Supplementary information

A genome-wide meta-analysis identifies 50 genetic loci associated with carpal tunnel syndrome

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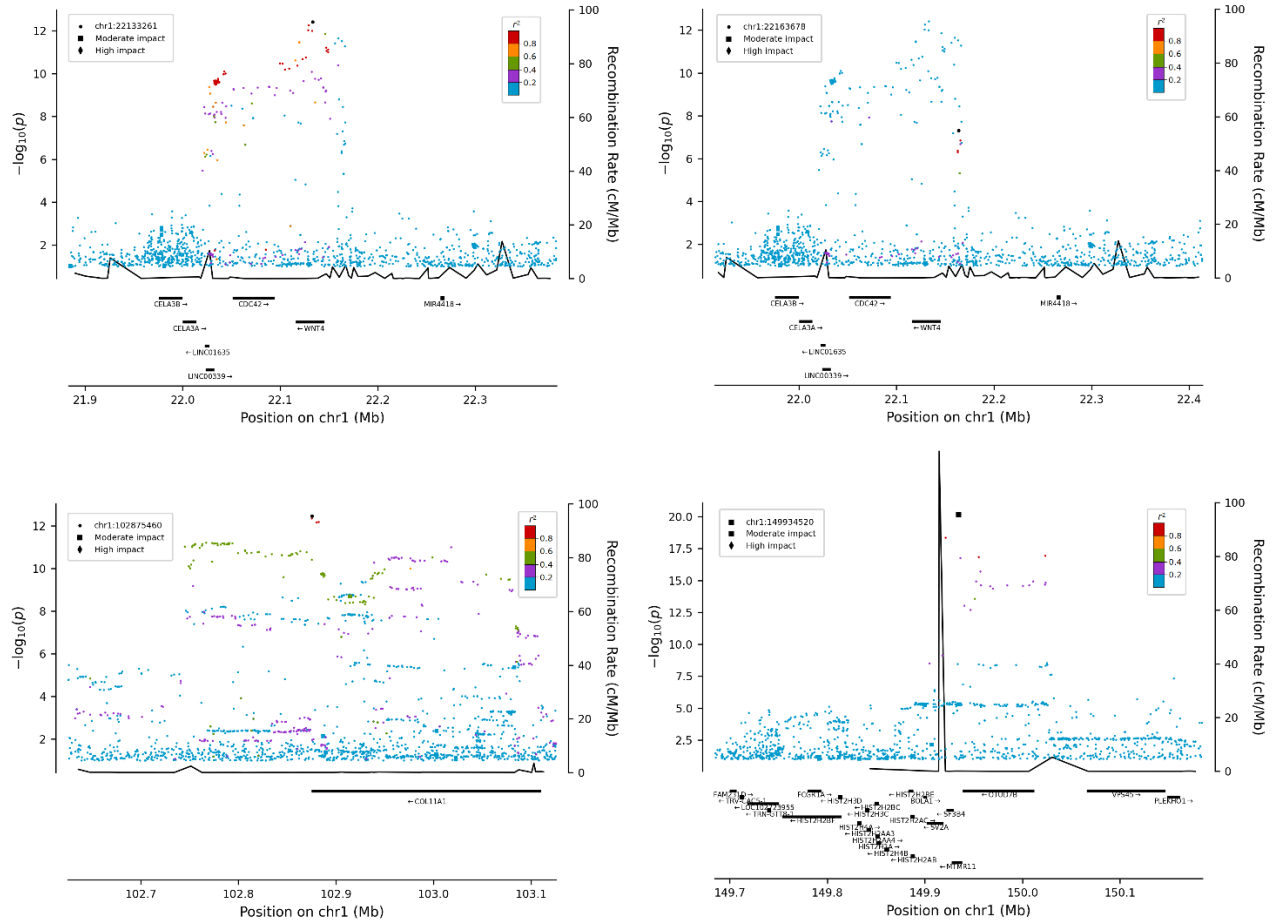
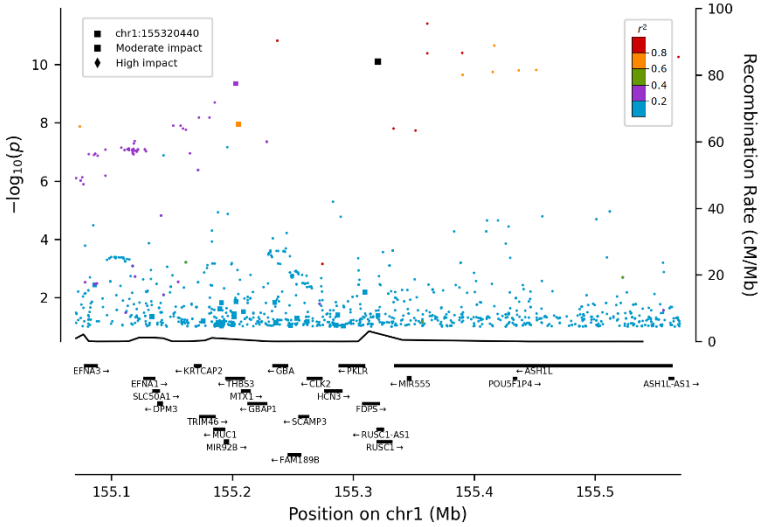
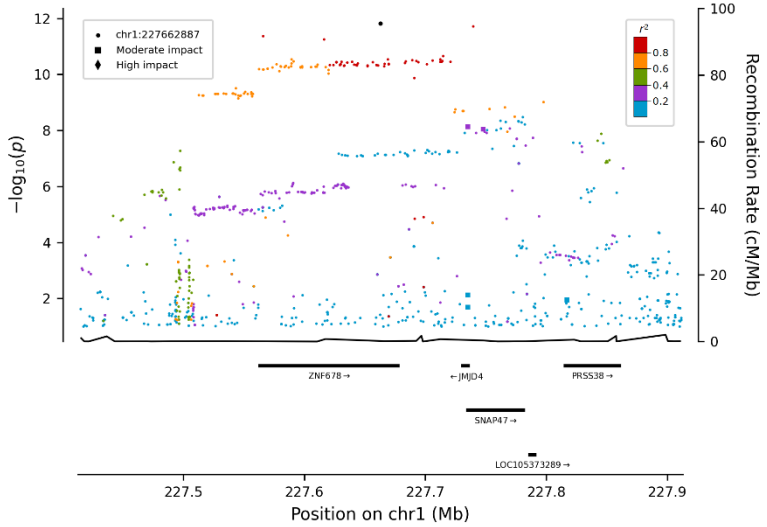
Contents

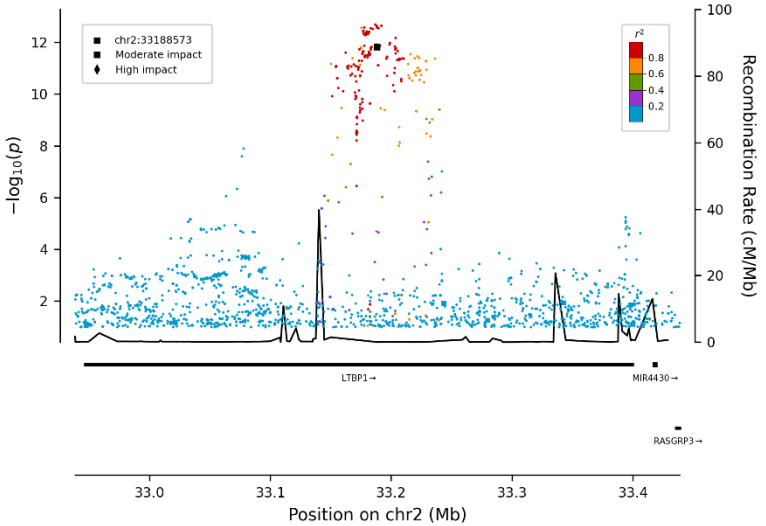
Supplementary Figure 1. Regional plots of the loci associating with CTS

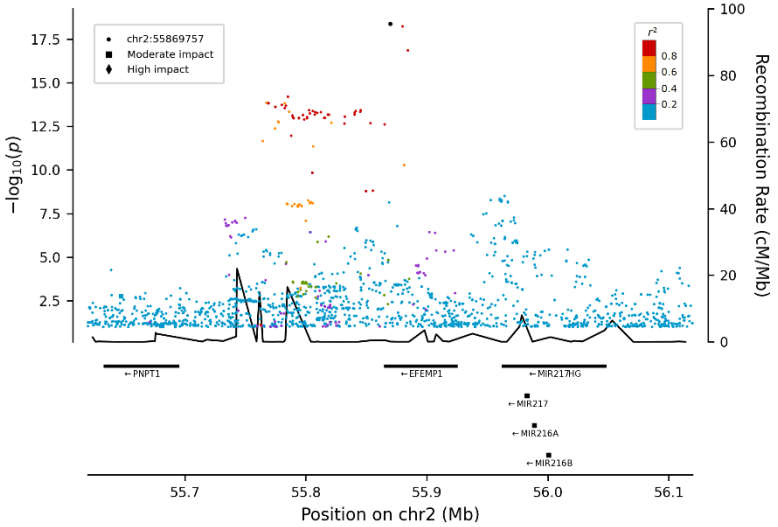
Variants are colored by the degree of correlation (r^2) with the lead variant, which is colored black. Functional variants have a squared (moderate impact) or a diamond shape (high impact). The -$\log_{10}P$-values on the left y-axis (two-sided logistic regression) are plotted for each variant against their chromosomal position (x axis). The right y-axis shows calculated recombination rates based on the Icelandic data at the chromosomal location, plotted as solid black lines. *P*-values are two-sided and derived from a likelihood-ratio test.

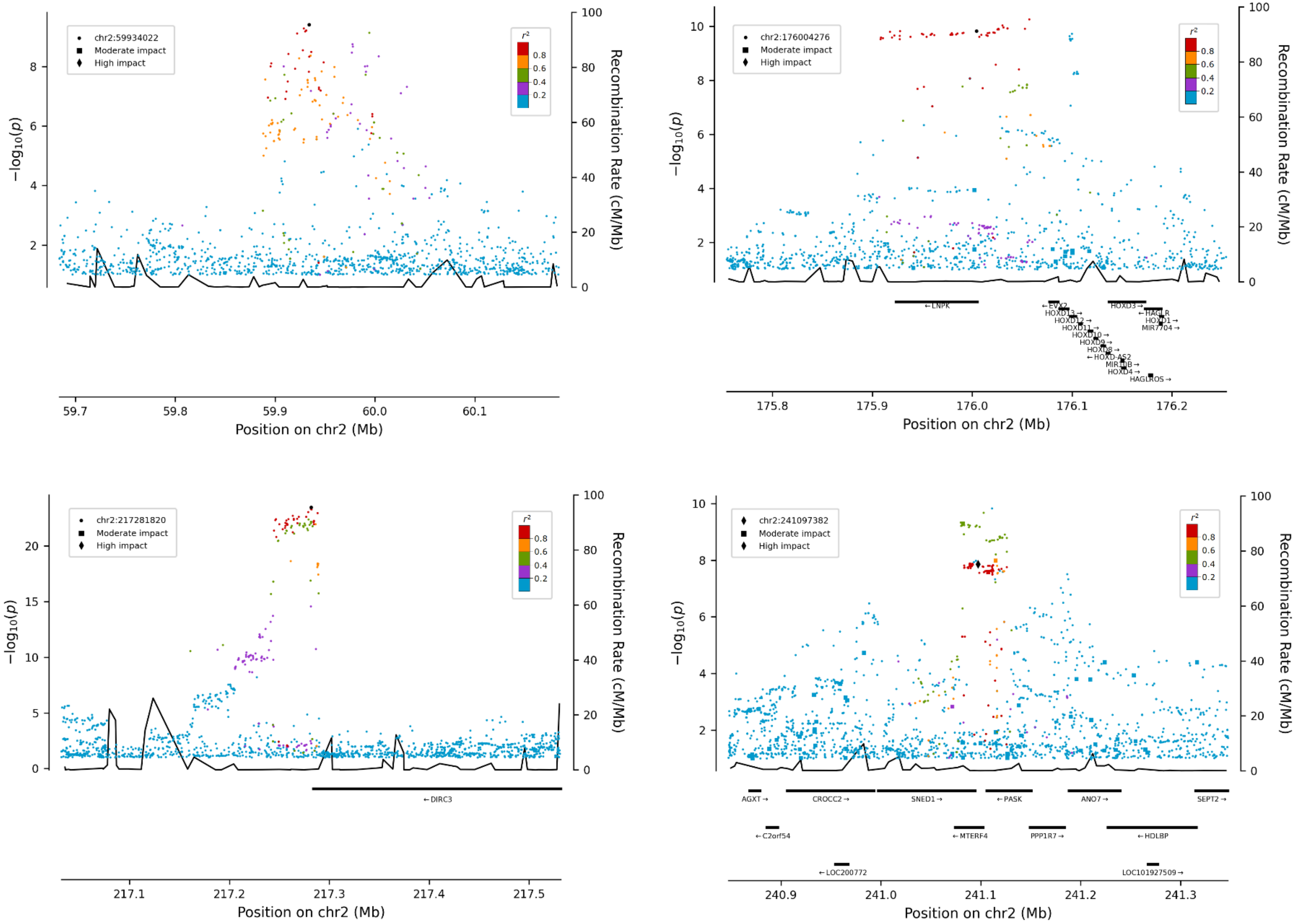


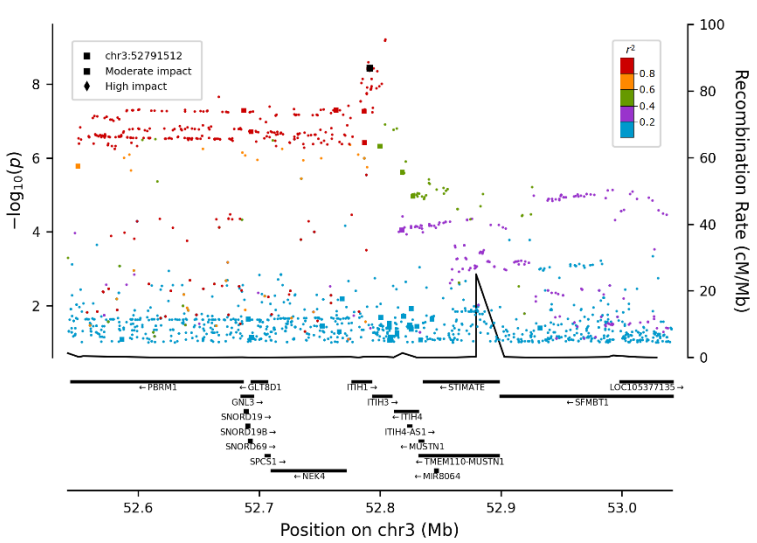

chr1:155320440
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
EFNA5→
←KRTCAP2
EFNA1→
←THBS3
←GBA
←CLK2
←PKLR
←ASH1L
←MIR555
POU5F1P4→
ASH1L-AS1→
SLC50A1→
MTX1→
HCN3→
←DPM3
←GBAP1
FDPS→
TRIM46→
←SCAMP3
←MUC1
←RUSC1-AS1
MIR92B→
RUSC1→
←FAM189B
155.1
155.2
155.3
155.4
155.5
Position on chr1 (Mb)

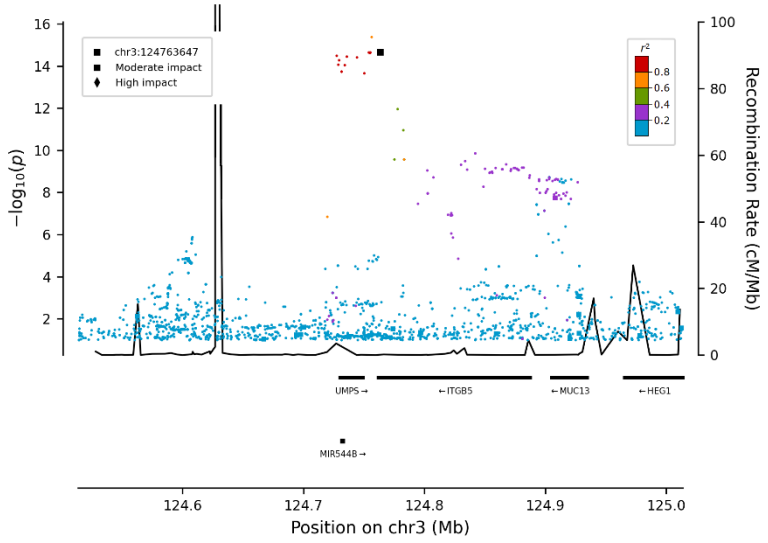

chr1:227662887
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
ZNF678→
←JMJD4
PRSS38→
SNAP47→
LOC105373289→
227.5
227.6
227.7
227.8
227.9
Position on chr1 (Mb)

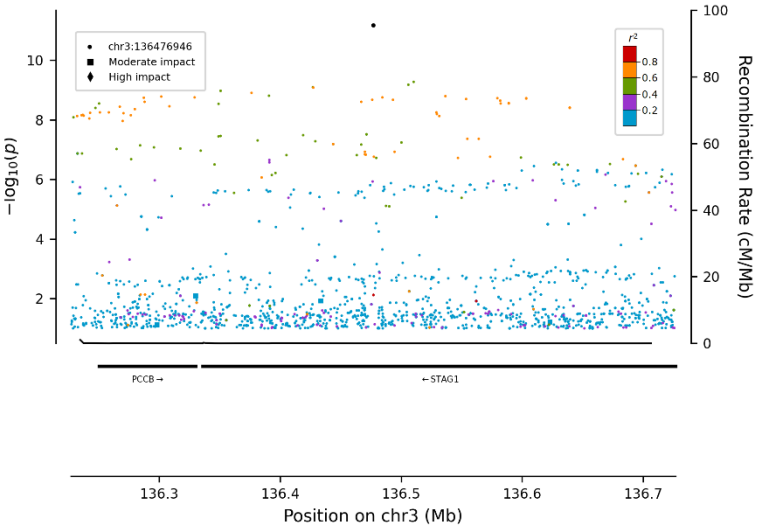

chr2:33188573
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
LTBP1→
MIR4430→
RASGRP3→
33.0
33.1
33.2
33.3
33.4
Position on chr2 (Mb)

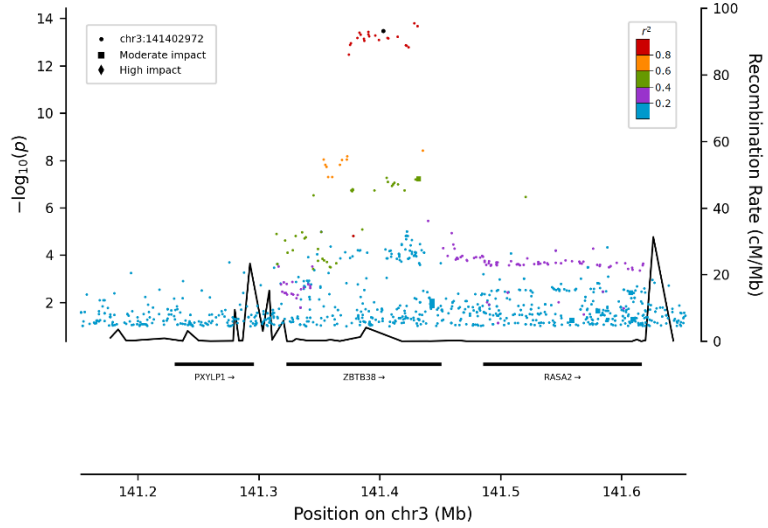

chr2:55869757
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
←PNPT1
←EFEMP1
←MIR217HG
←MIR217
←MIR216A
←MIR216B
55.7
55.8
55.9
56.0
56.1
Position on chr2 (Mb)

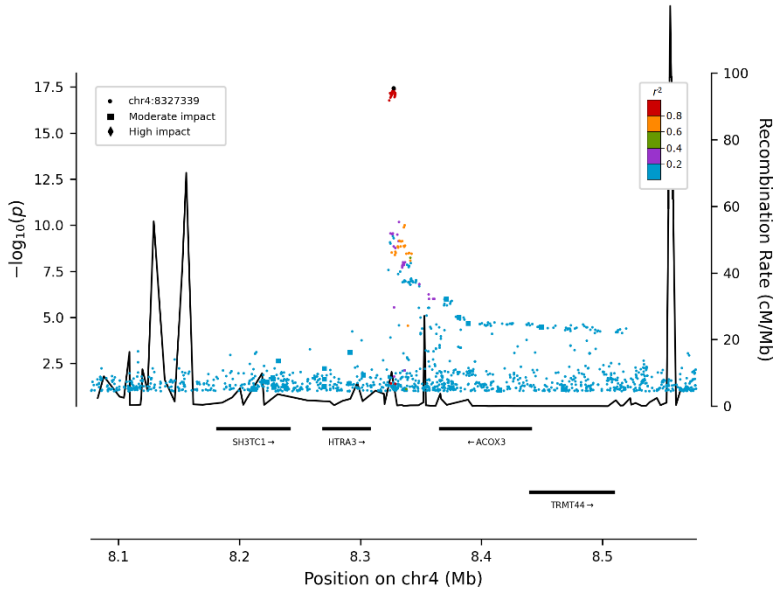

chr2:59934022
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
Position on chr2 (Mb)
chr2:176004276
Moderate impact
High impact
←LNPK
HOXD3→
Position on chr2 (Mb)
chr2:217281820
Moderate impact
High impact
←DIRC3
Position on chr2 (Mb)
chr2:241097382
Moderate impact
High impact
AGXT→
CROCC2→
SNED1→
←PASK
ANO7→
SEPT2→
←C2orf54
←MTERF4
PPP1R7→
←HDLBP
←LOC200772
LOC101927509→
Position on chr2 (Mb)

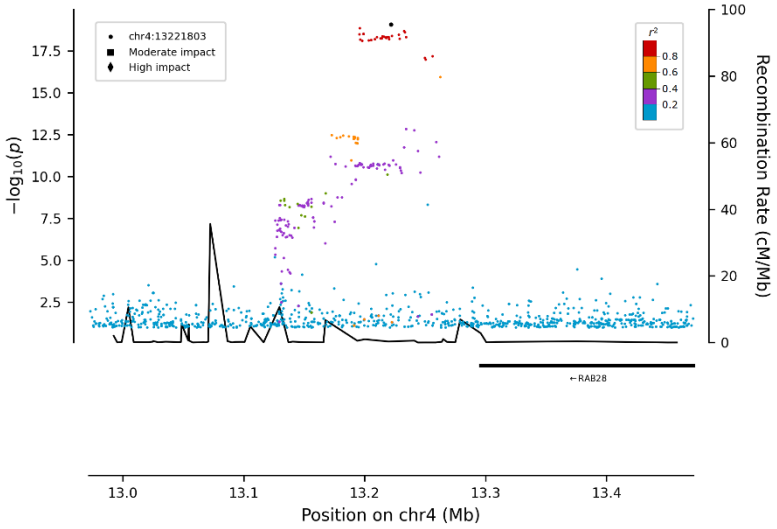

chr3:52791512
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
← PBRM1
← GLTSD1
GNL3→
SNORD19→
SNORD19B→
SNORD69→
SPCS1→
← NEK4
ITIH1→
ITIH3→
← ITIH4
ITIH4-AS1→
← MUSTN1
← TMEM110-MUSTN1
← MIR8064
← STIMATE
LOC105377135→
← SFMBT1
52.6
52.7
52.8
52.9
53.0
Position on chr3 (Mb)

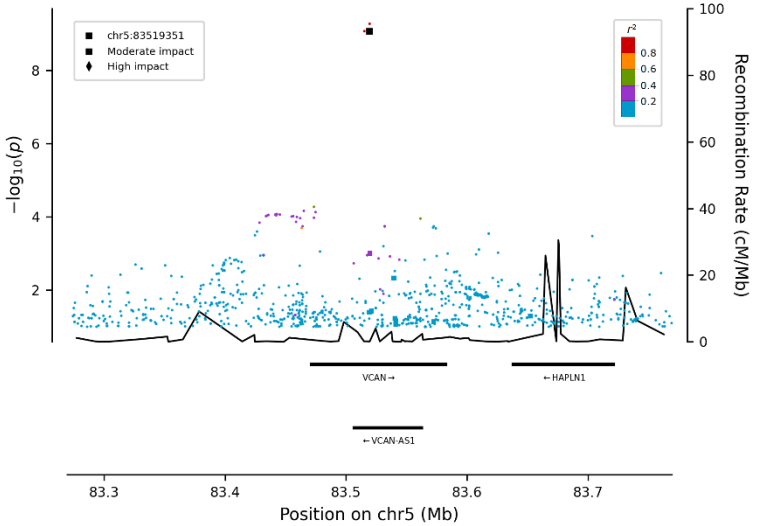

chr3:124763647
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
UMPS→
← ITGB5
← MUC13
← HEG1
MIR544B→
124.6
124.7
124.8
124.9
125.0
Position on chr3 (Mb)

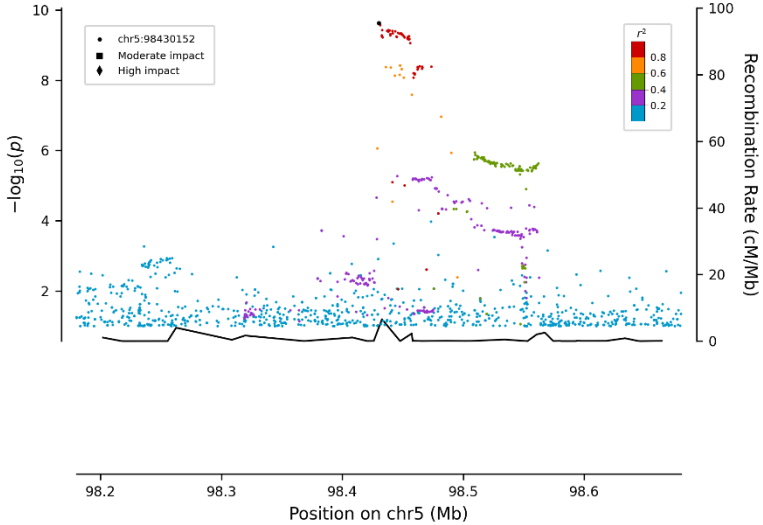

chr3:136476946
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
PCCB→
← STAG1
136.3
136.4
136.5
136.6
136.7
Position on chr3 (Mb)

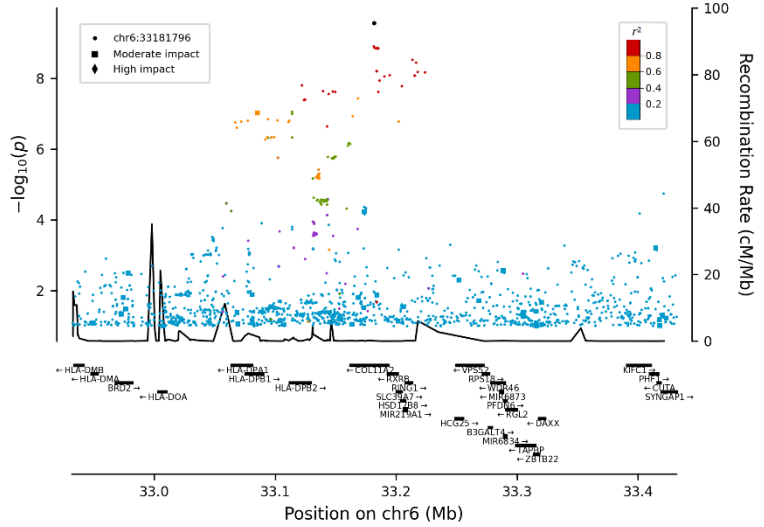

chr3:141402972
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
PXYLP1→
ZBTB38→
RASA2→
141.2
141.3
141.4
141.5
141.6
Position on chr3 (Mb)

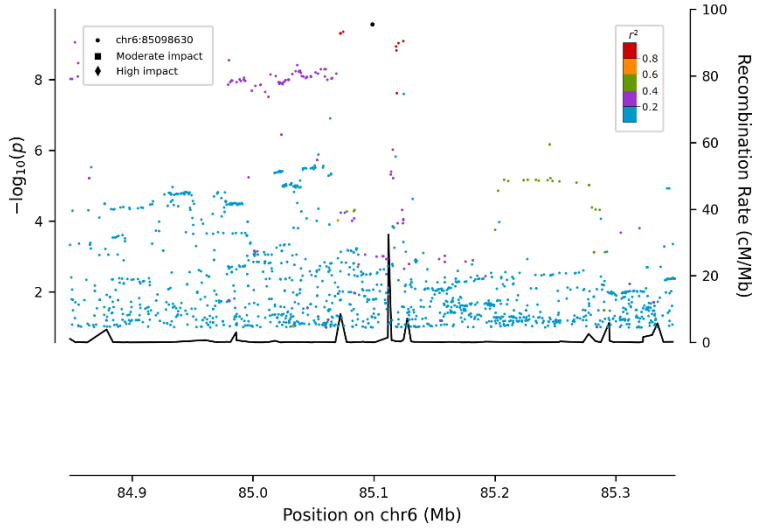

chr4:8327339
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
SH3TC1→
HTRA3→
←ACOX3
TRMT44→
Position on chr4 (Mb)

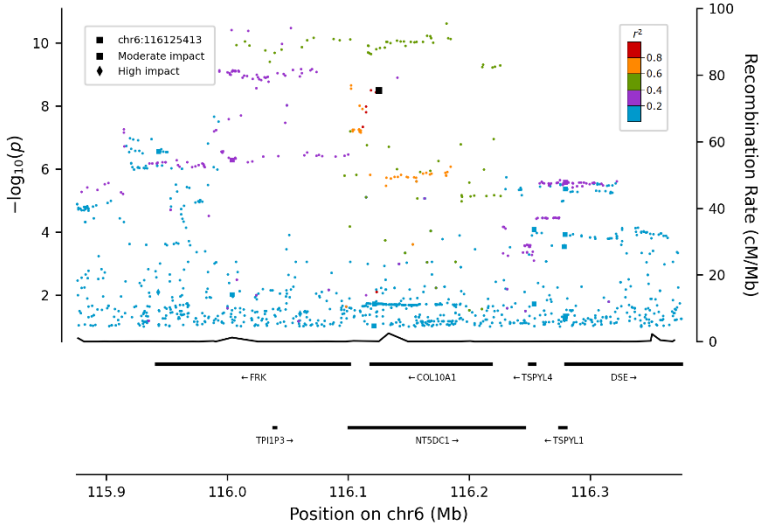

chr4:13221803
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
←RAB28
Position on chr4 (Mb)

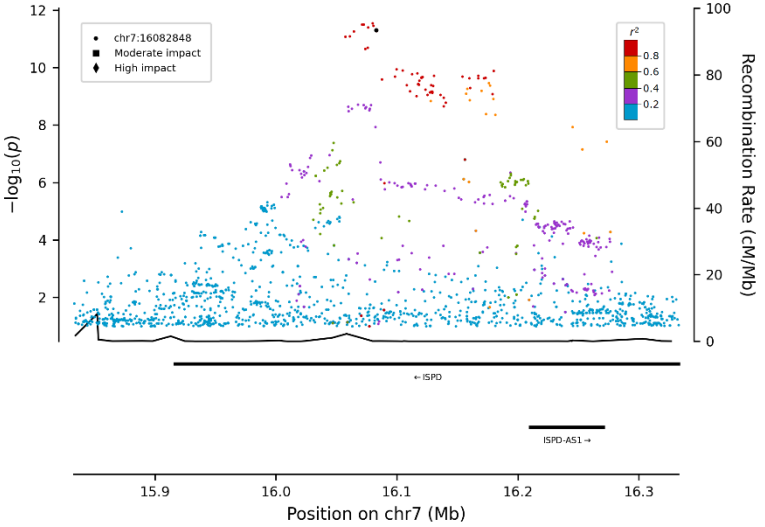

chr5:83519351
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
VCAN→
←HAPLN1
←VCAN-AS1
Position on chr5 (Mb)

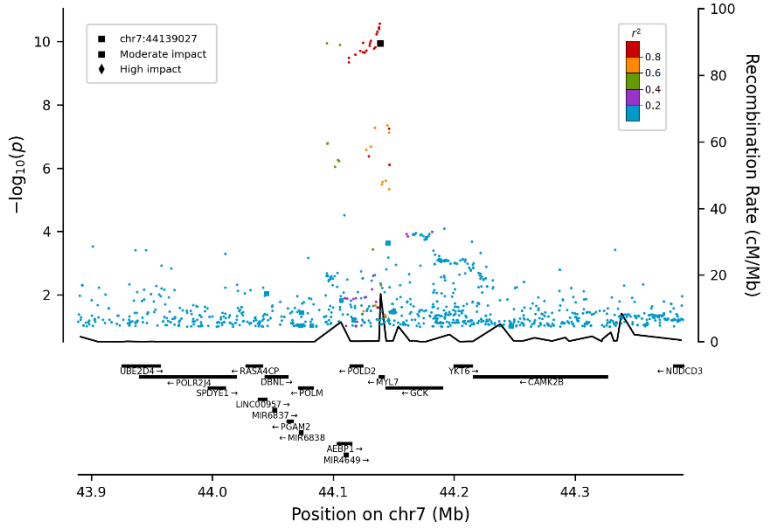

chr5:98430152
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
Position on chr5 (Mb)

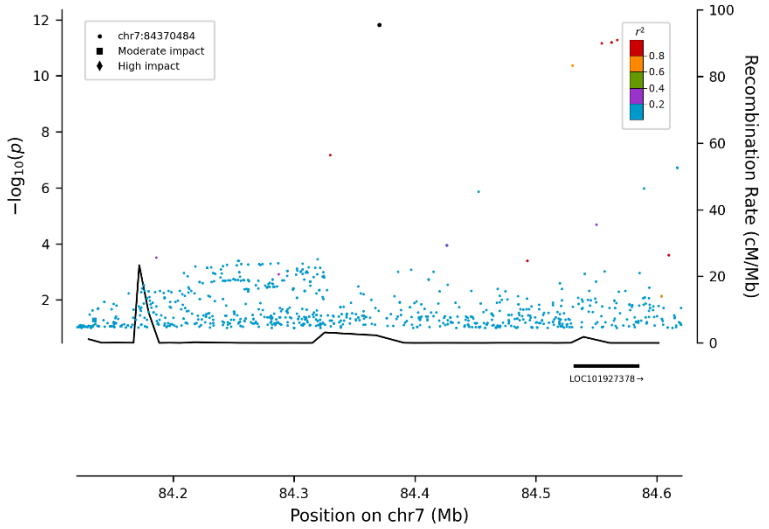

chr6:33181796
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
Position on chr6 (Mb)

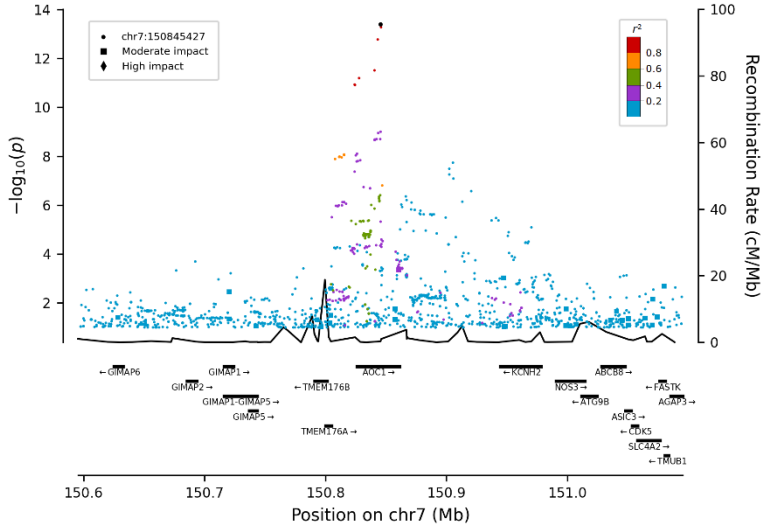

chr6:85098630
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
Position on chr6 (Mb)

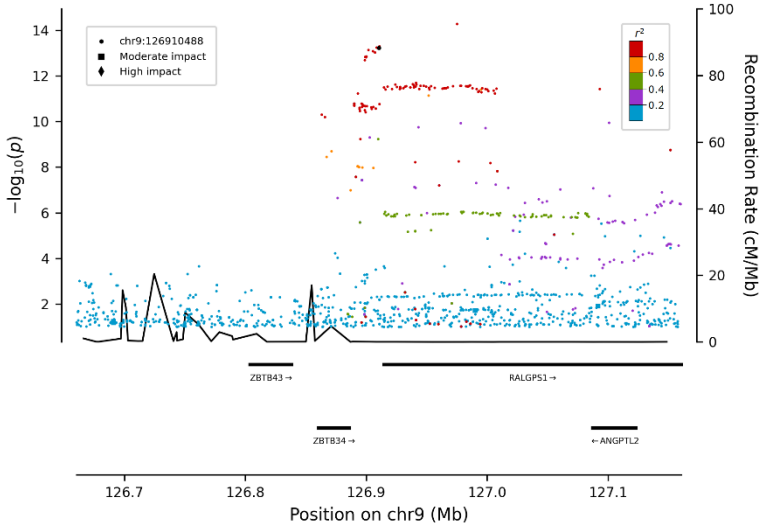

chr6:116125413
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
Position on chr6 (Mb)

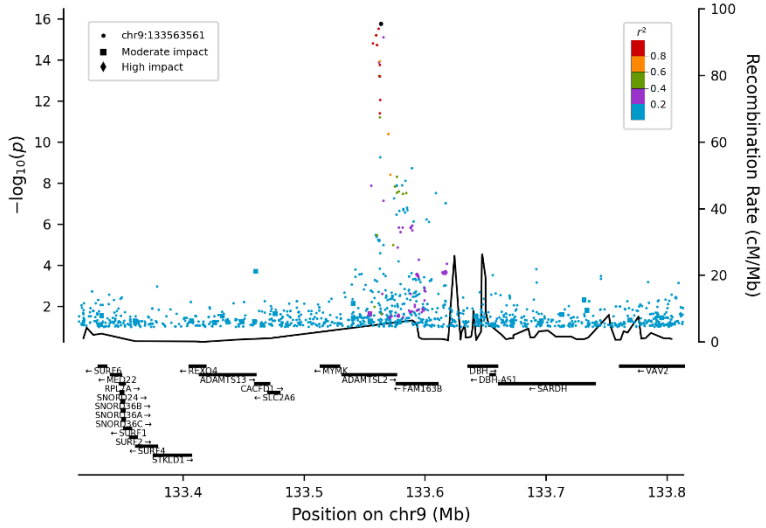

chr7:16082848
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
Position on chr7 (Mb)

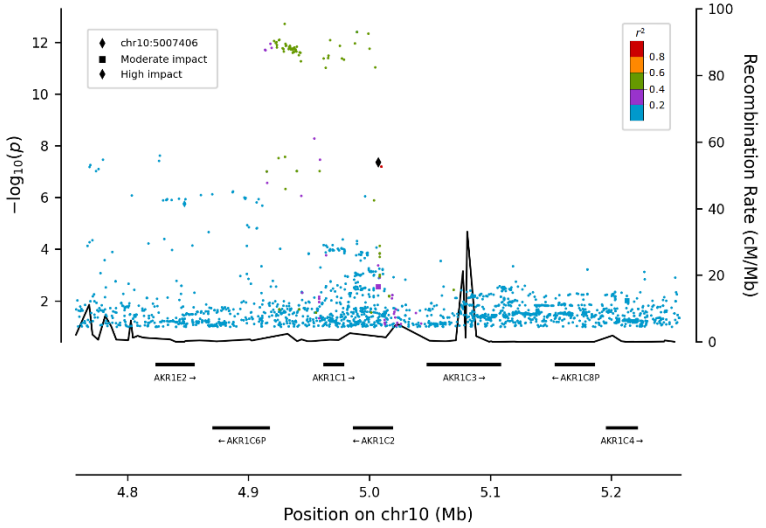

chr7:44139027
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
UBE2D4→
←POLR2J4
SPDYE1→
LINC00957→
MIR6837→
←PGAM2
←MIR6838
AEBP1→
MIR4649→
←RASA4CP
DBNL→
←POLM
←POLD2
←MYL7
←GCK
YKT6→
←CAMK2B
←NUDCD3
43.9
44.0
44.1
44.2
44.3
Position on chr7 (Mb)

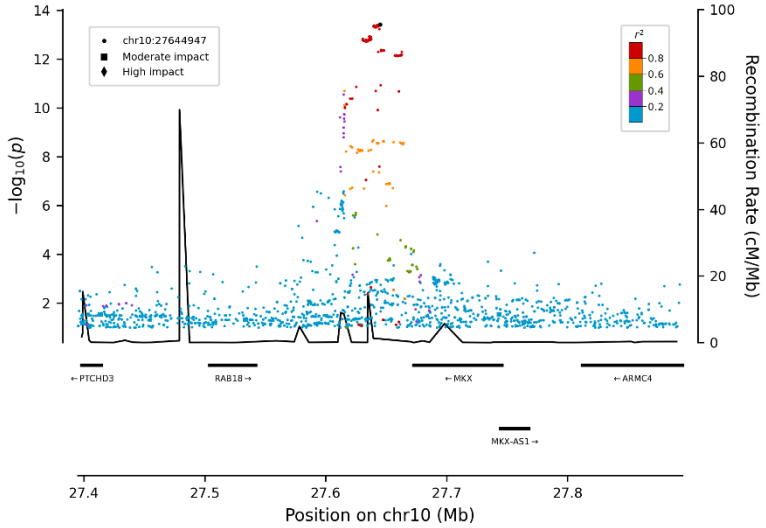

chr7:84370484
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
LOC101927378→
84.2
84.3
84.4
84.5
84.6
Position on chr7 (Mb)

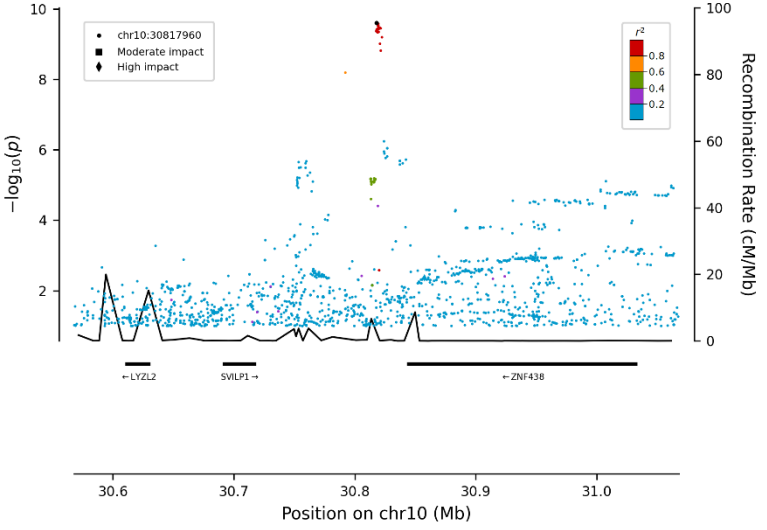

chr7:150845427
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
←GIMAP6
GIMAP1→
GIMAP2→
GIMAP1-GIMAP5→
GIMAP5→
←TMEM176B
TMEM176A→
A0C1→
←KCNH2
NOS3→
←ATG9B
ABCB8→
←FASTK
ACAP3→
ASIC3→
←CDK5
SLC4A2→
←TMUB1
150.6
150.7
150.8
150.9
151.0
Position on chr7 (Mb)

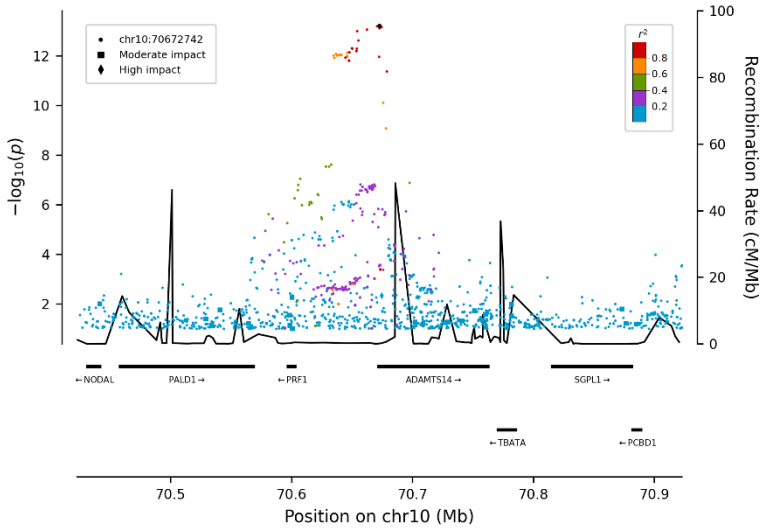

chr9:126910488
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
ZBTB43→
RALGPS1→
ZBTB34→
←ANGPTL2
126.7
126.8
126.9
127.0
127.1
Position on chr9 (Mb)

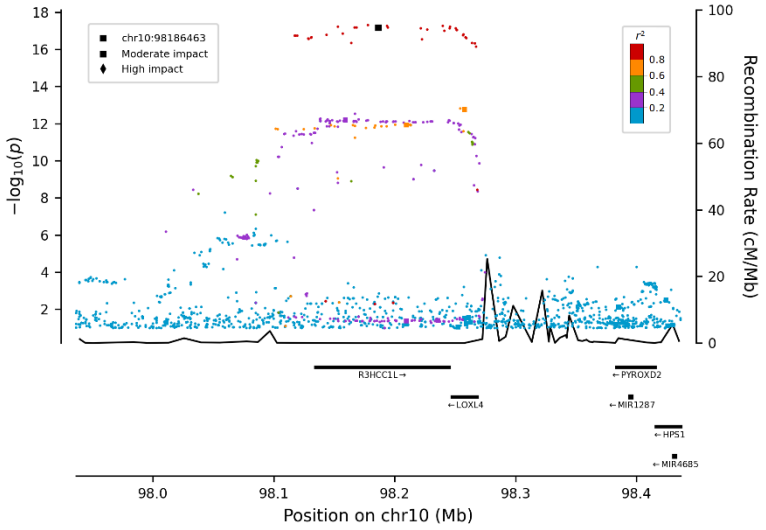

chr9:133563561
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
Position on chr9 (Mb)
133.4
133.5
133.6
133.7
133.8

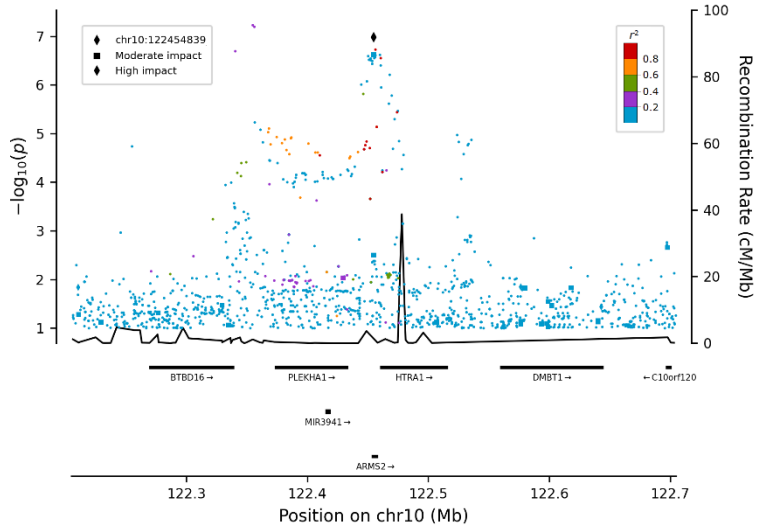

chr10:5007406
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
Position on chr10 (Mb)
4.8
4.9
5.0
5.1
5.2

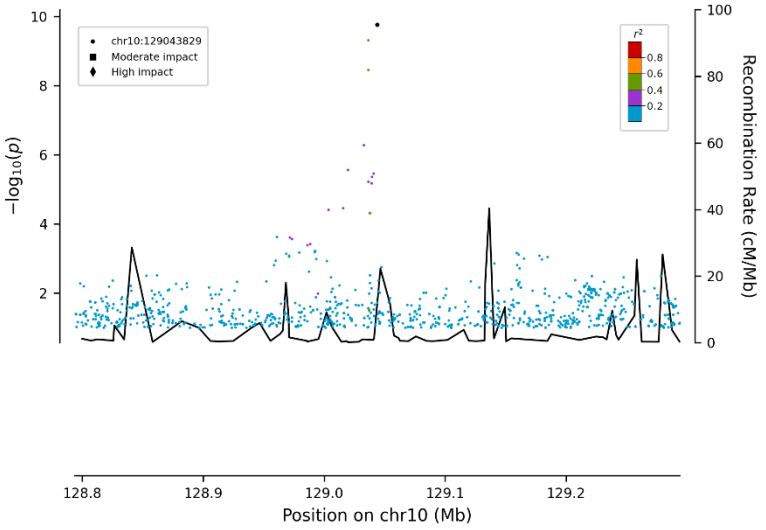

chr10:27644947
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
Position on chr10 (Mb)
27.4
27.5
27.6
27.7
27.8

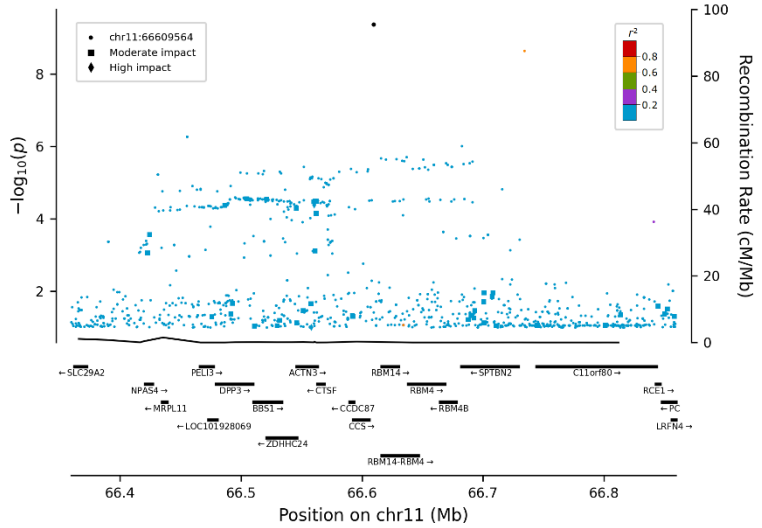

chr10:30817960
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
Position on chr10 (Mb)
30.6
30.7
30.8
30.9
31.0

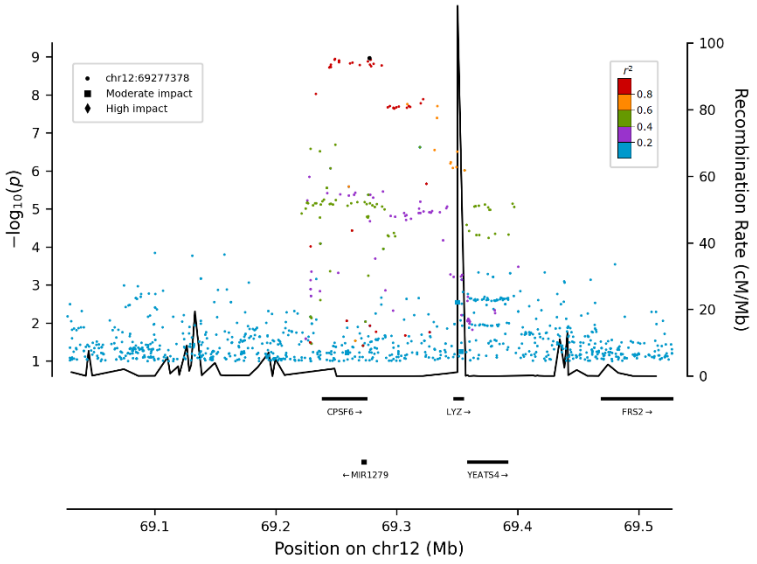

chr10:70672742
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
←NODAL
PALD1→
←PRF1
ADAMTS14→
SGPL1→
←TBATA
←PCBD1
Position on chr10 (Mb)

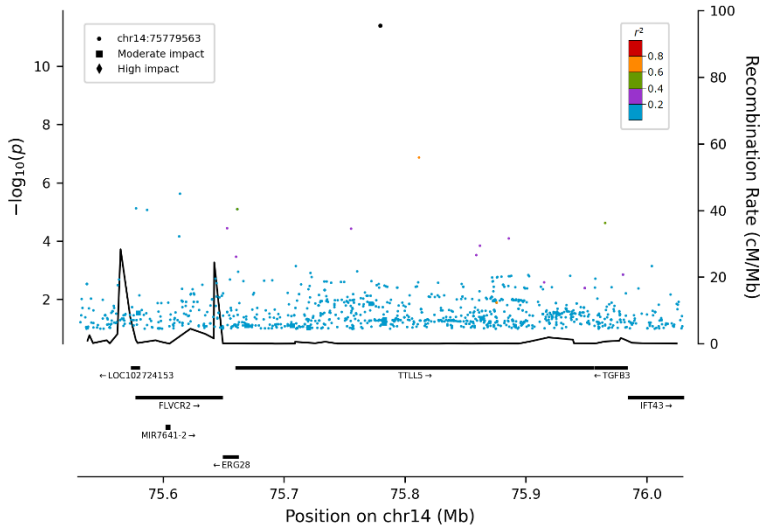

chr10:98186463
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
R3HCC1L→
←PYROXD2
←LOXL4
←MIR1287
←HPS1
←MIR4685
Position on chr10 (Mb)

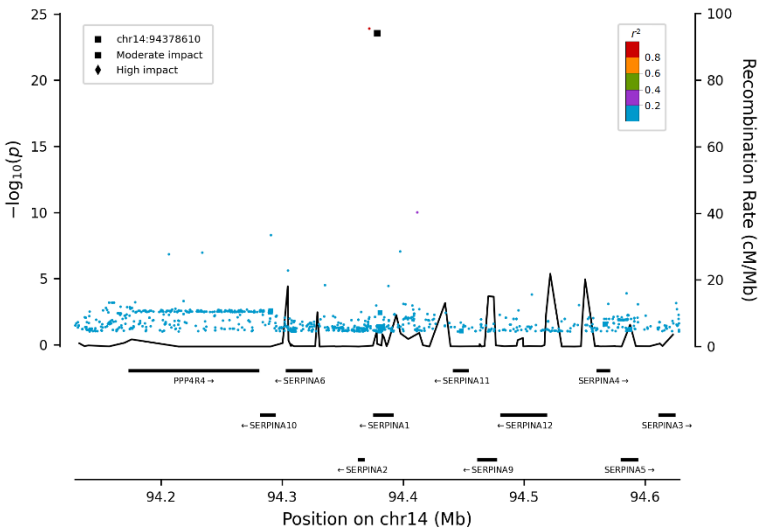

chr10:122454839
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
BTBD16→
PLEKHA1→
HTRA1→
DMBT1→
←C10orf120
MIR3941→
ARMS2→
Position on chr10 (Mb)

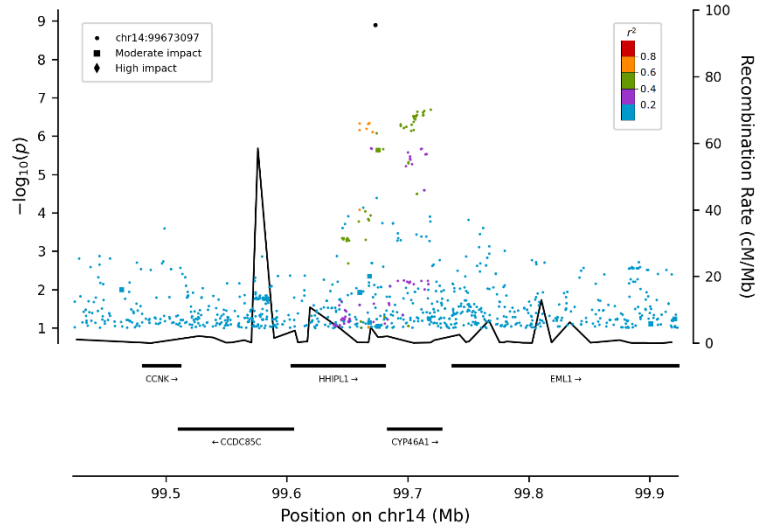

chr10:129043829
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
Position on chr10 (Mb)

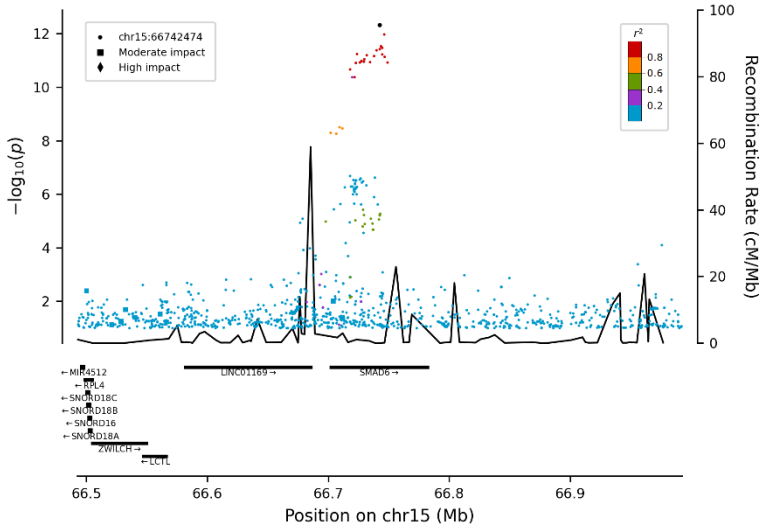

chr11:66609564
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
SLC29A2
NPAS4
MRPL11
LOC101928069
PELI3
DPP3
BBS1
ZDHHC24
ACTN3
CTSF
CCDC87
CCS
RBM14
RBM4
RBM4B
RBM14-RBM4
SPTBN2
C11orf80
RCE1
PC
LRFN4
66.4
66.5
66.6
66.7
66.8
Position on chr11 (Mb)

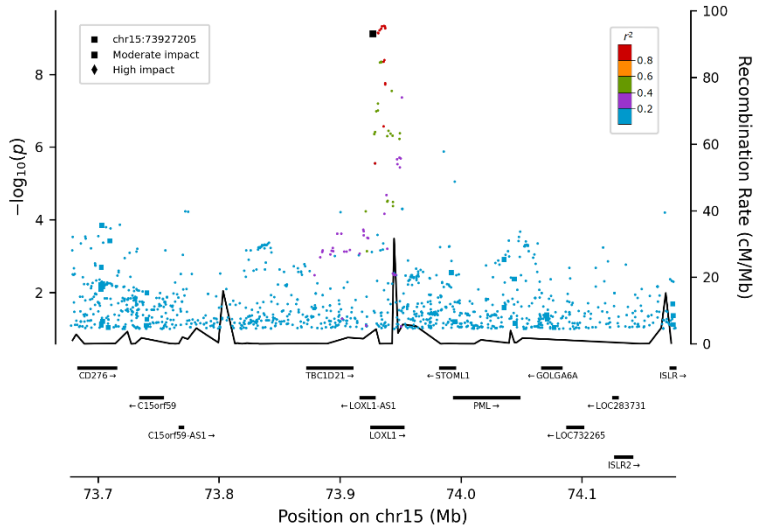

chr12:69277378
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
CPSF6
LYZ
FRS2
MIR1279
YEATS4
69.1
69.2
69.3
69.4
69.5
Position on chr12 (Mb)

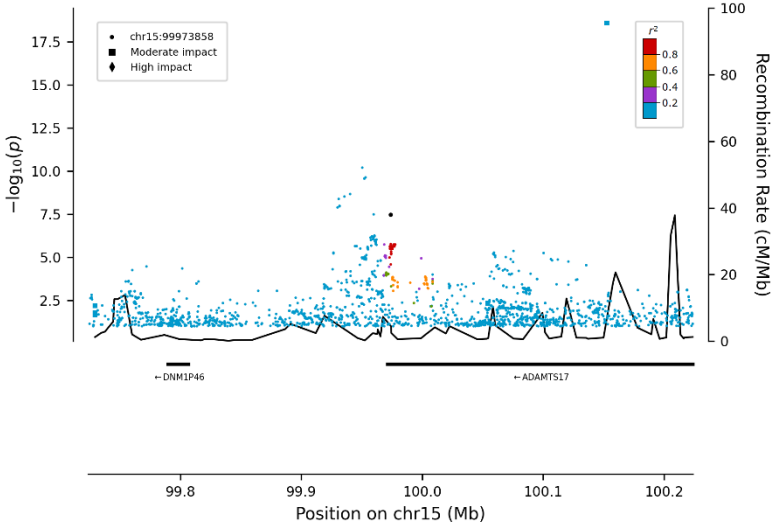

chr14:75779563
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
LOC102724153
FLVCR2
MIR7641-2
ERG28
TTLL5
TGFB3
IFT43
75.6
75.7
75.8
75.9
76.0
Position on chr14 (Mb)

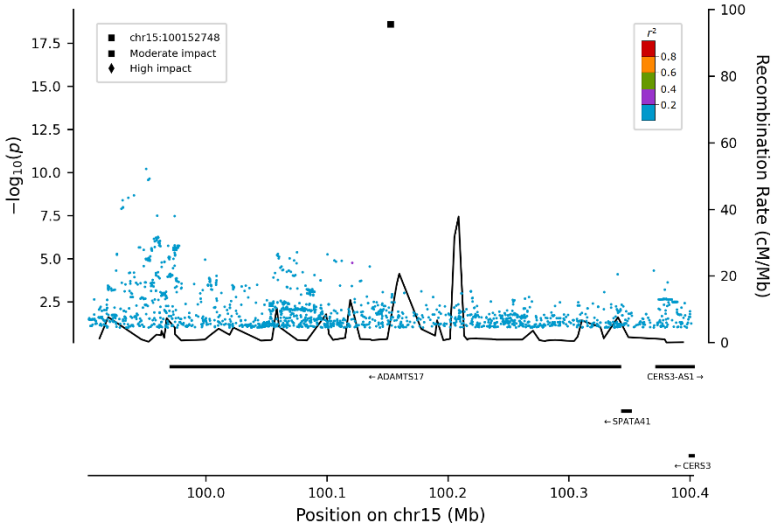

chr14:94378610
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
PPP4R4
SERPINA6
SERPINA11
SERPINA4
SERPINA10
SERPINA1
SERPINA12
SERPINA3
SERPINA2
SERPINA9
SERPINA5
94.2
94.3
94.4
94.5
94.6
Position on chr14 (Mb)

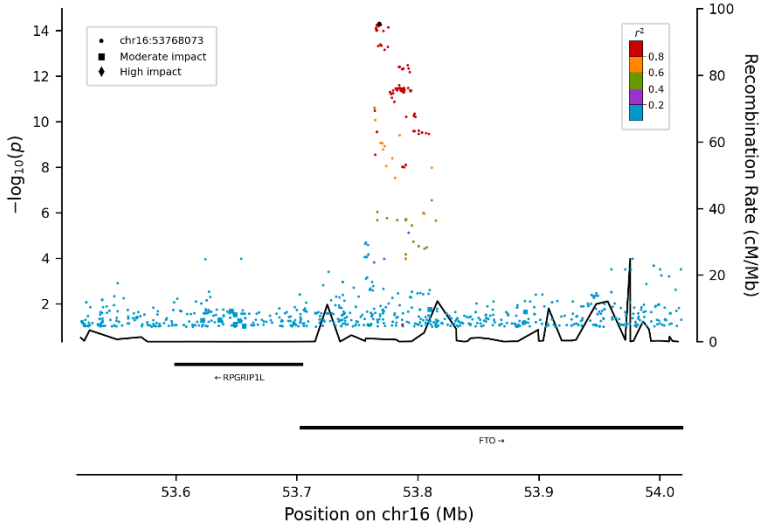

chr14:99673097
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
CCNK→
HHIPL1→
EML1→
←CCDC85C
CYP46A1→
99.5
99.6
99.7
99.8
99.9
Position on chr14 (Mb)

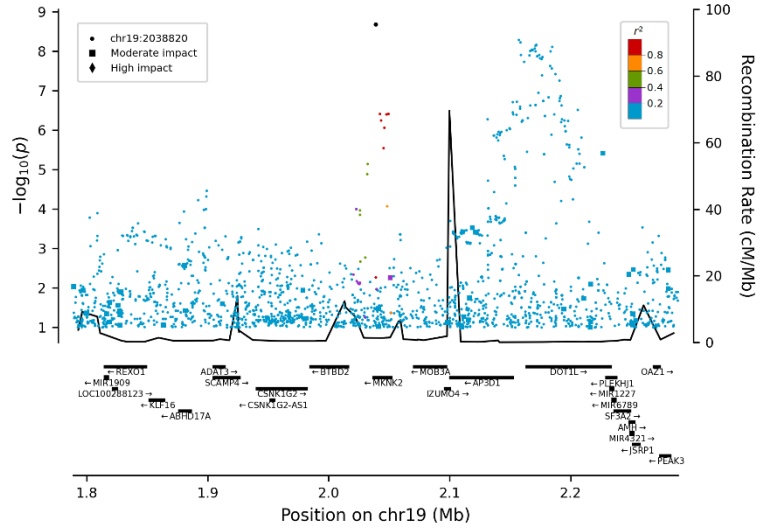

chr15:66742474
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
←MIR4512
←RPL4
←SNORD18C
←SNORD18B
←SNORD16
←SNORD18A
ZWILCH→
←LCTL
LINC01169→
SMAD6→
66.5
66.6
66.7
66.8
66.9
Position on chr15 (Mb)

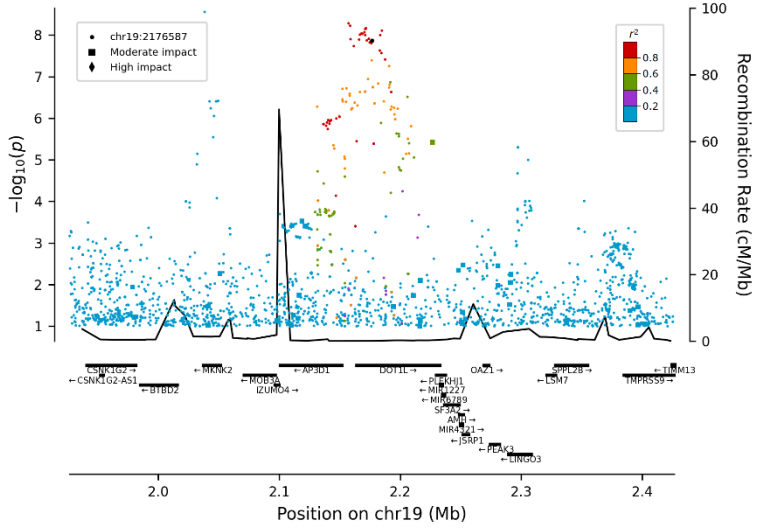

chr15:73927205
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
CD276→
TBC1D21→
←STOML1
←GOLGA6A
ISLR→
←C15orf59
←LOXL1-AS1
PML→
←LOC283731
C15orf59-AS1→
LOXL1→
←LOC732265
ISLR2→
73.7
73.8
73.9
74.0
74.1
Position on chr15 (Mb)

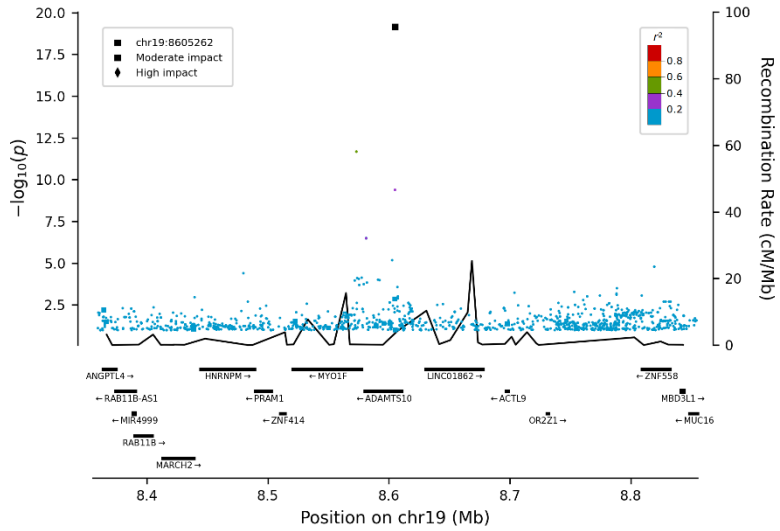

chr15:99973858
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
←DNM1P46
←ADAMTS17
99.8
99.9
100.0
100.1
100.2
Position on chr15 (Mb)

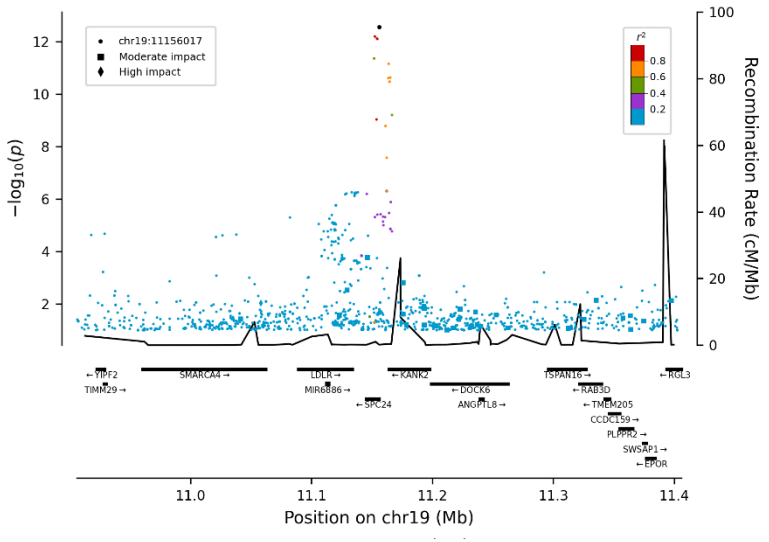

chr15:100152748
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
←ADAMTS17
CERS3-AS1→
←SPATA41
←CERS3
Position on chr15 (Mb)

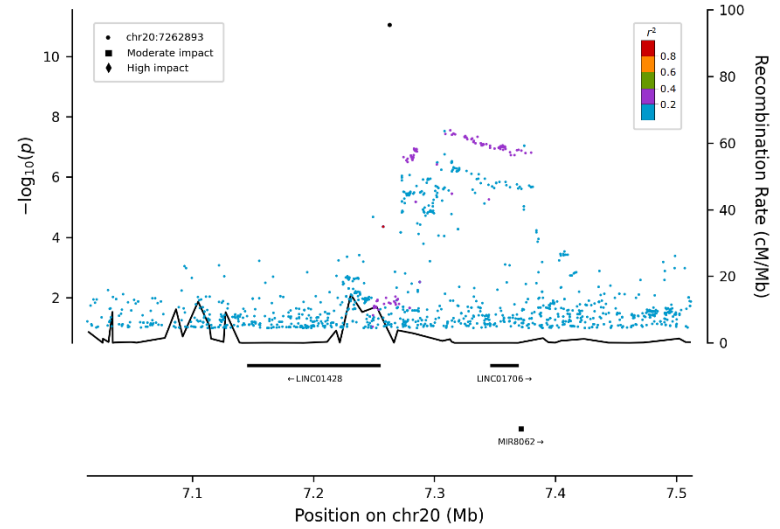

chr16:53768073
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
←RPGRIP1L
FTO→
Position on chr16 (Mb)

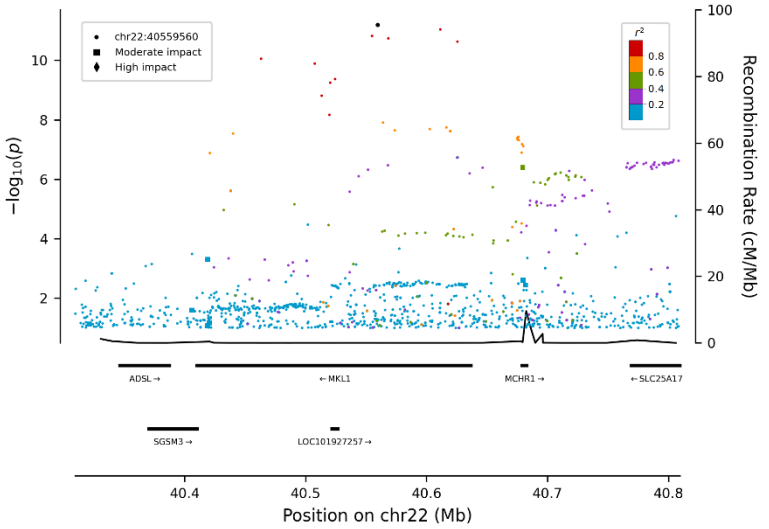

chr19:2038820
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
Position on chr19 (Mb)

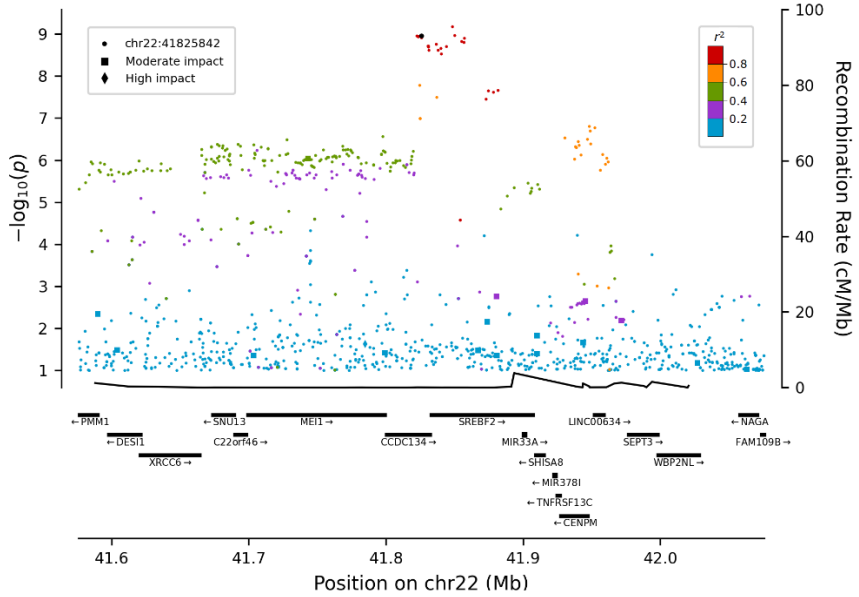

chr19:2176587
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
Position on chr19 (Mb)


chr19:8605262
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
ANGPTL4→
←RAB11B-AS1
←MIR4999
RAB11B→
MARCH2→
HNRNPM→
←PRAM1
←ZNF414
←MYO1F
←ADAMTS10
LINC01862→
←ACTL9
OR2Z1→
←ZNF558
MBD3L1→
←MUC16
Position on chr19 (Mb)


chr19:11156017
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
←YIPF2
TIMM29→
SMARCA4→
LDLR→
MIR6886→
←SPC24
←KANK2
←DOCK6
ANGPTL8→
TSPAN16→
←RAB3D
←TMEM205
CCDC159→
PLPPR2→
SWSAP1→
←EPOR
←RGL3
Position on chr19 (Mb)

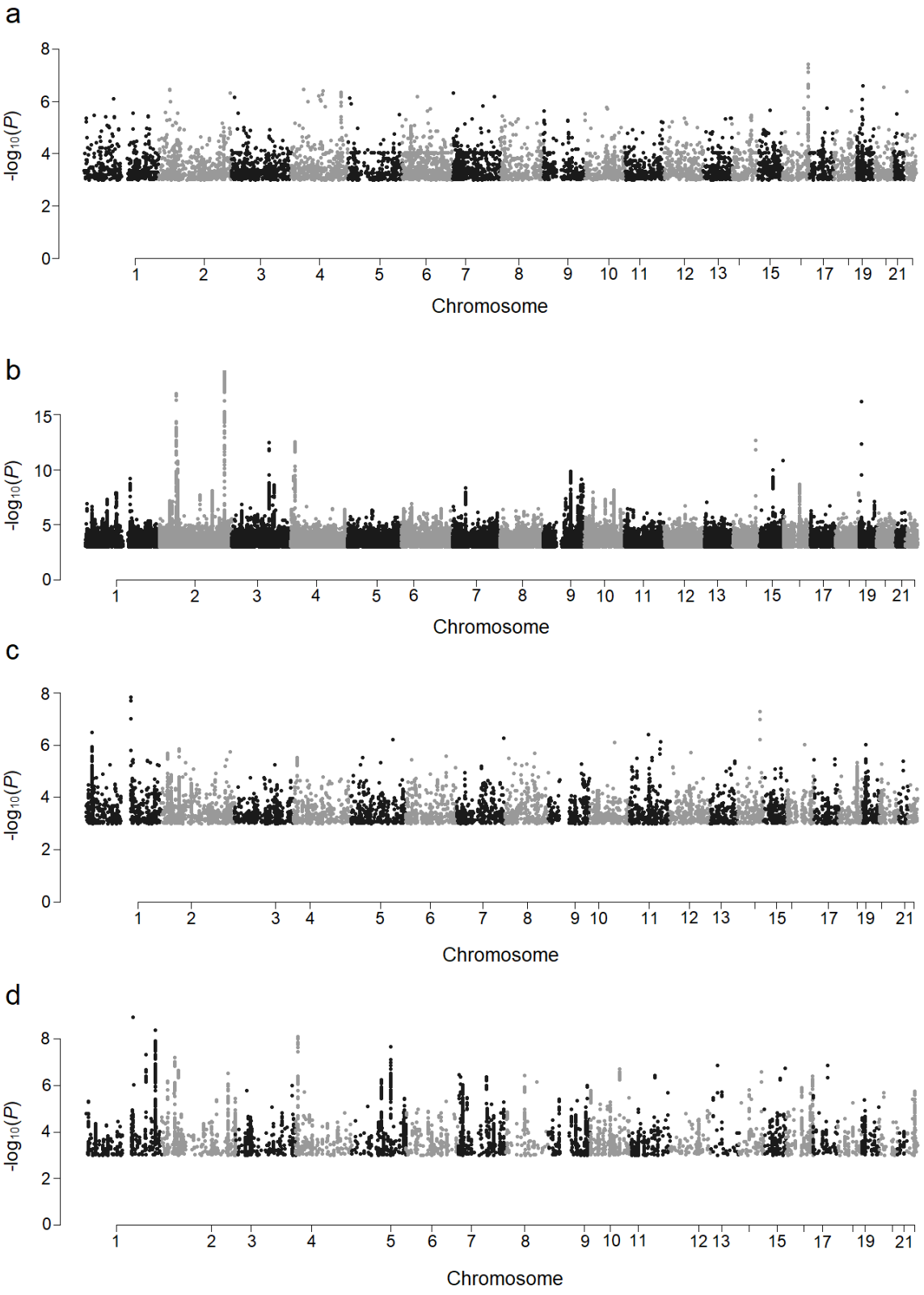

chr20:7262893
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
←LINC01428
LINC01706→
MIR8062→
Position on chr20 (Mb)


chr22:40559560
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
ADSL→
←MKL1
MCHR1→
←SLC25A17
SGSM3→
LOC101927257→
Position on chr22 (Mb)


chr22:41825842
Moderate impact
High impact
r^2
0.8
0.6
0.4
0.2
$-\log_{10}(p)$
Recombination Rate (cM/Mb)
PMM1
SNU13
MEI1
SREBF2
LINC00634
NAGA
DESI1
C22orf46
CCDC134
MIR33A
SEPT3
FAM109B
XRCC6
SHISA8
WBP2NL
MIR378I
TNFRSF13C
CENPM
41.6
41.7
41.8
41.9
42.0
Position on chr22 (Mb)

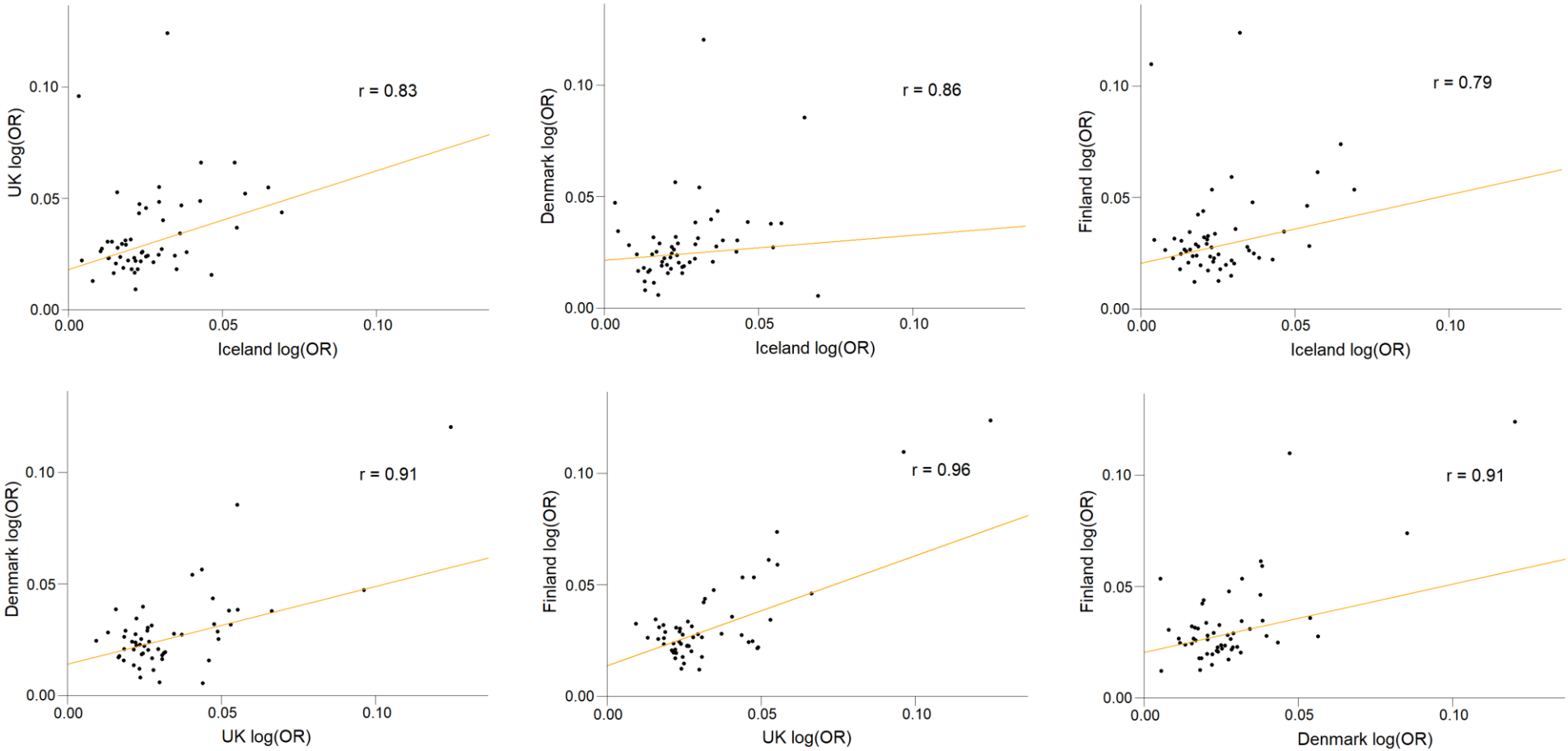
Supplementary Figure 2. Manhattan plot for individual datasets

Manhattan plots showing GWAS results under an additive model for a) Iceland, b) the UK, c) Denmark, and d) Finland. The -$\log_{10}$*P*-values (y-axis) are plotted for each variant against their chromosomal position (x-axis). *P*-values are two-sided and derived from a likelihood-ratio test.



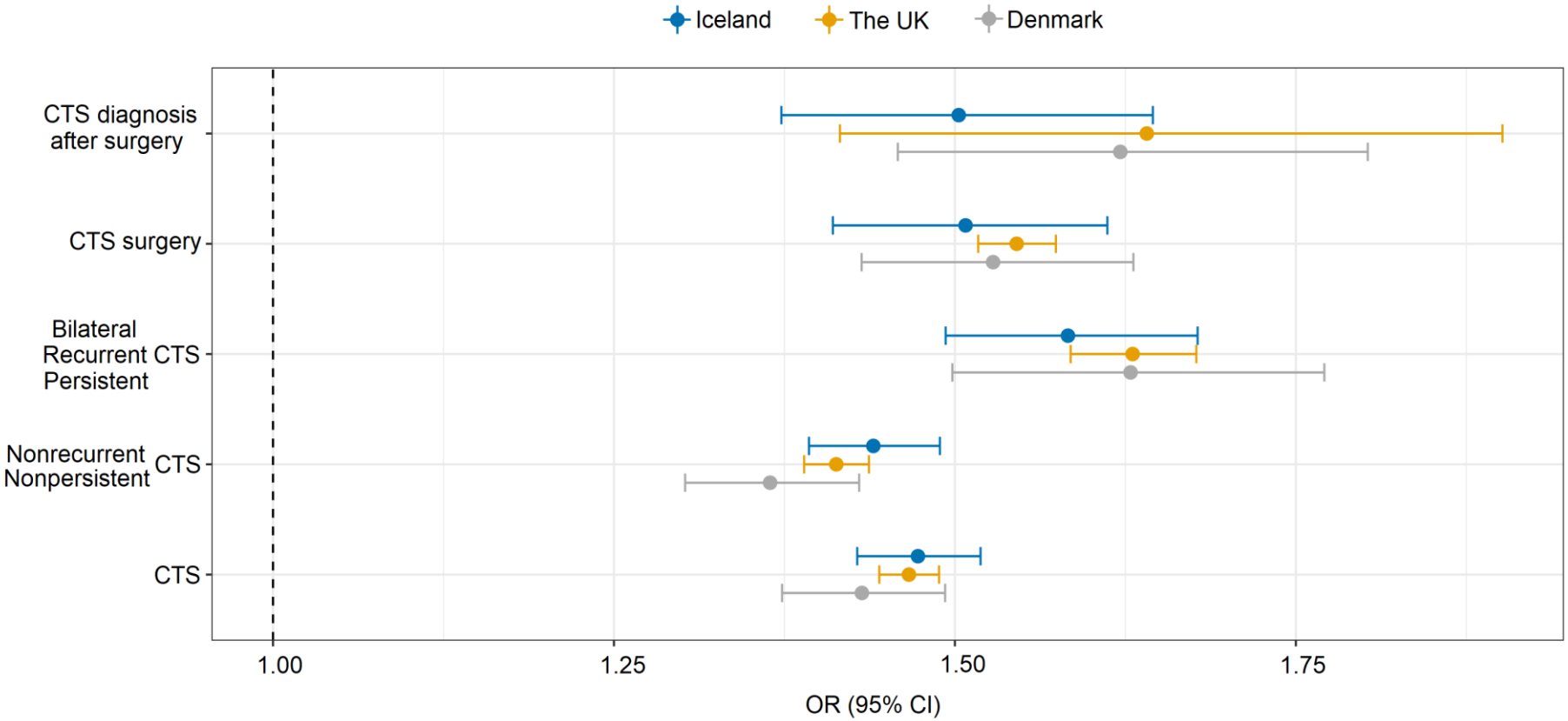
Supplementary Figure 3. Correlation of effects

The correlation of effect sizes for the 53 CTS variants is plotted for the four datasets. The orange line represents results from two-sided weighted linear regression using MAF(1-MAF) as weight. Pearson‘s correlation coefficient (r) is shown in each plot

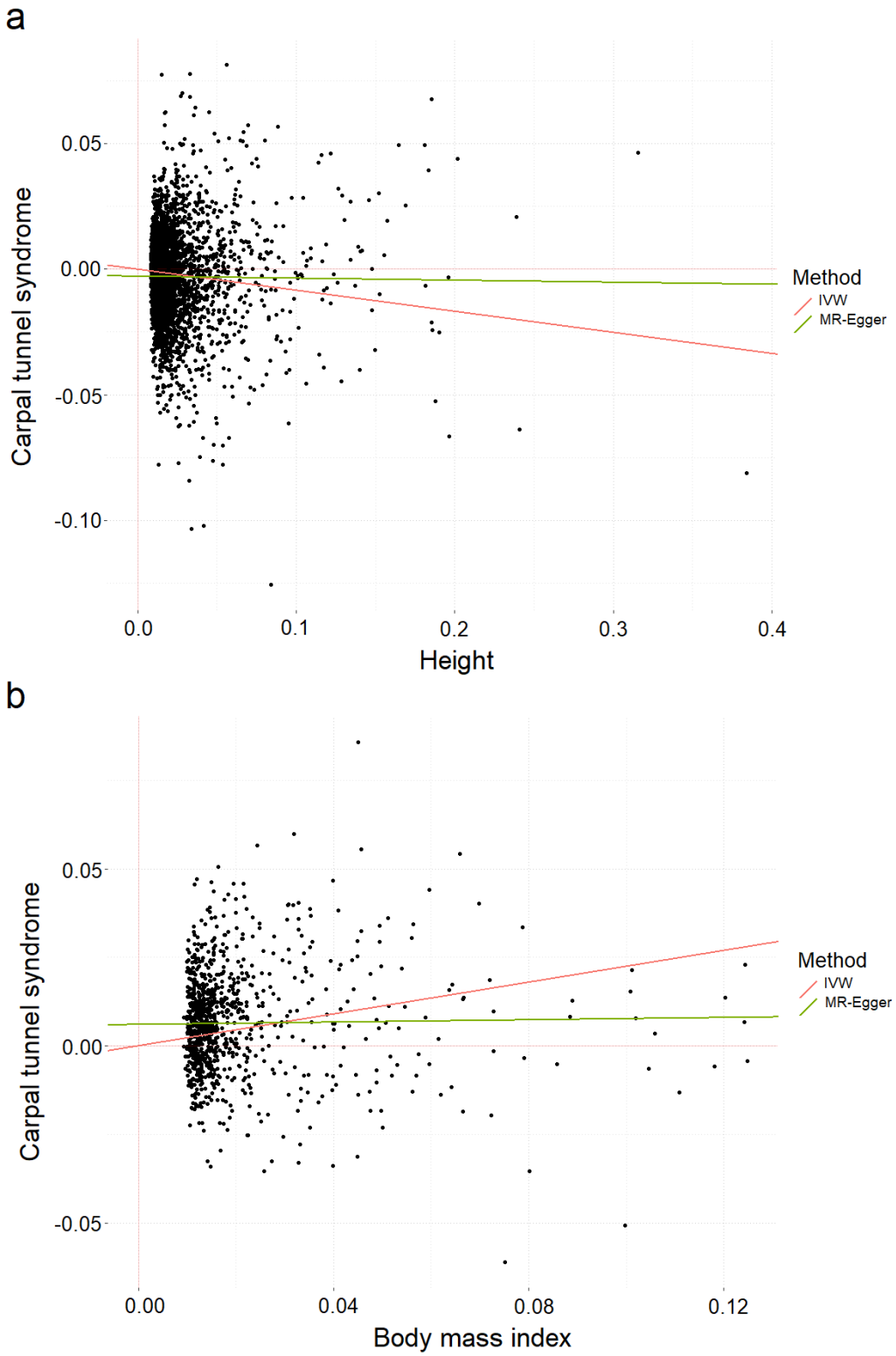


Supplementary Figure 4. Genetic propensity for CTS in different groups

CTS PRSs were constructed for Iceland (navy), The UK (orange), and Denmark (gray). Bilateral, recurrent, or persistent CTS cases had higher PRS than nonrecurrent or nonpersistent cases in all three datasets (Iceland *P*-het = 0.0019, The UK *P*-het = 4.3×10^{-18}, and Denmark *P*-het = 3.6×10^{-4}). The point estimate of OR and 95% CI (error bars) adjusted for genomic inflation on x-axis, were estimated in suggested severity groups, y-axis.



Supplementary Figure 5. Mendelian randomization
Mendelian randomization analyses using inverse variance-weighted (IVW) and MR-Egger methods where the exposure variables were a) height and b) body mass index (BMI) and the outcome variable CTS. We used 3290 variants previously associated with height and 941 variants previously associated with BMI.



Supplementary Table 1. Demographics of the carpal tunnel syndrome datasets
We had patient onset information for 8077 from Iceland, 18.880 from the UK, and 9323 from Denmark. The bilateral, recurrent, or persistent cases were defined as having at least 6 months in between health encounters. Demographic numbers for the Finnish dataset were accessed at https://r5.risteys.finngen.fi/phenocode/G6_CARPTU.

Dataset	Sex	Count (%)	Mean age at first diagnosis	Median age at first diagnosis	Bilateral, recurrent, or persistent cases (%)
Iceland	Females	5038 (62.0)	51.3	51	23.4
	Males	3084 (38.0)	53.1	53	19.7
The UK	Females	13514 (68.1)	56.3	57	27.2
	Males	6335 (31.9)	59.0	60	25.1
Denmark	Females	5881 (60.9)	55.9	55	28.0
	Males	3783 (39.1)	57.4	58	27.4
Finland	Females	7761 (69.2)	52.5	-	-
	Males	3447 (30.8)	55.4	-	-
Total	Females	32.194 (65.9)	55.1	56	27.1
	Males	16.649 (34.1)	57.1	58	25.4

Supplementary Table 2. Weighted genome-wide significance thresholds
The thresholds were estimated from the Icelandic data. DHS Dnase I hypersensitivity sites

Impact	Type of variants	Broad DHS	Significance threshold
High	Splice donor, splice acceptor, stop gained, frameshift, stop lost, initiator codon	-	1.3×10^{-7}
Moderate	Inframe indels, missense, splice region, stop retained	-	2.6×10^{-8}
Low	Synonymous, 5' UTR, 3' UTR, up- and downstream	-	2.4×10^{-9}
Other	Intronic, intergenic	Yes	1.2×10^{-9}
		No	4.0×10^{-10}

Supplementary Table 3. Mendelian randomization

Mendelian randomization analyses using inverse variance-weighted (IVW) and MR-Egger methods where the exposure variables were a) height and b) body mass index (BMI) and the outcome variable CTS. We used 3290 variants previously associated with height[1] and 941 variants previously associated with BMI[1]. The confidence intervals (CI) were calculated with t-distribution.

Exposure	Method	Estimate	SE	95% CI	*P*-value
Height	IVW	-0.083	0.010	-0.10, -0.064	1.3×10^{-16}
	MR-Egger	-0.008	0.015	-0.037, 0.022	0.60
	Intercept	-0.003	0.000	-0.004, -0.002	1.1×10^{-11}
BMI	IVW	0.23	0.020	0.19, 0.26	3.2×10^{-30}
	MR-Egger	0.016	0.032	-0.045, 0.078	0.604
	Intercept	0.006	0.001	0.005, 0.007	2.2×10^{-16}