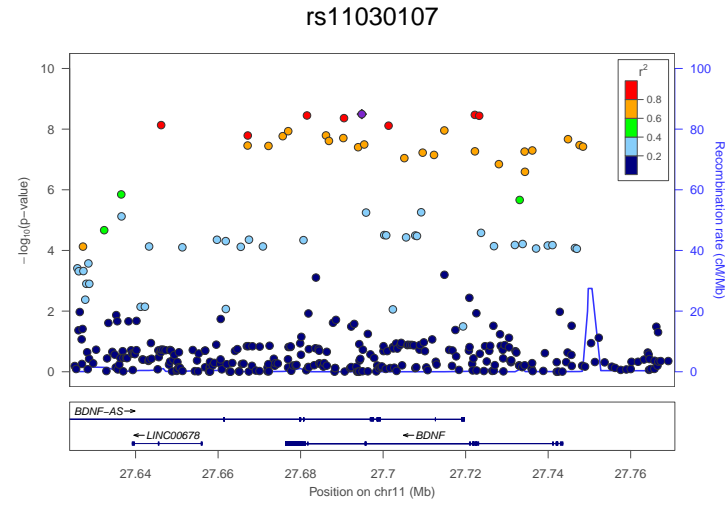
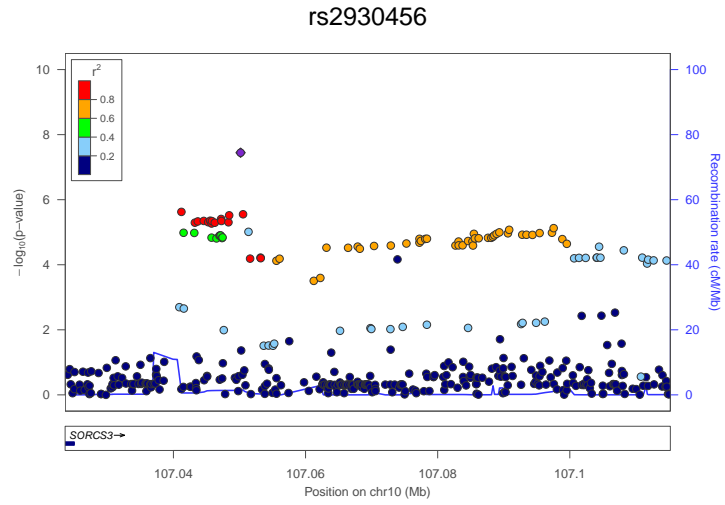
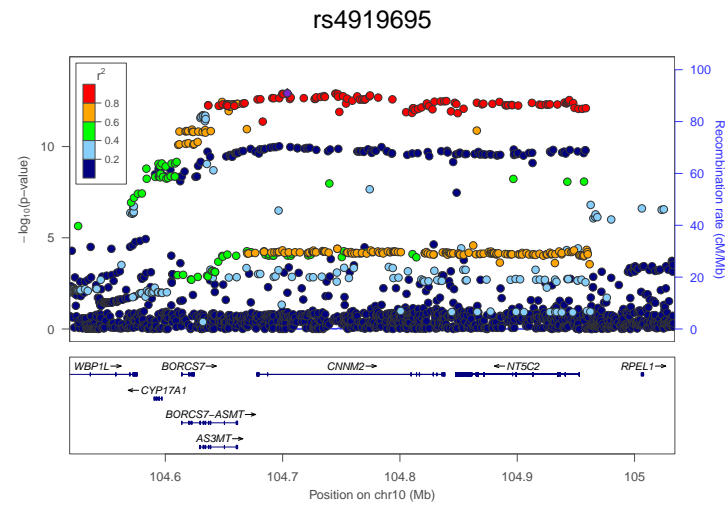
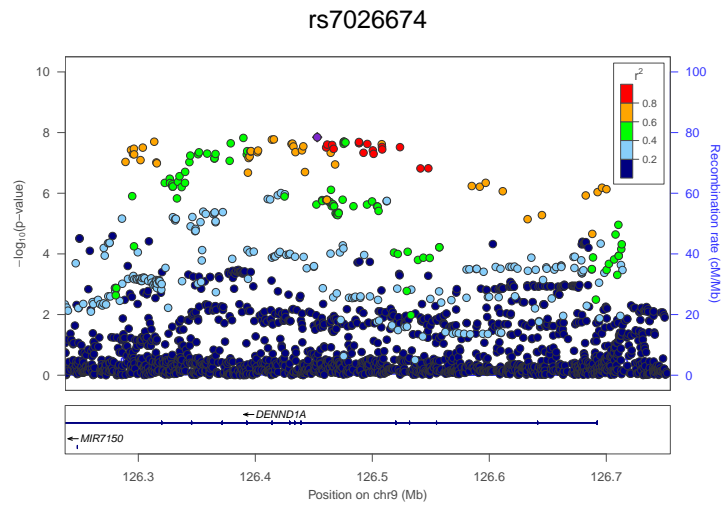


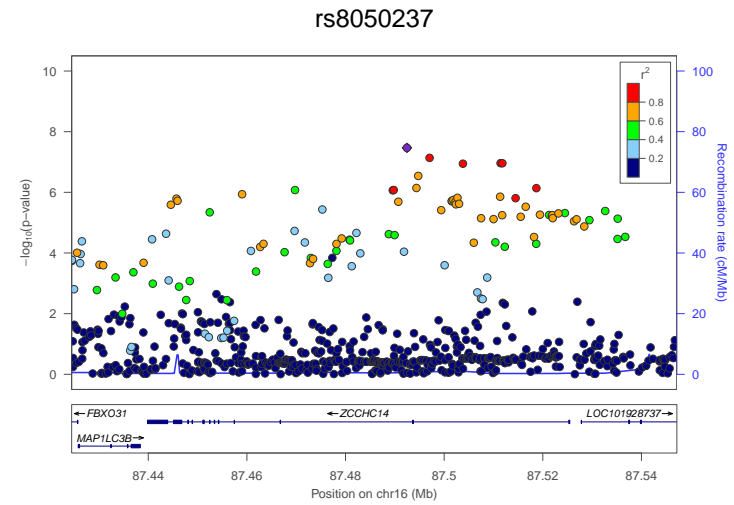
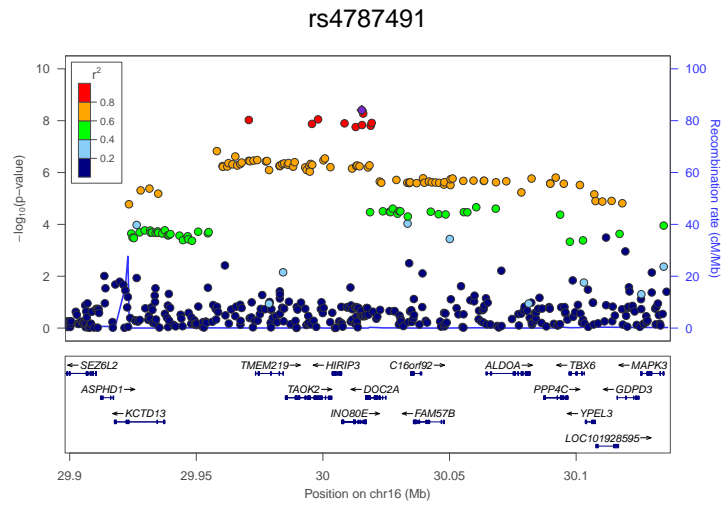
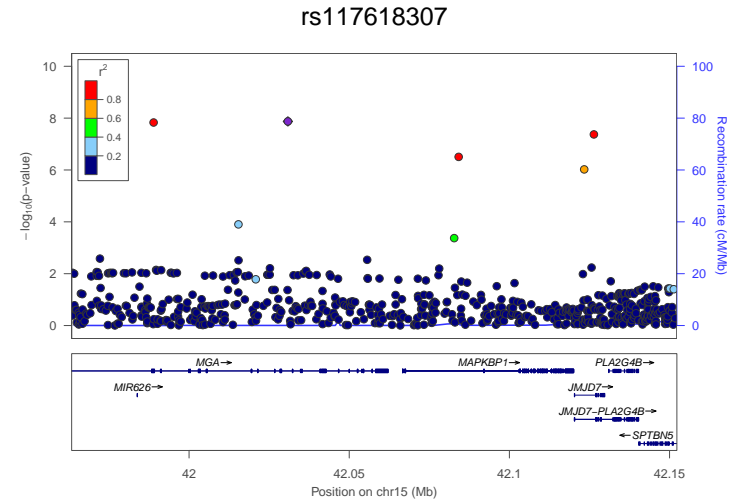
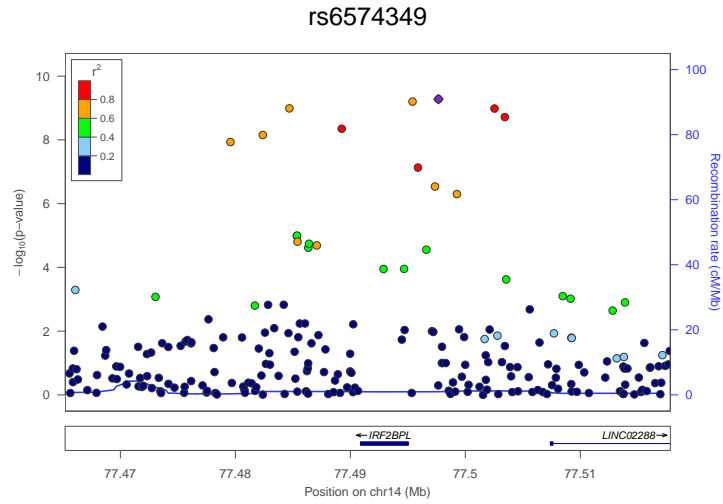
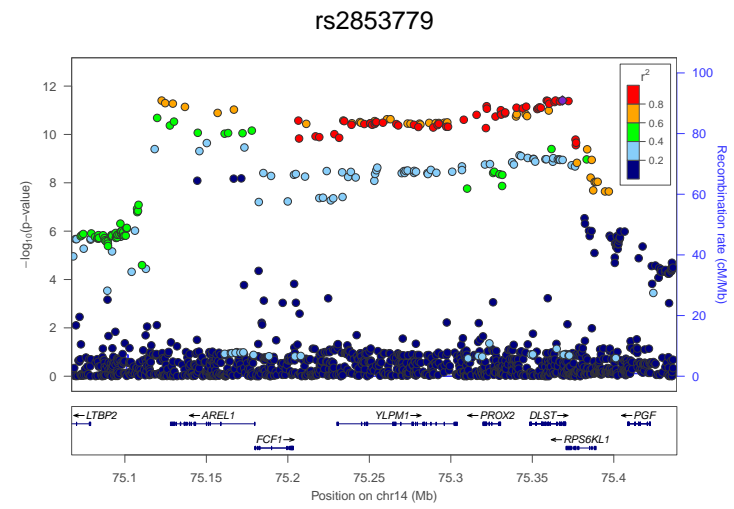
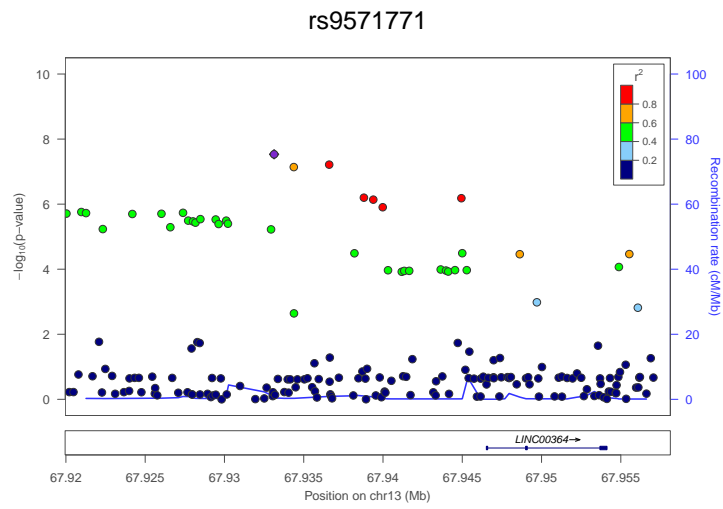
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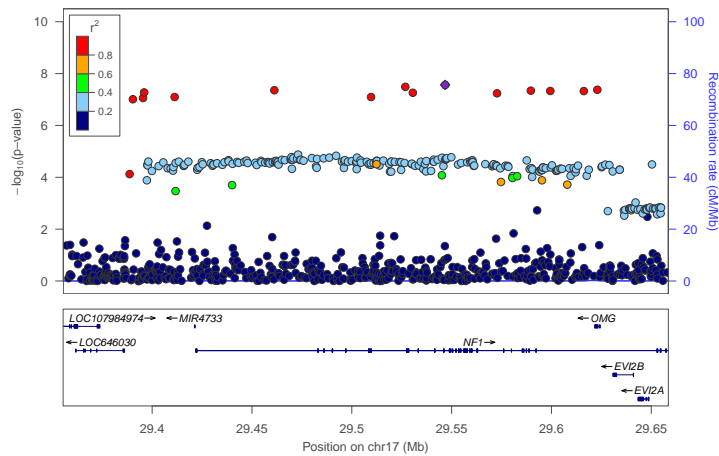




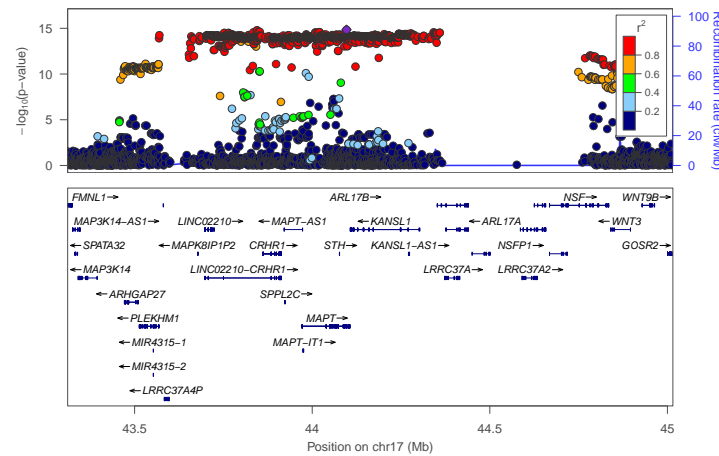




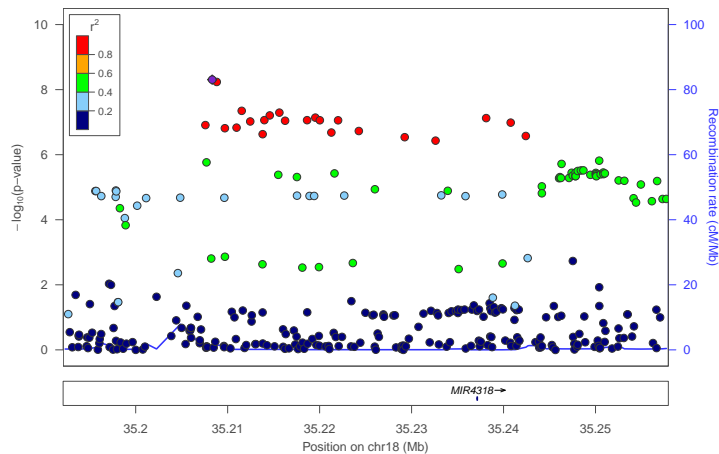
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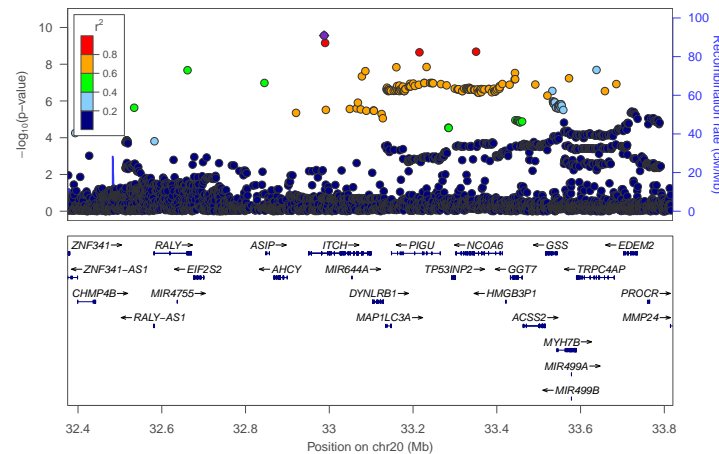
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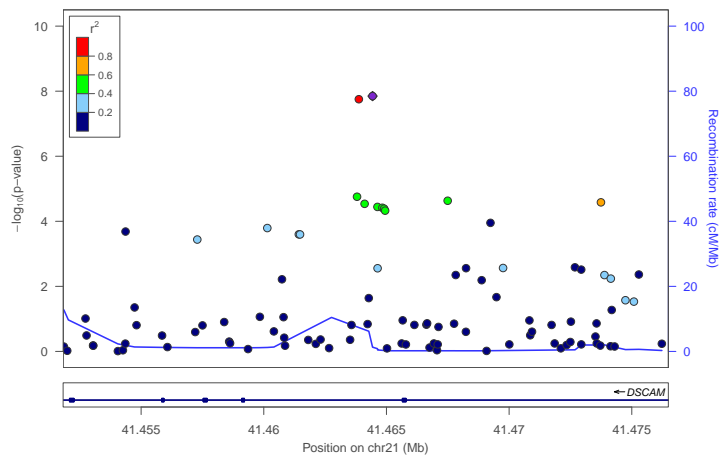
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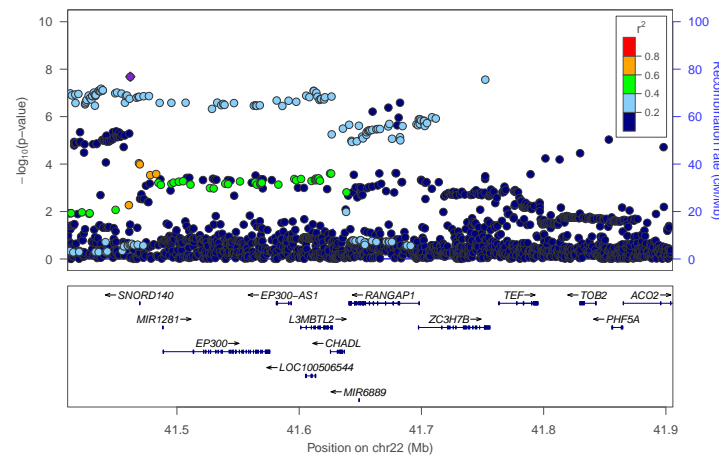
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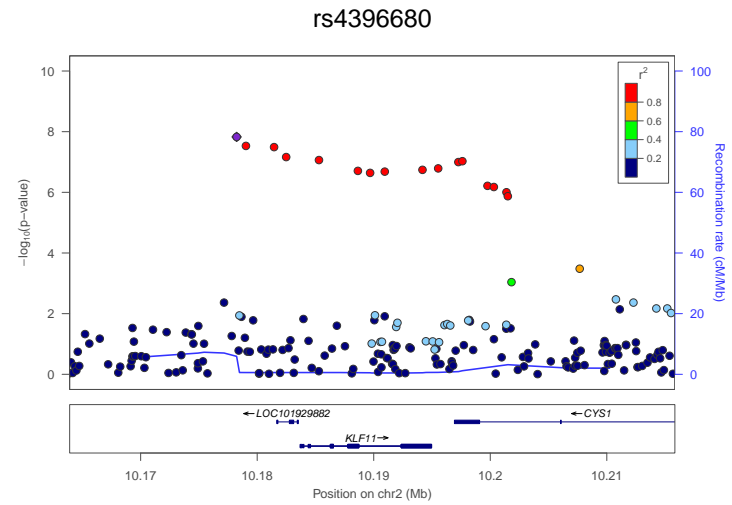
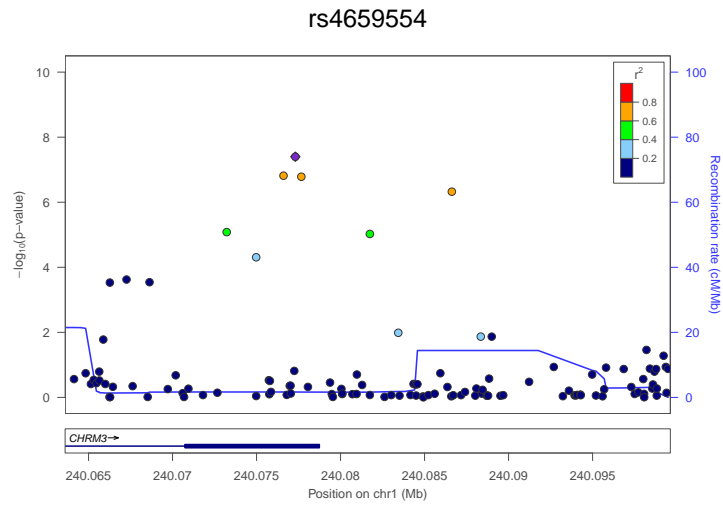
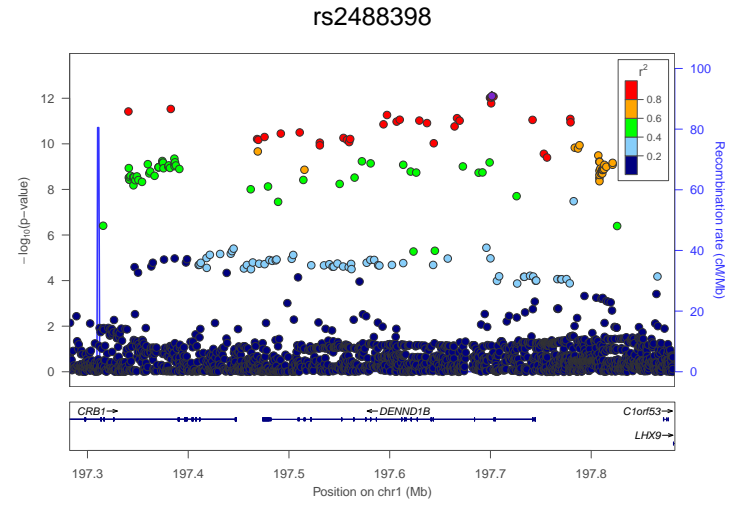
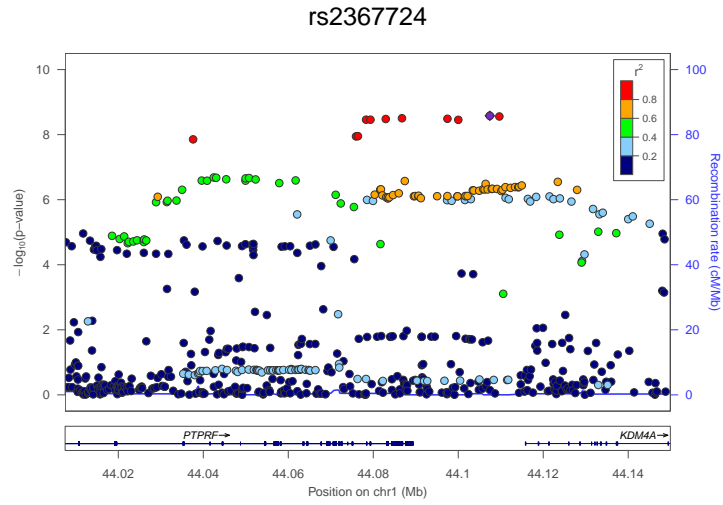
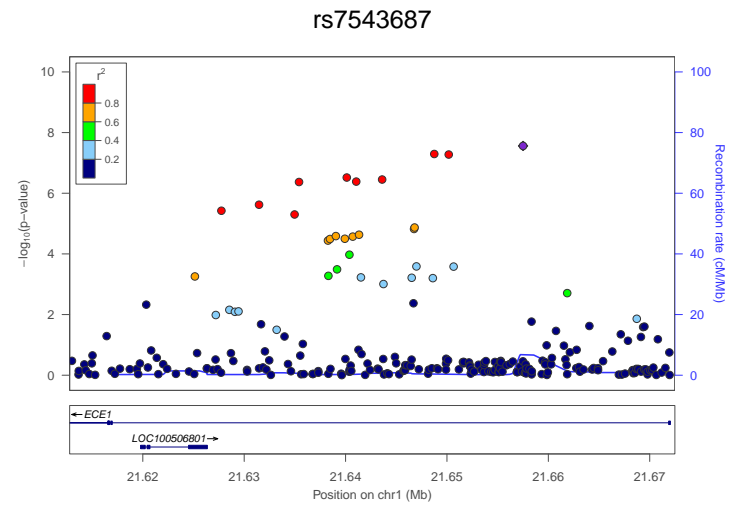
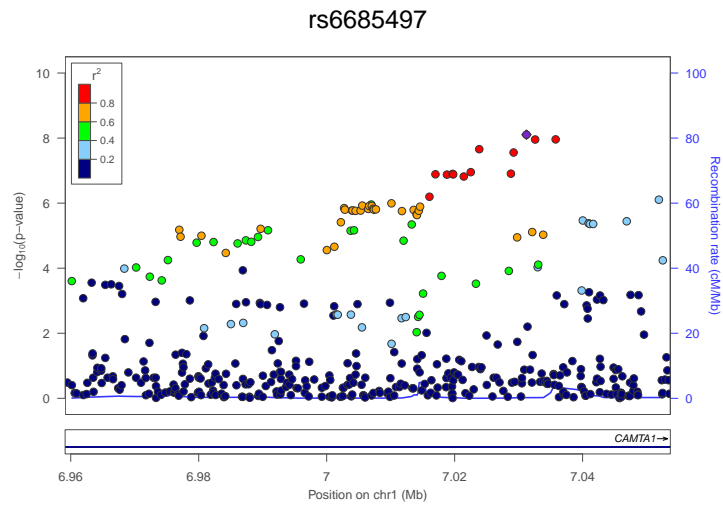


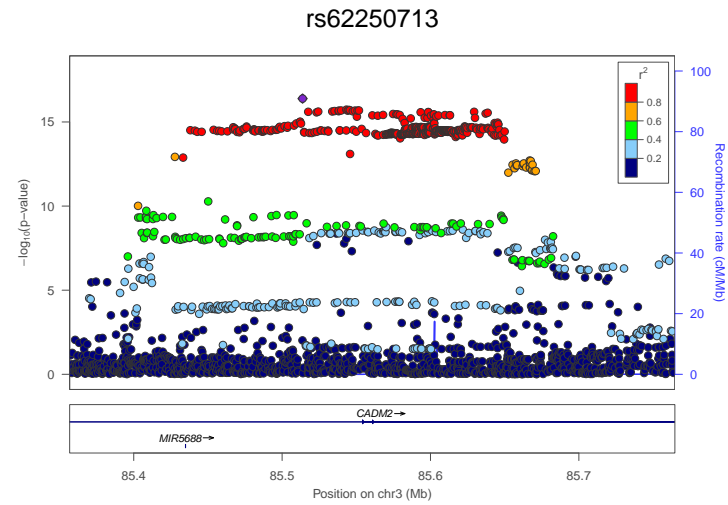
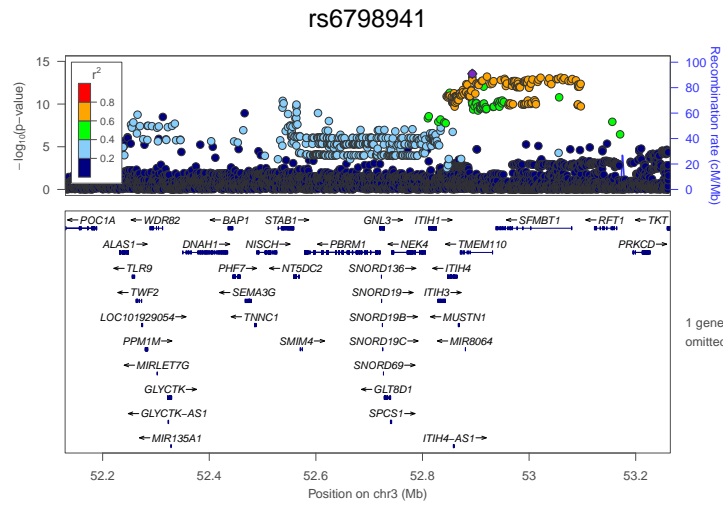
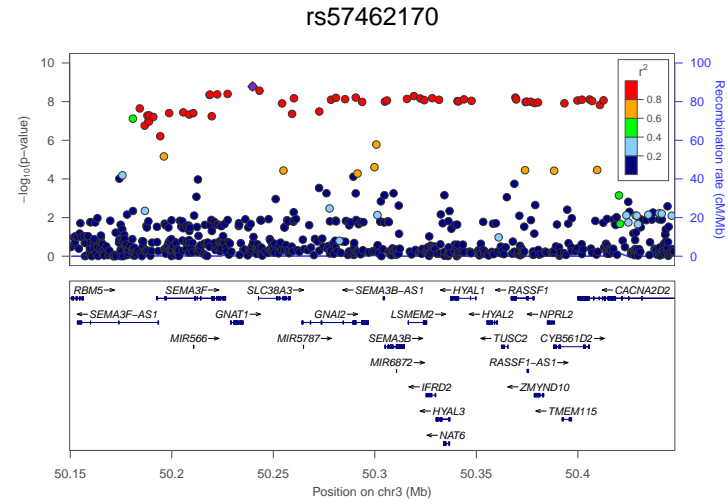
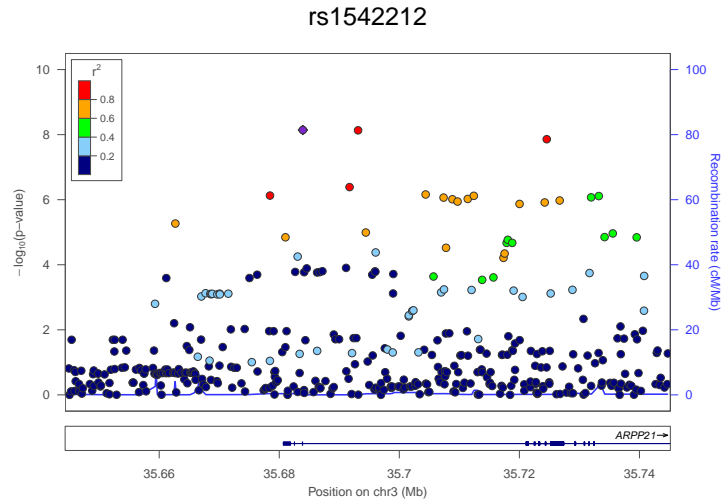
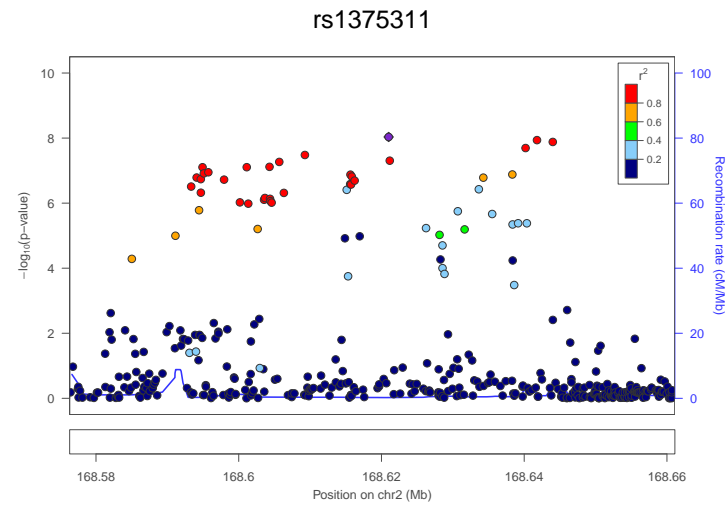
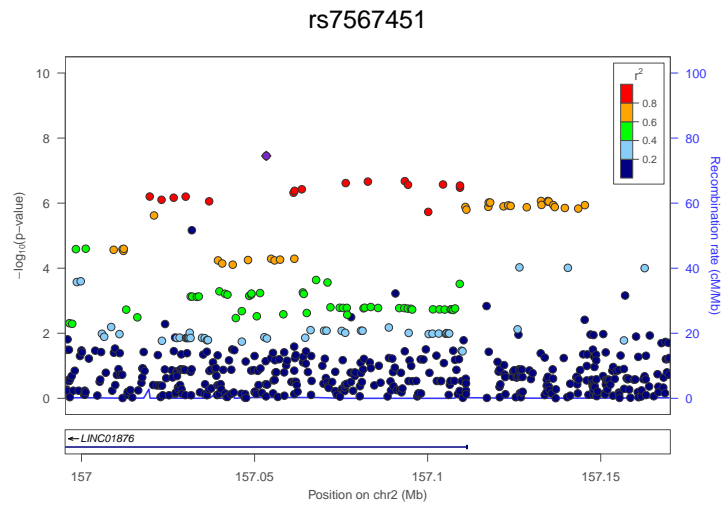
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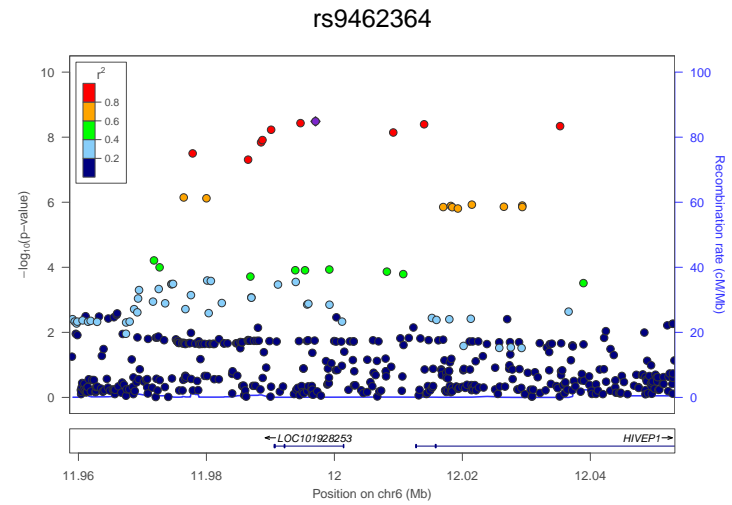
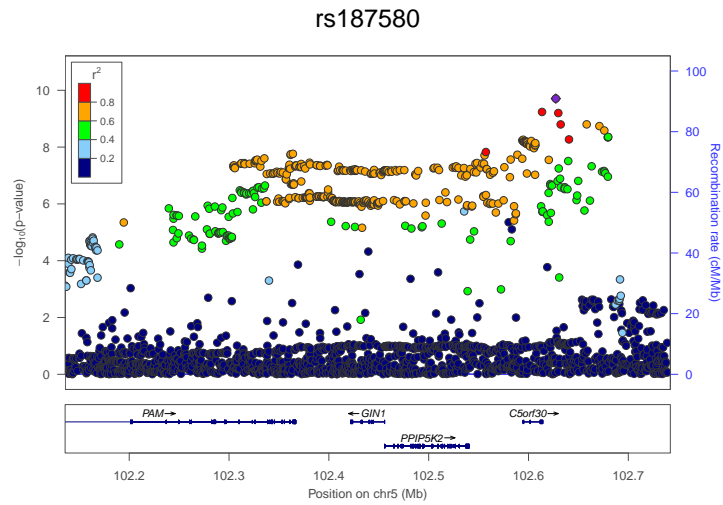
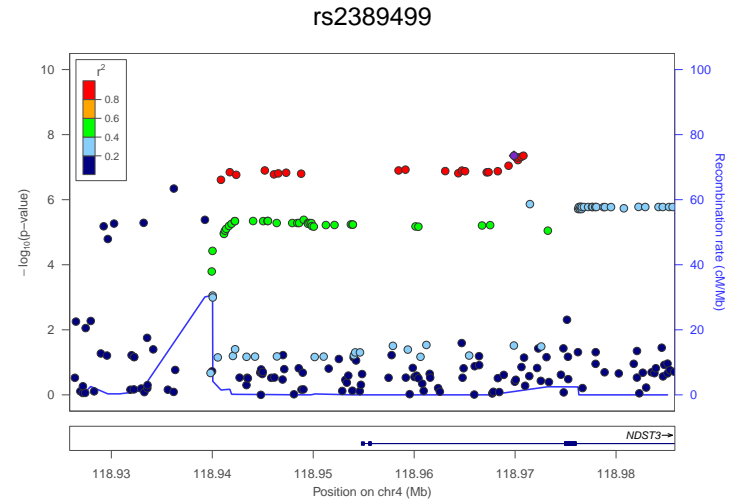
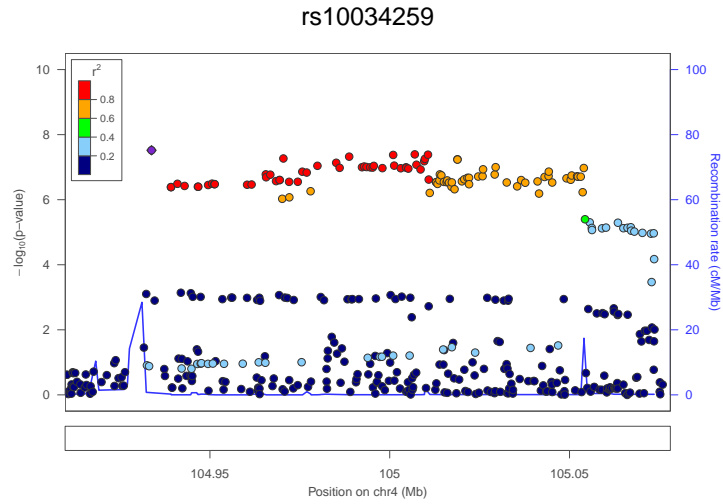
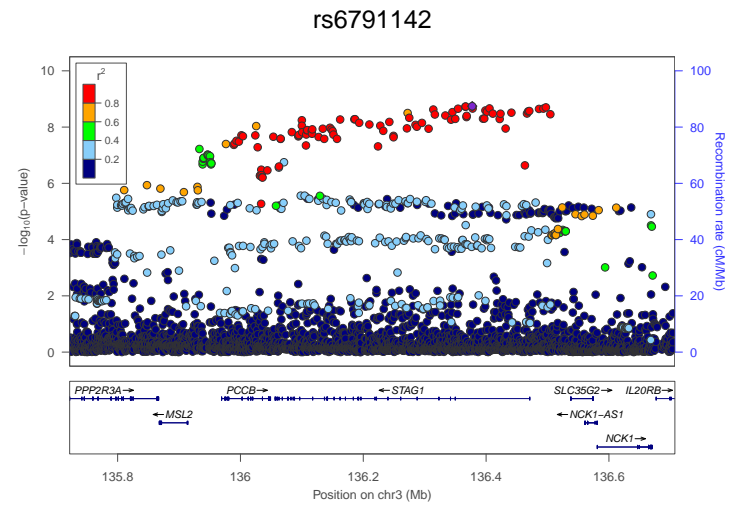
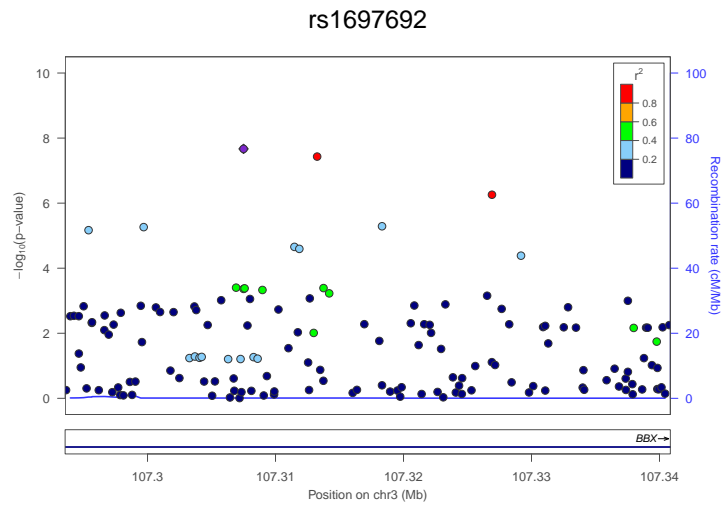


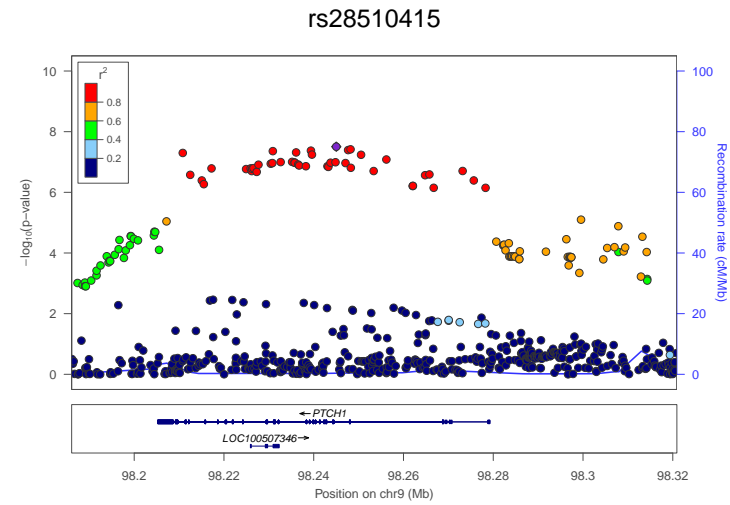
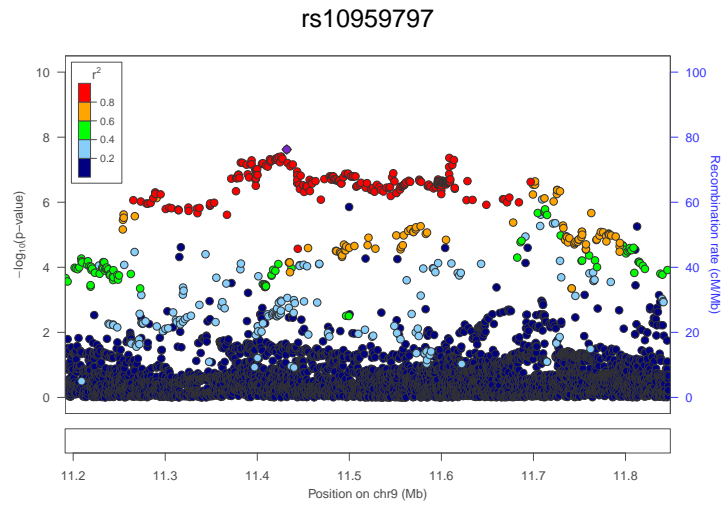
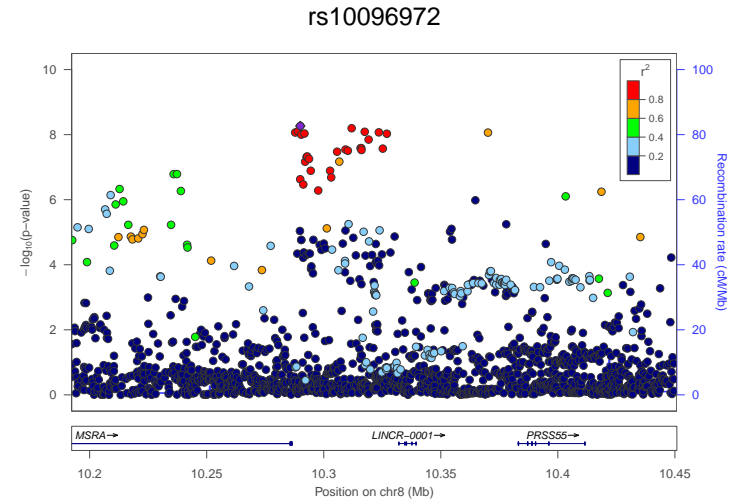
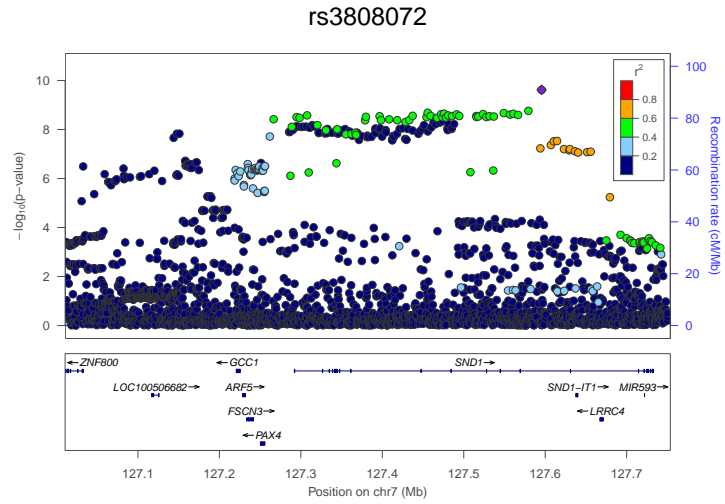
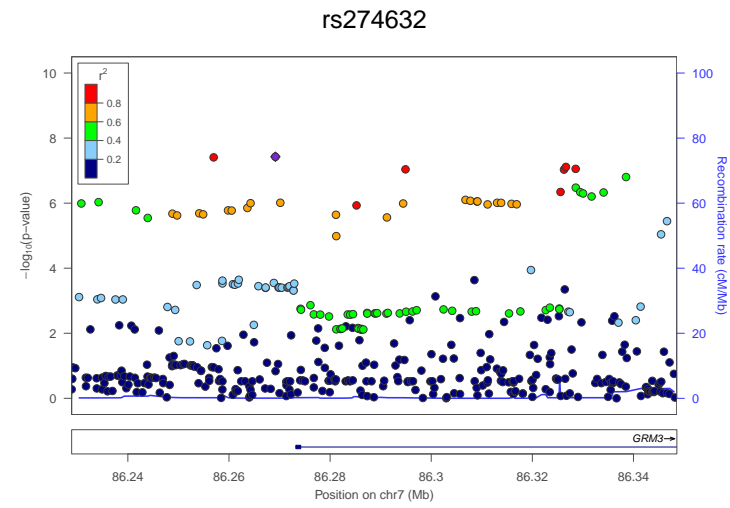
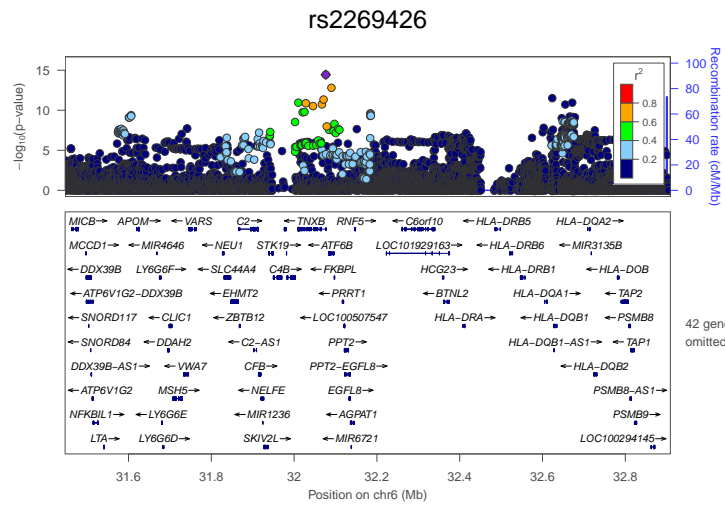
Supplementary Figure 10. Regional plots of GWA analyses of item NERV-FEEL.

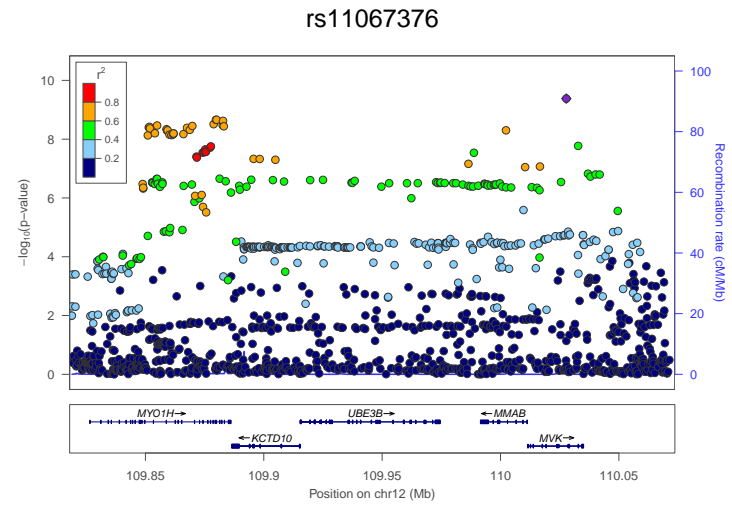
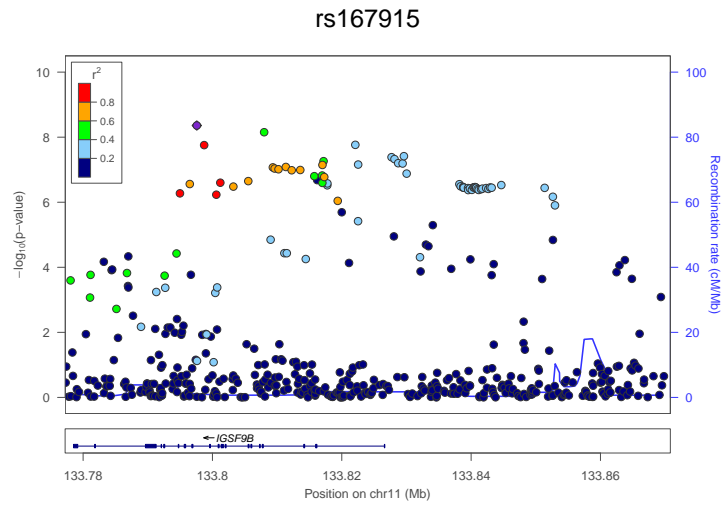
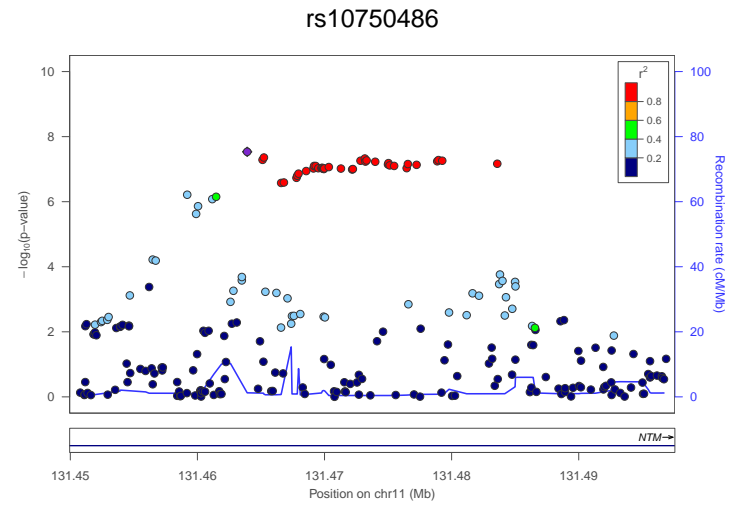
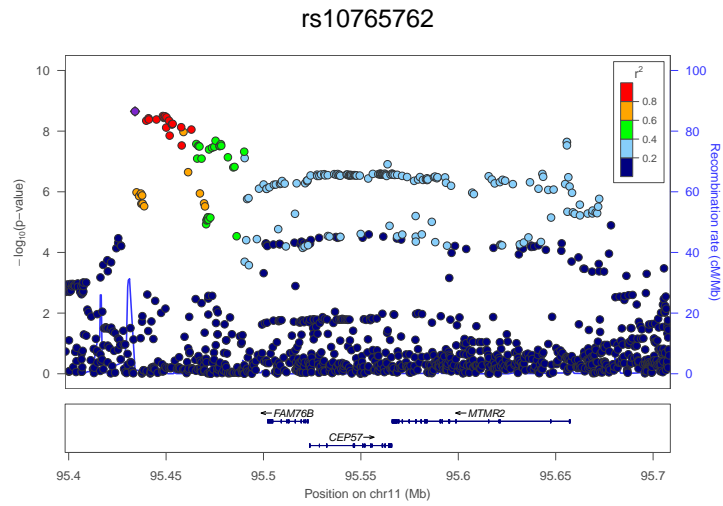
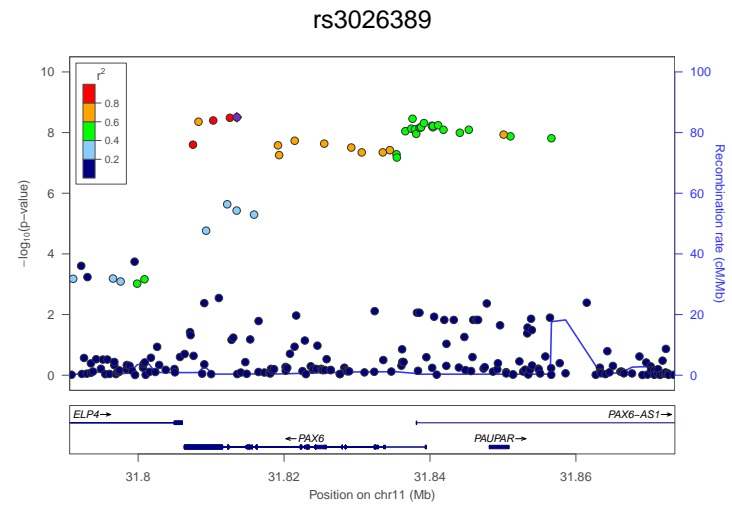
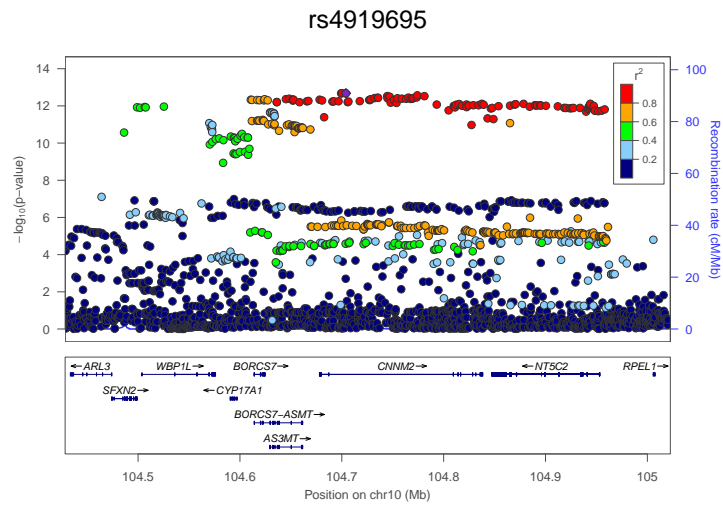
The y -axis represents the negative logarithm (base 10) of the SNP P value and the x -axis the position on the chromosome, with the name and location of genes in the UCSC Genome Browser in the bottom panel. The SNP with the lowest P value in the region is marked by a purple diamond. The colors of the other SNPs indicate the r^2 of these SNPs with the lead SNP, with grey color indicating SNPs below the user-defined r^2 . Plots are generated with LocusZoom. See **Supplementary Data 2** for an overview of all lead SNPs for which a regional plot is presented above. For excluded loci (see **Methods**; **Supplementary Data 3-4**) the rsID's are marked yellow.



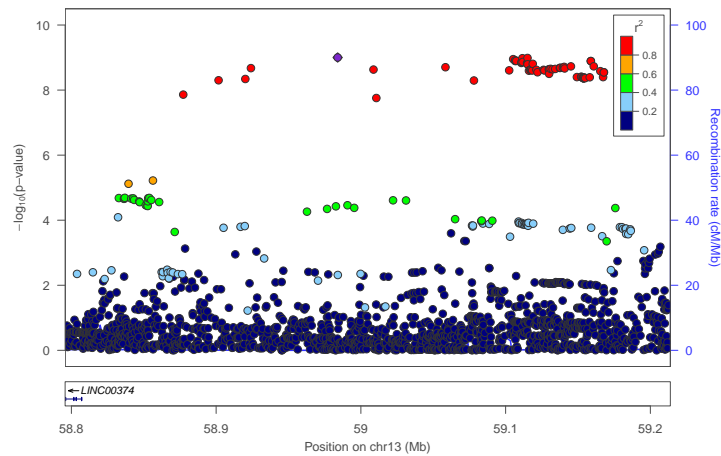




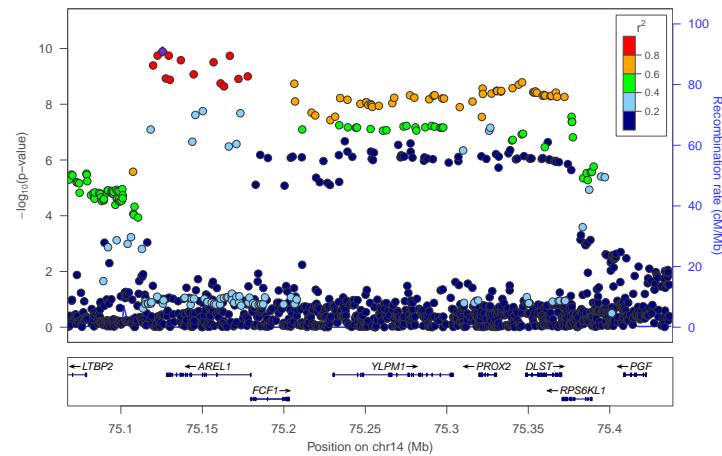




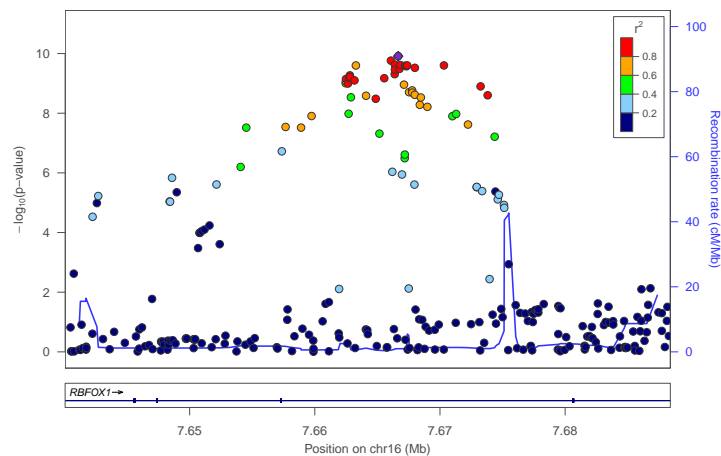
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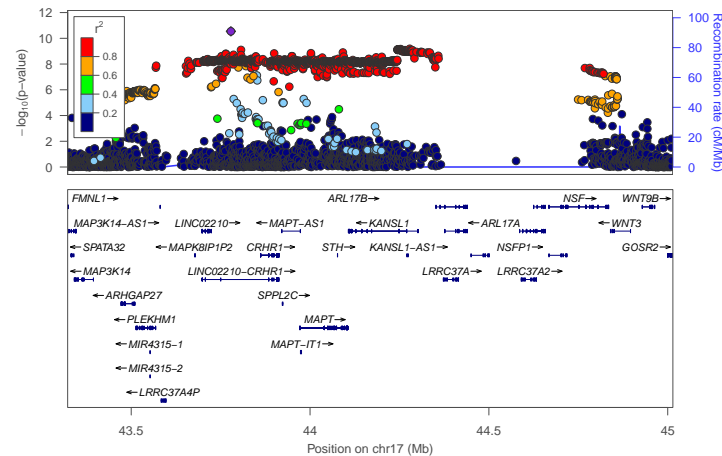
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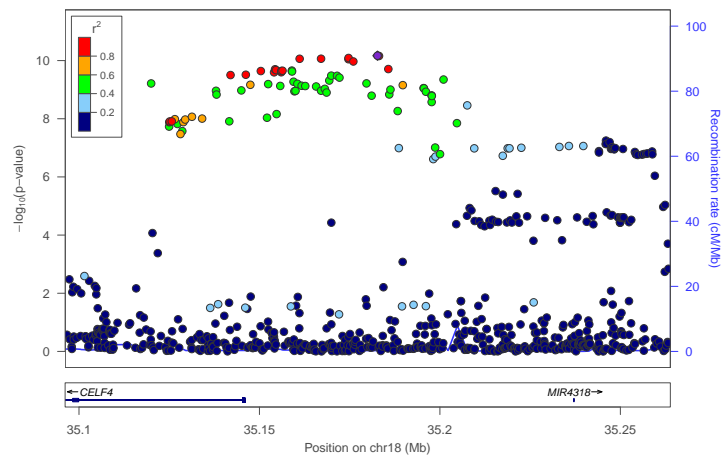
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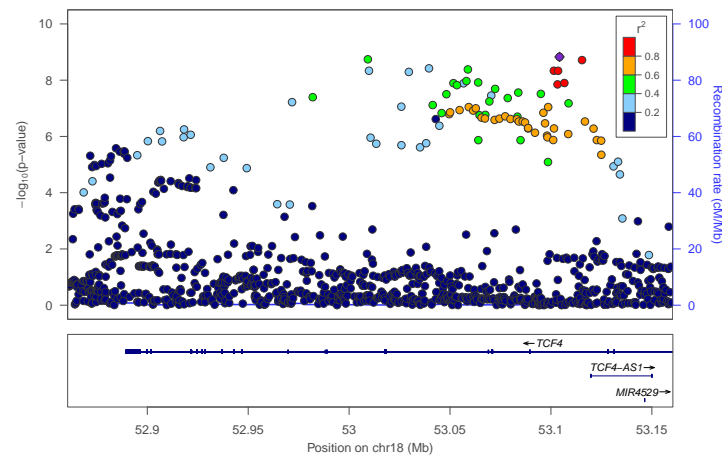
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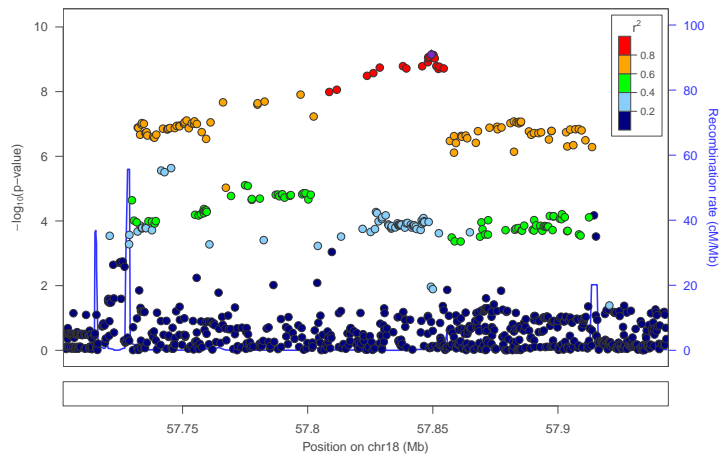
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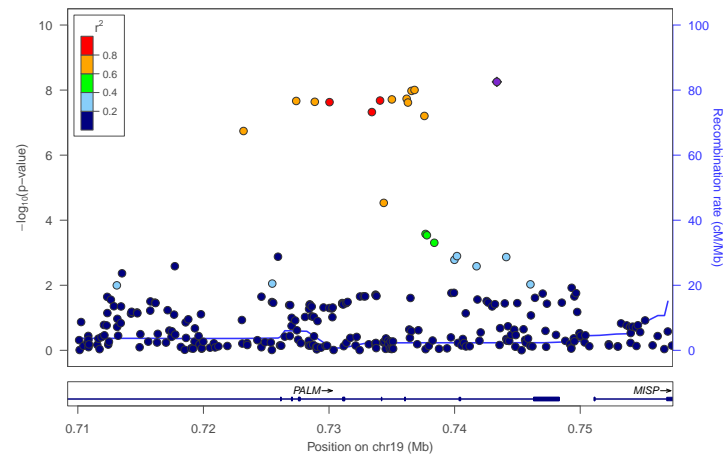
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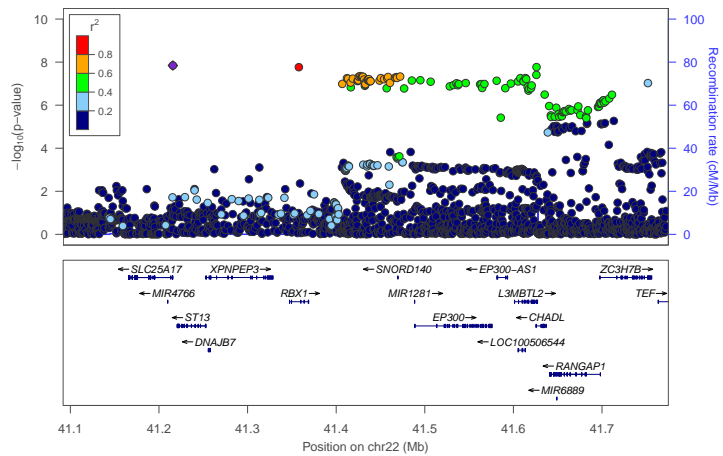
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rs116962250

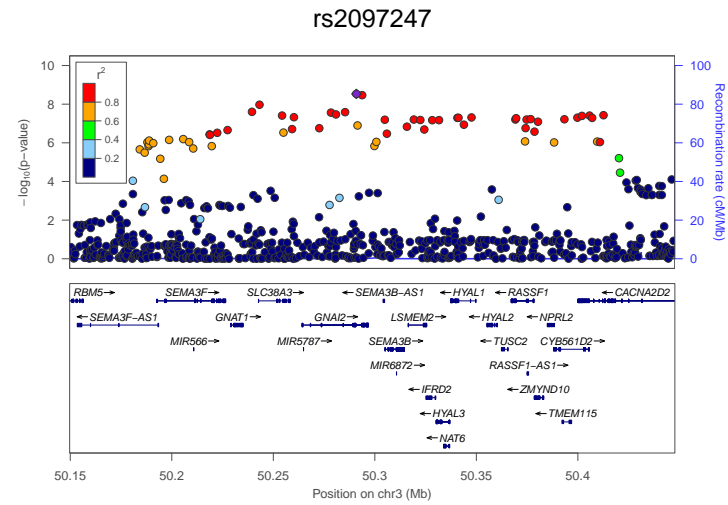
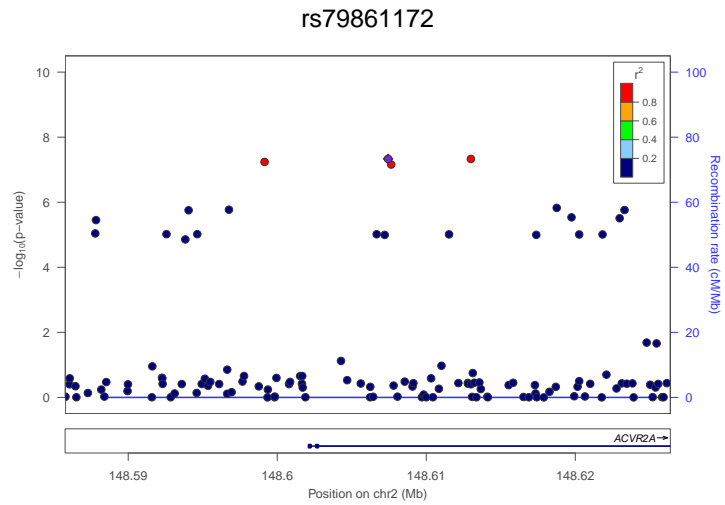
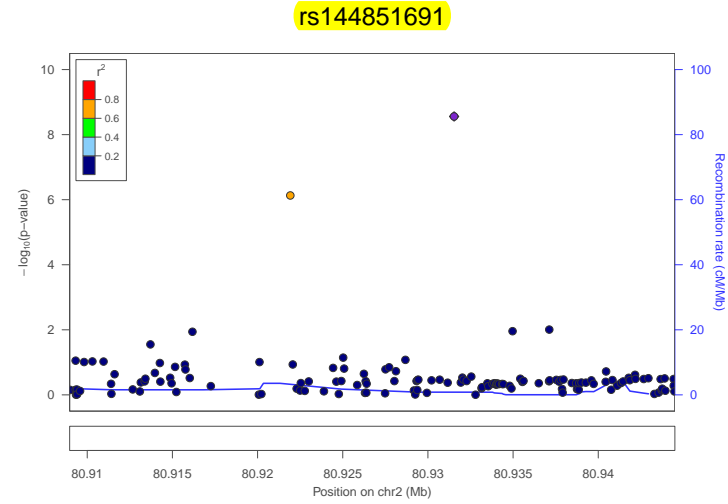
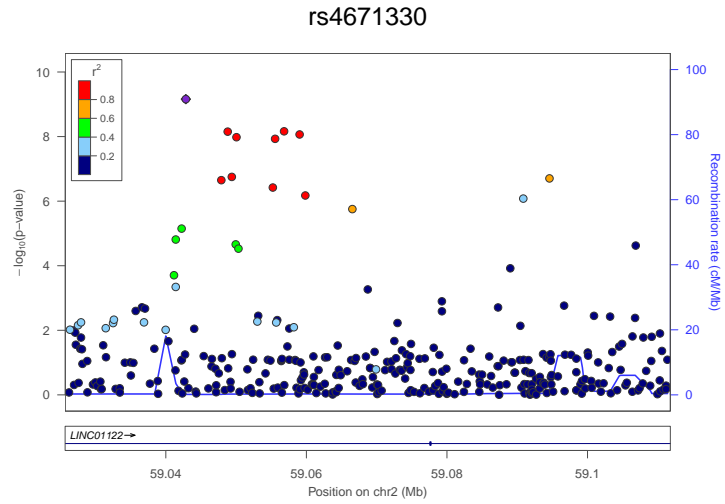
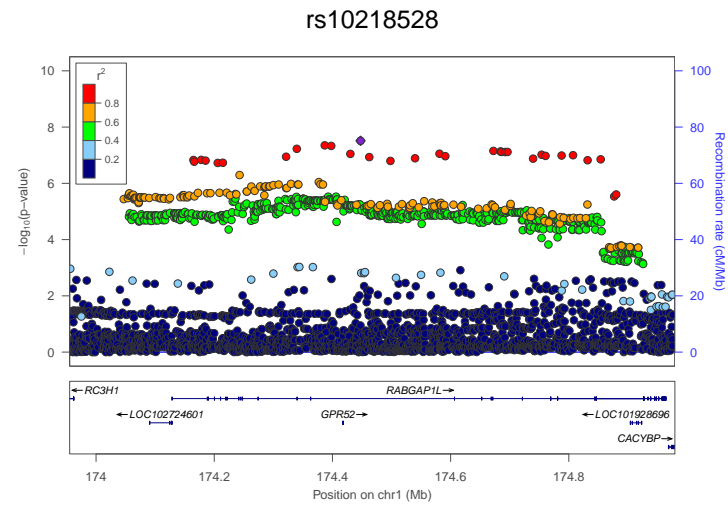
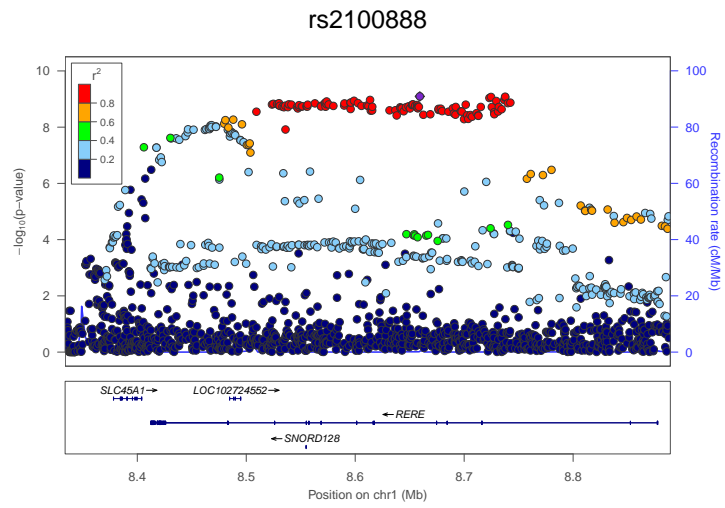


rs13054099

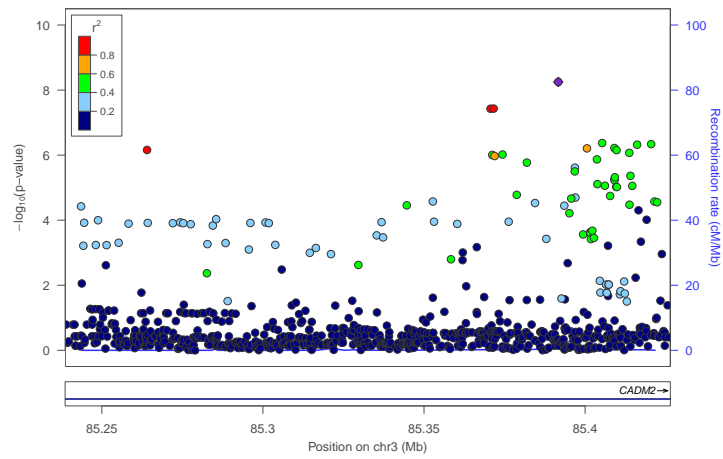


Supplementary Figure 11. Regional plots of GWA analyses of item WORRY.

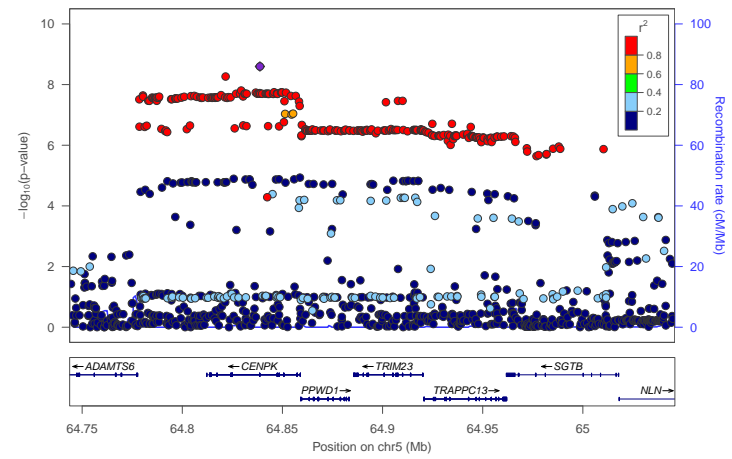
The y -axis represents the negative logarithm (base 10) of the SNP P value and the x -axis the position on the chromosome, with the name and location of genes in the UCSC Genome Browser in the bottom panel. The SNP with the lowest P value in the region is marked by a purple diamond. The colors of the other SNPs indicate the r^2 of these SNPs with the lead SNP, with grey color indicating SNPs below the user-defined r^2 . Plots are generated with LocusZoom. See **Supplementary Data 2** for an overview of all lead SNPs for which a regional plot is presented above.



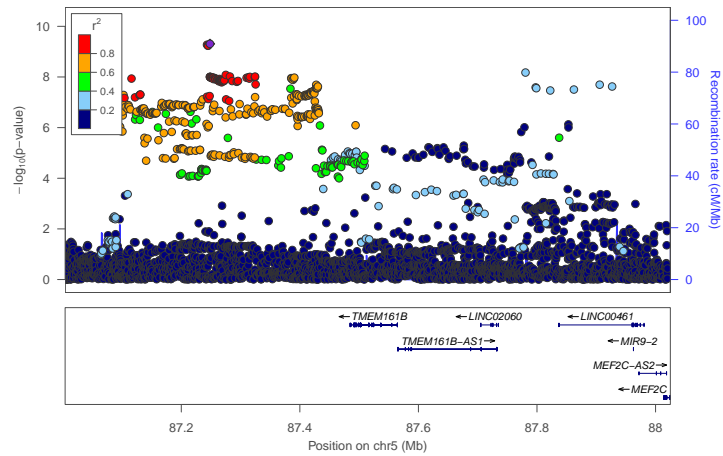
rs9811546



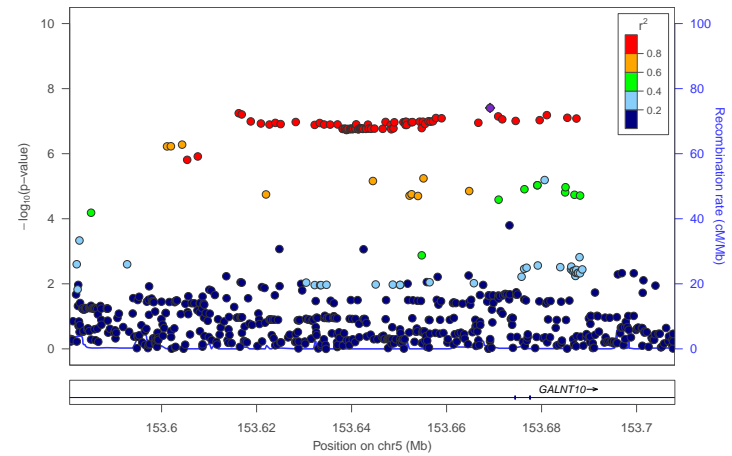
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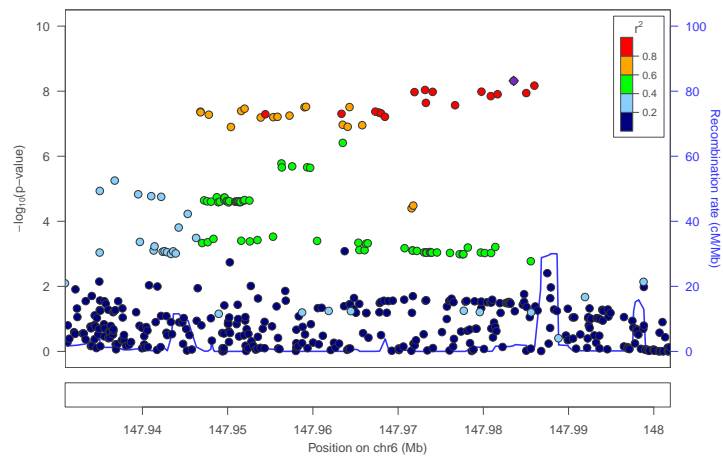
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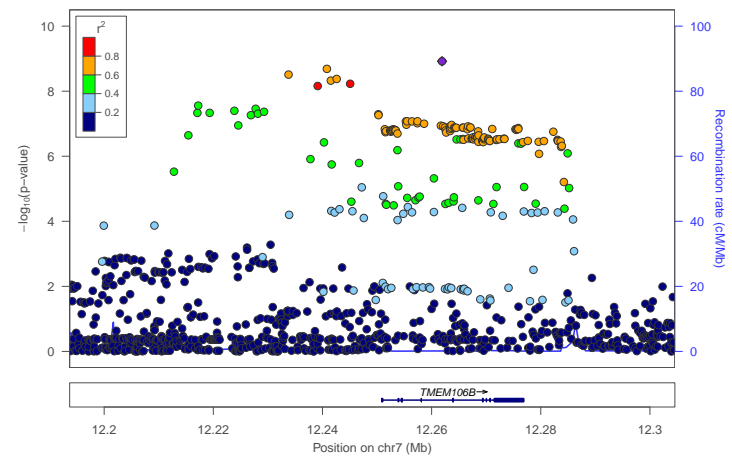
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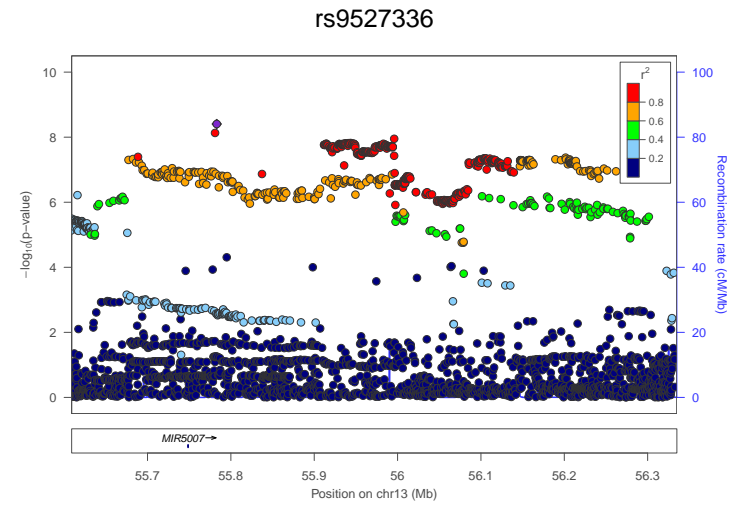
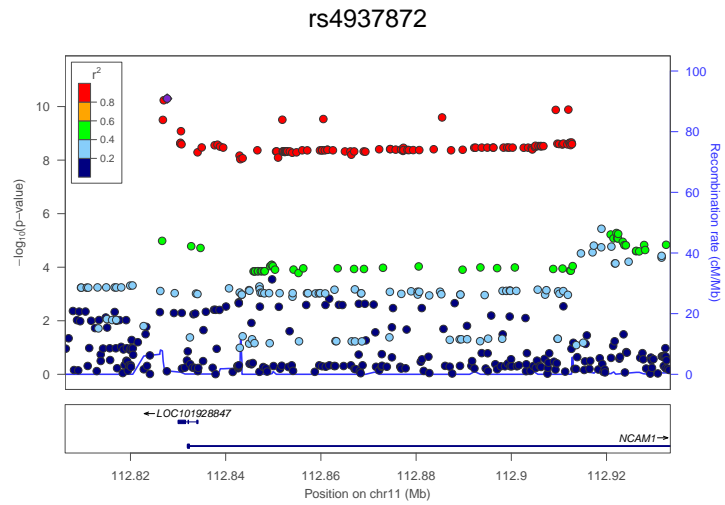
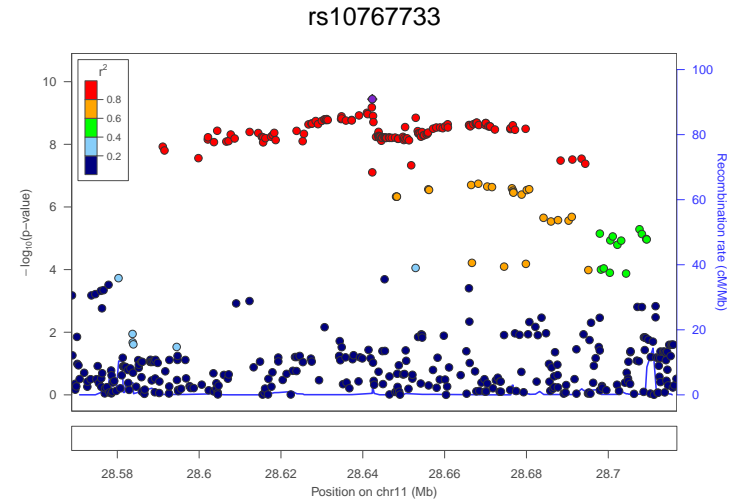
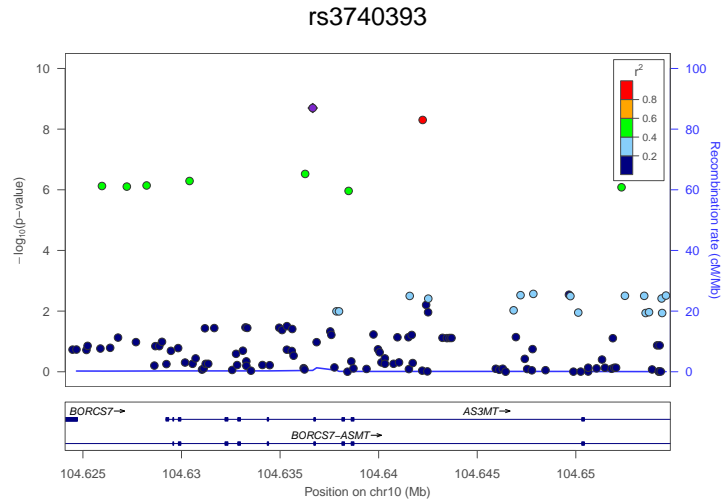
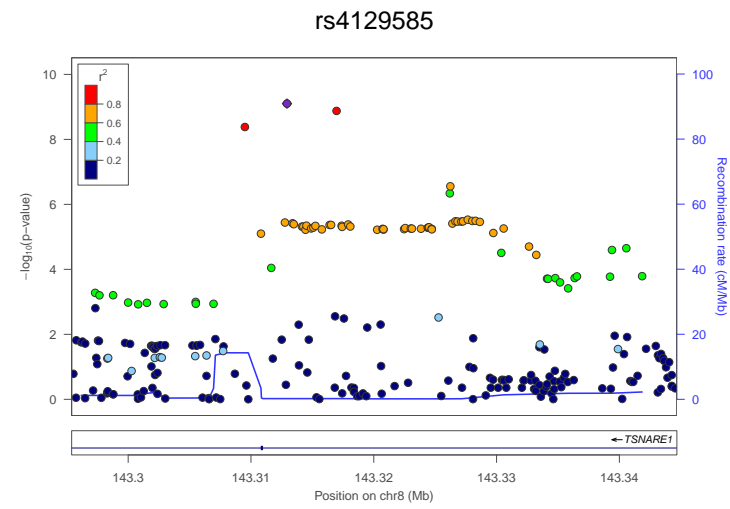
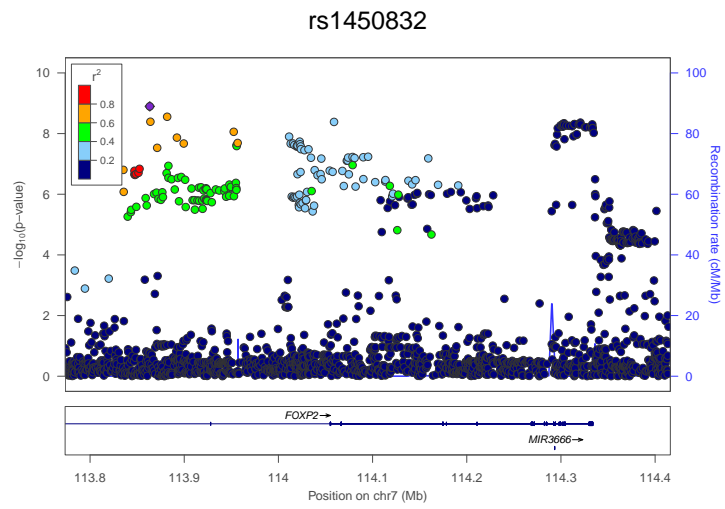


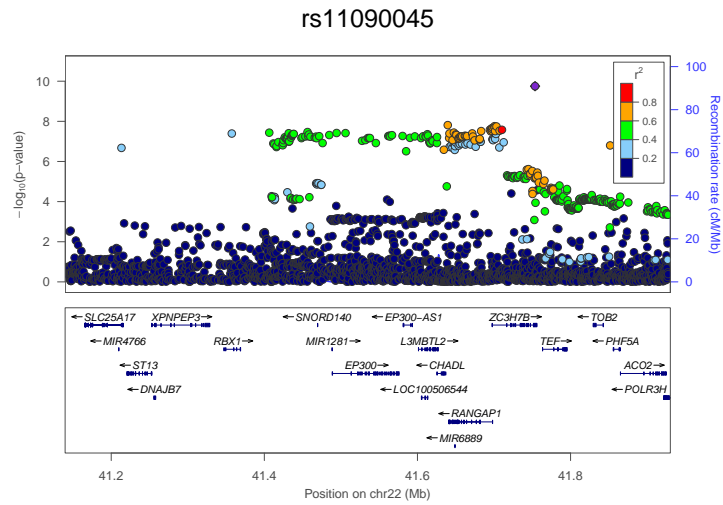
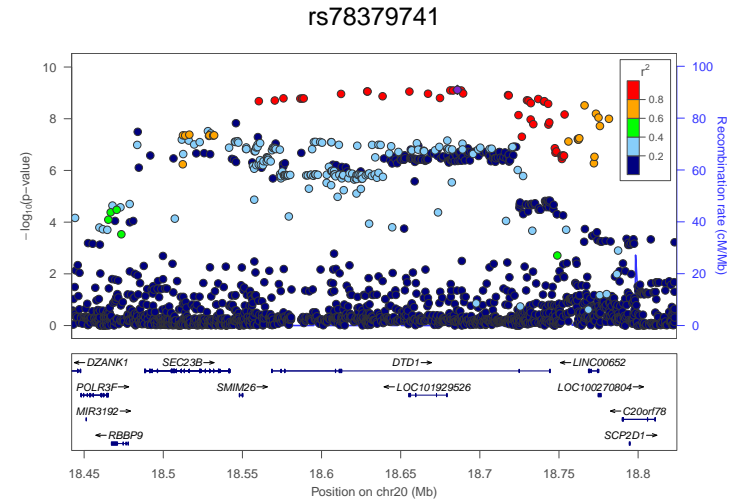
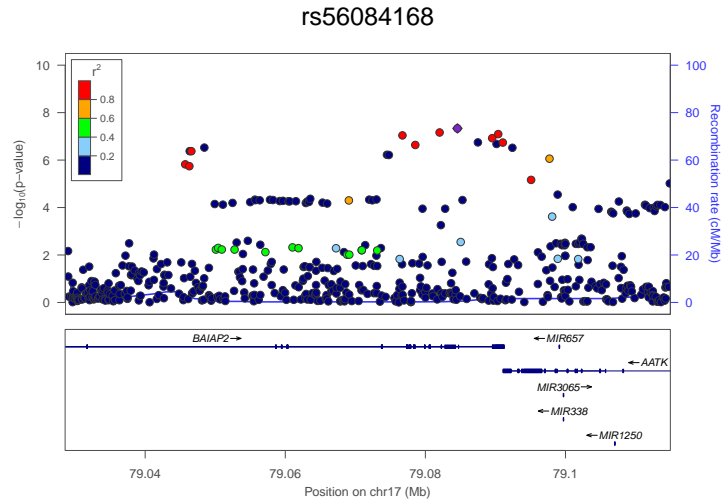
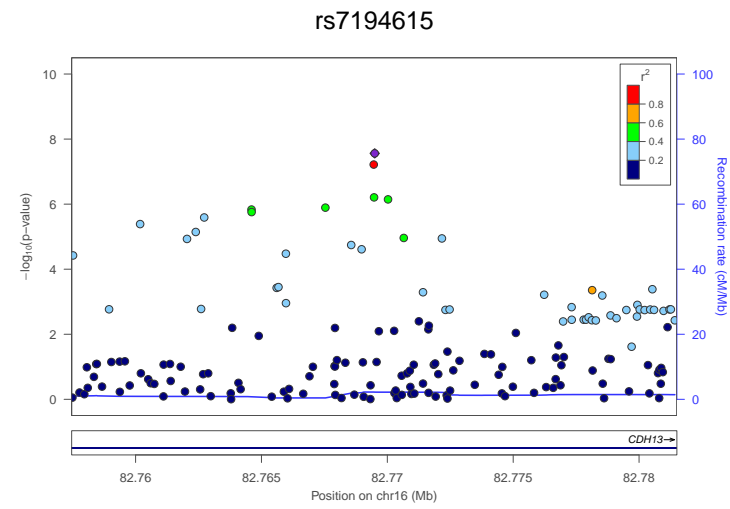
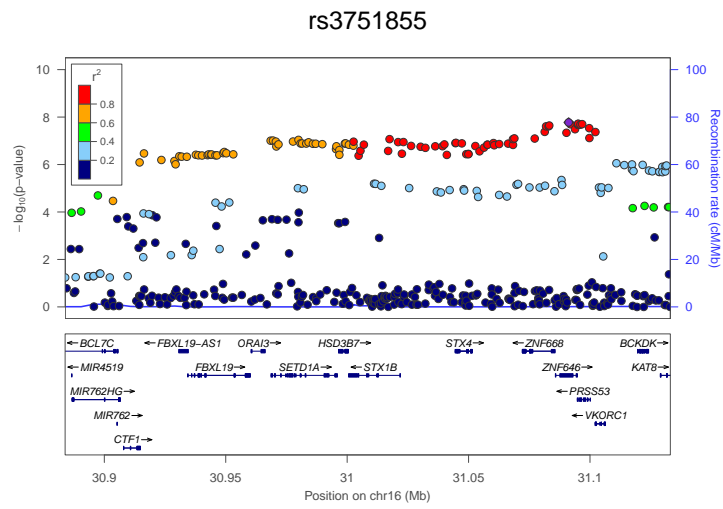
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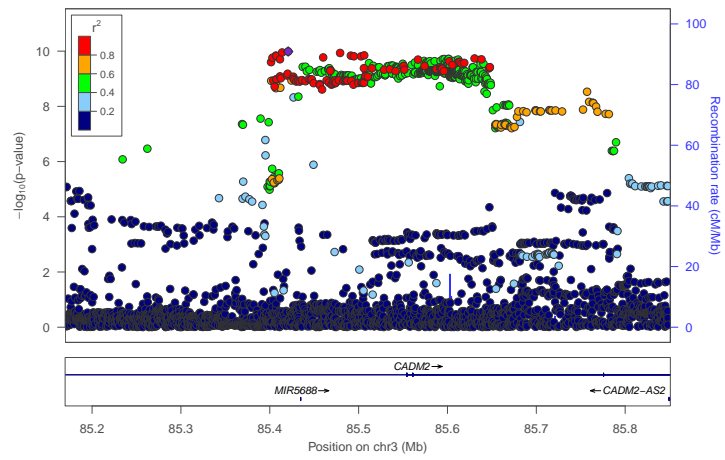




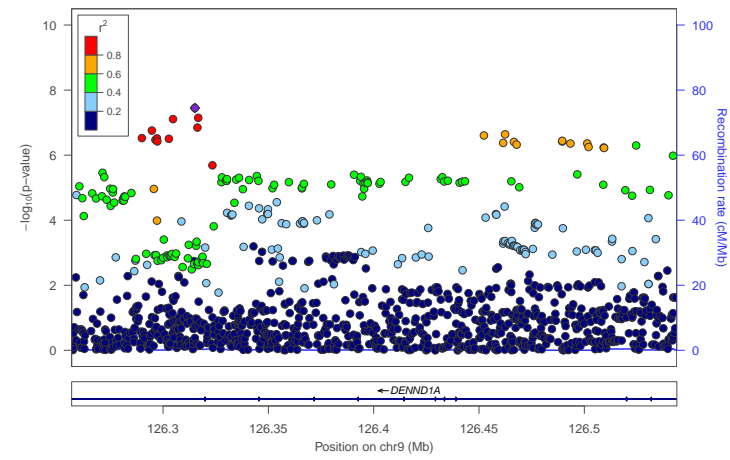
Supplementary Figure 12. Regional plots of GWA analyses of item TENSE.

The y -axis represents the negative logarithm (base 10) of the SNP P value and the x -axis the position on the chromosome, with the name and location of genes in the UCSC Genome Browser in the bottom panel. The SNP with the lowest P value in the region is marked by a purple diamond. The colors of the other SNPs indicate the r^2 of these SNPs with the lead SNP, with grey color indicating SNPs below the user-defined r^2 . Plots are generated with LocusZoom. See **Supplementary Data 2** for an overview of all lead SNPs for which a regional plot is presented above. For excluded loci (see **Methods**; **Supplementary Data 3-4**) the rsID's are marked yellow.

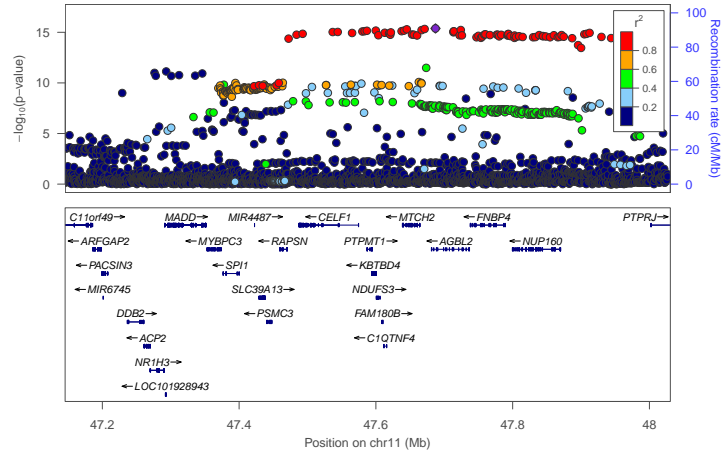
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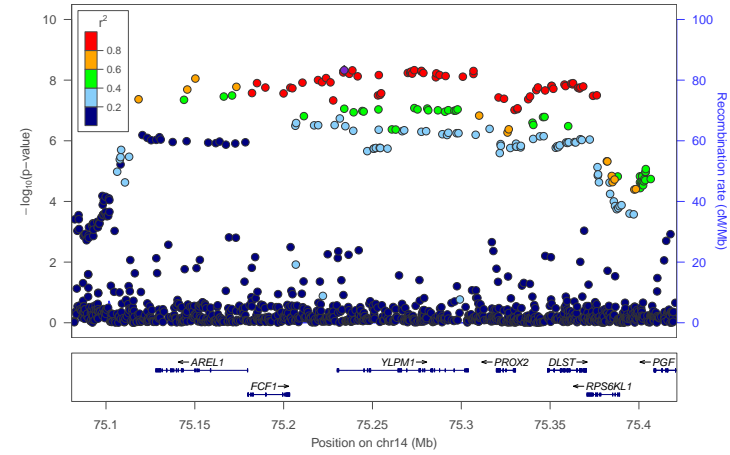
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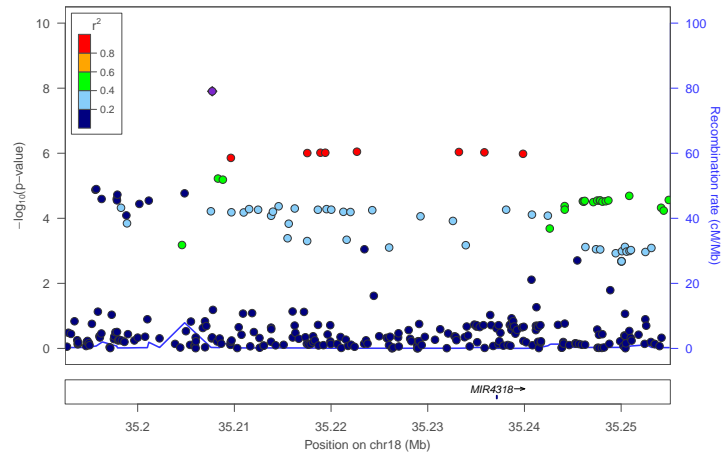
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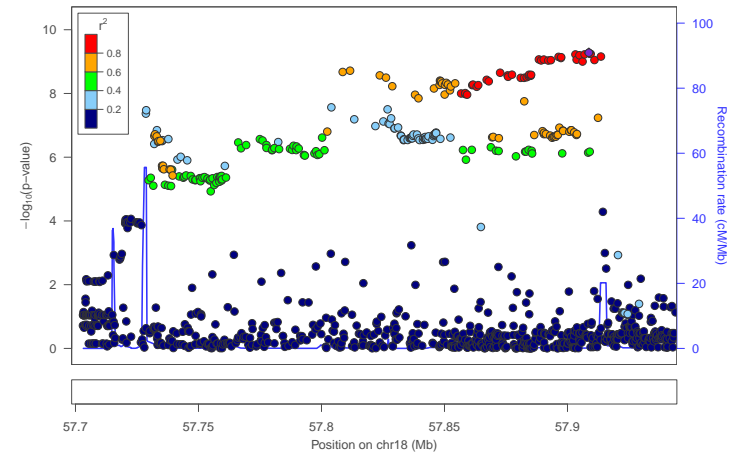
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rs62081501



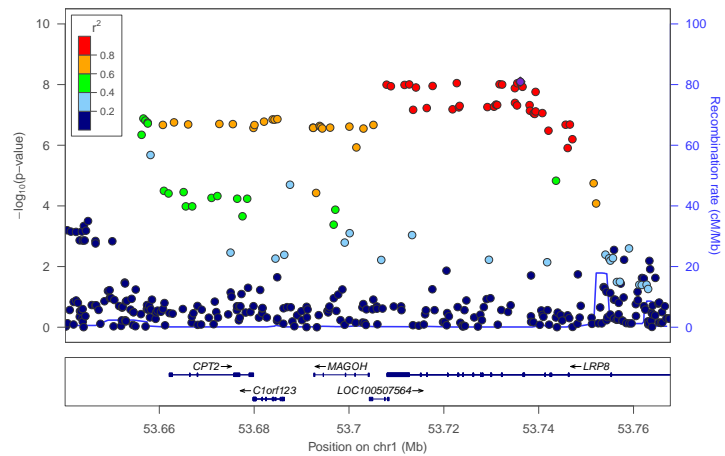
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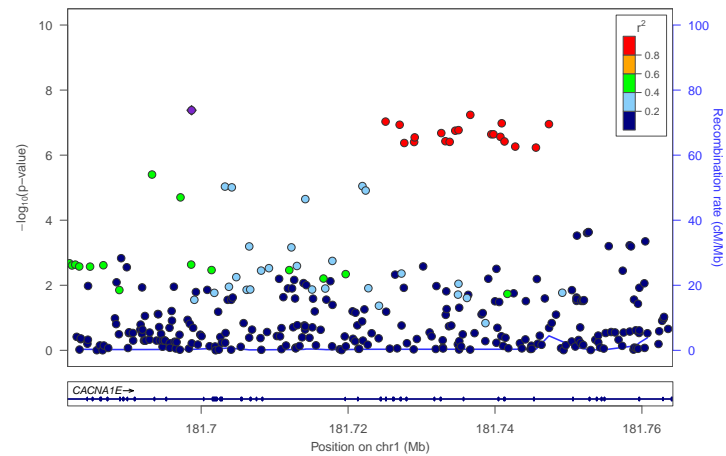
Supplementary Figure 13. Regional plots of GWA analyses of item SUF-NERV.

The y -axis represents the negative logarithm (base 10) of the SNP P value and the x -axis the position on the chromosome, with the name and location of genes in the UCSC Genome Browser in the bottom panel. The SNP with the lowest P value in the region is marked by a purple diamond. The colors of the other SNPs indicate the r^2 of these SNPs with the lead SNP, with grey color indicating SNPs below the user-defined r^2 . Plots are generated with LocusZoom. See **Supplementary Data 2** for an overview of all lead SNPs for which a regional plot is presented above.

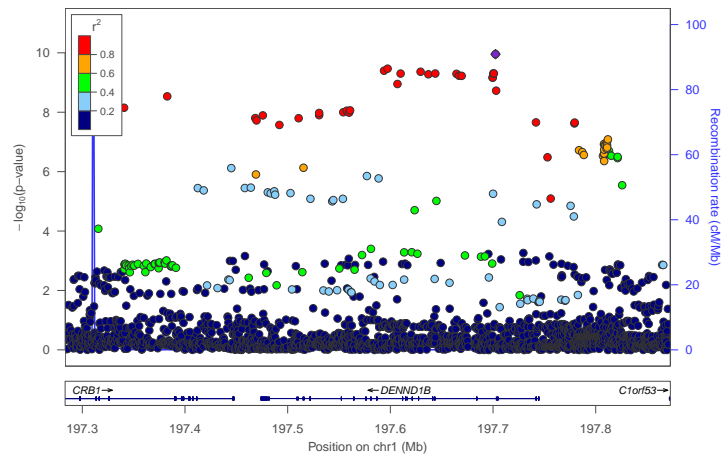
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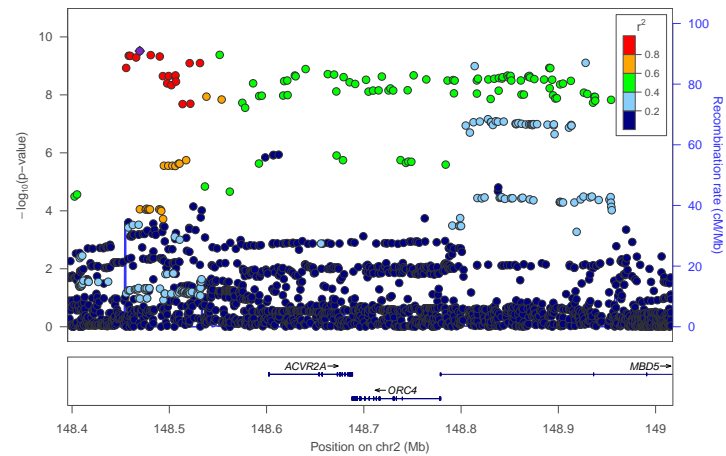
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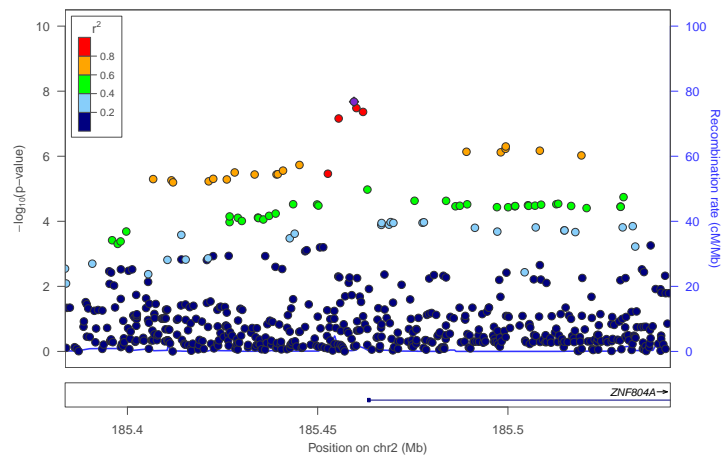
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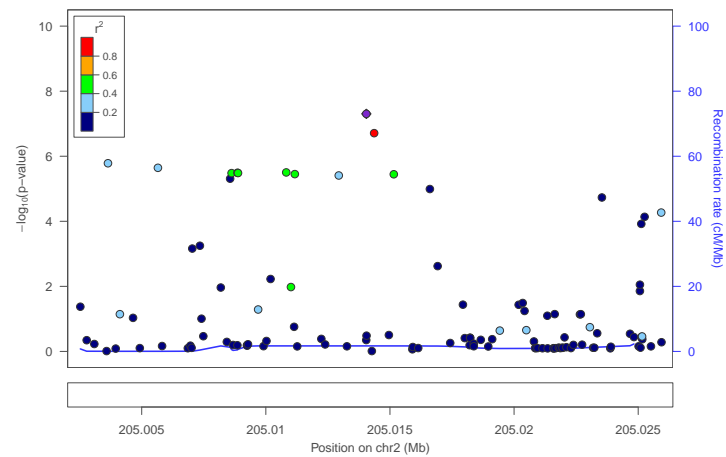
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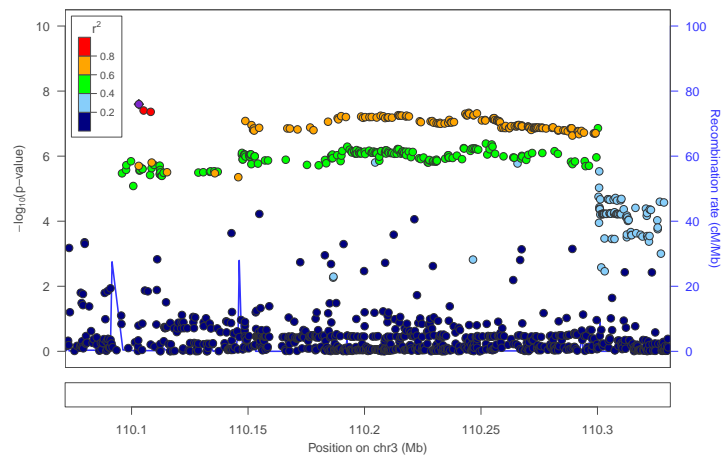
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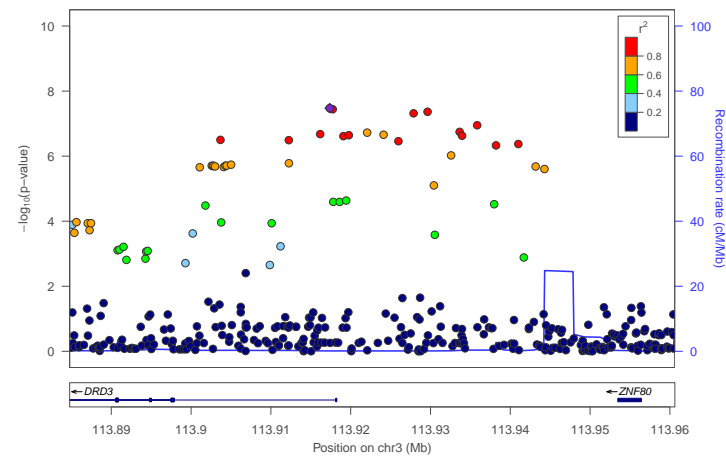
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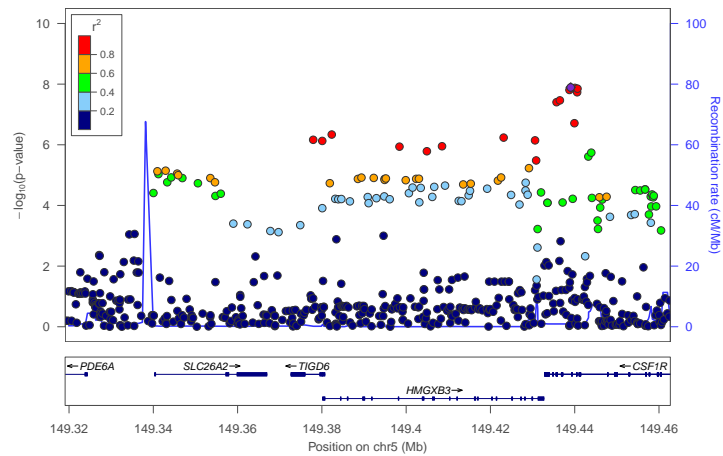
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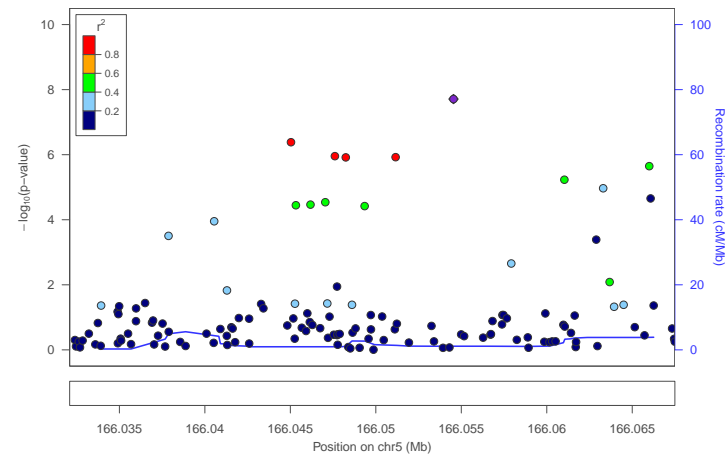
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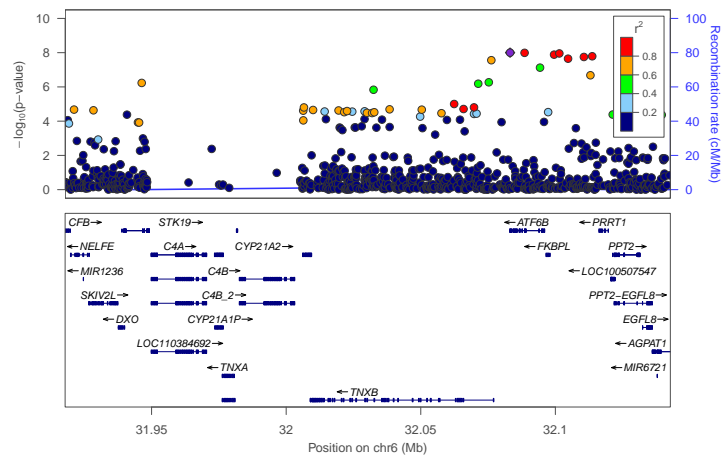
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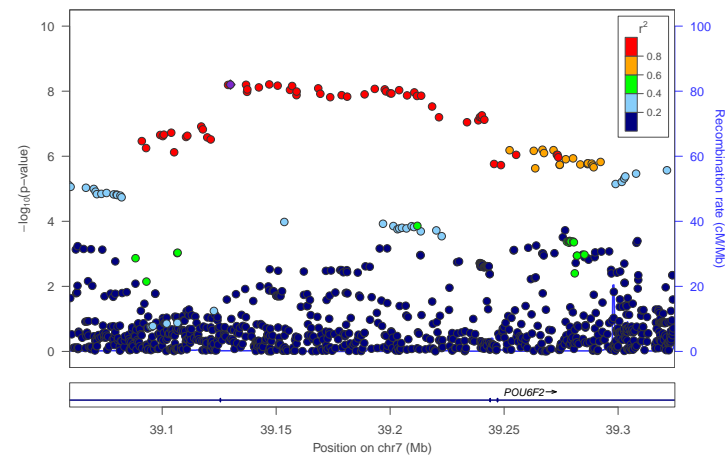
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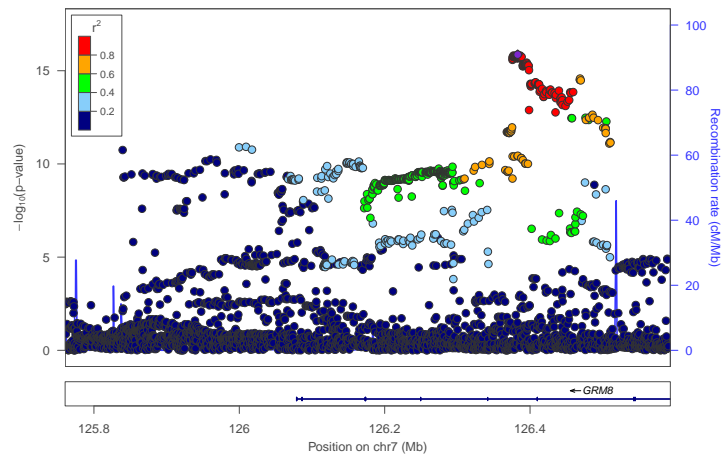
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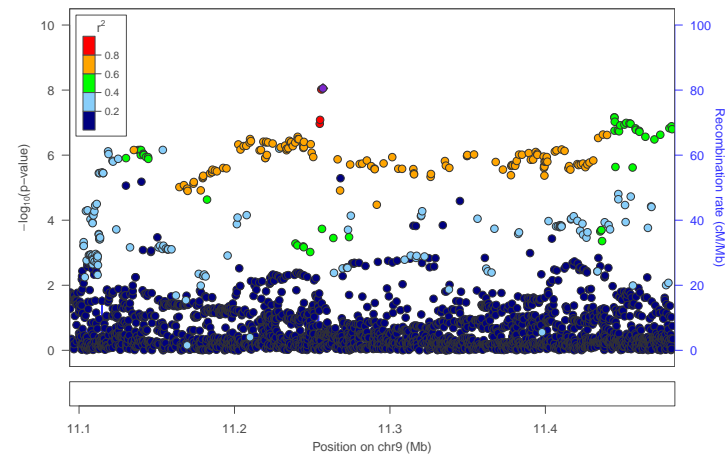
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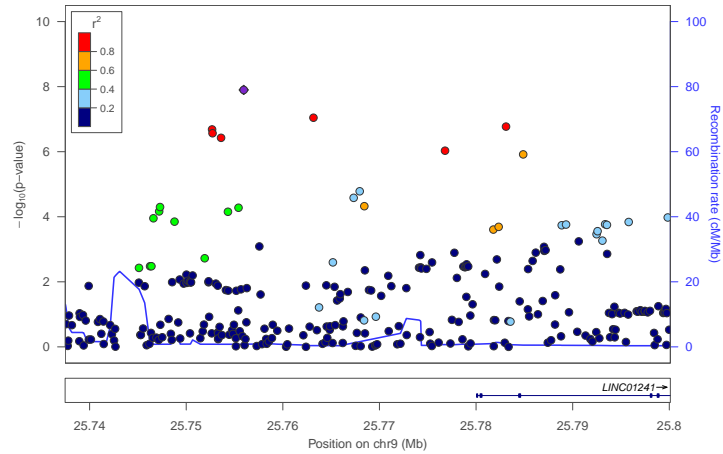
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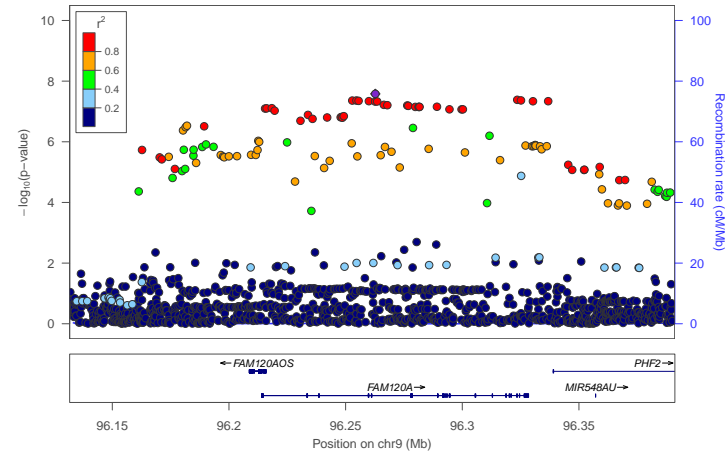
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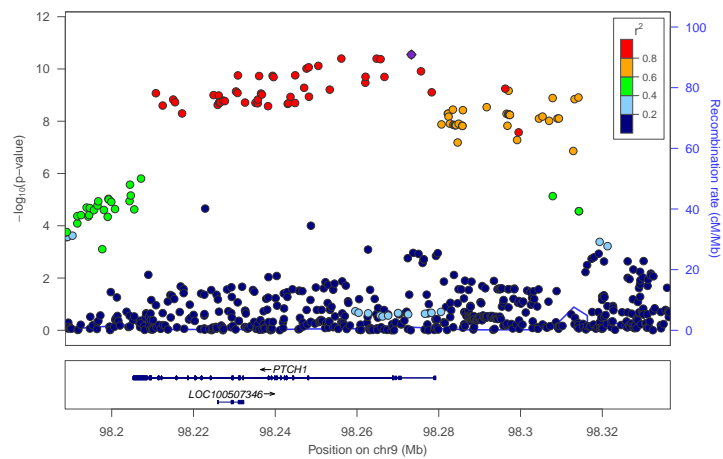
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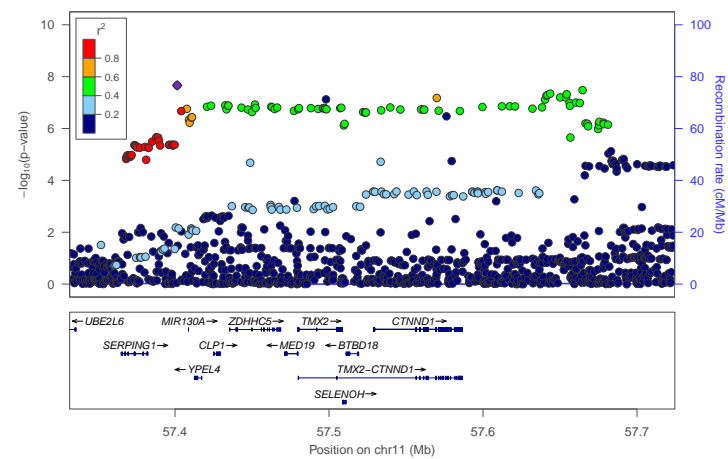
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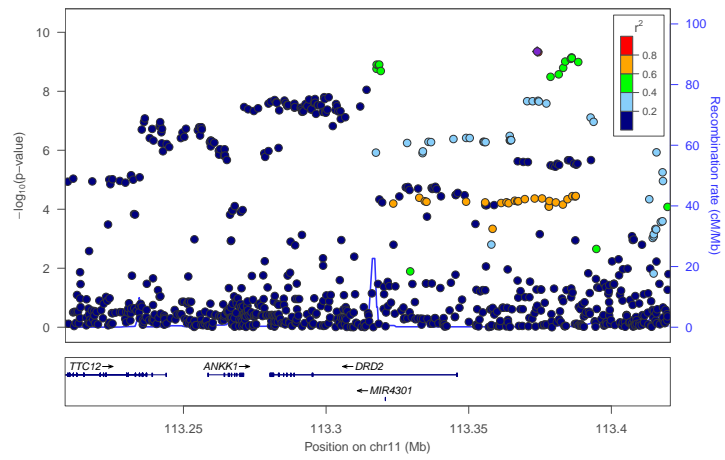
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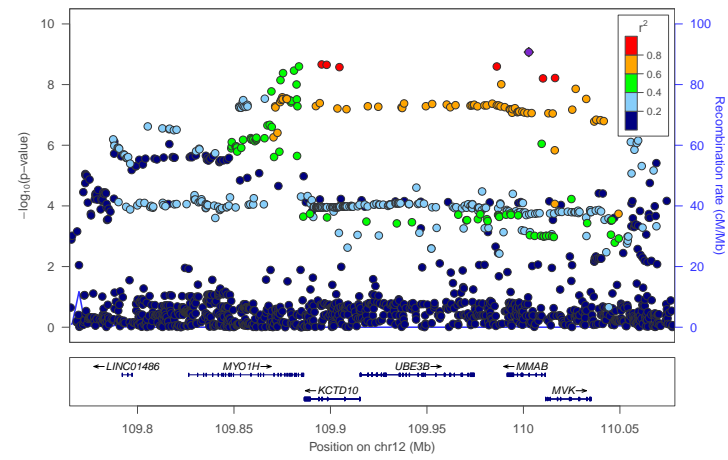
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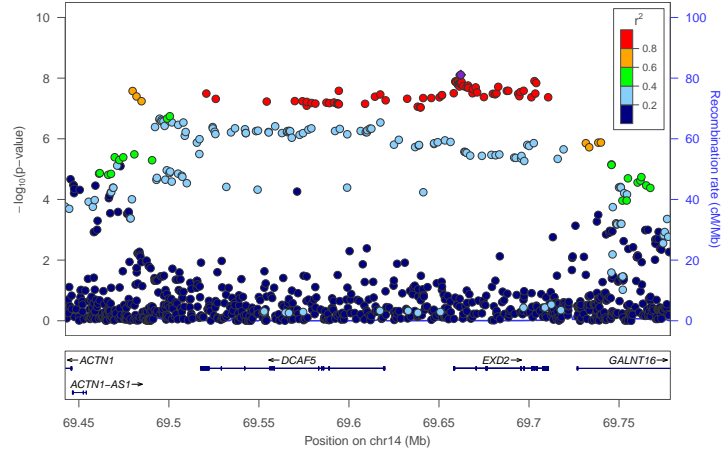
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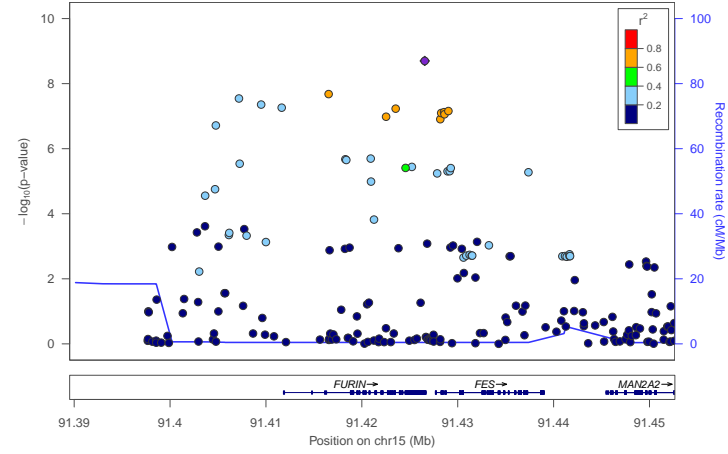
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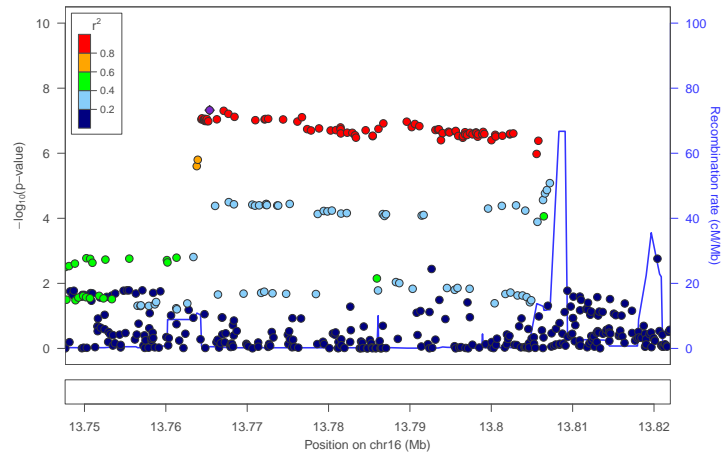
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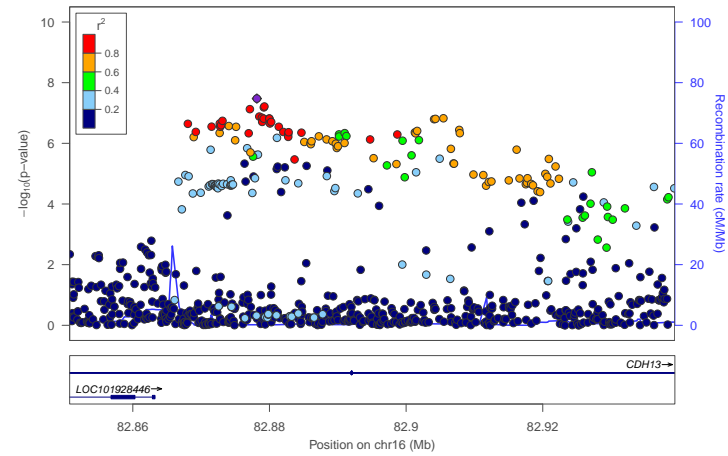
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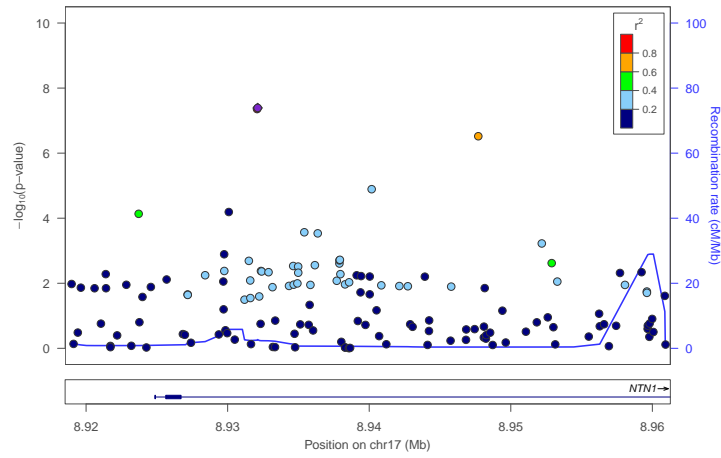
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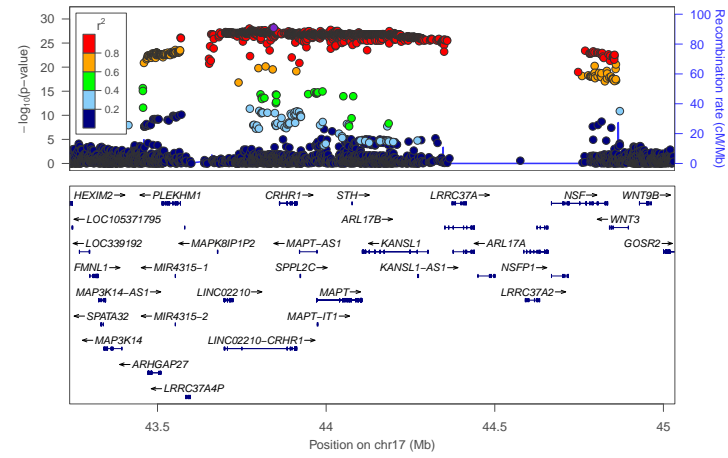
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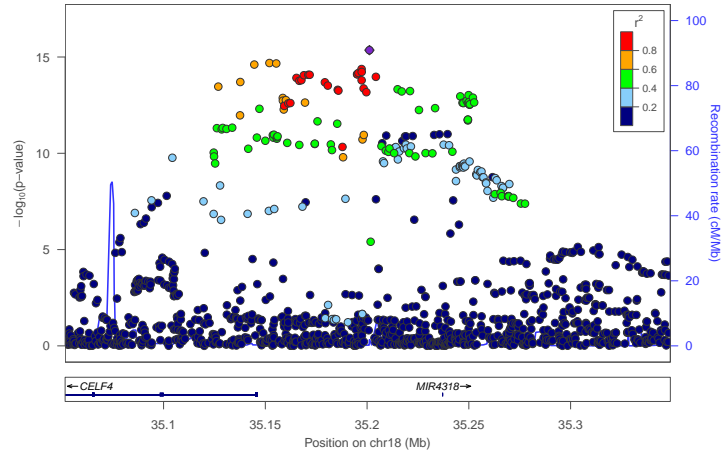
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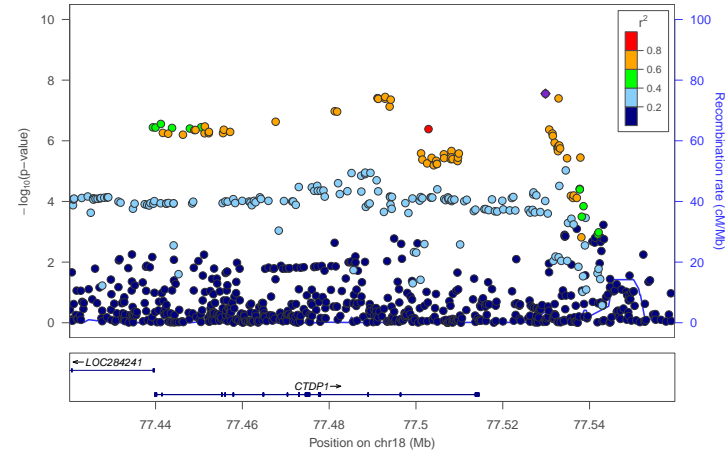
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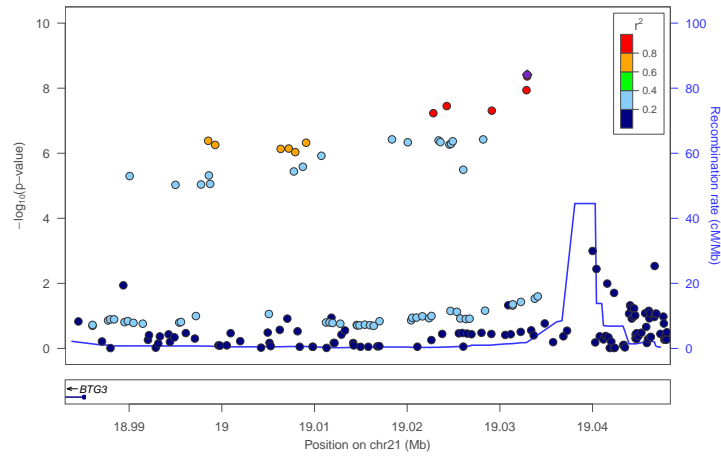
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rs545853



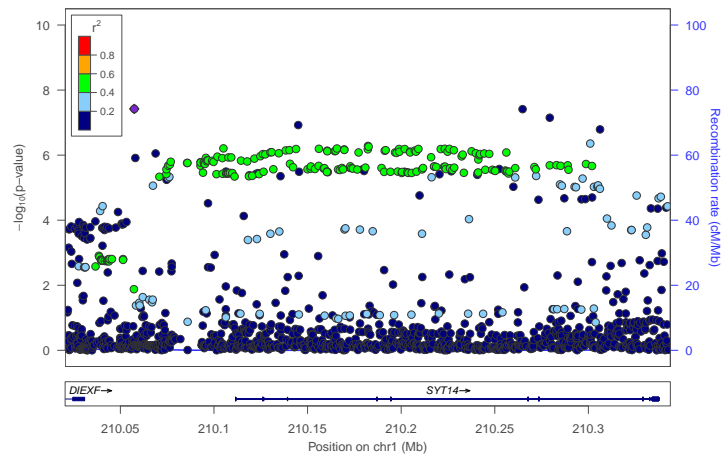
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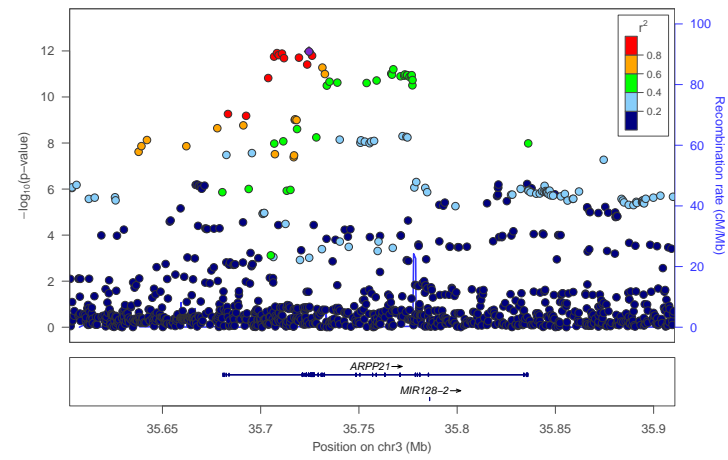
Supplementary Figure 14. Regional plots of GWA analyses of item HURT.

The y -axis represents the negative logarithm (base 10) of the SNP P value and the x -axis the position on the chromosome, with the name and location of genes in the UCSC Genome Browser in the bottom panel. The SNP with the lowest P value in the region is marked by a purple diamond. The colors of the other SNPs indicate the r^2 of these SNPs with the lead SNP, with grey color indicating SNPs below the user-defined r^2 . Plots are generated with LocusZoom. See **Supplementary Data 2** for an overview of all lead SNPs for which a regional plot is presented above.

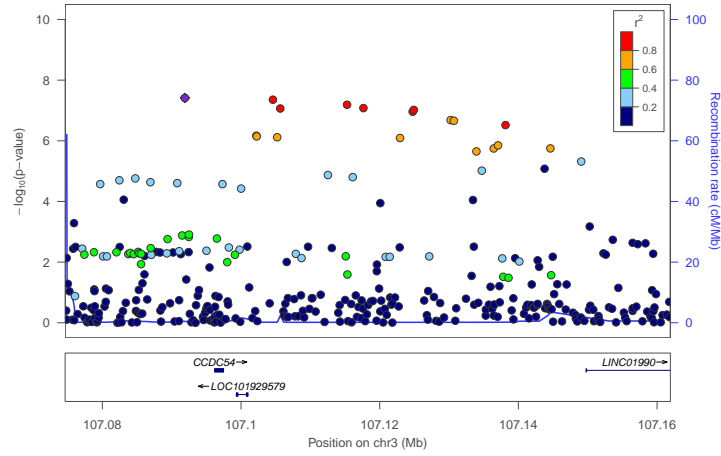
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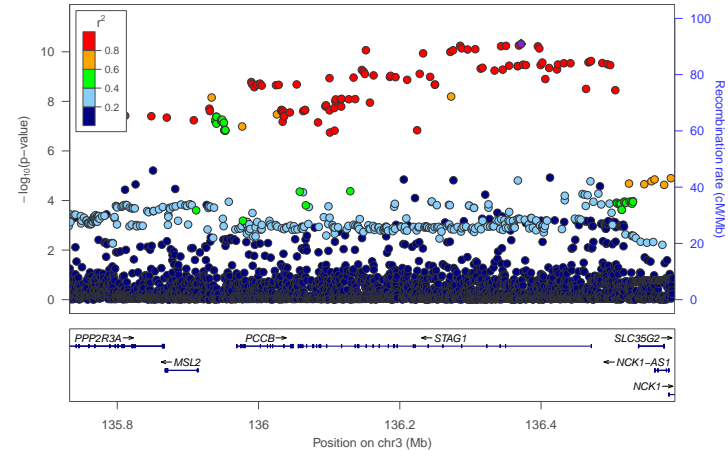
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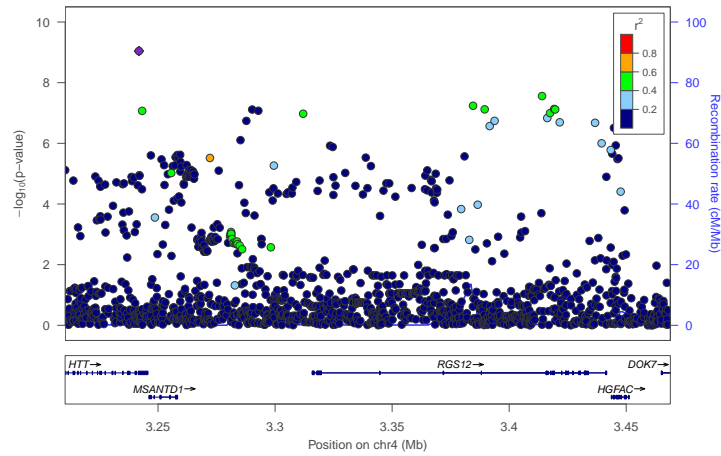
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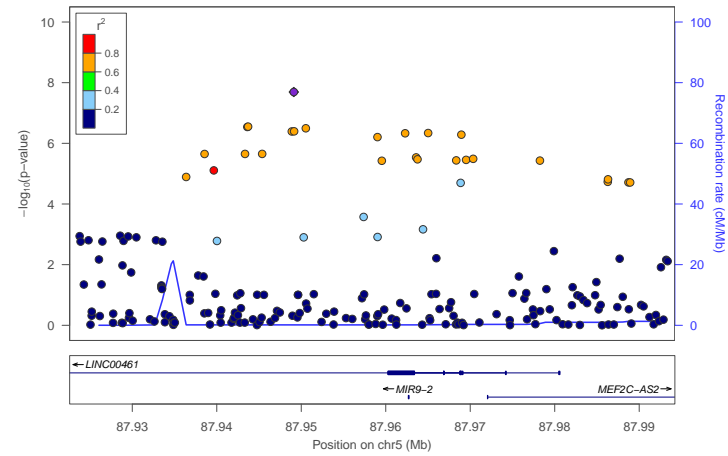
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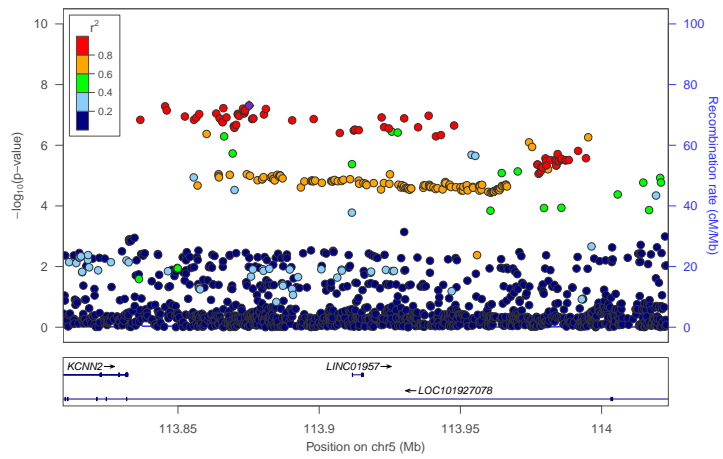
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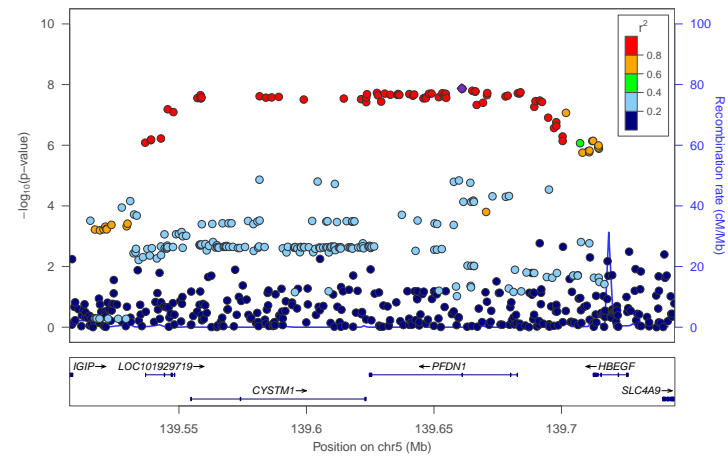
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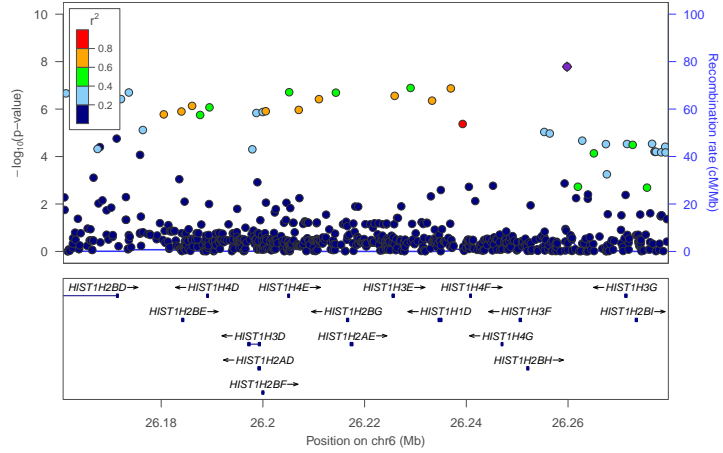
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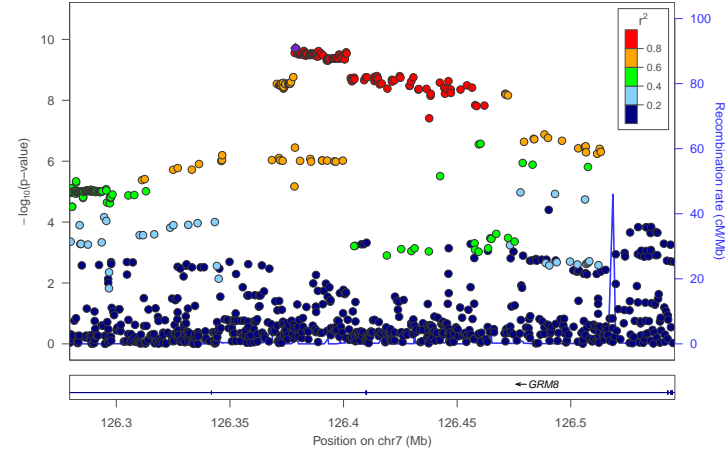
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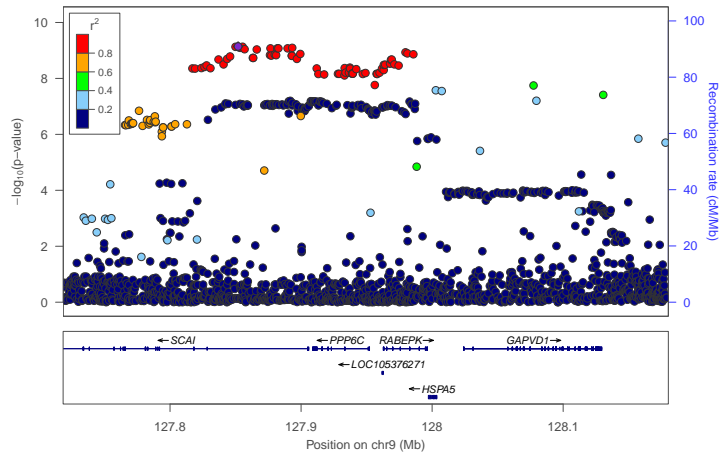
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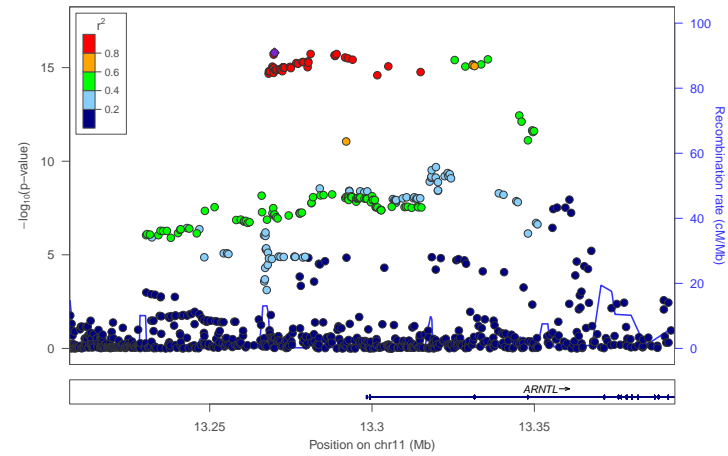
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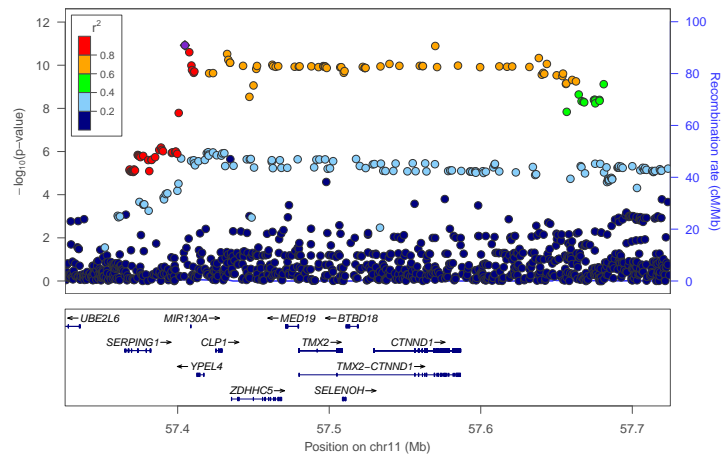
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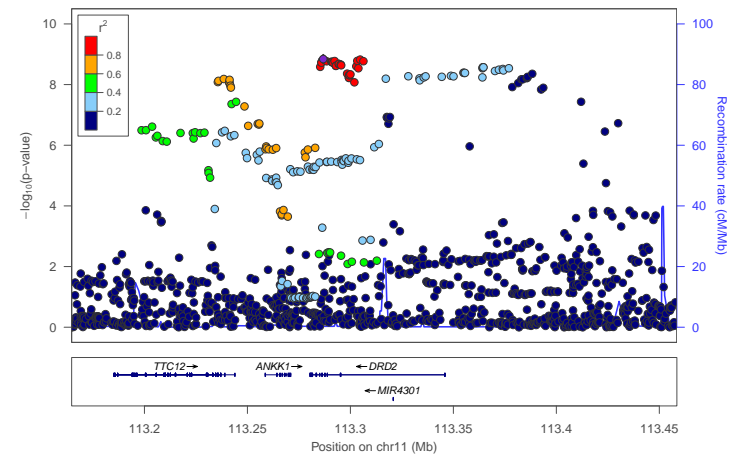
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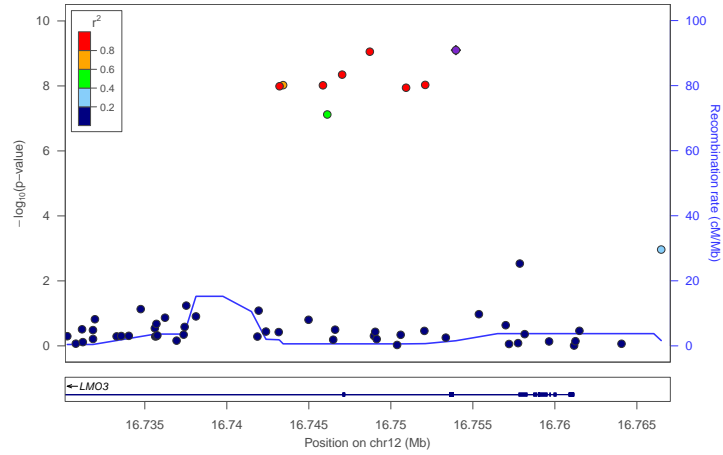
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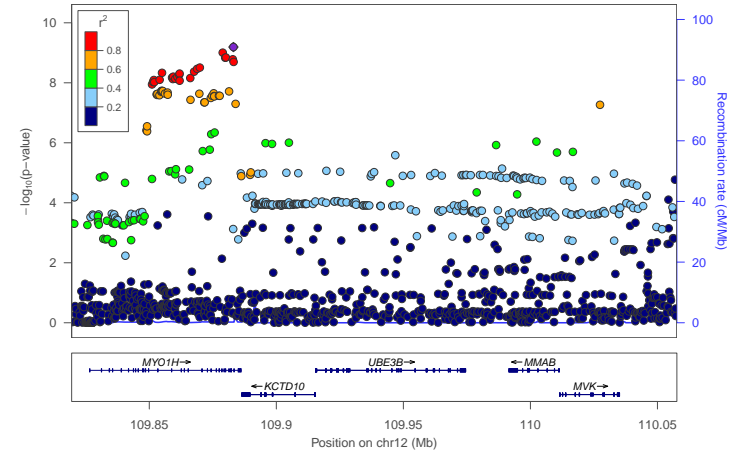
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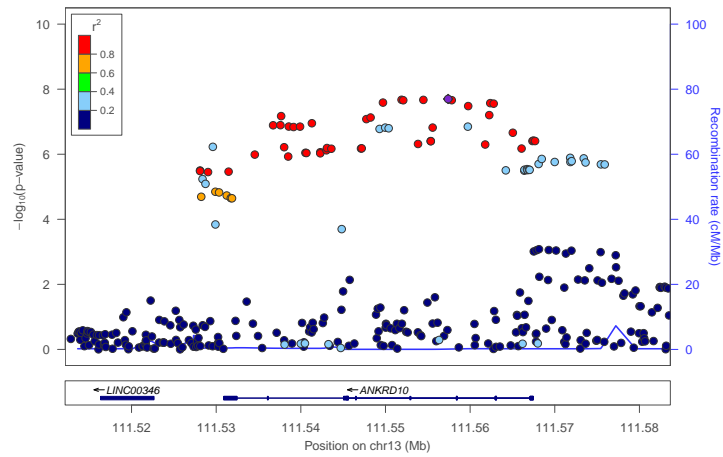
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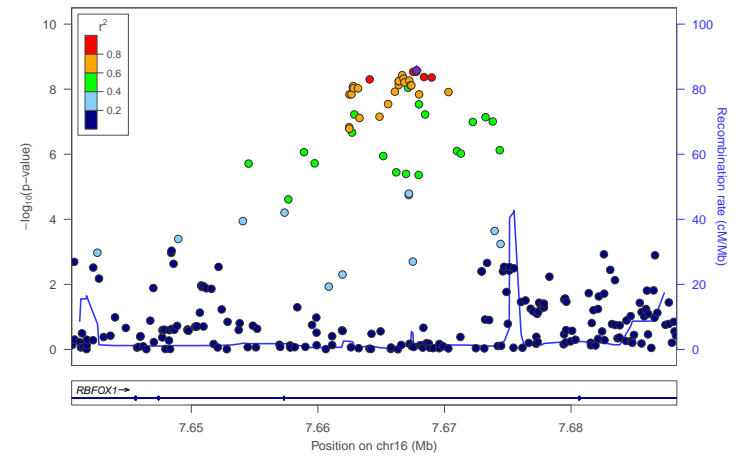
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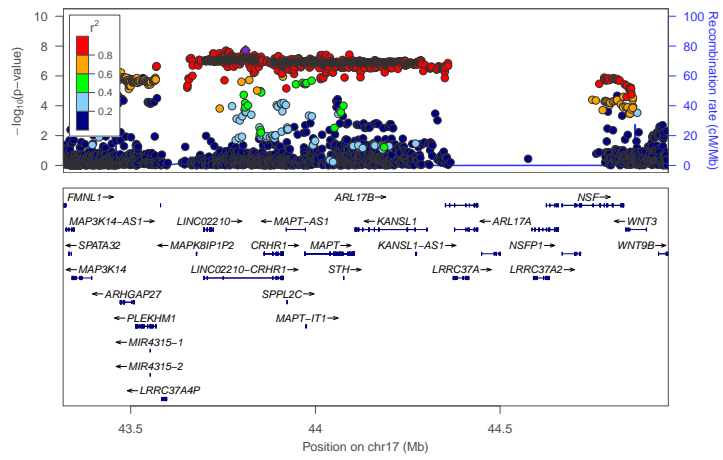
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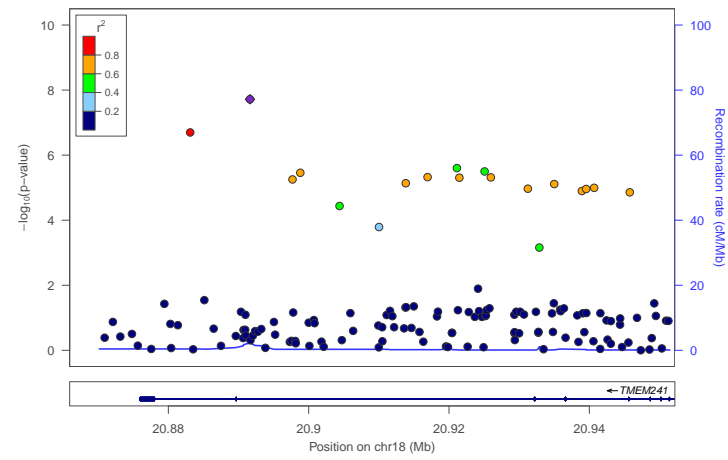
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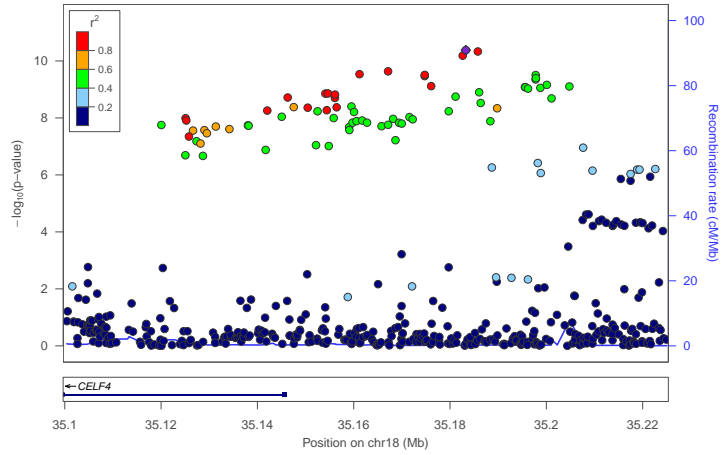
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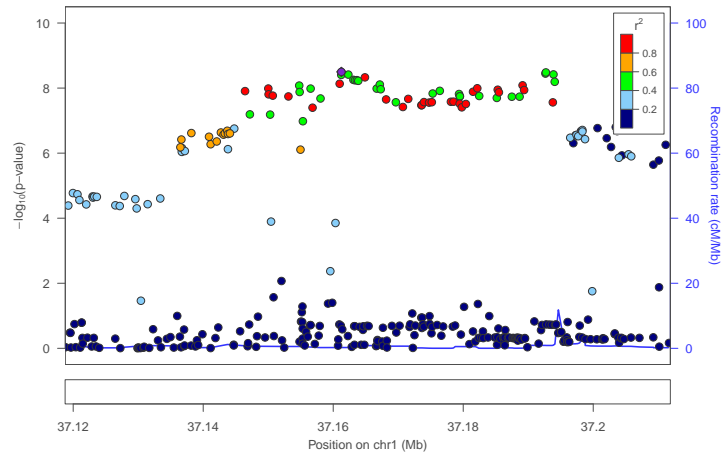
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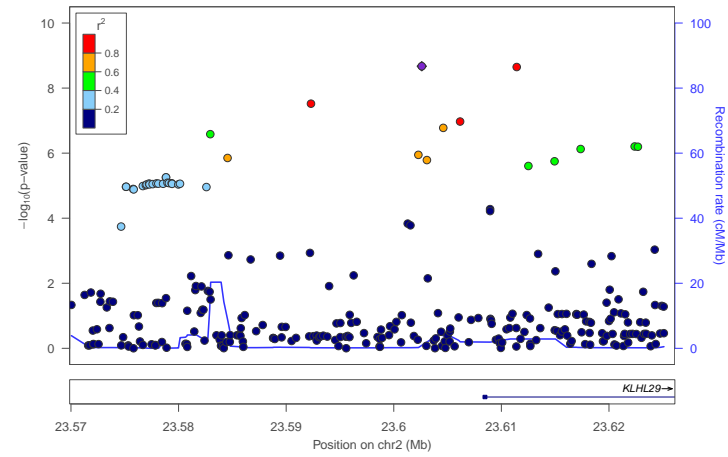
Supplementary Figure 15. Regional plots of GWA analyses of item WORR-EMB.

The y -axis represents the negative logarithm (base 10) of the SNP P value and the x -axis the position on the chromosome, with the name and location of genes in the UCSC Genome Browser in the bottom panel. The SNP with the lowest P value in the region is marked by a purple diamond. The colors of the other SNPs indicate the r^2 of these SNPs with the lead SNP, with grey color indicating SNPs below the user-defined r^2 . Plots are generated with LocusZoom. See **Supplementary Data 2** for an overview of all lead SNPs for which a regional plot is presented above.

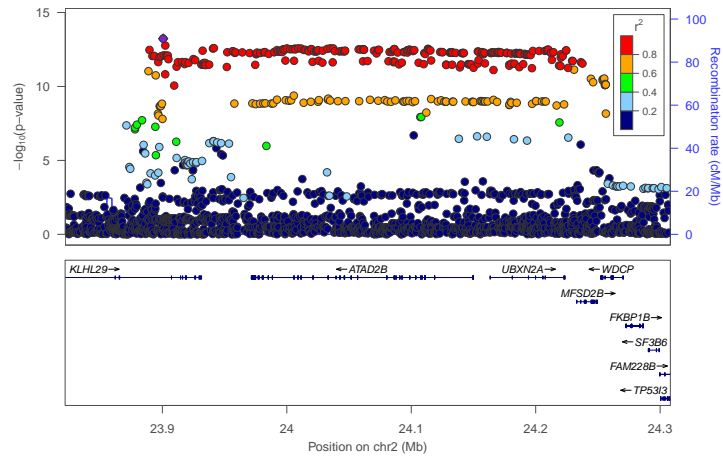
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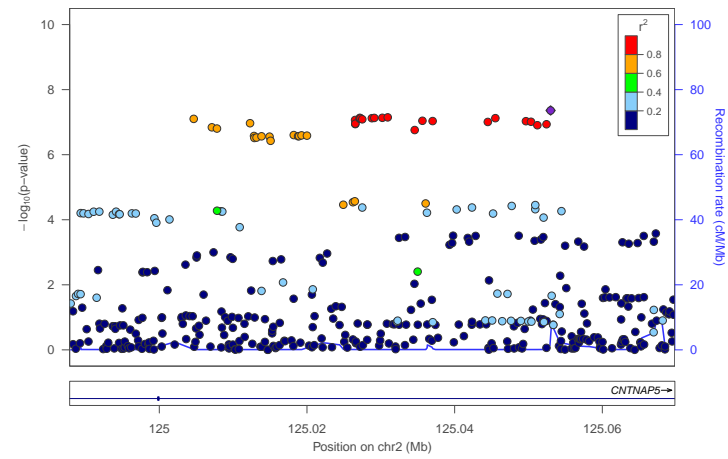
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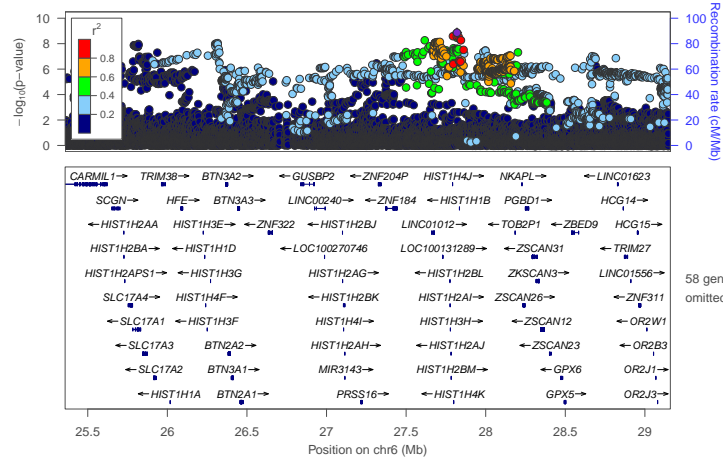
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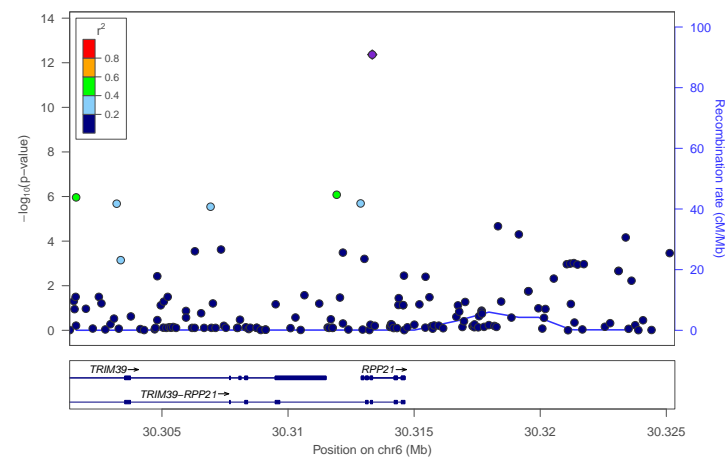
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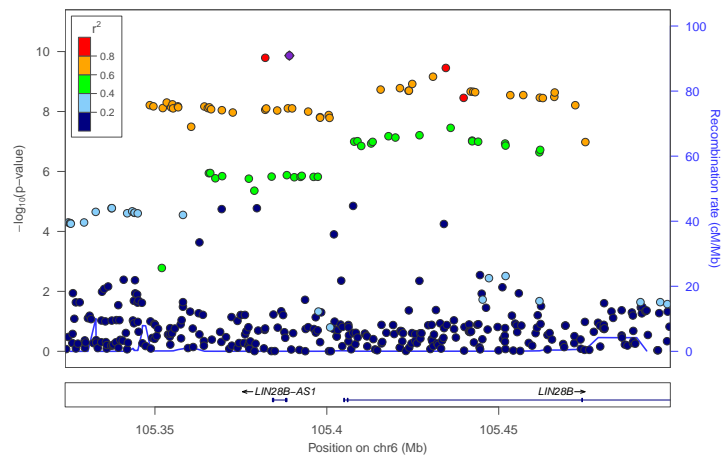
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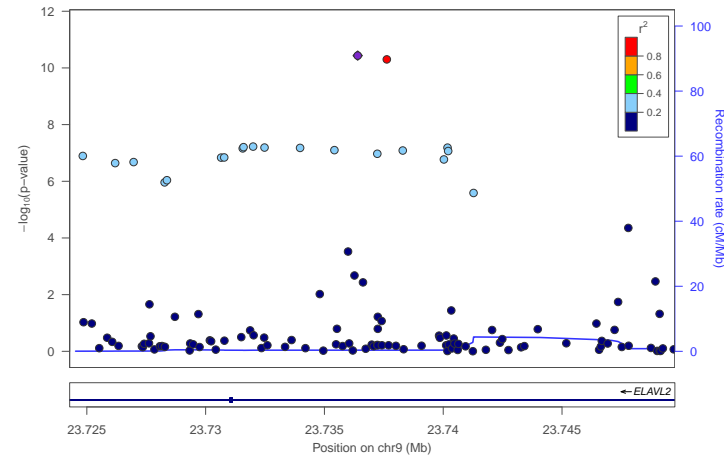
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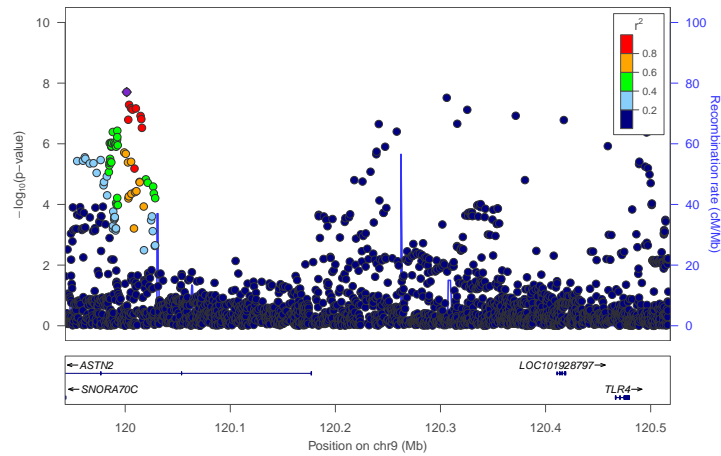
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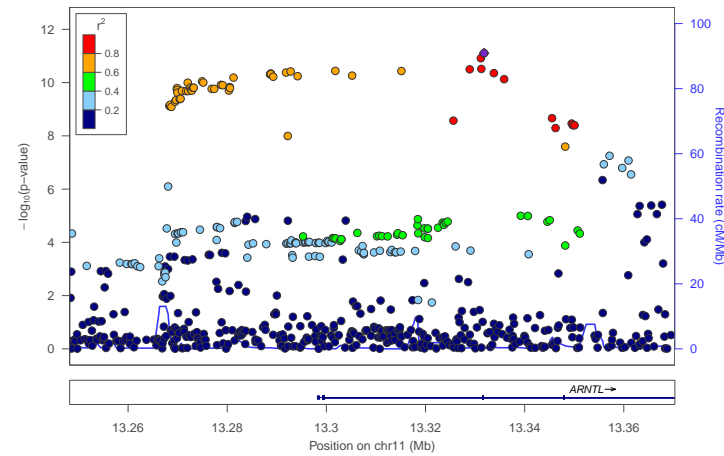
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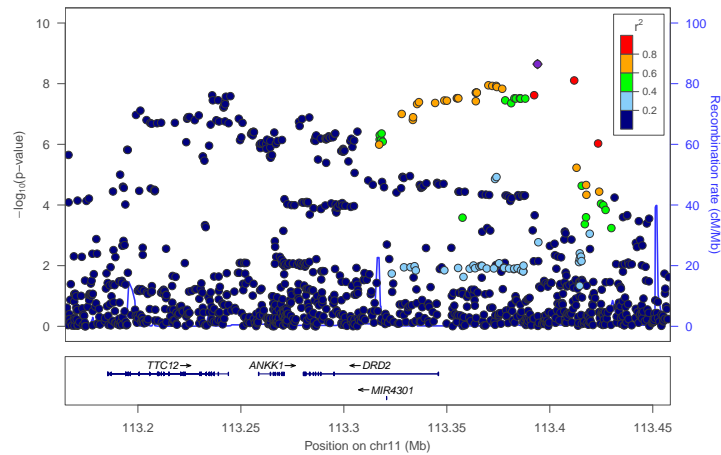
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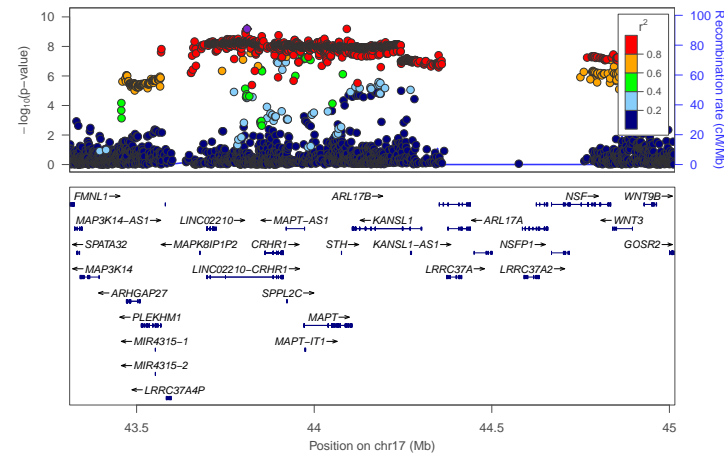
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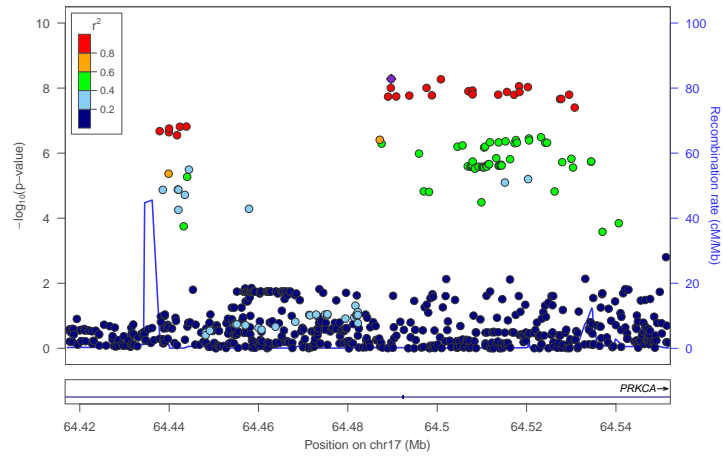
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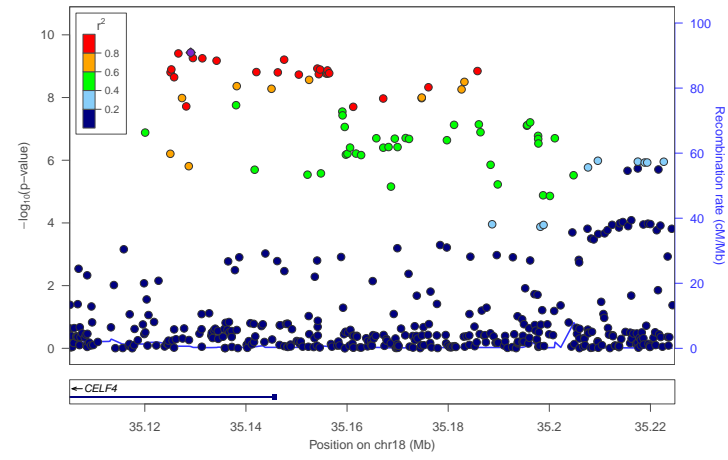
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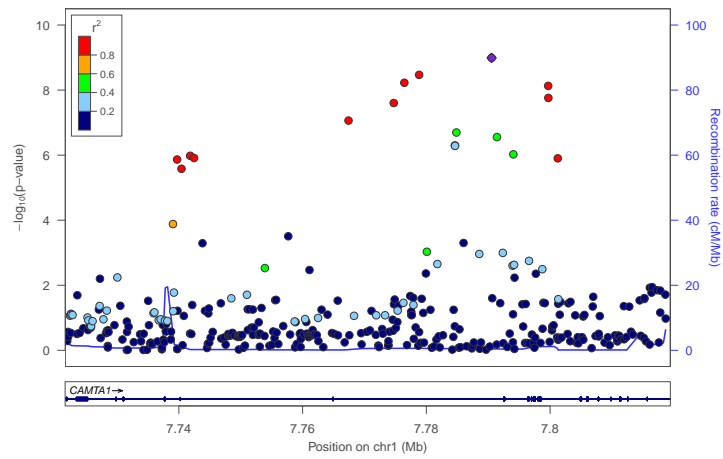
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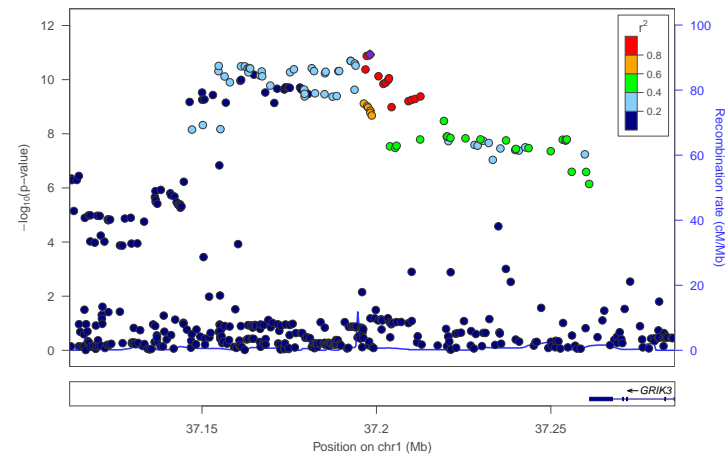
Supplementary Figure 16. Regional plots of GWA analyses of item GUILT.

The y -axis represents the negative logarithm (base 10) of the SNP P value and the x -axis the position on the chromosome, with the name and location of genes in the UCSC Genome Browser in the bottom panel. The SNP with the lowest P value in the region is marked by a purple diamond. The colors of the other SNPs indicate the r^2 of these SNPs with the lead SNP, with grey color indicating SNPs below the user-defined r^2 . Plots are generated with LocusZoom. See **Supplementary Data 2** for an overview of all lead SNPs for which a regional plot is presented above.

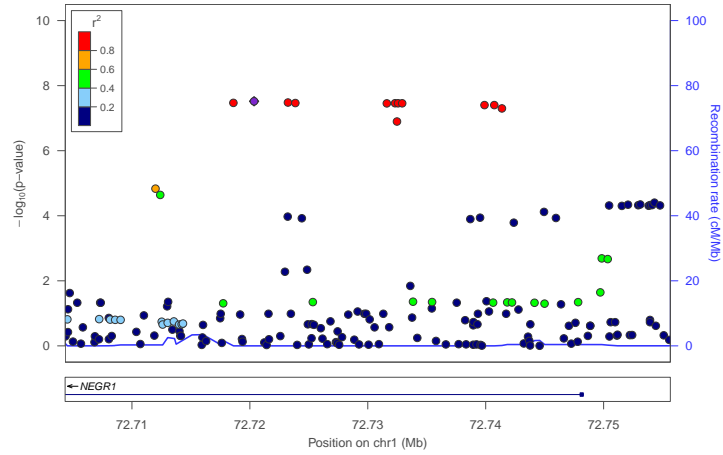
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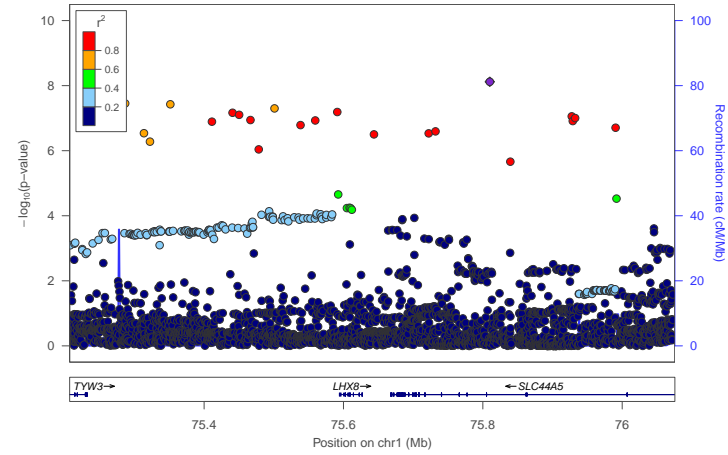
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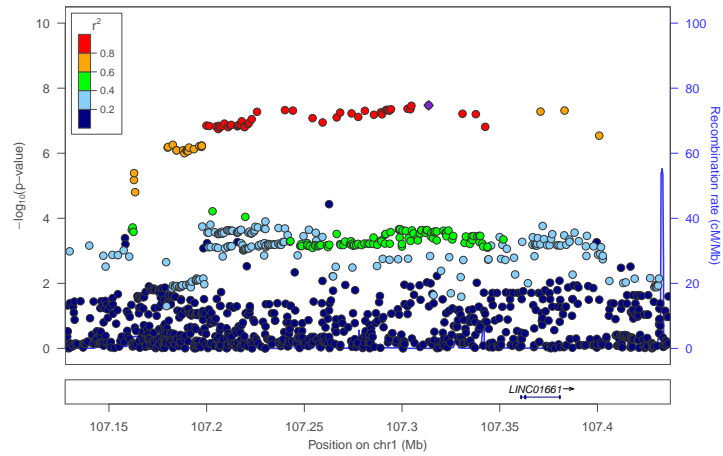
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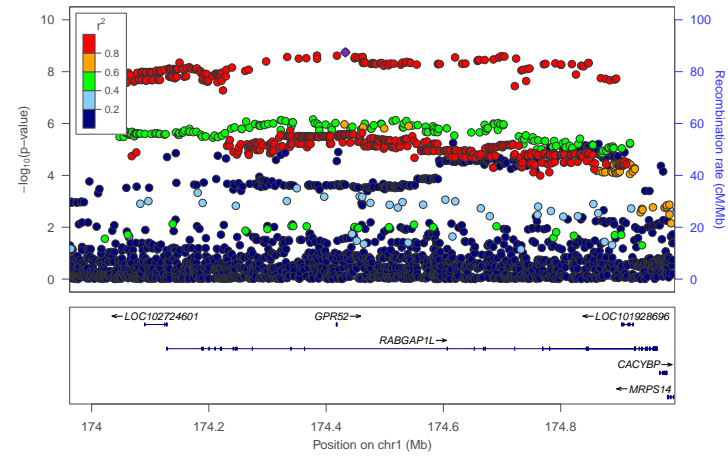
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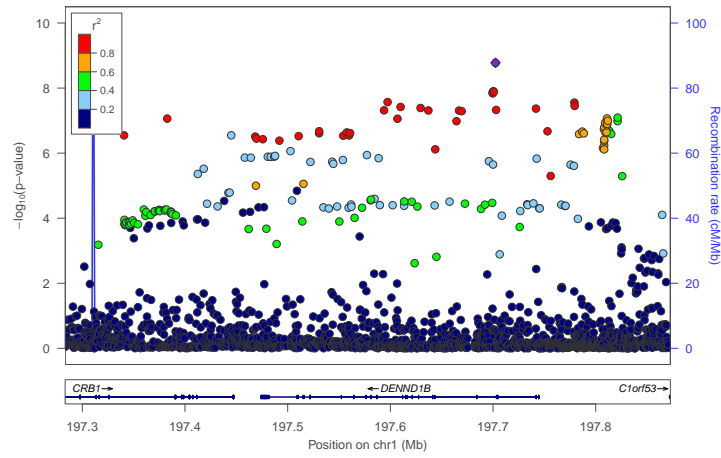
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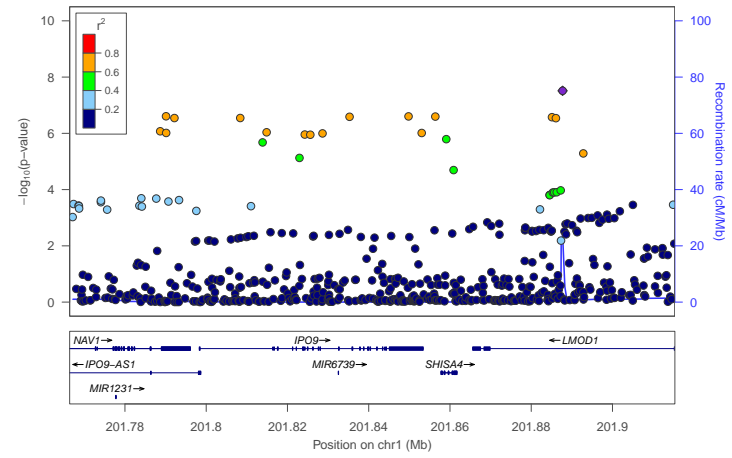
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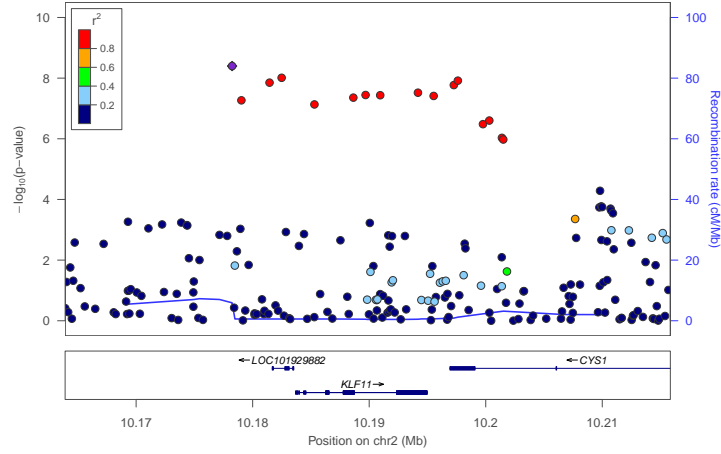
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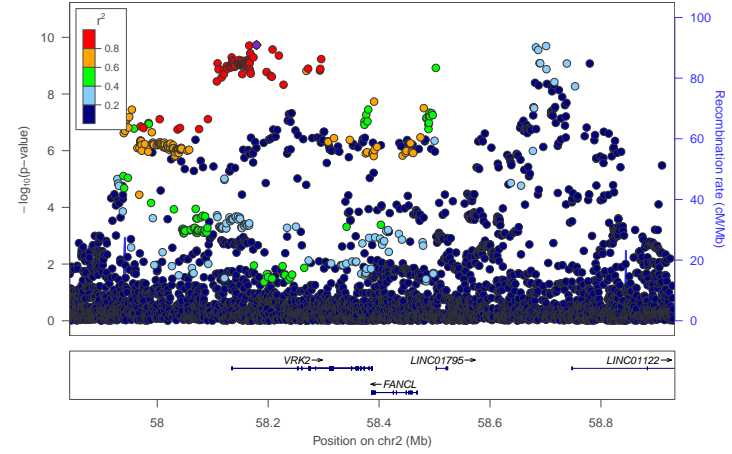
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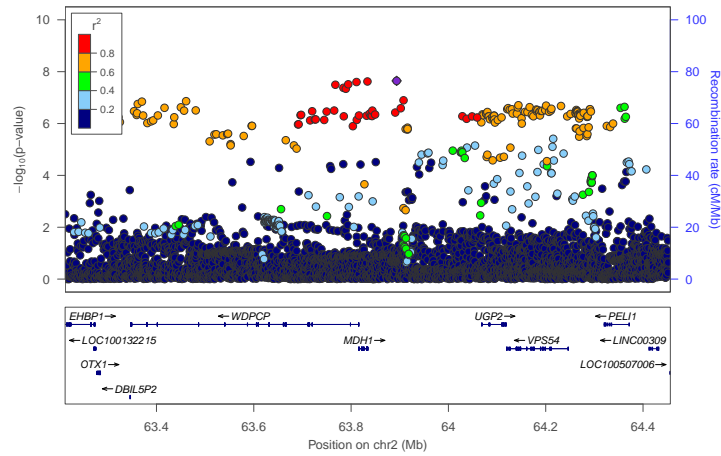
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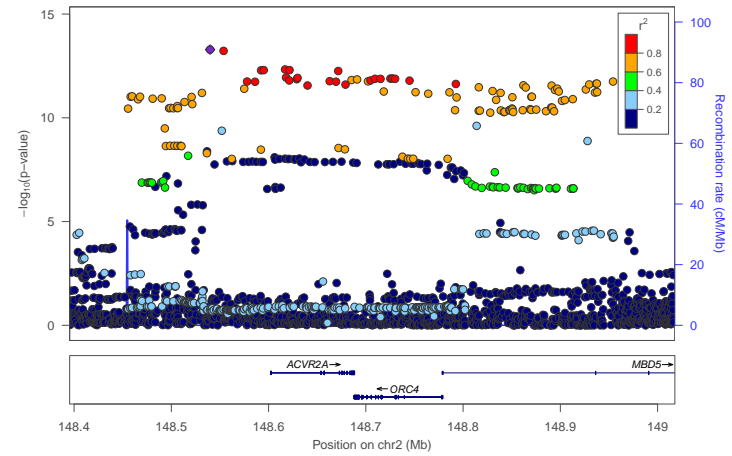
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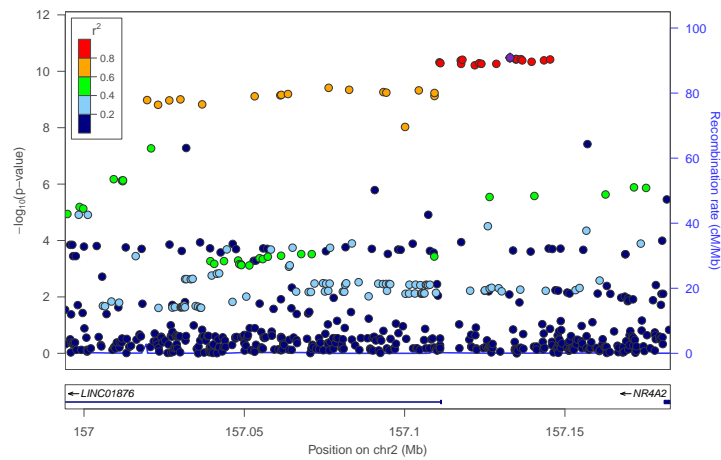
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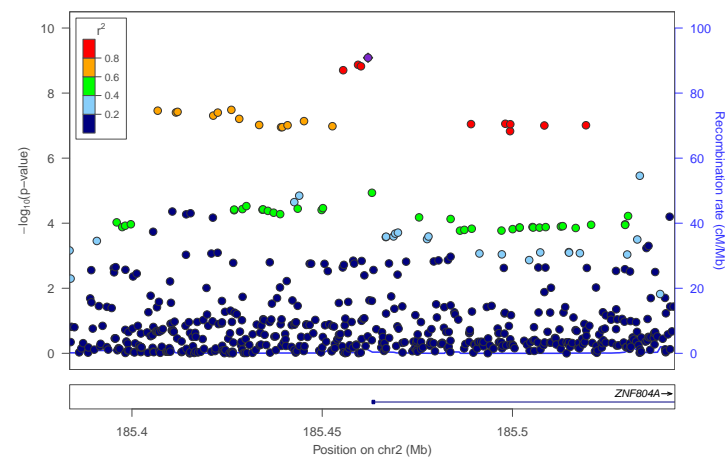
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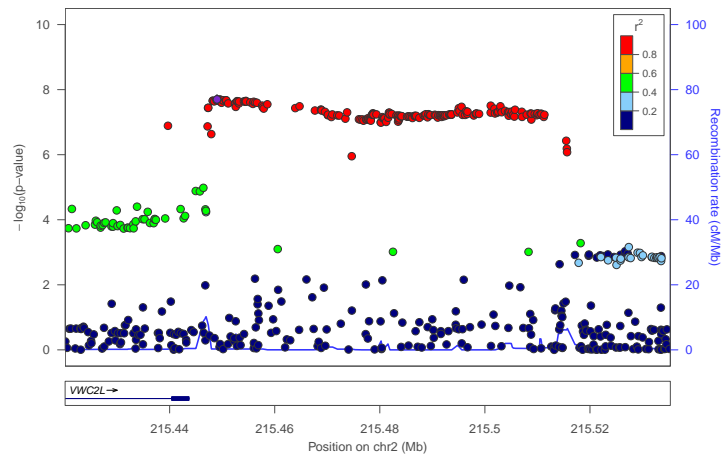
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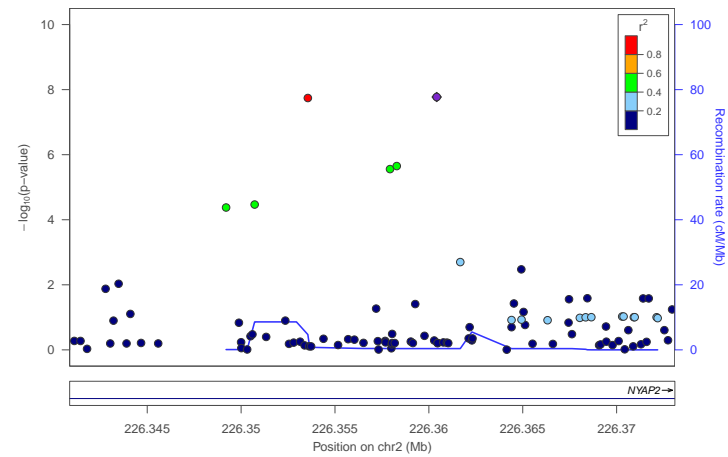
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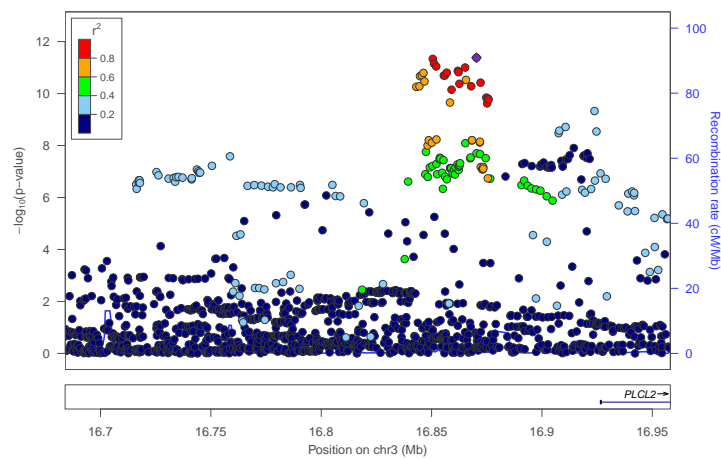
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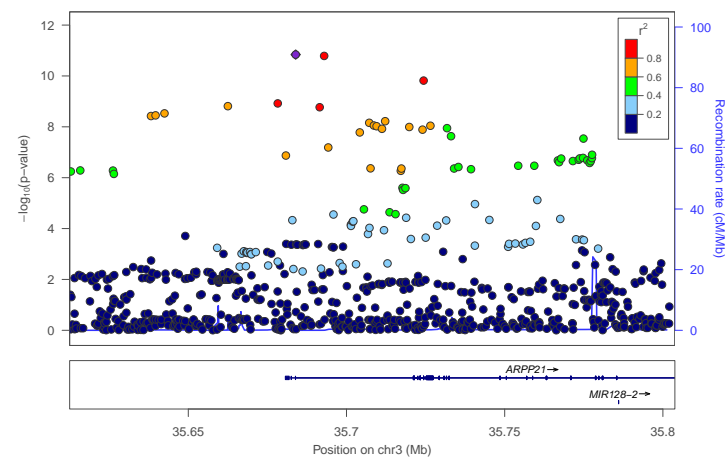
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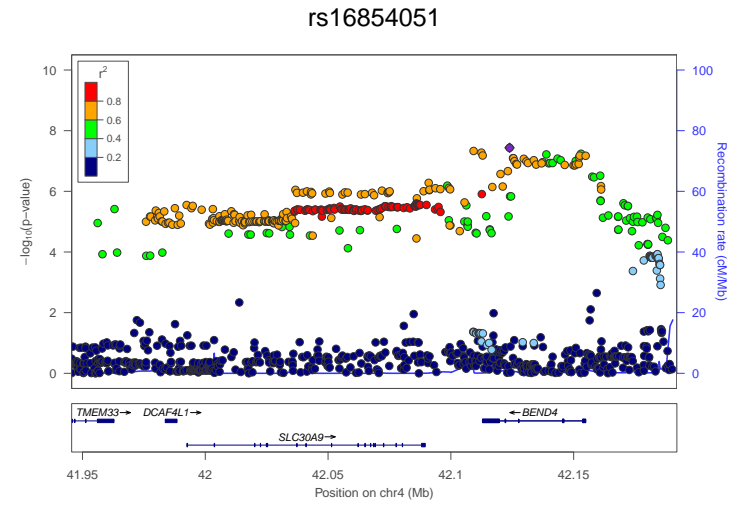
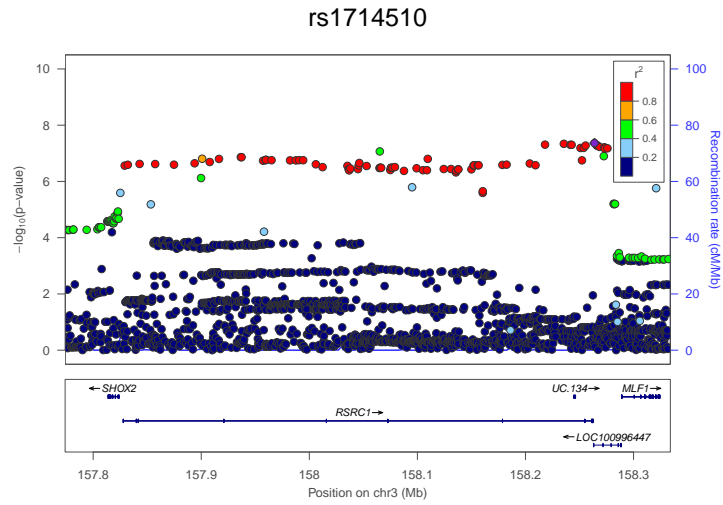
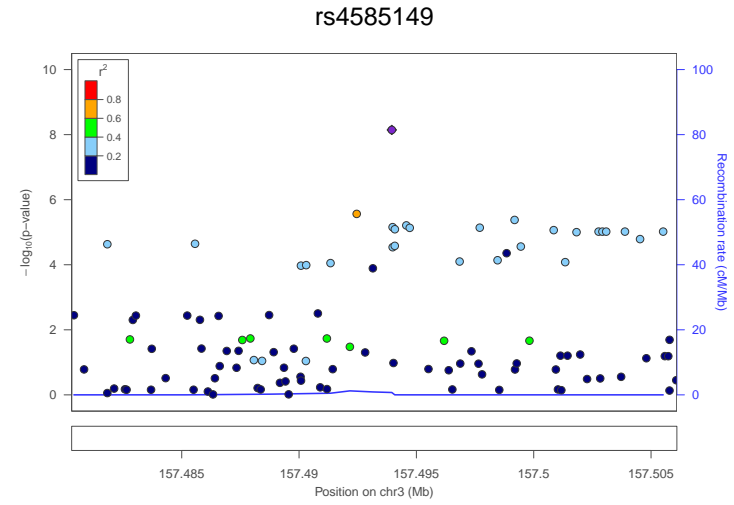
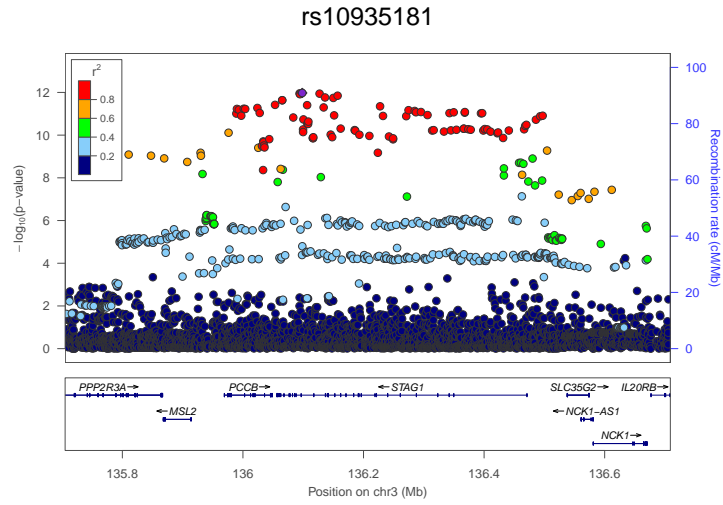
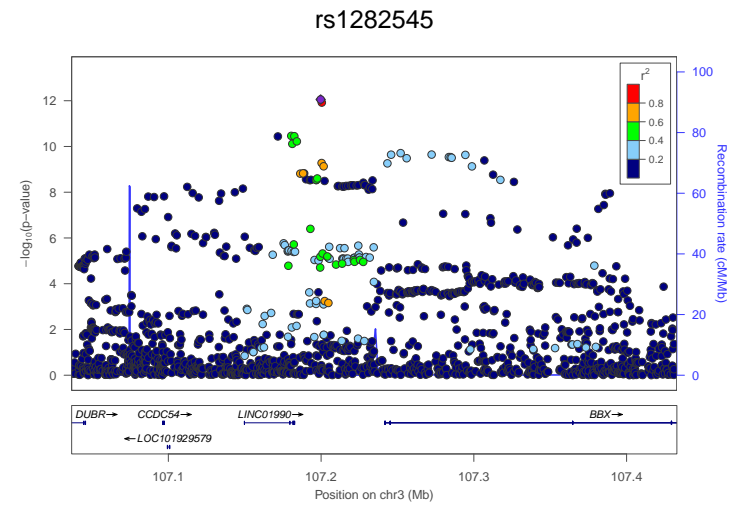
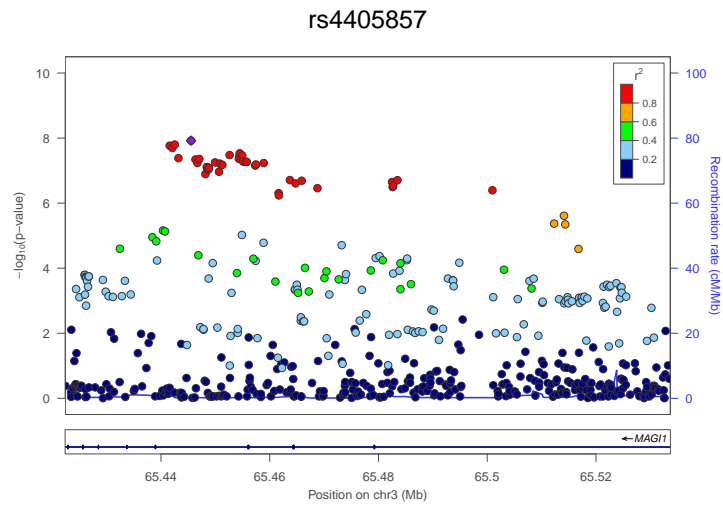


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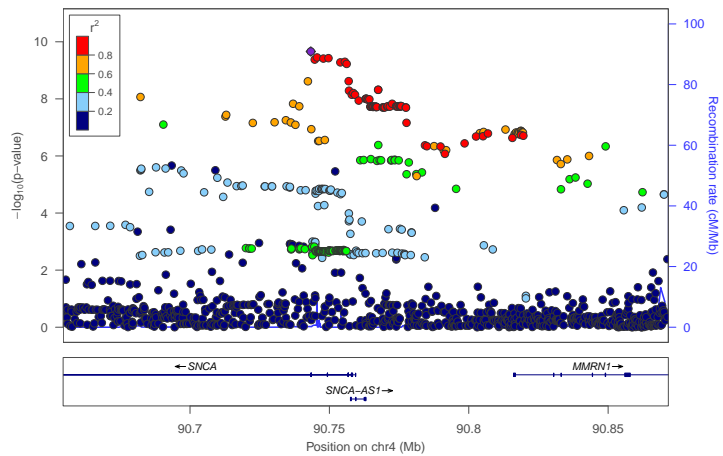


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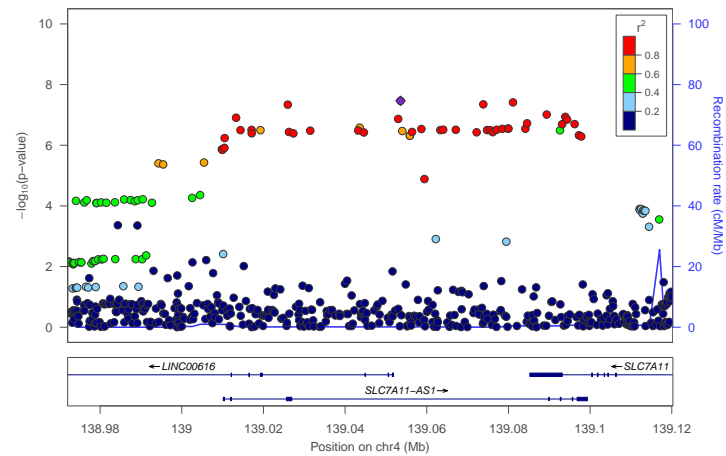




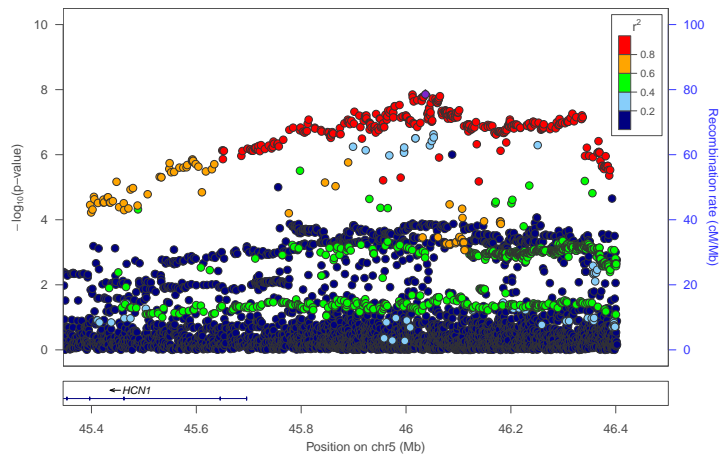
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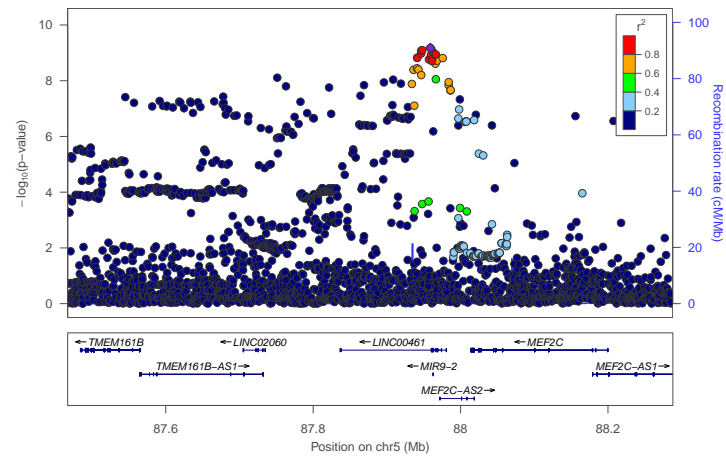
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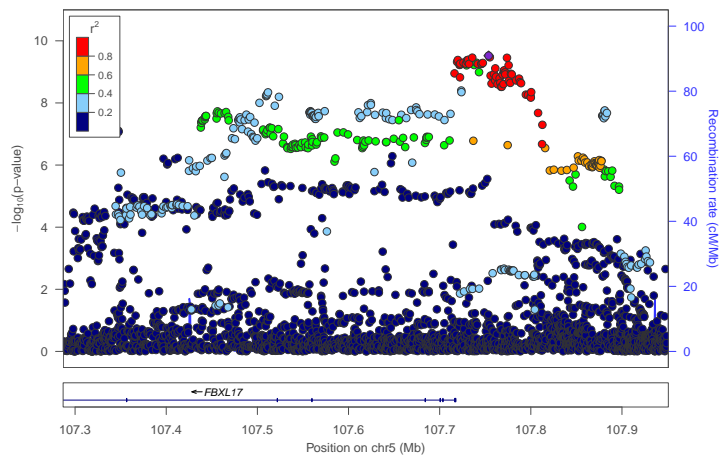
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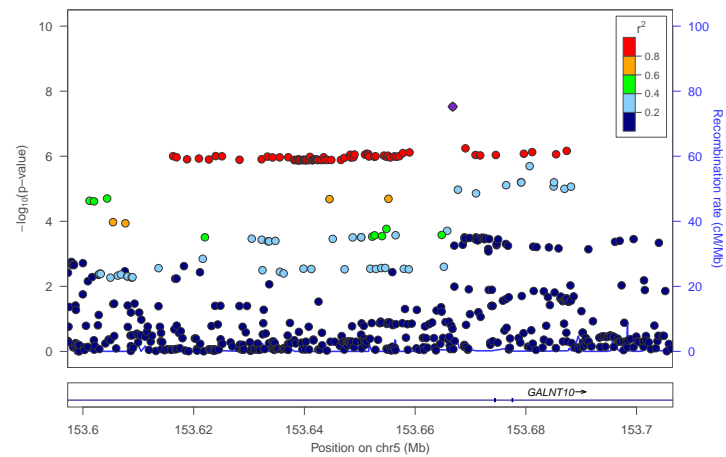
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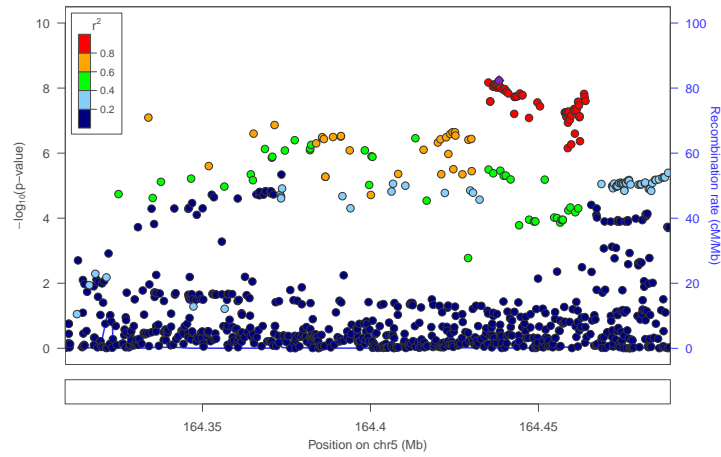
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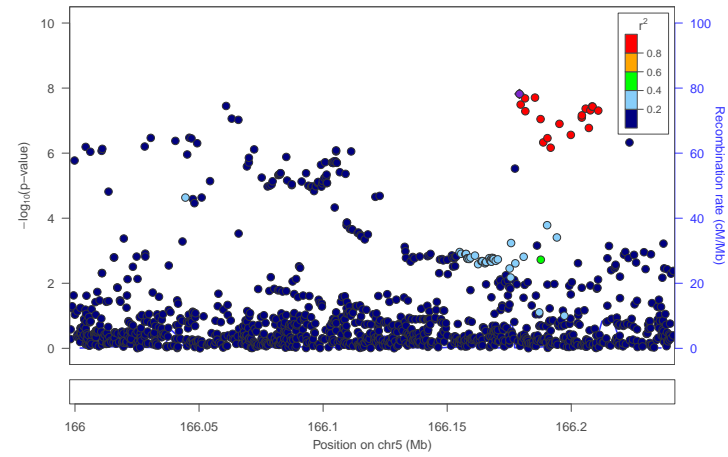
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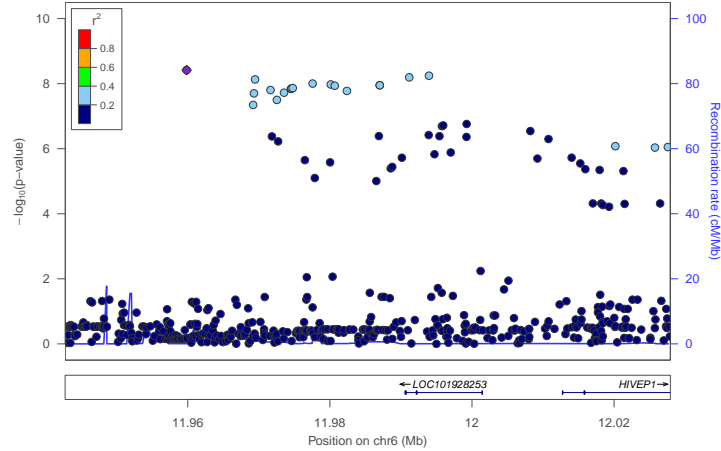
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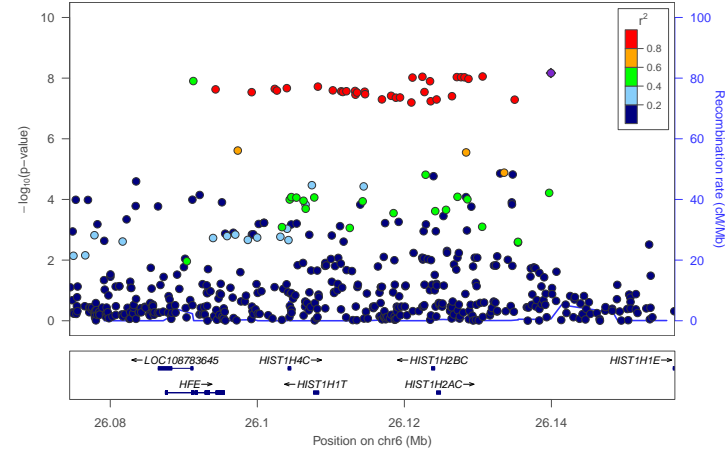
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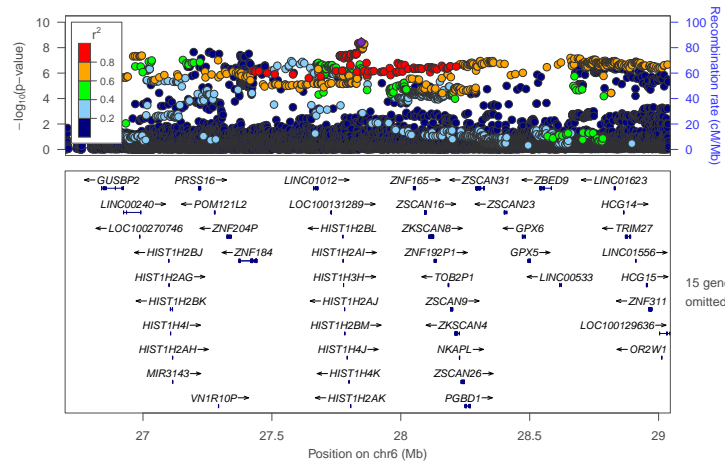
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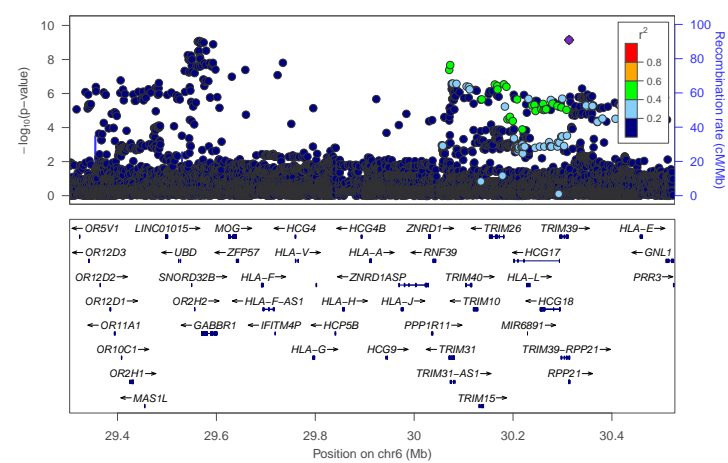
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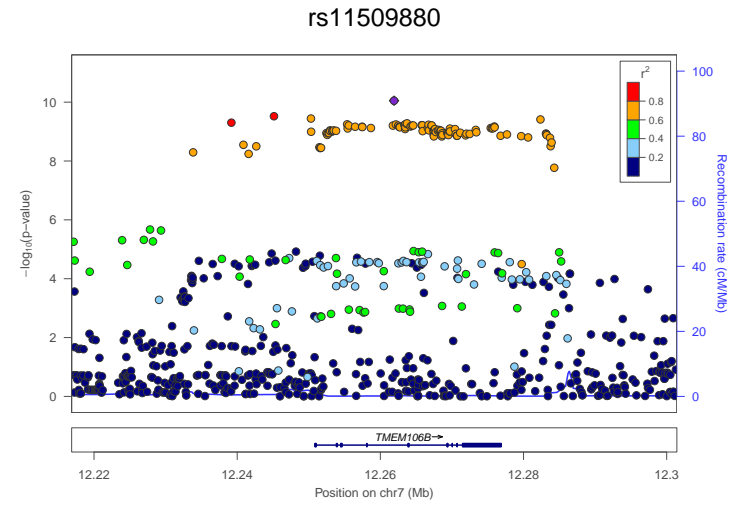
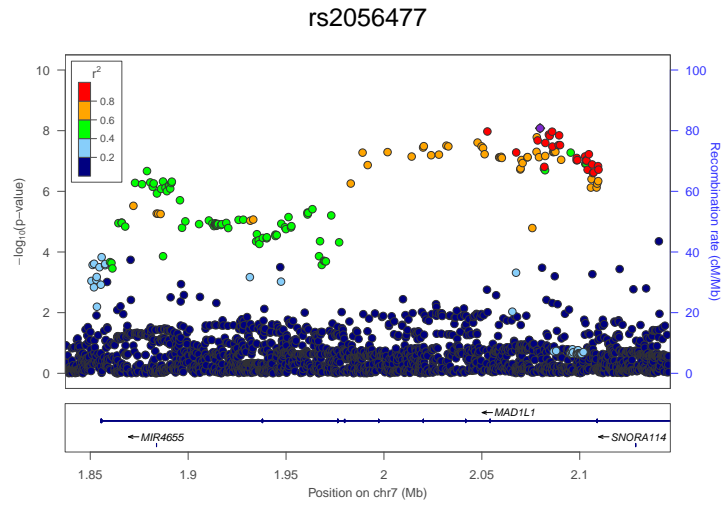
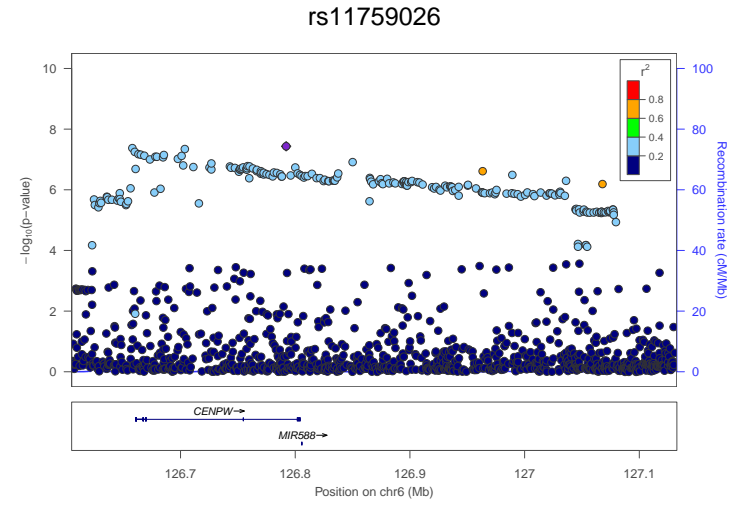
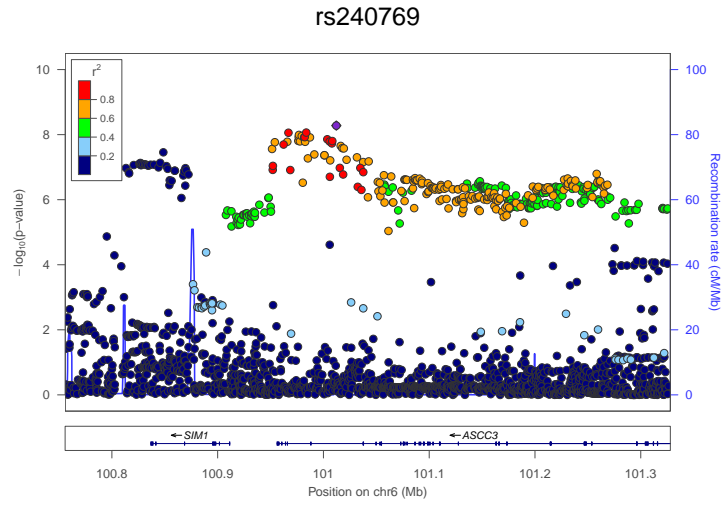
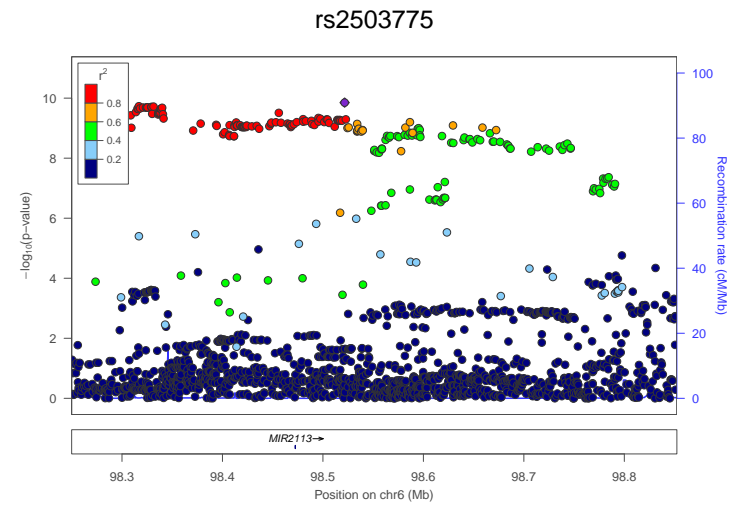
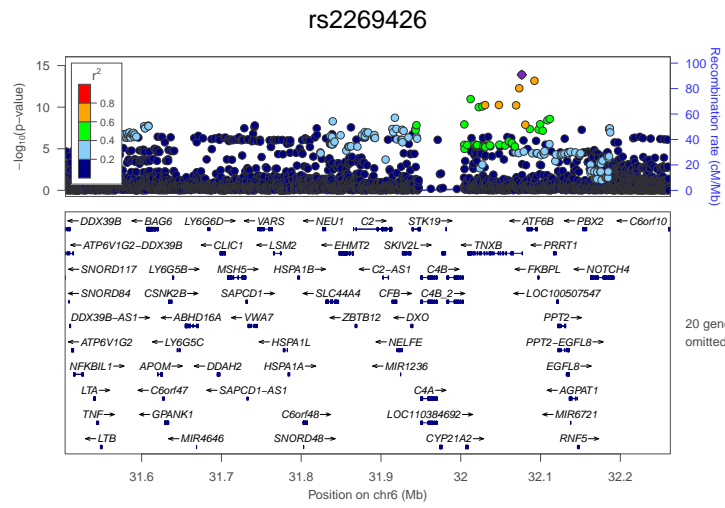


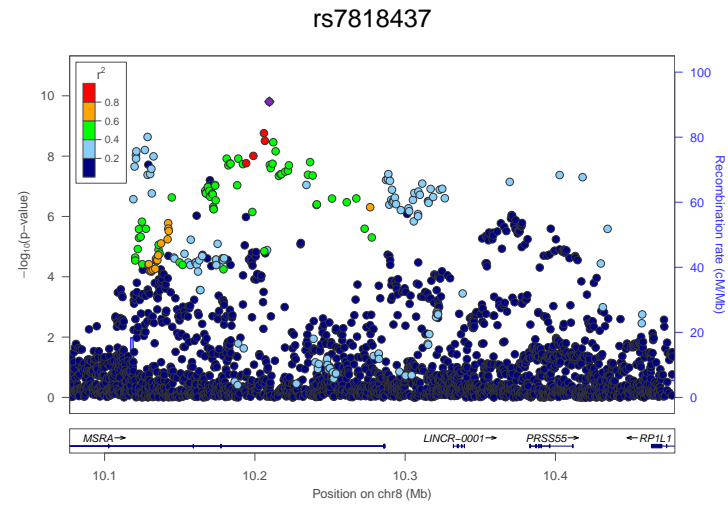
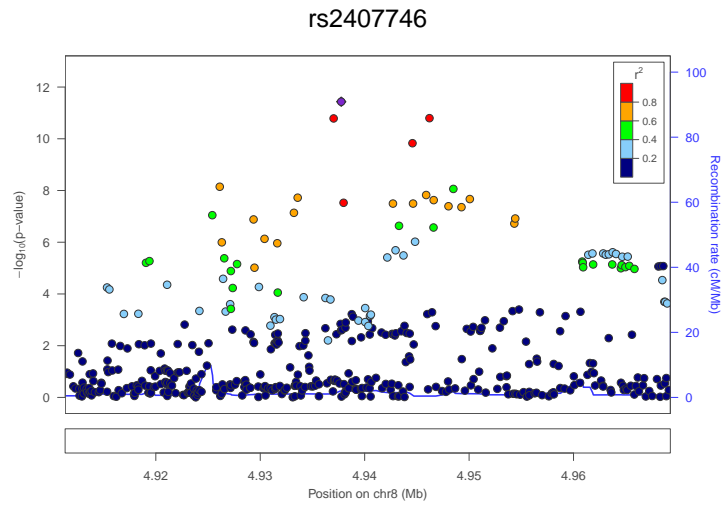
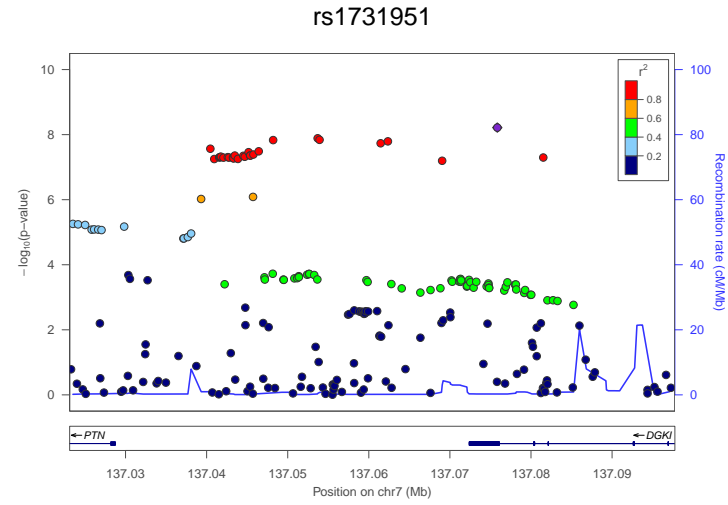
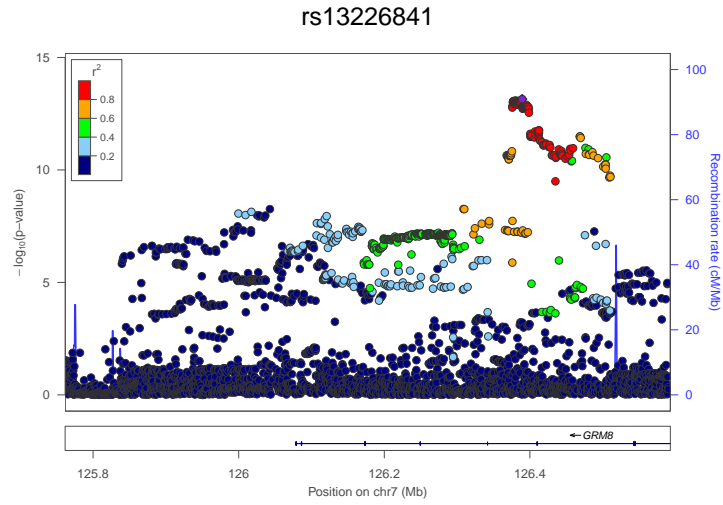
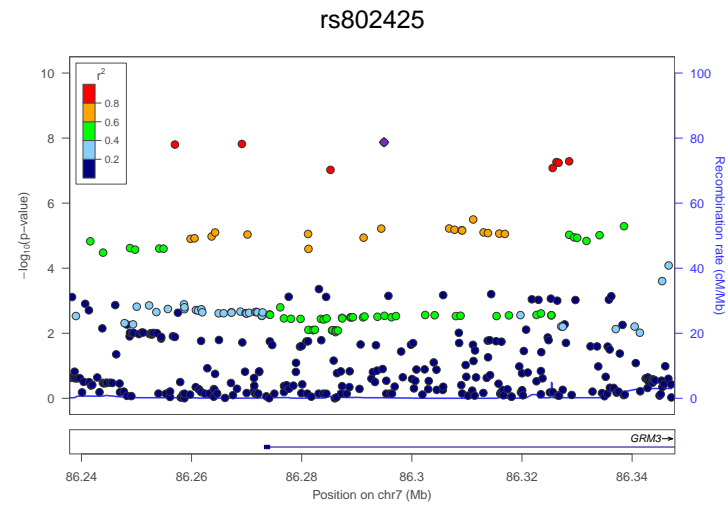
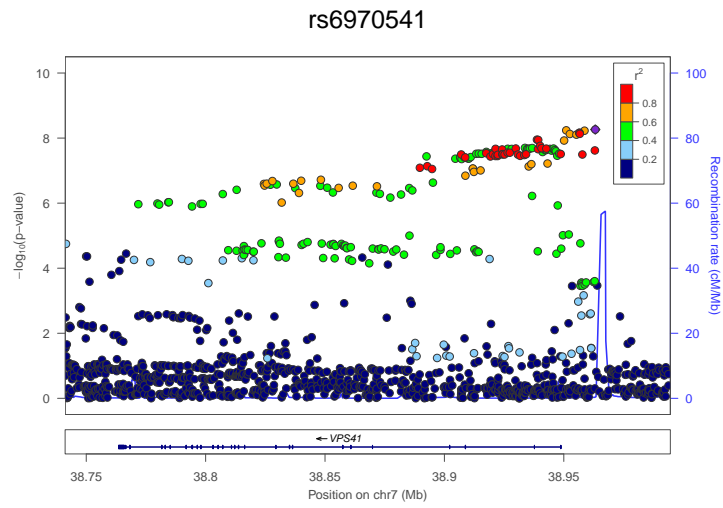
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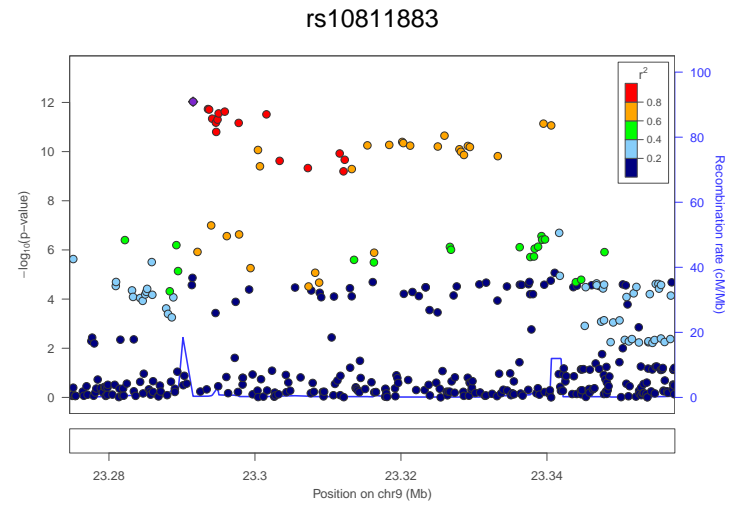
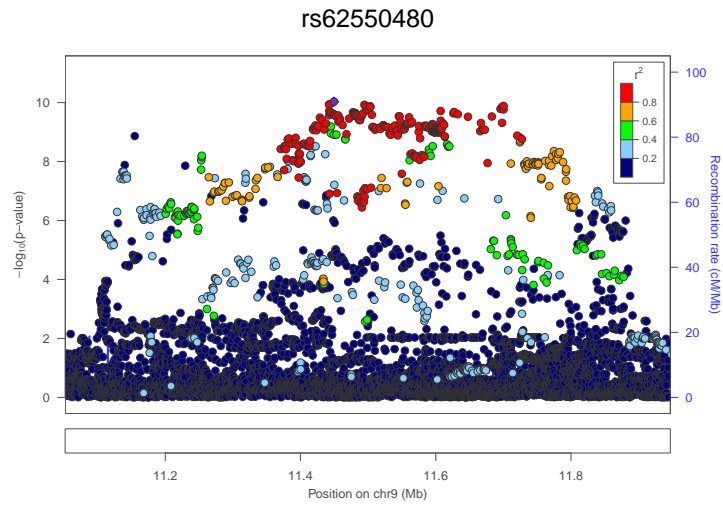
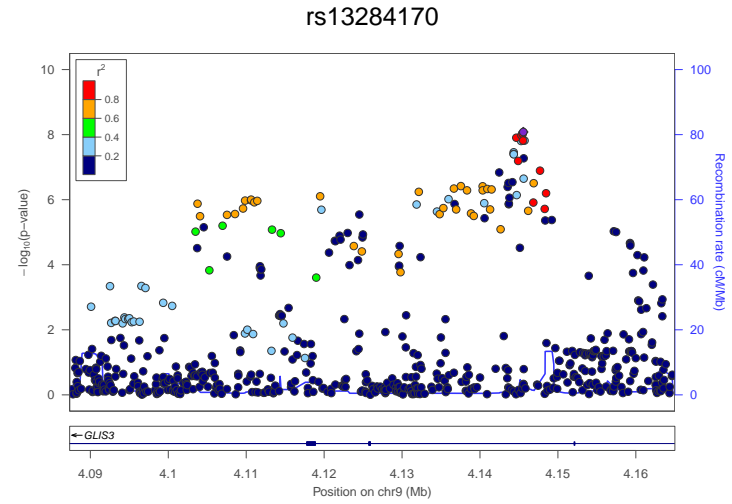
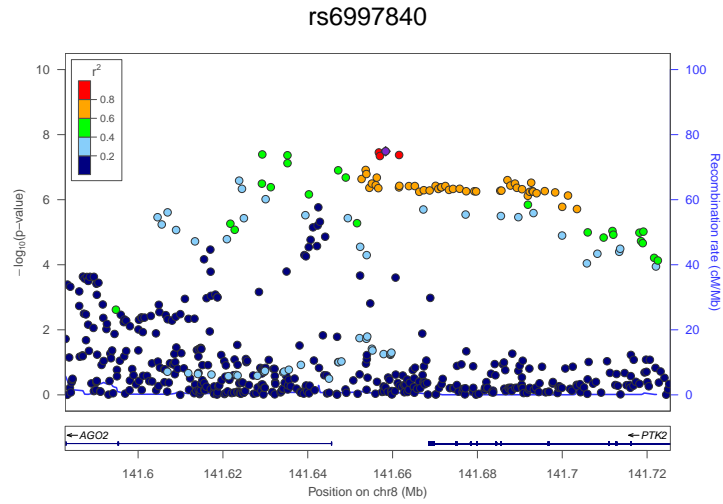
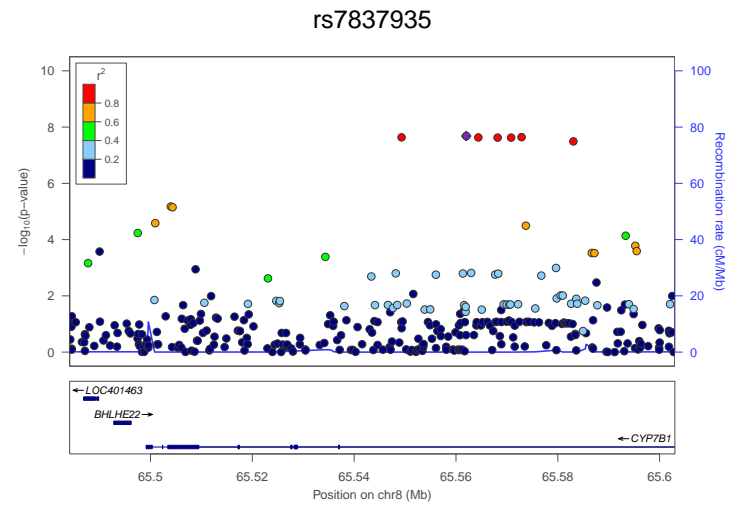
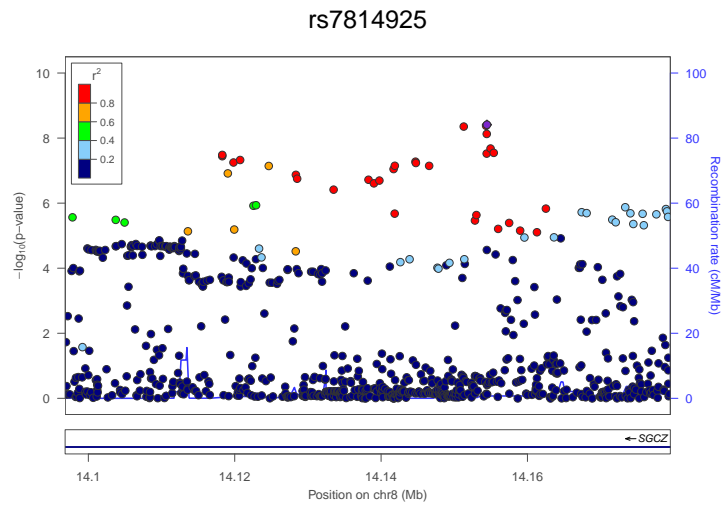


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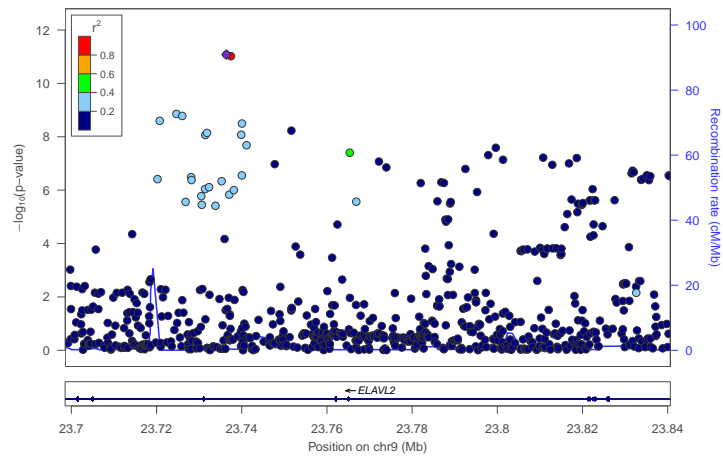




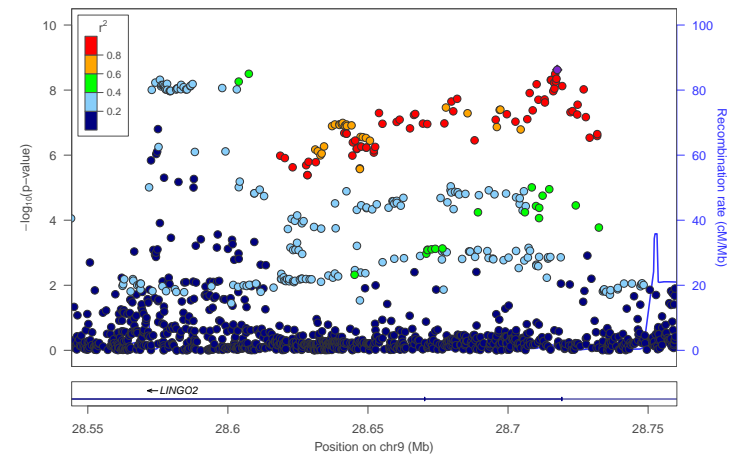




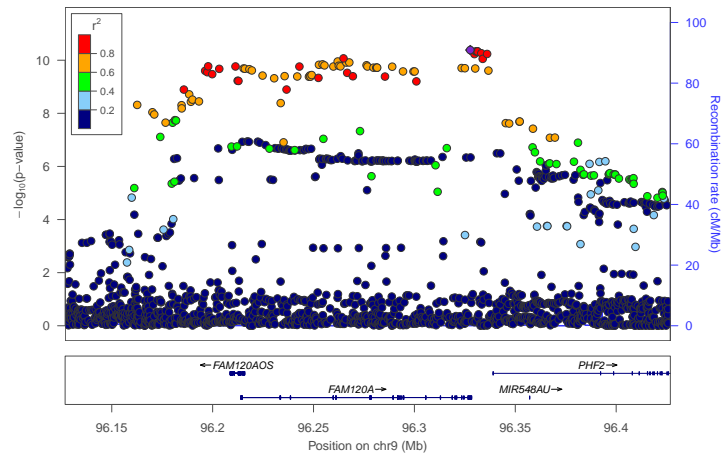
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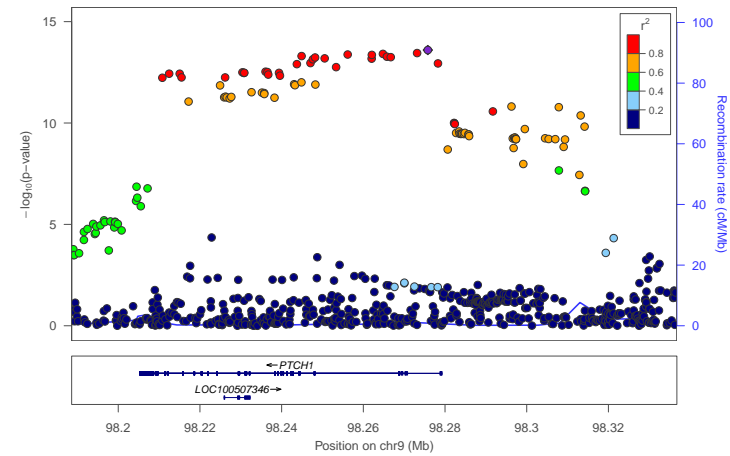
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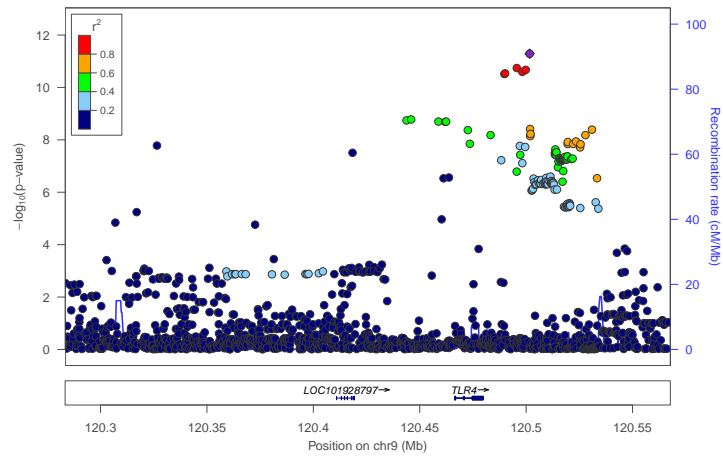
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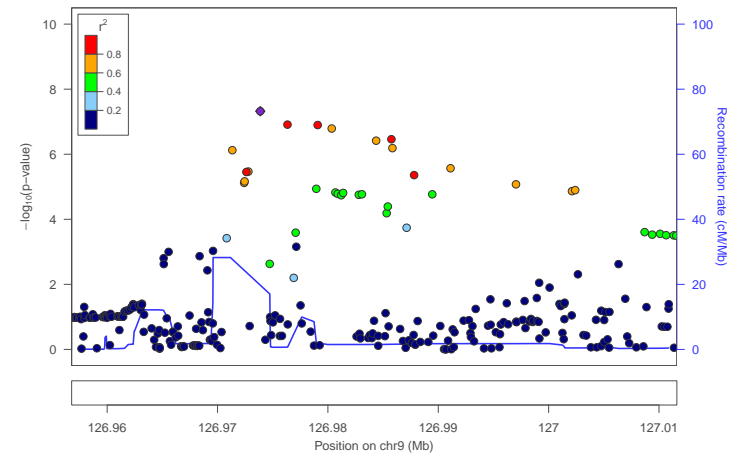
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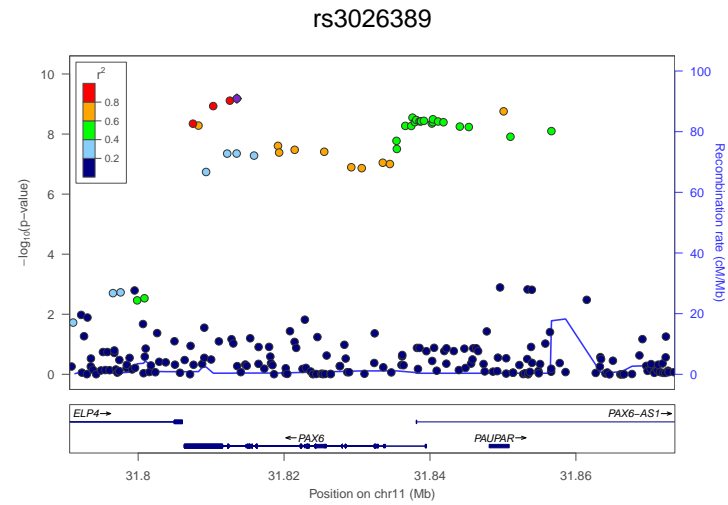
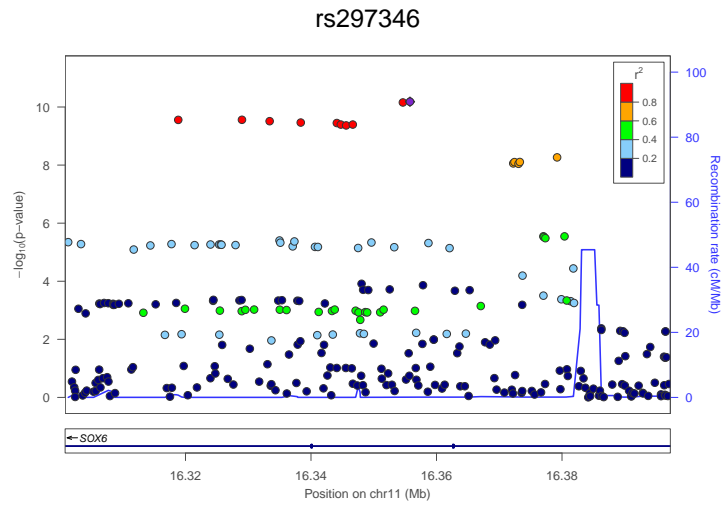
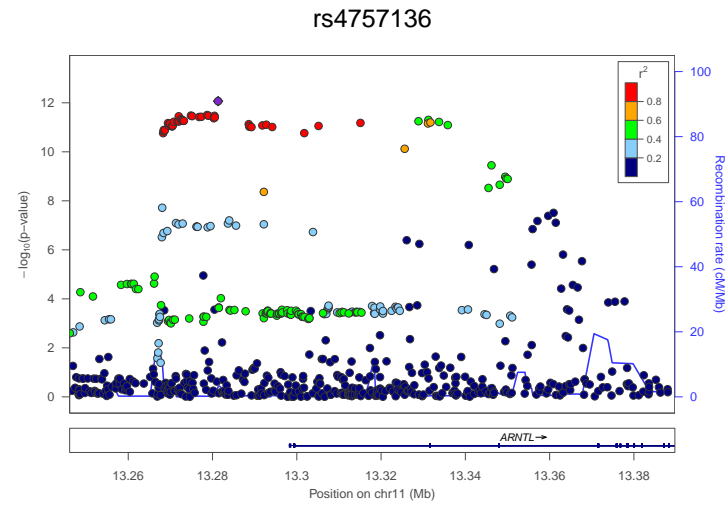
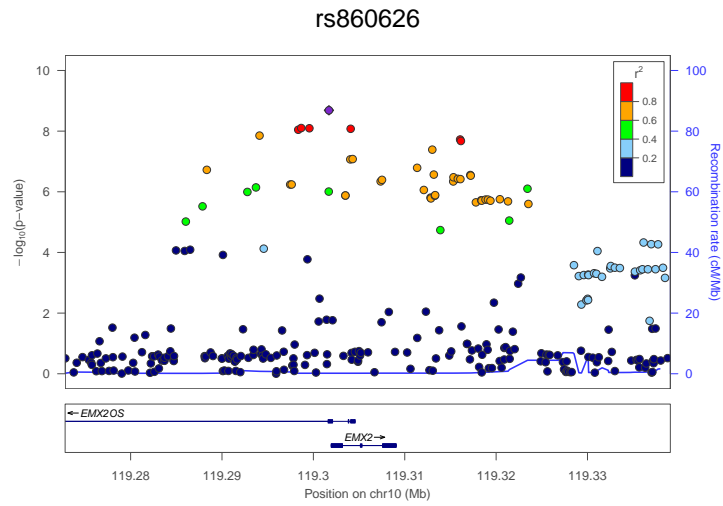
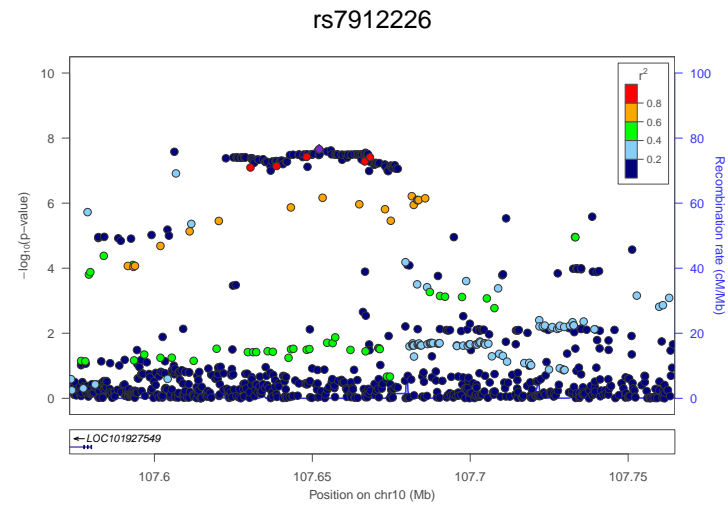
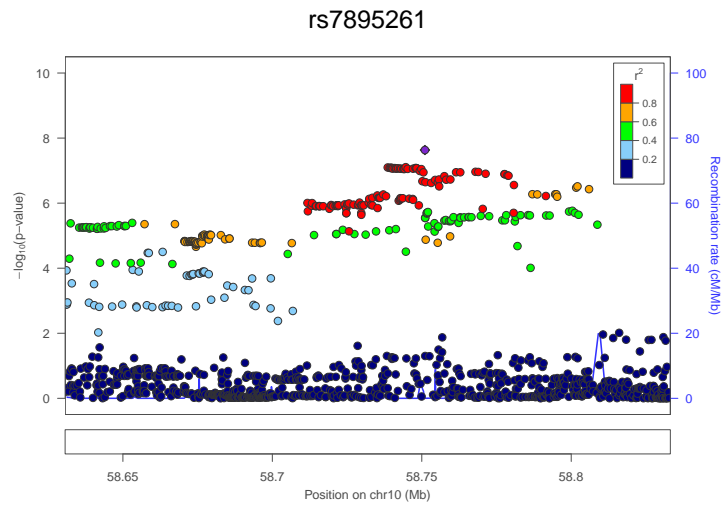


rs2149351

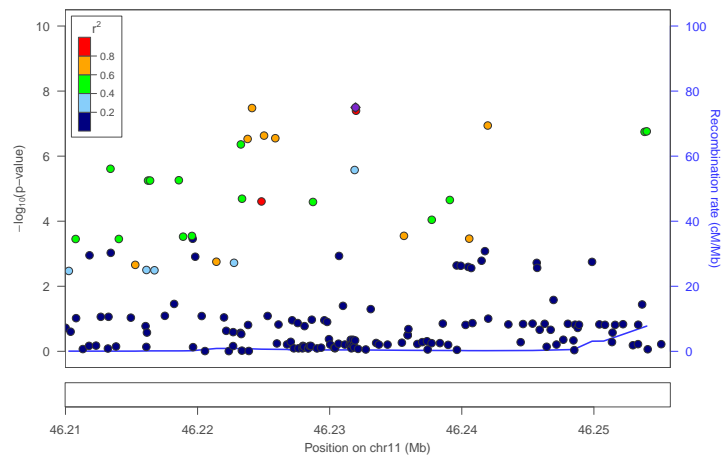


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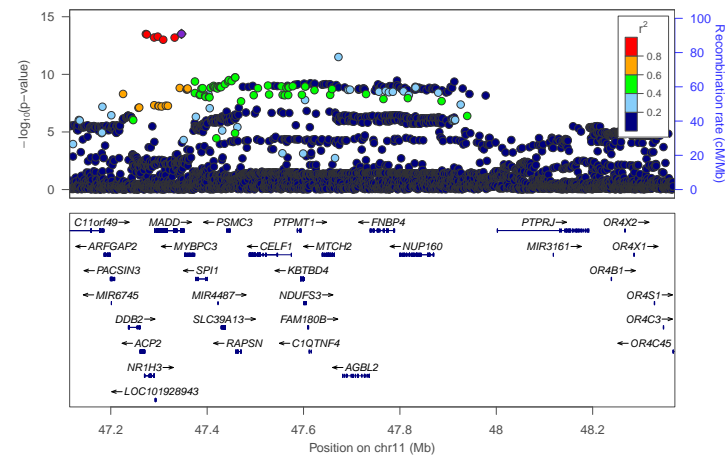




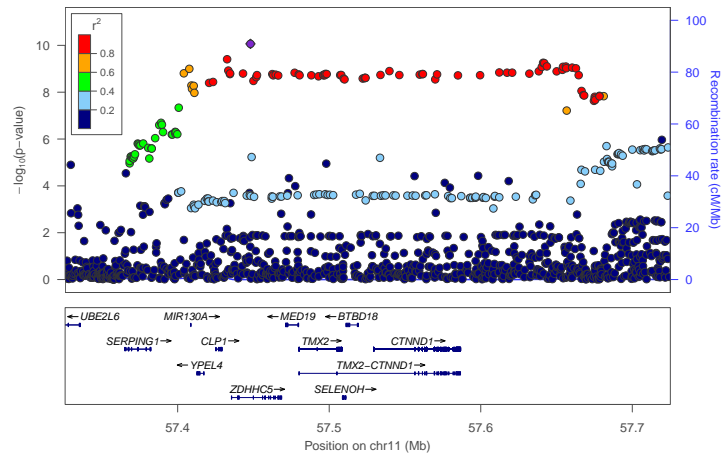
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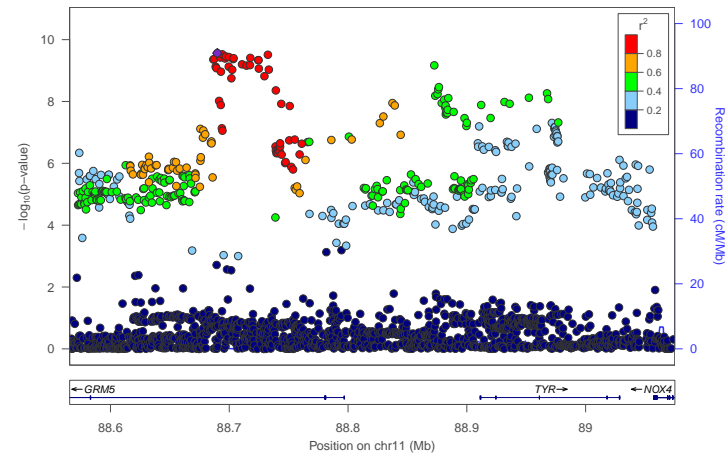
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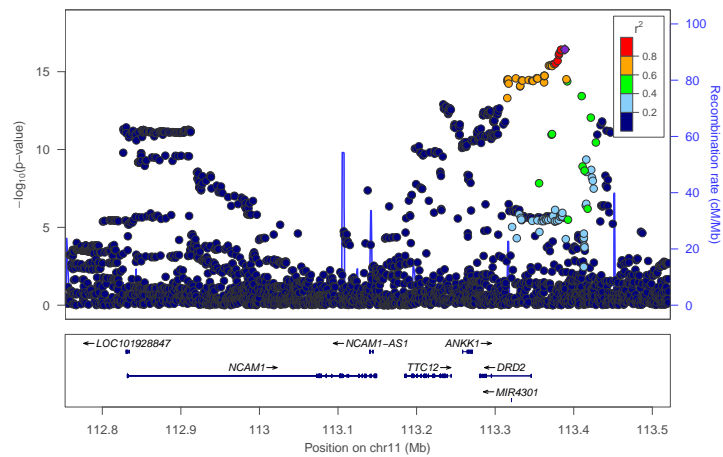
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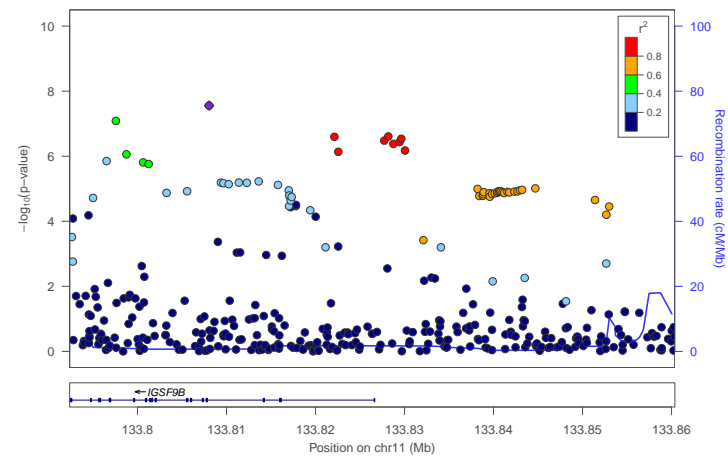
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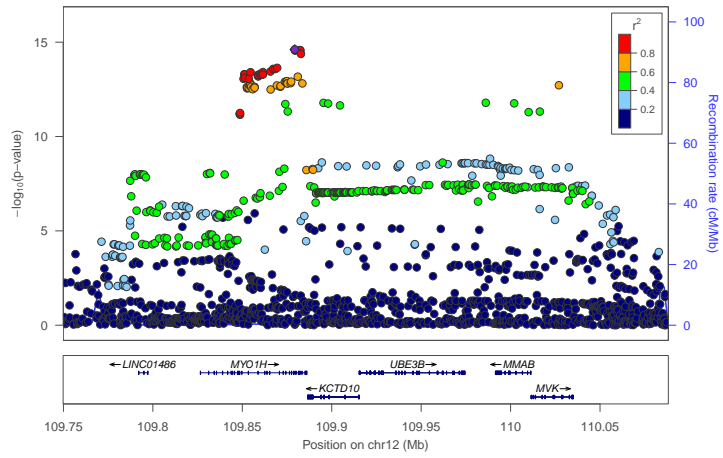
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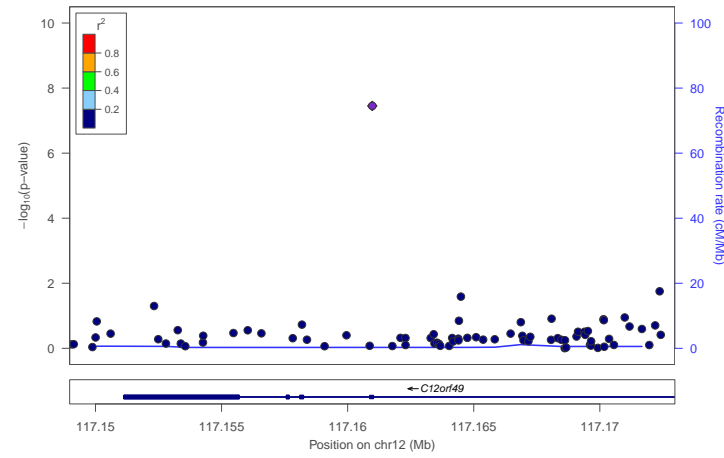
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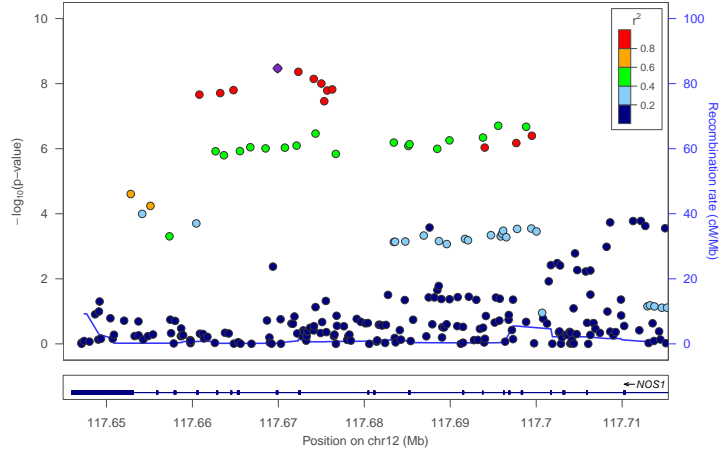
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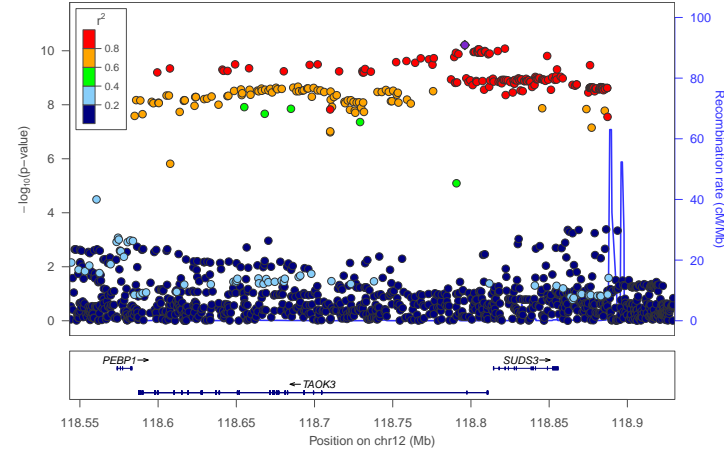
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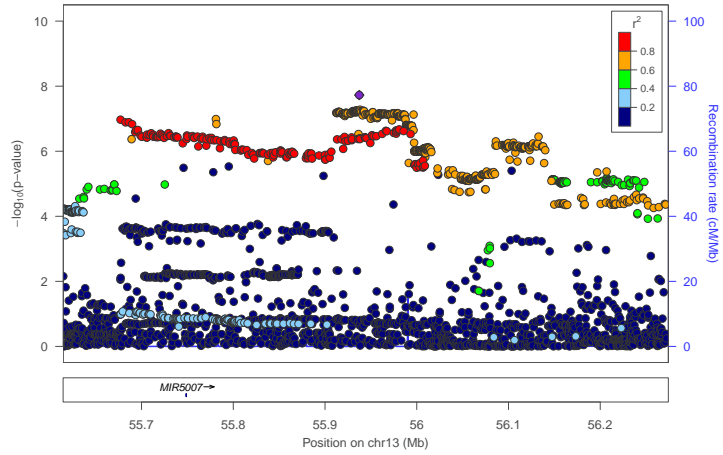
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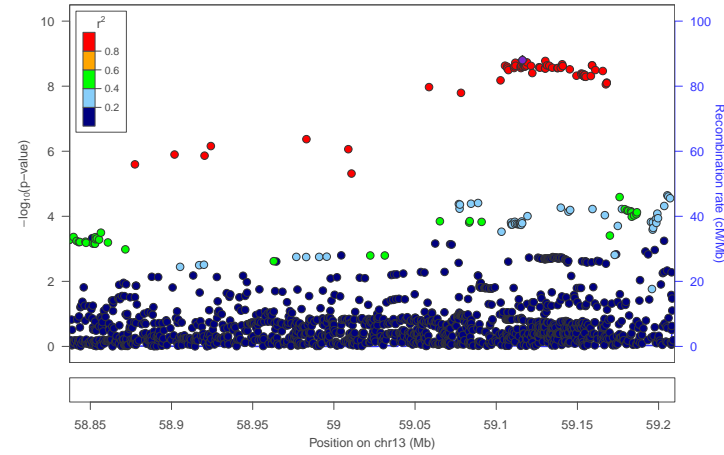
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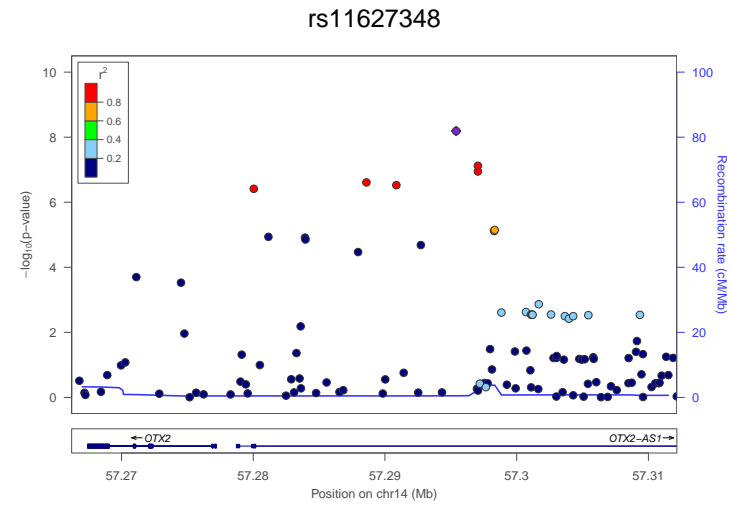
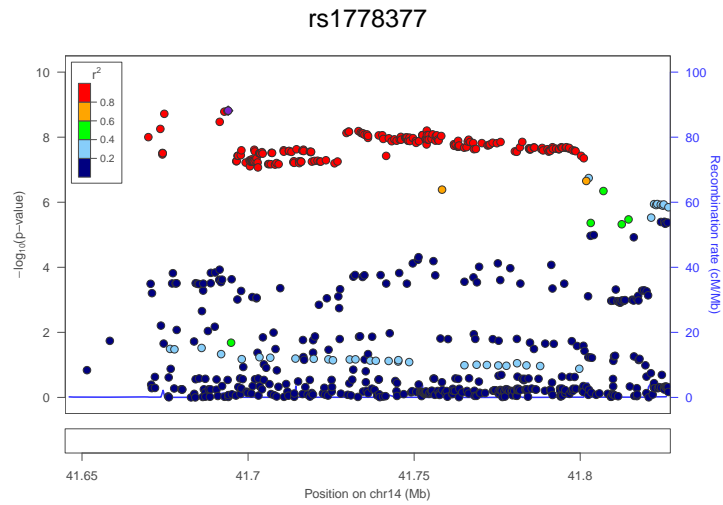
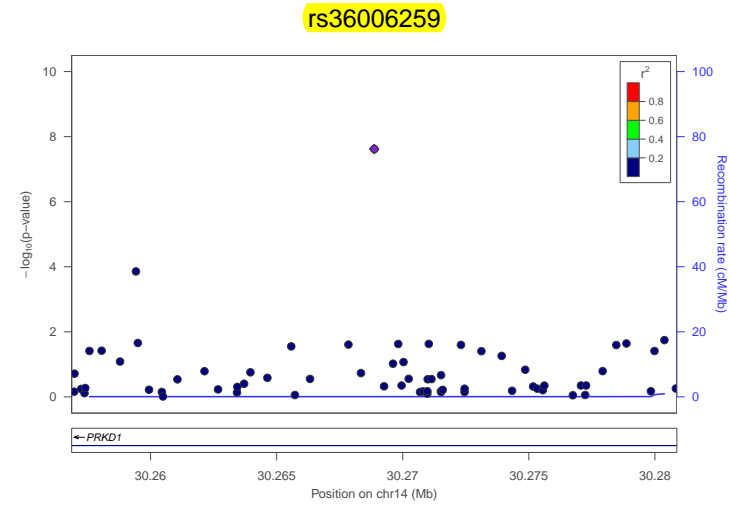
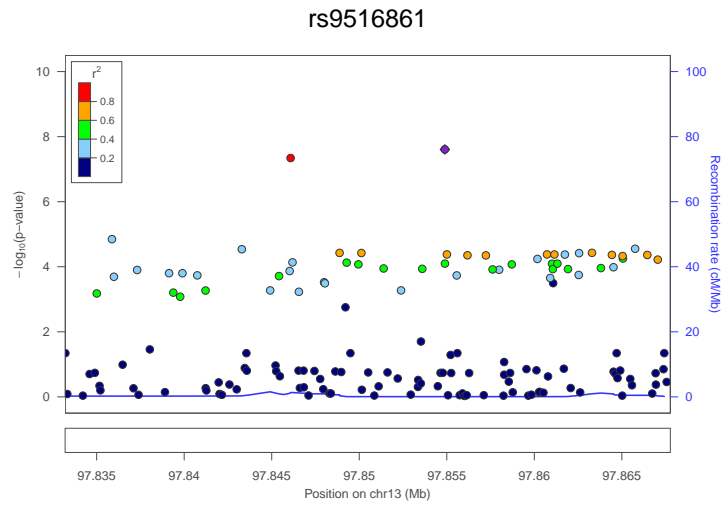
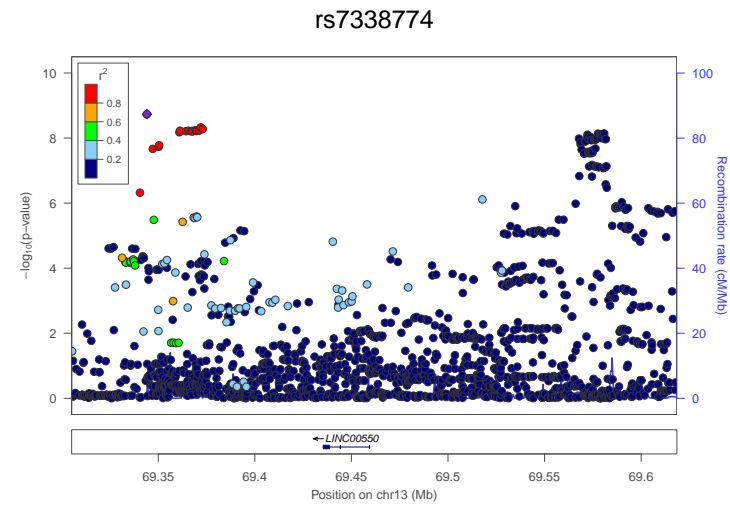
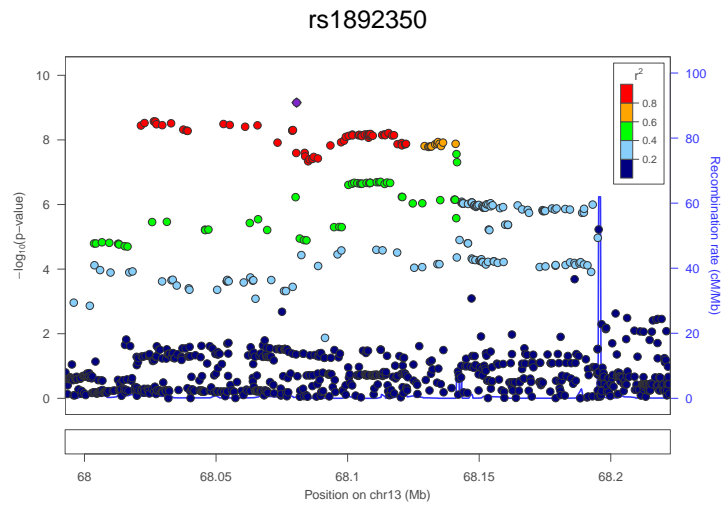


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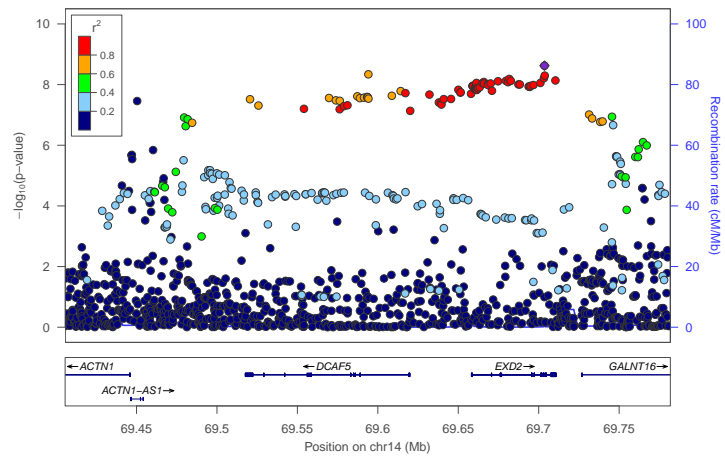


rs4444227

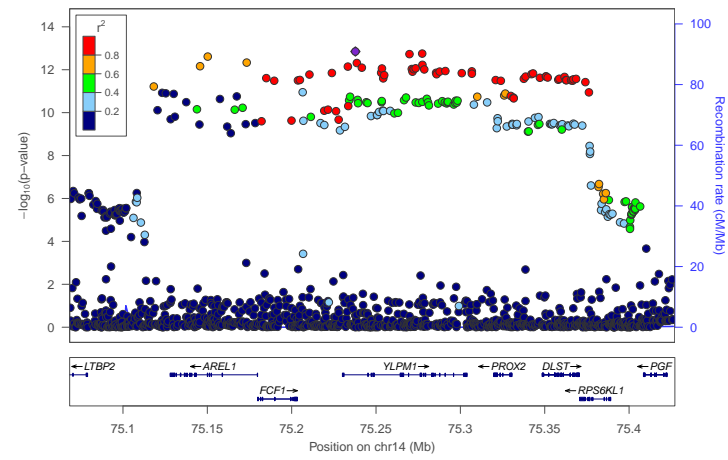




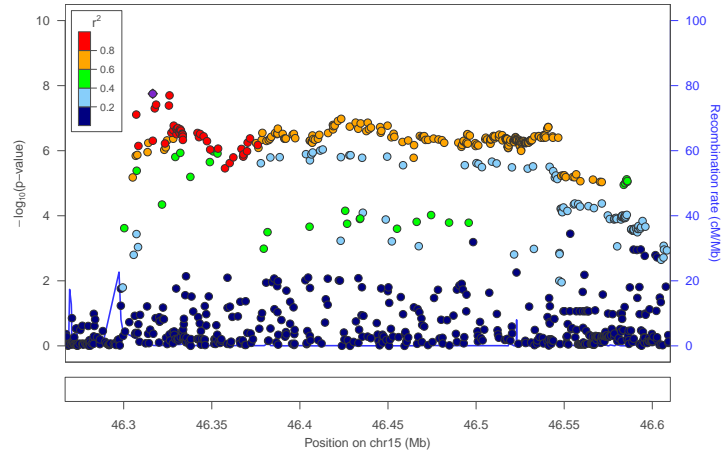
rs4902704



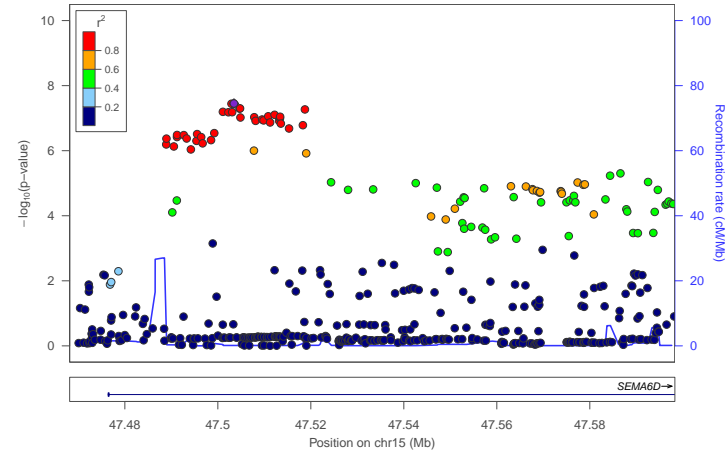
rs10144845



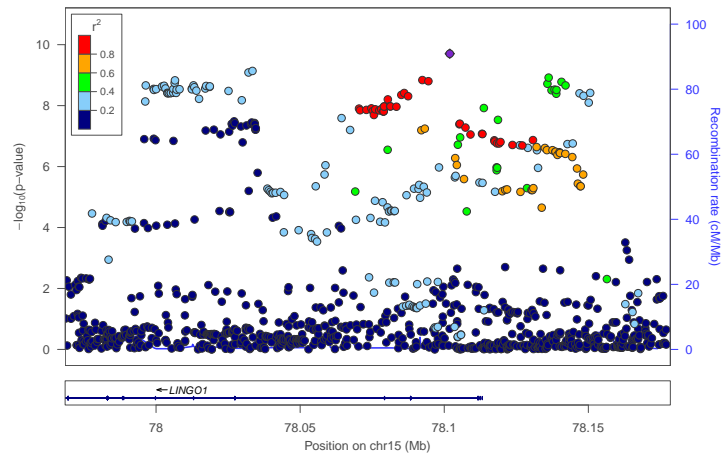
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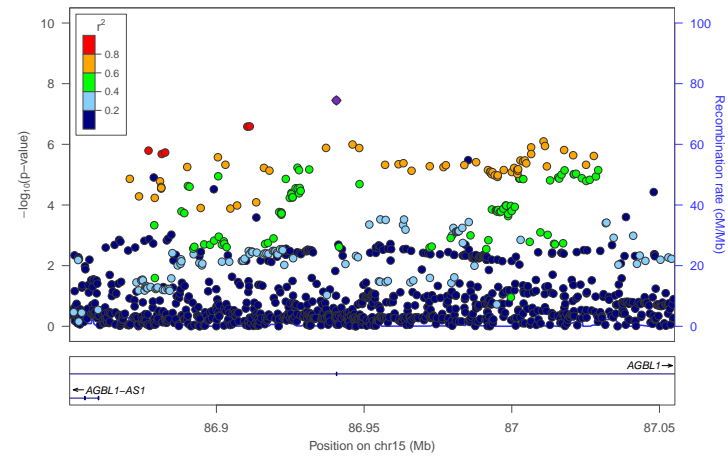
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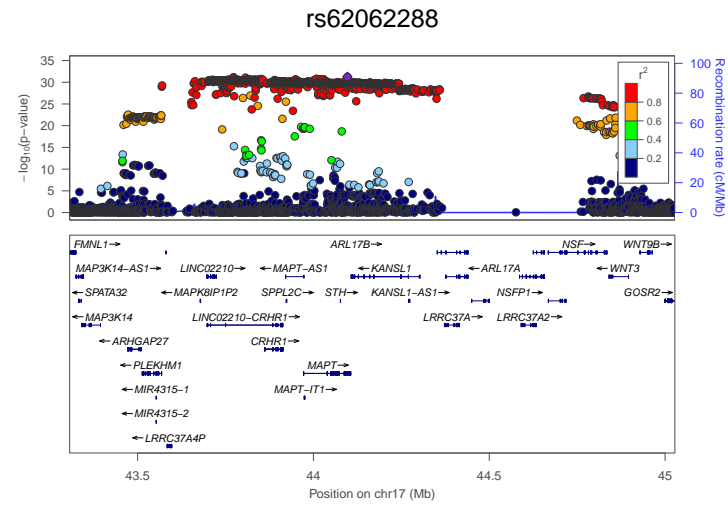
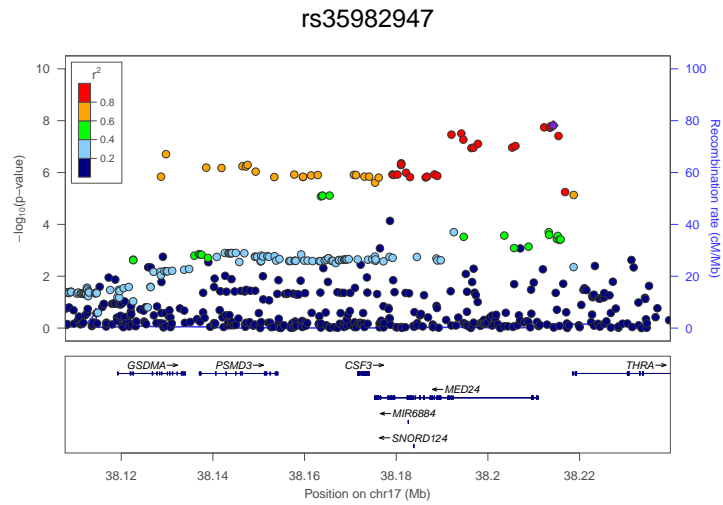
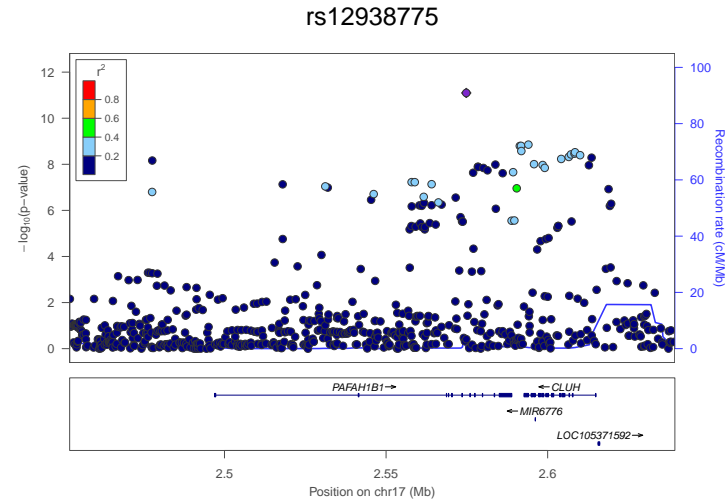
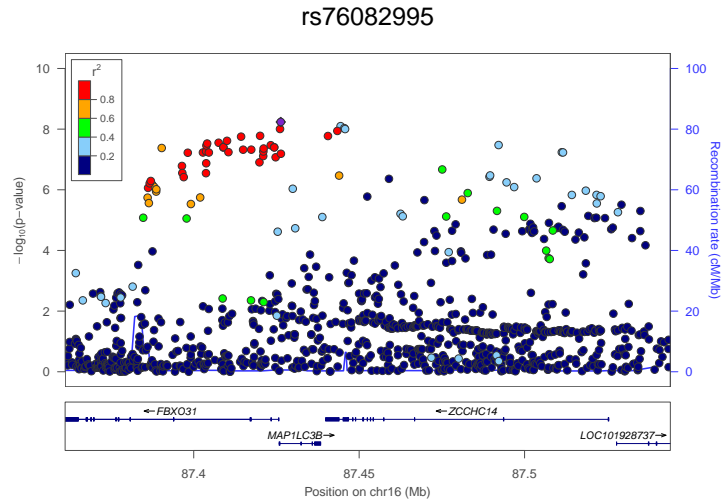
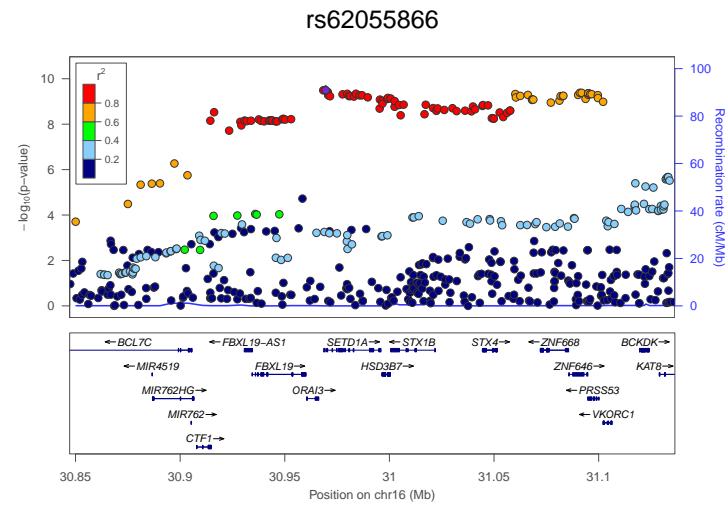
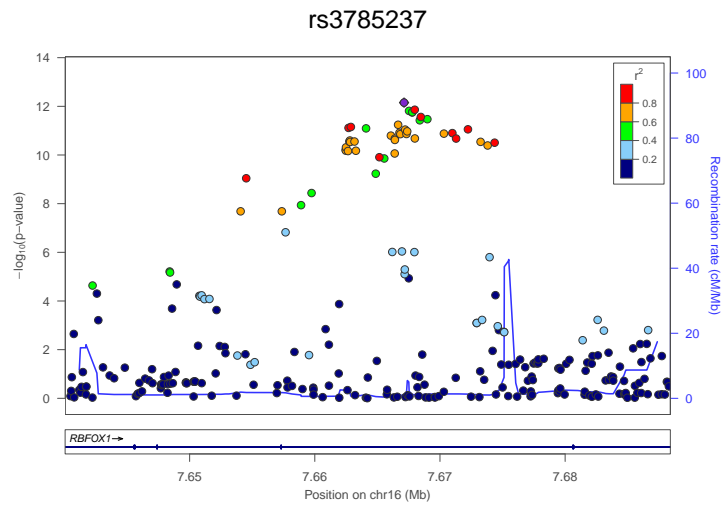


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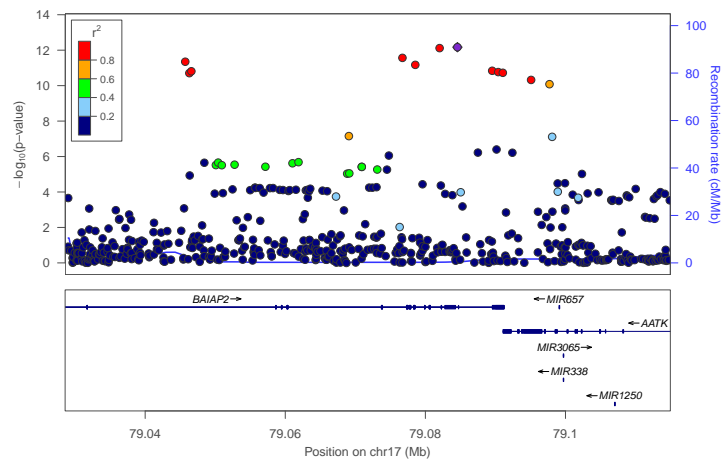


rs4362360

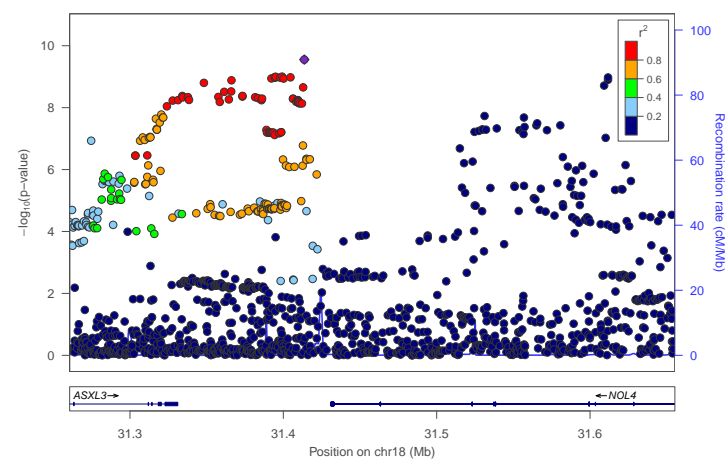




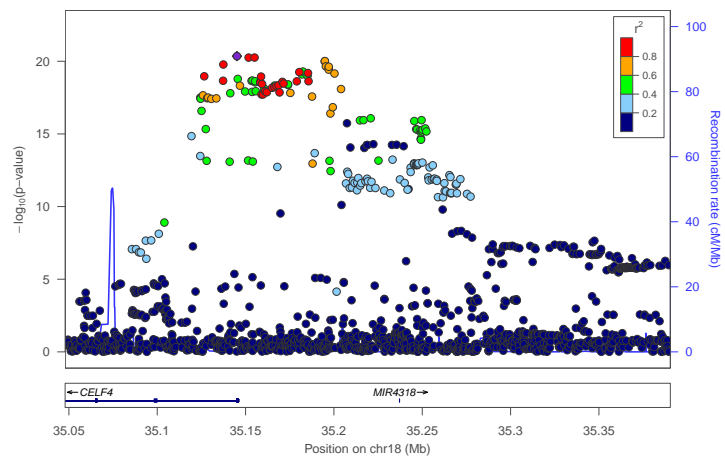
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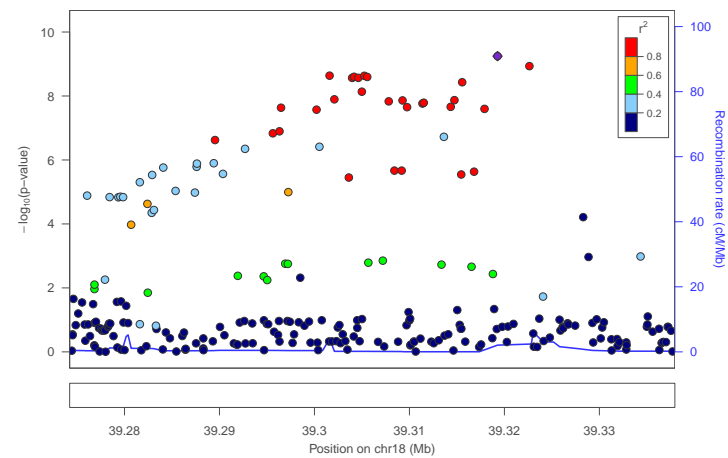
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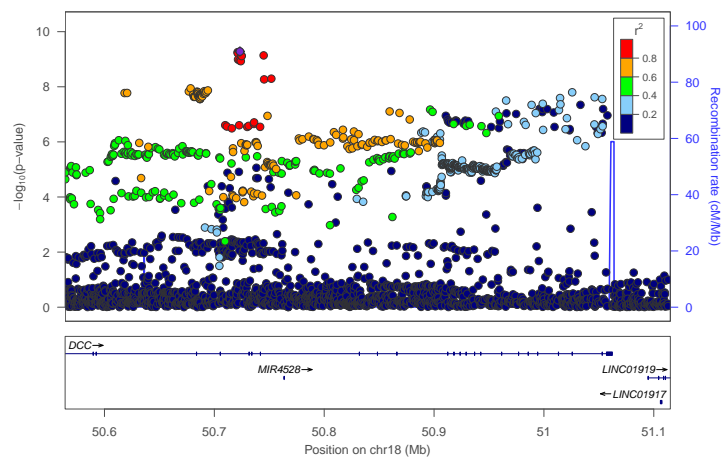
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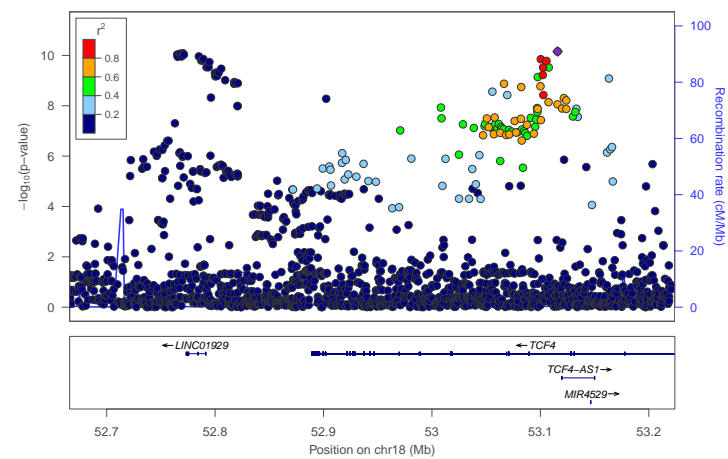
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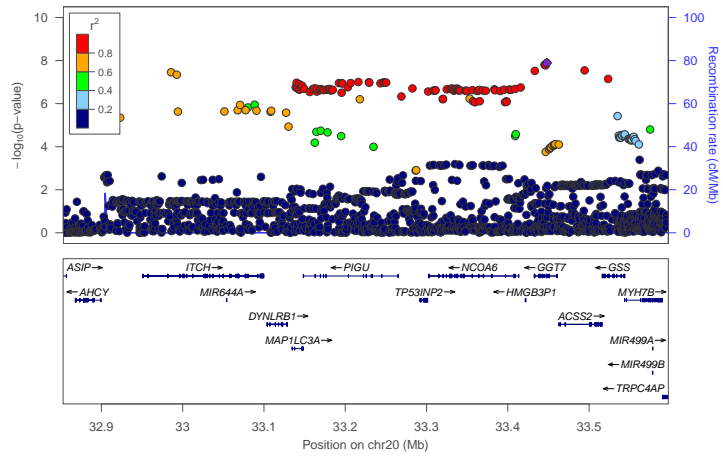
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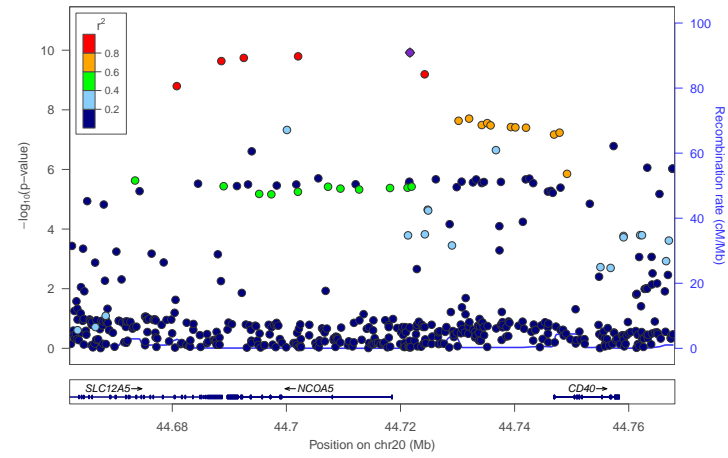
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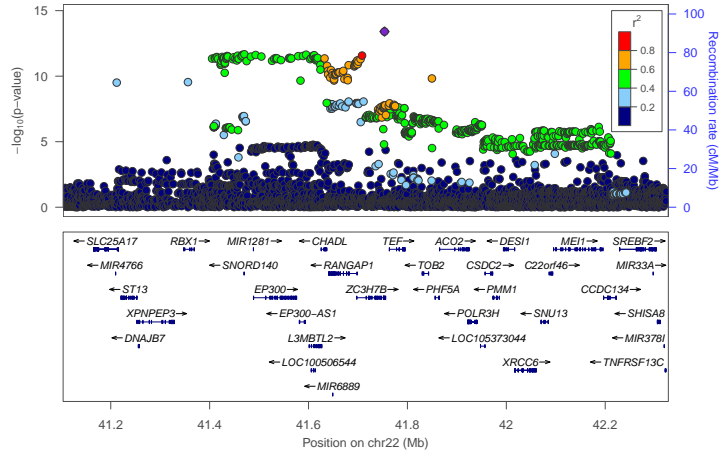
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rs4578918

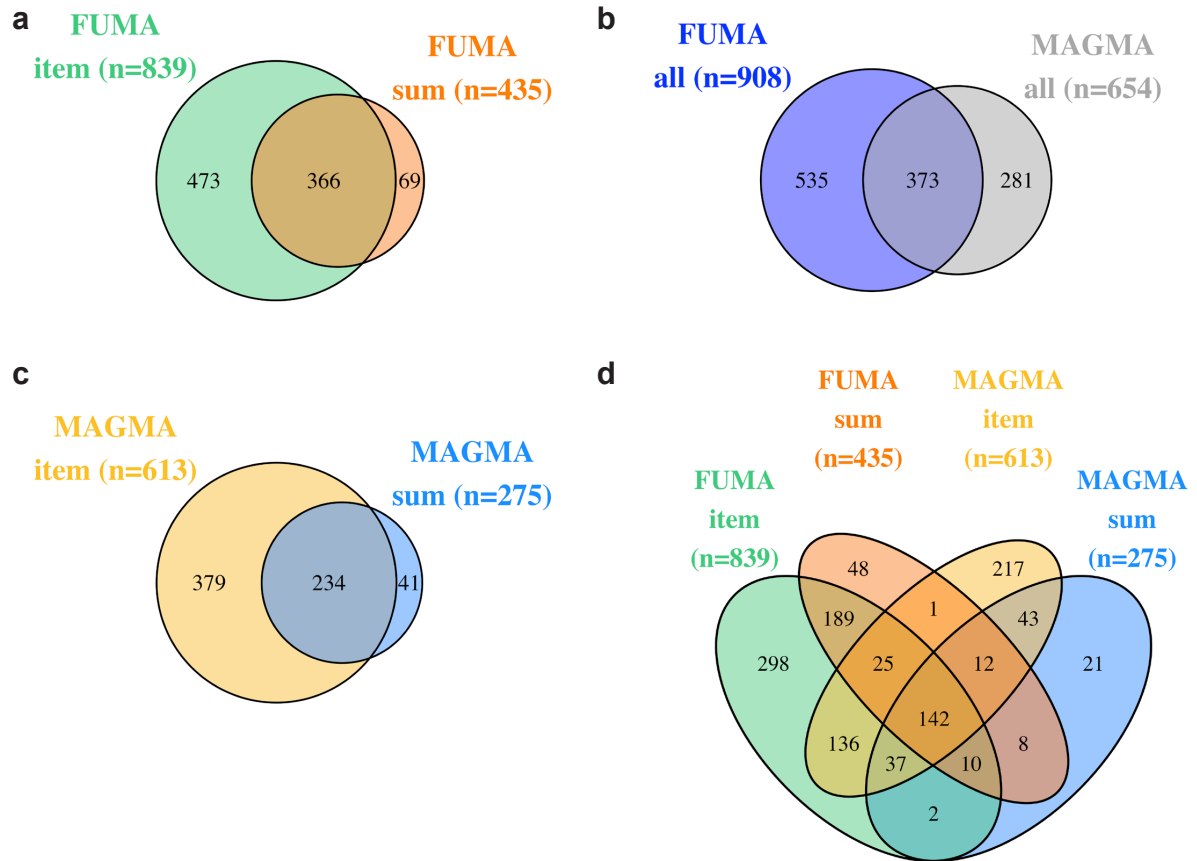


rs11090045



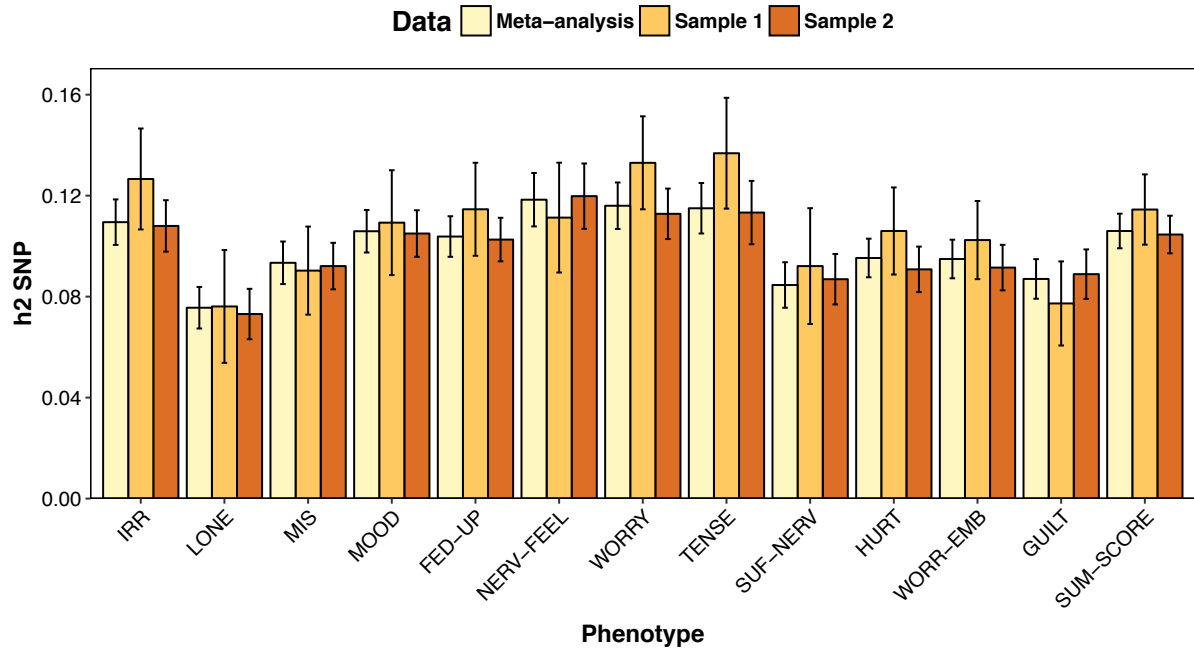
Supplementary Figure 17. Regional plots of GWA analyses of the neuroticism sum-score.

The y -axis represents the negative logarithm (base 10) of the SNP P value and the x -axis the position on the chromosome, with the name and location of genes in the UCSC Genome Browser in the bottom panel. The SNP with the lowest P value in the region is marked by a purple diamond. The colors of the other SNPs indicate the r^2 of these SNPs with the lead SNP, with grey color indicating SNPs below the user-defined r^2 . Plots are generated with LocusZoom. See **Supplementary Data 2** for an overview of all lead SNPs for which a regional plot is presented above. For excluded loci (see **Methods; Supplementary Data 3-4**) the rsID's are marked yellow.



Supplementary Figure 18. Venn diagrams of overlap between genes implicated by SNP-based (FUMA) versus gene-based (MAGMA) analyses of the 12 neuroticism items and the sum-score.

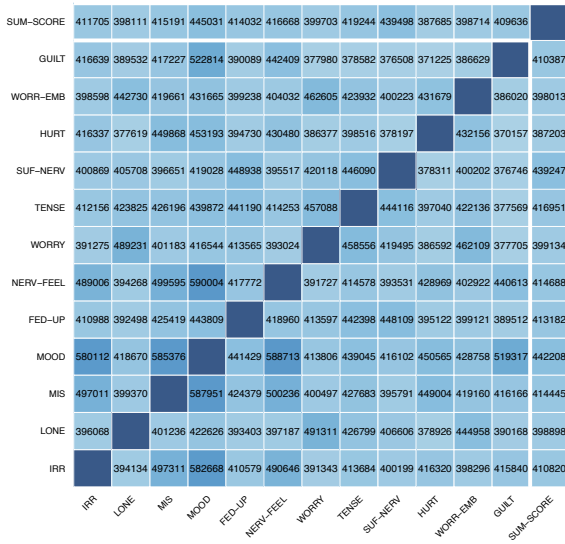
(a) Overlap in number of genes implicated by FUMA in SNP-based analyses of the 12 neuroticism items and the sum-score. (b) Overlap in number of genes implicated by SNP-based analyses in FUMA versus gene-based analyses in MAGMA. (c) Overlap in number of genes identified in MAGMA's gene-based analyses of the 12 neuroticism items and the sum-score. (d) Overlap between genes implicated by FUMA and MAGMA for the 12 neuroticism items and the neuroticism sum-score.



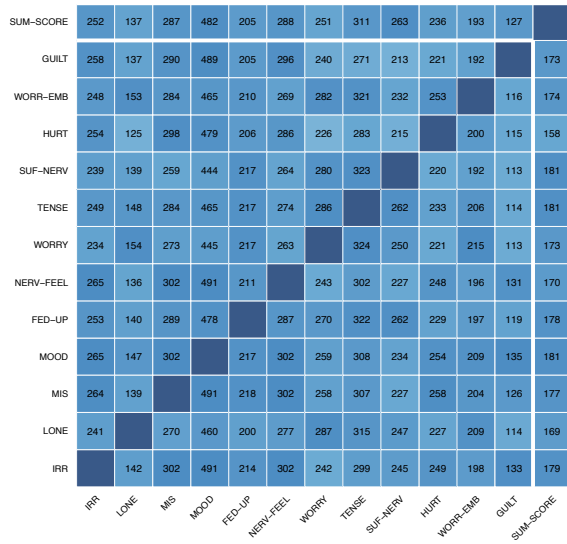
Supplementary Figure 19. SNP-based heritability for the 12 neuroticism items and the sum-score.

SNP-based heritability was computed on summary statistics of sample 1, sample 2, and the meta-analysis results of both samples, using LD score regression⁶. Error bars represent 95% confidence intervals.

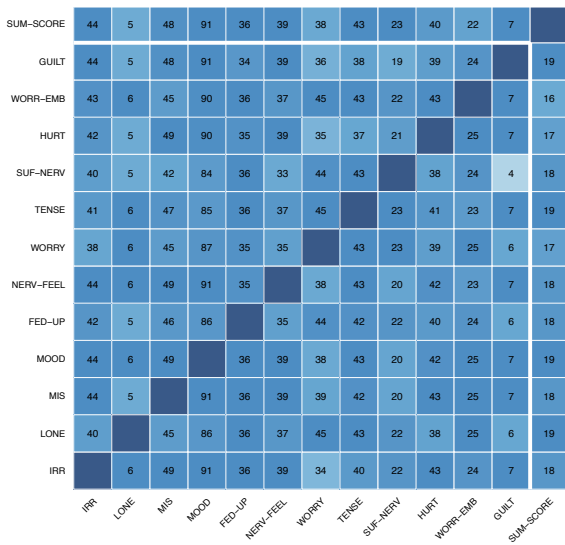
$P < 0.5$



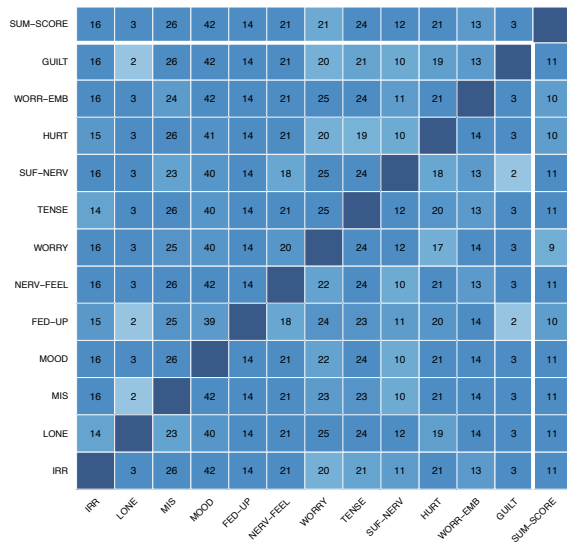
$P < 1e-5$



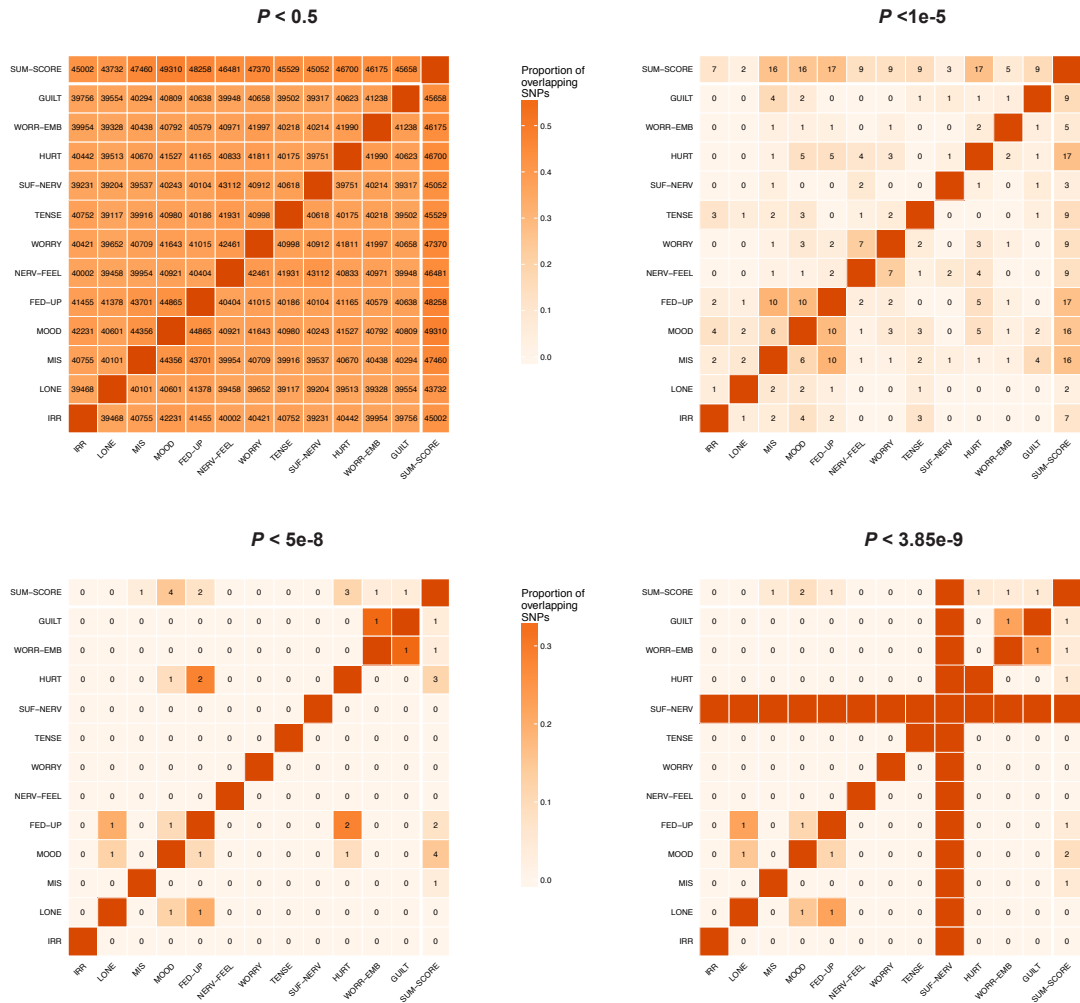
$P < 5e-8$



$P < 3.85e-9$



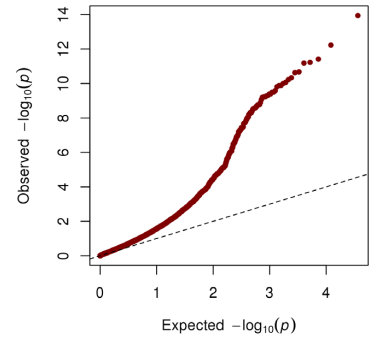
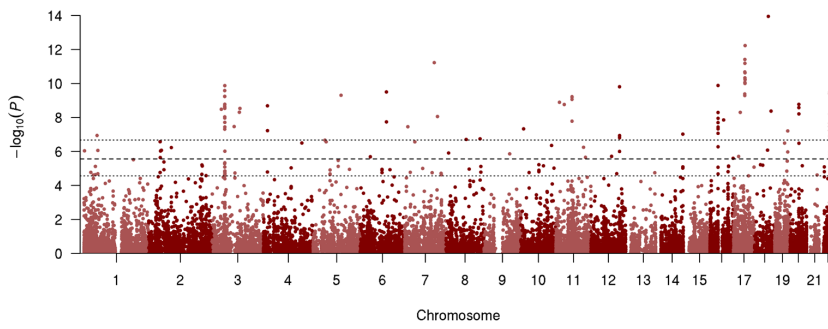
Digits in the cells indicate the number of SNPs for that specific combination of phenotypes that exceeded the given P value threshold. The depicted heatmaps are not symmetrical, as LD-based clumping was performed on both phenotypes (see **Methods** and **Supplementary Note 1**).



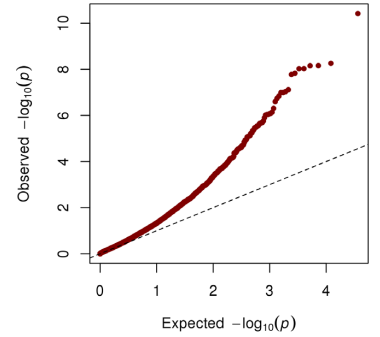
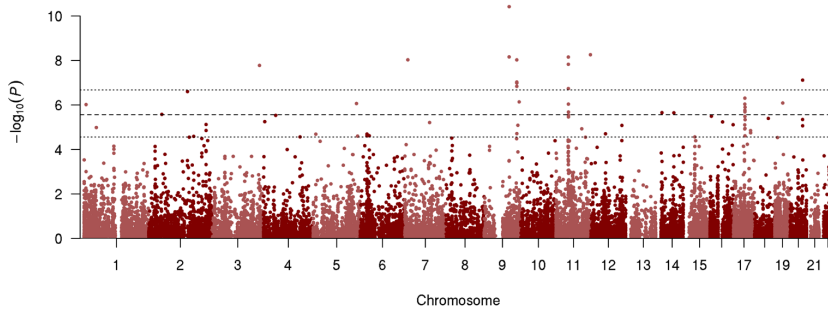
Supplementary Figure 21. Heatmaps showing the results from Fisher’s exact test for overlap in the top SNPs (for different P value thresholds).

Digits in the cells indicate the number of SNPs for that specific combination of phenotypes that exceeded the given P value threshold (see **Methods** and **Supplementary Note 1**). If an off-diagonal cell contains no value this indicates that there were no SNPs with a P value lower than the given threshold for that phenotype. A value ‘0’ indicates that although there were SNPs with P values lower than the threshold for both phenotypes, these were not the same SNPs. All heatmaps in this figure are symmetric.

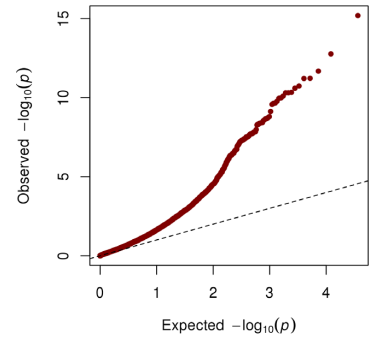
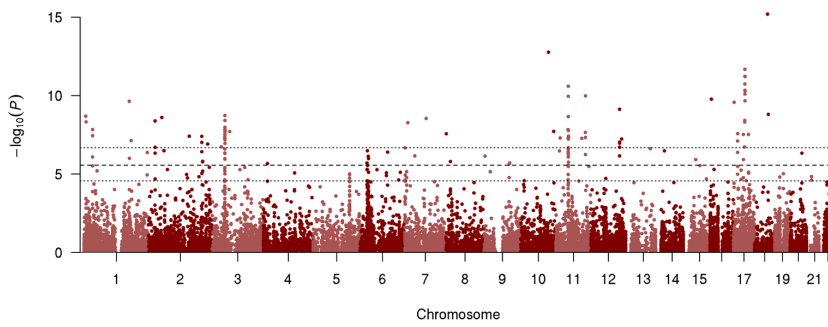
IRR - Are you an irritable person?



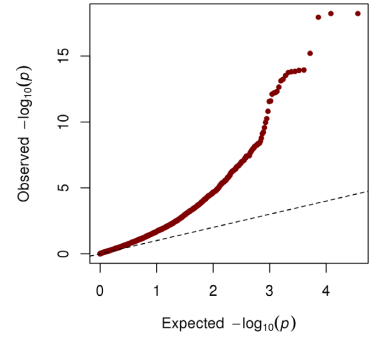
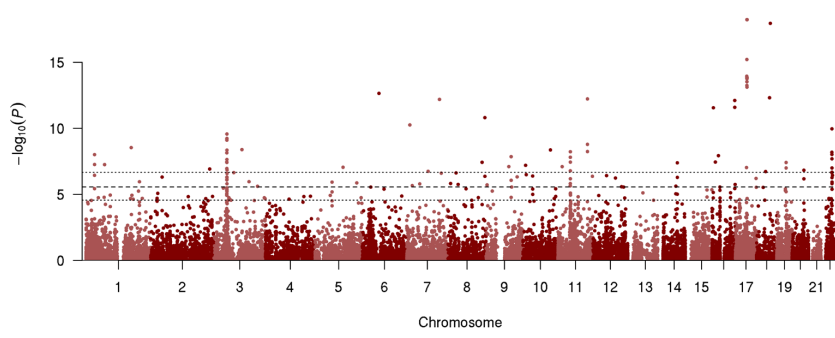
LONE - Do you often feel lonely?



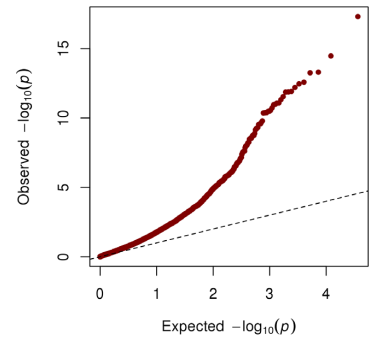
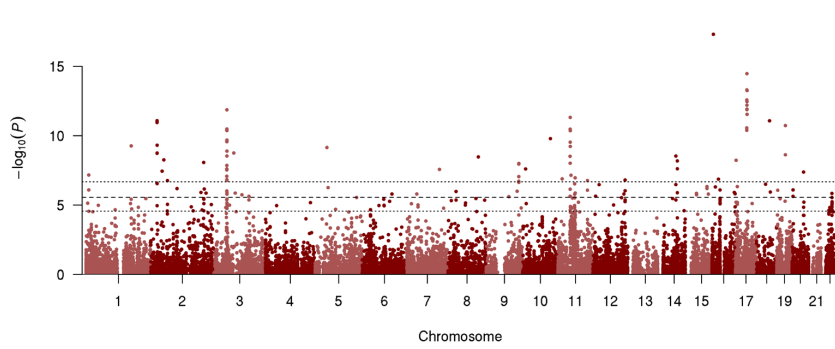
MIS - Do you ever feel 'just miserable' for no reason?



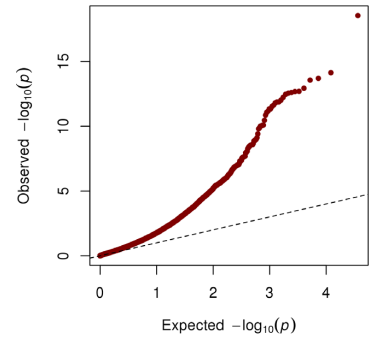
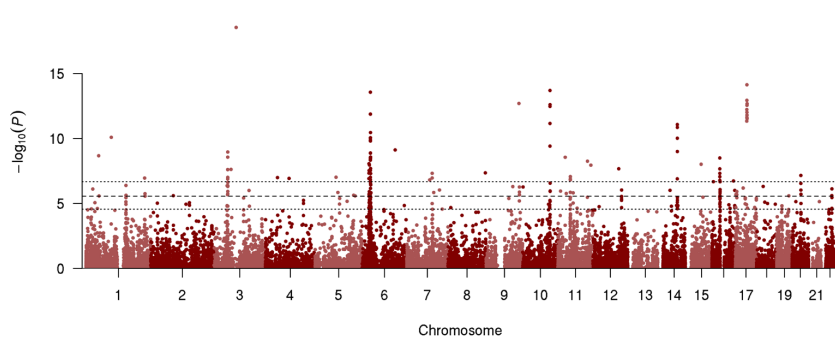
MOOD - Does your mood often go up and down?



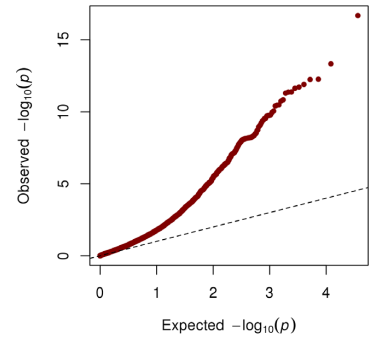
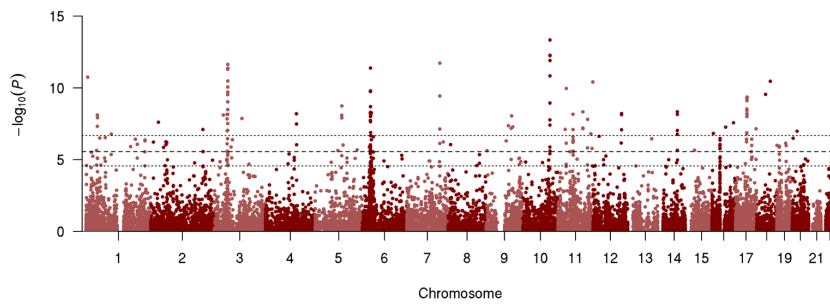
FED-UP - Do you often feel 'fed-up'?



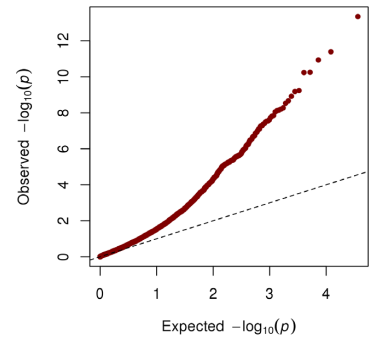
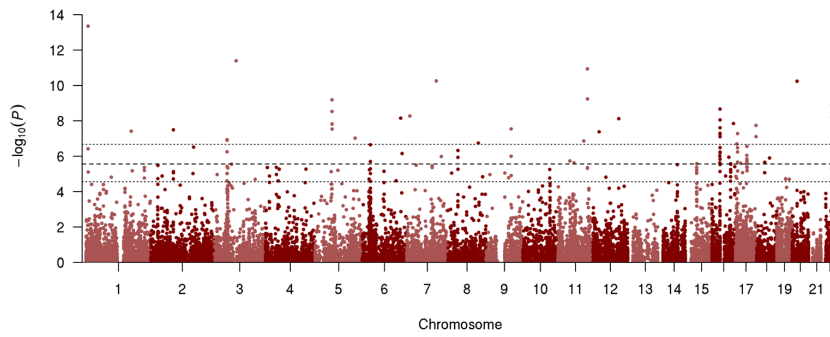
NERV-FEEL - Would you call yourself a nervous person?



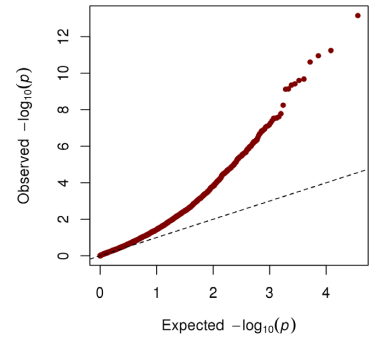
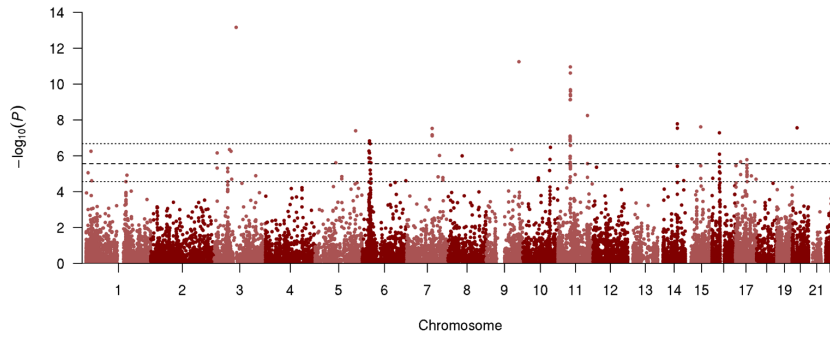
WORRY - Are you a worrier?



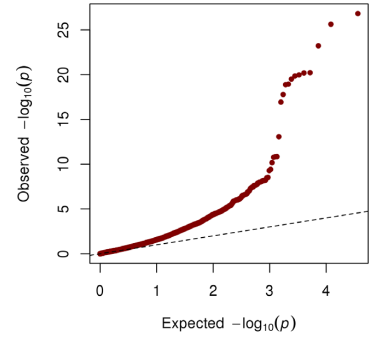
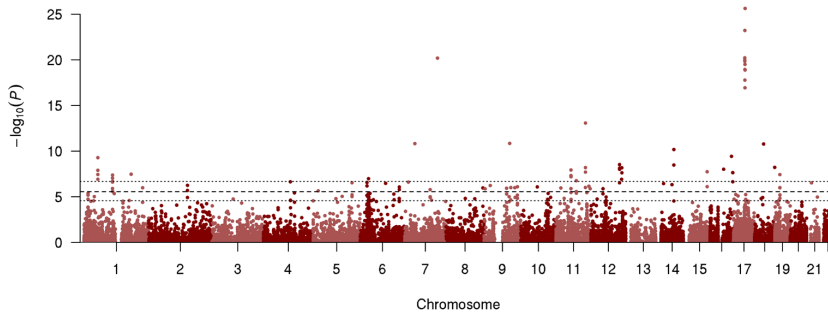
TENSE - Would you call yourself tense or 'highly strung'?



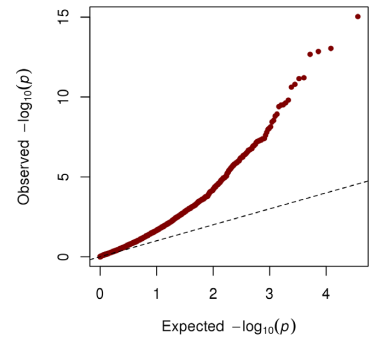
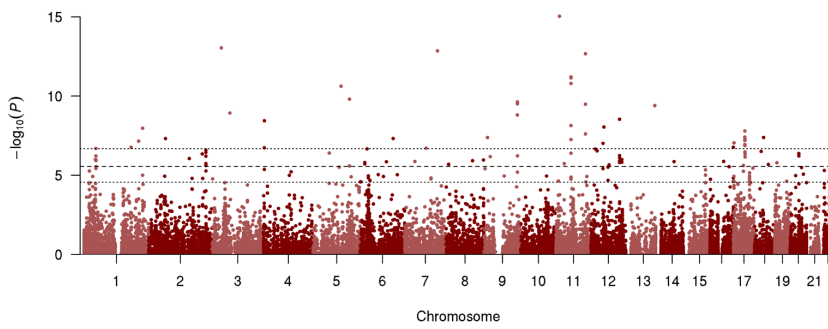
SUF-NERV - Do you suffer from 'nerves'?



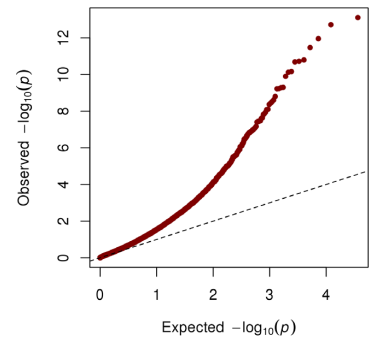
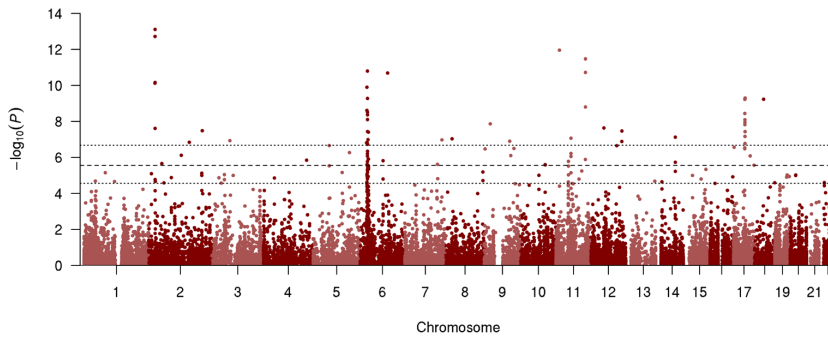
HURT - Are your feelings easily hurt?

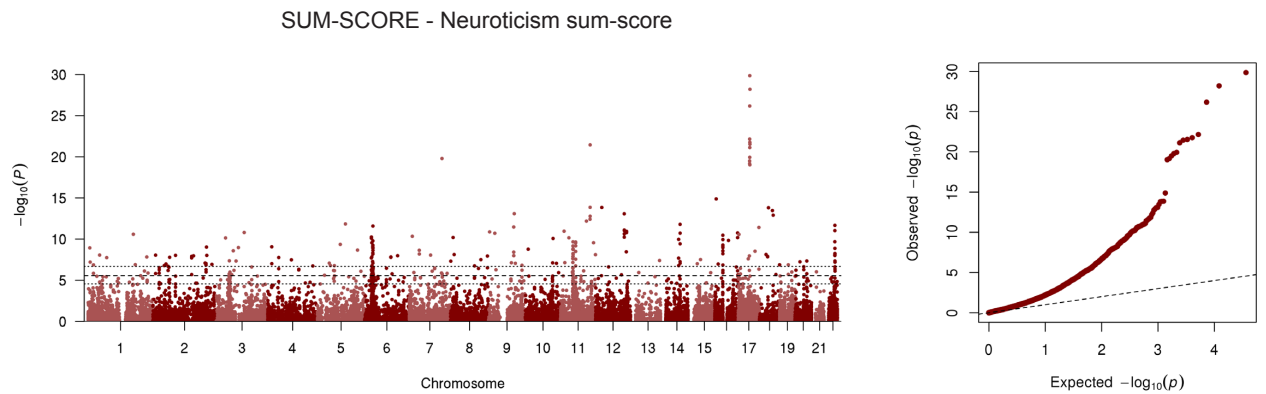


WORR-EMB - Do you worry too long after an embarrassing experience?



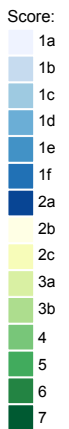
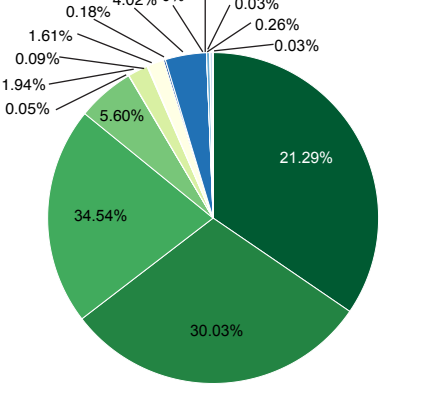
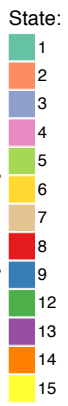
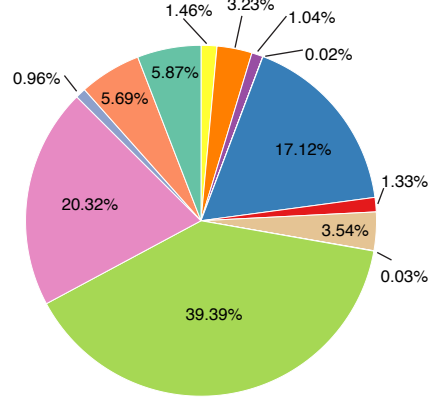
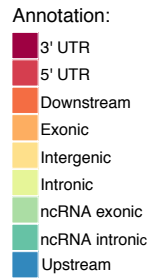
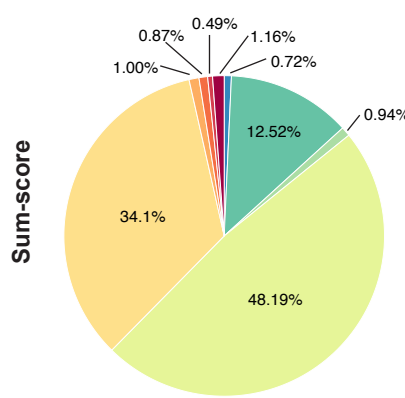
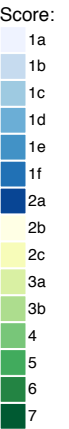
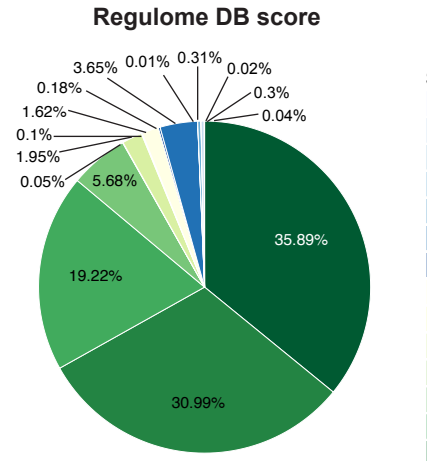
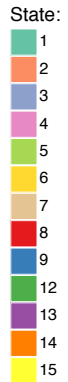
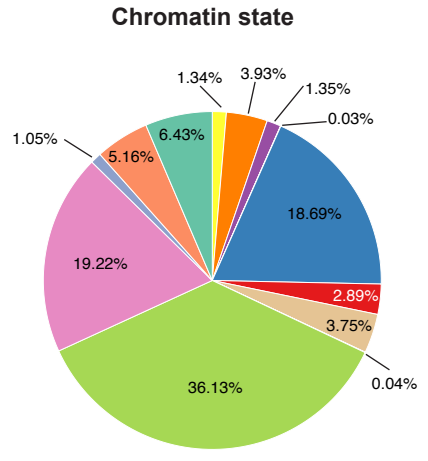
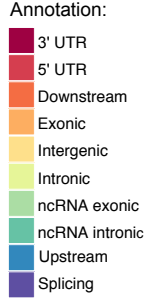
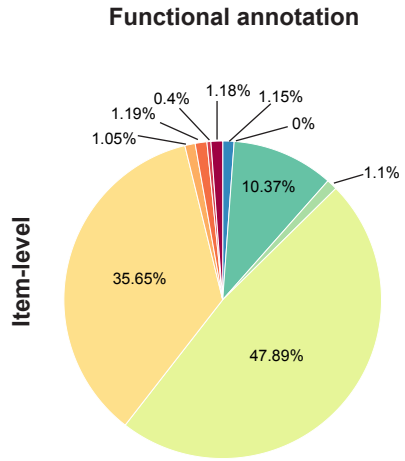
GUILT - Are you often troubled by feelings of guilt?





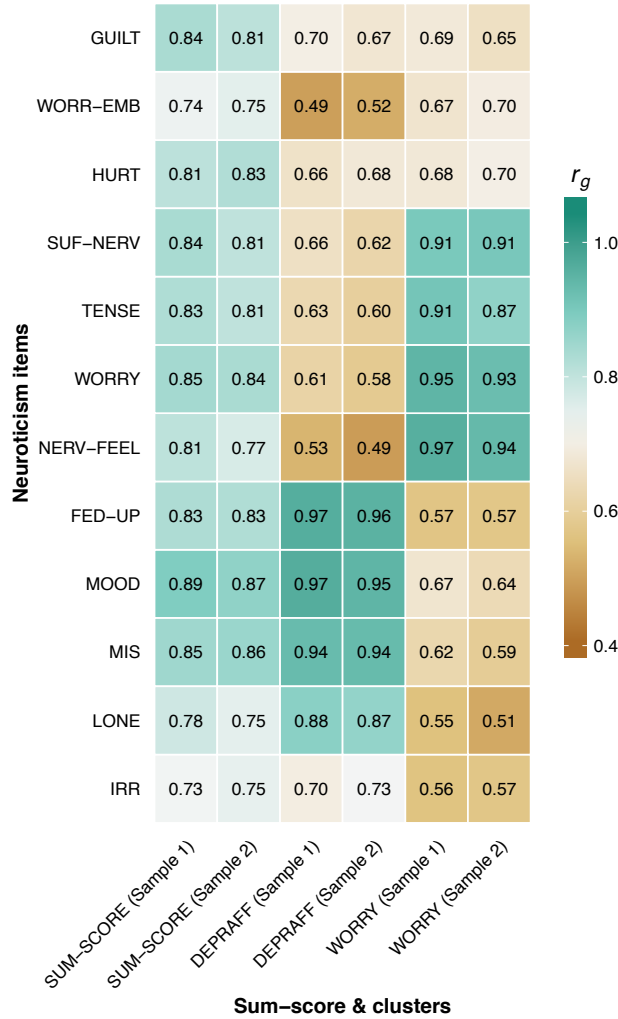
Supplementary Figure 22. Manhattan and quantile-quantile (Q-Q) plots of the gene-based association results for the individual items and the neuroticism sum-score.

Gene association results from the MAGMA gene-based tests, which are based on the summary statistics of the meta-analyses of the 12 neuroticism items and the sum-score. Each dot represents a gene. The y-axis shows the $-\log_{10} P$ values and the x-axis the chromosomal position of a given gene. Dashed lines indicate genome-wide significance ($P < 2.75 \times 10^{-6}$). The upper dotted line indicates a more stringent Bonferroni-corrected significance threshold, where we corrected for testing 13 phenotypes; $P < 2.12 \times 10^{-7}$ ($2.75 \times 10^{-6}/13$) whereas the lower dotted line indicates the ‘suggestive’ significance threshold ($P < 2.75 \times 10^{-5}$). See **Supplementary Table 1** for an explanation of item labels.



Supplementary Figure 23. Functional categories, chromatin state and regulome DB score for SNPs that were GWS in item-level analyses versus analysis of the neuroticism sum-score.

The functional annotation indicates the functional consequences on the gene to which a given SNP was annotated (**Supplementary Table 6**). The chromatin state refers to the minimum (i.e., most active) chromatin state across 127 tissues for all genome-wide significant SNPs. The lower the regulome DB (database) score, the more likely it is that the SNP has a regulatory function. Coding of the chromatin states and regulome DB scores is presented in **Supplementary Tables 7-8**. Annotation was performed in FUMA⁷.



Supplementary Figure 24. Genetic correlations between the 12 neuroticism items and the sum- and cluster-scores in samples 1 and 2.

Genetic correlations between the 12 neuroticism items and the sum- and cluster-scores in both samples. The genetic correlations of the same items measured in both samples are presented on the diagonal. All reported genetic correlations, computed with bivariate LD score regression, are significantly different from zero after Bonferroni correction ($P < 2.22 \times 10^{-4}$).

See **Supplementary Table 1** for a description of the item labels.

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