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Supplemental Data

A Genome-wide Association Study of Dupuytren Disease Reveals 17 Additional Variants Implicated in Fibrosis

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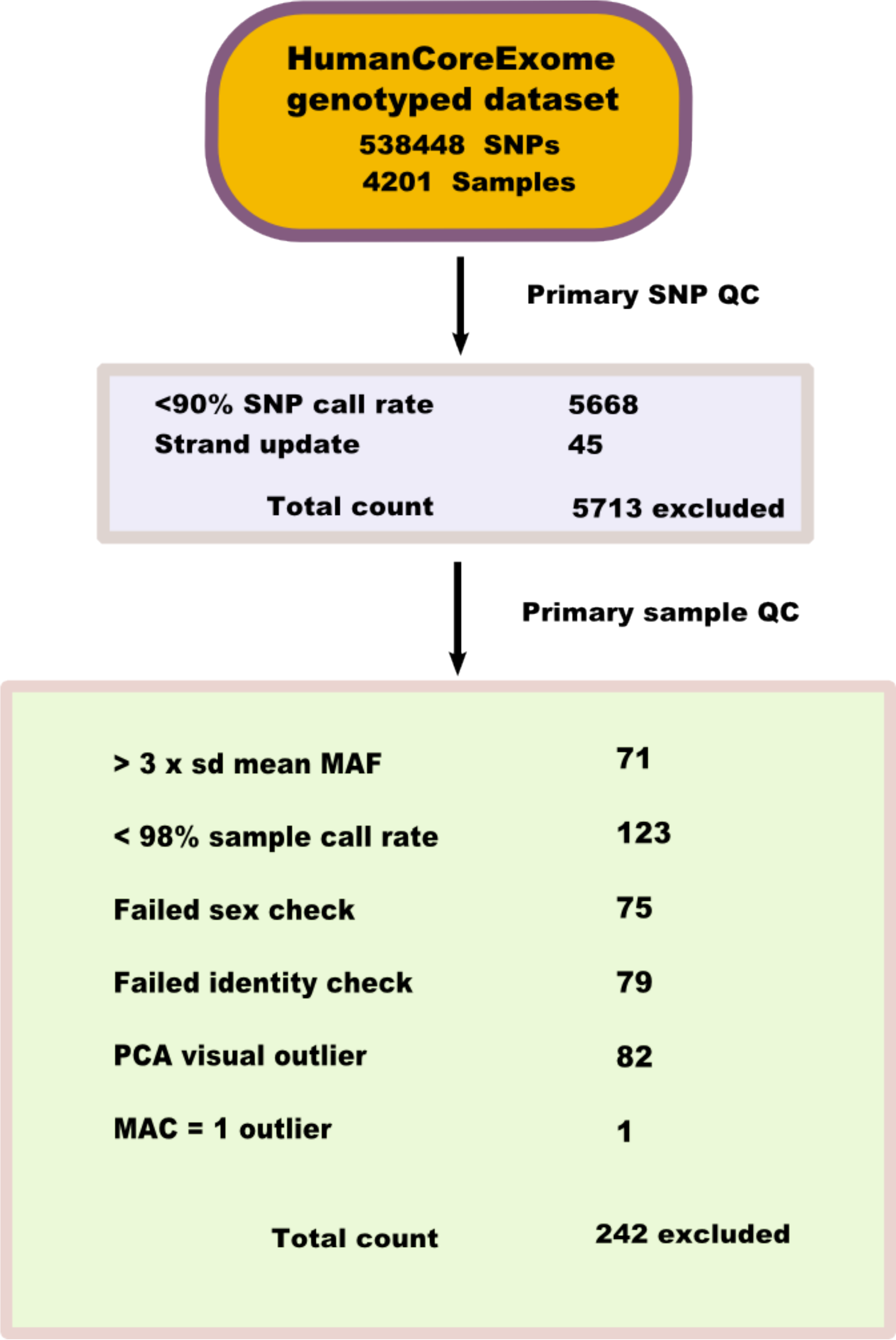
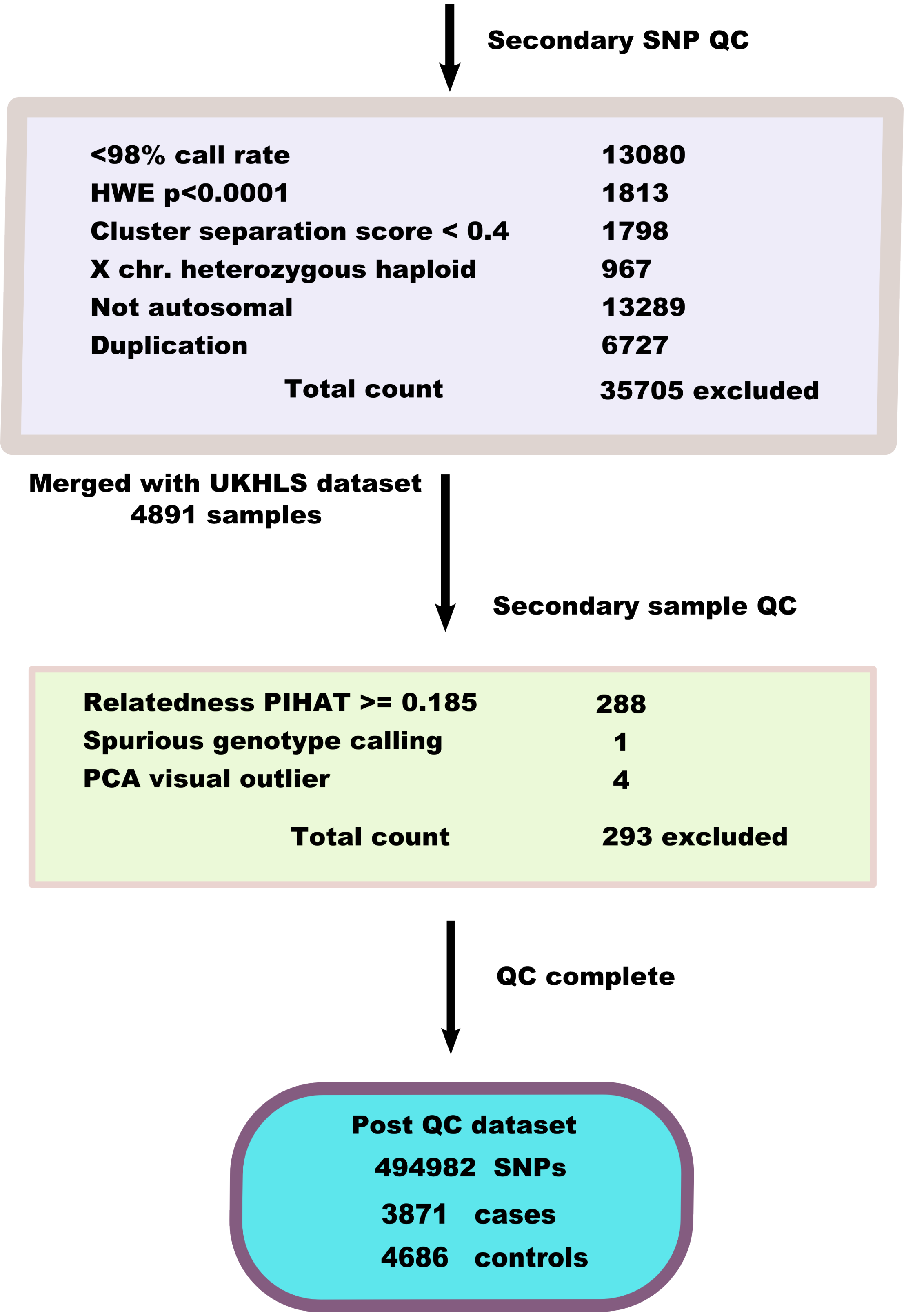
Figure S1. Quality control summary flowchart.





Secondary SNP QC

<98% call rate	13080
HWE p<0.0001	1813
Cluster separation score < 0.4	1798
X chr. heterozygous haploid	967
Not autosomal	13289
Duplication	6727
Total count	35705 excluded

Merged with UKHLS dataset
4891 samples

Secondary sample QC

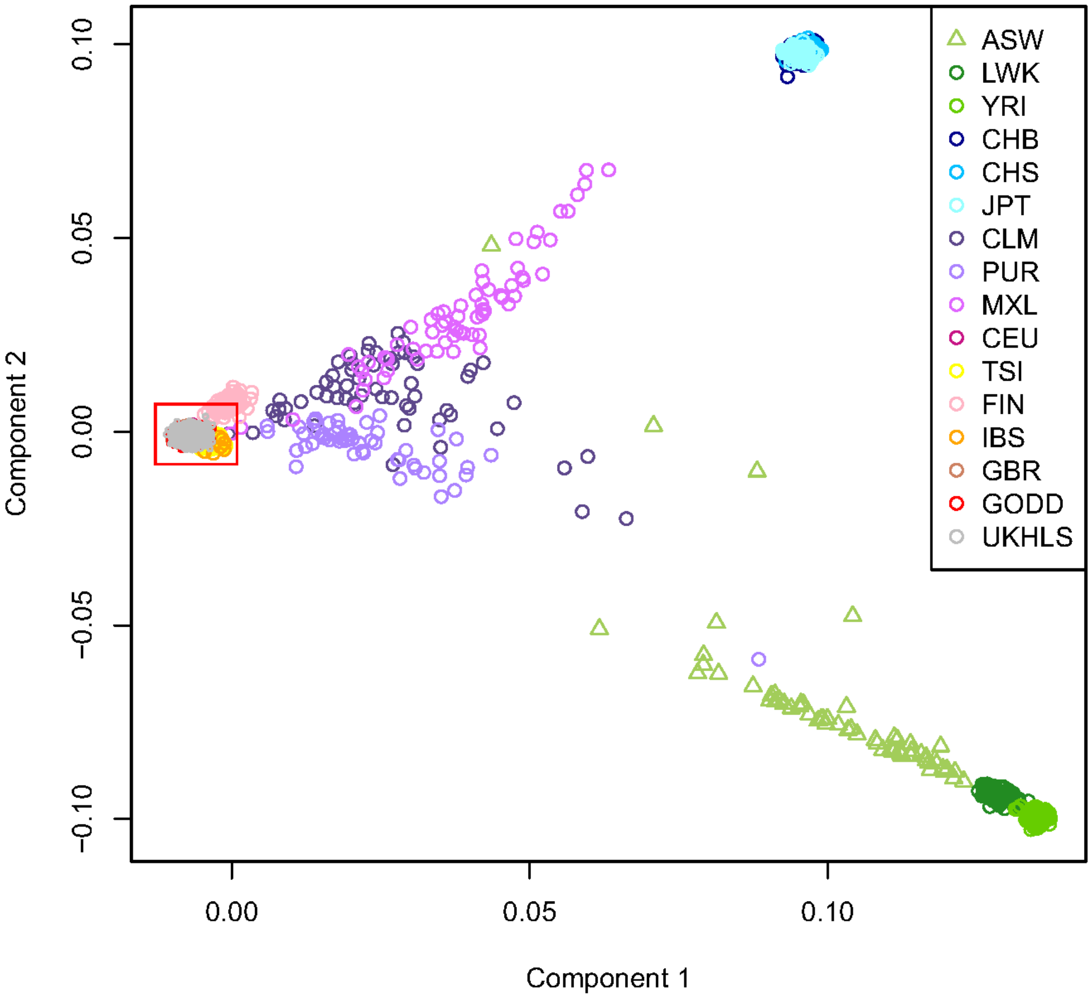
Relatedness PIHAT >= 0.185	288
Spurious genotype calling	1
PCA visual outlier	4
Total count	293 excluded

QC complete

Post QC dataset
494982 SNPs
3871 cases
4686 controls

Figure S2. Principal component analysis plots. a) Principle components 1 and 2 plotted for cases and controls and the 1000 genomes project samples. b) Close-up view of the area highlighted in (a) demonstrating overlap of BSSH-GODD (case) and UKHLS (control) samples. Three-letter abbreviations are those used in the 1000 Genomes Project. GODD – cases from the BSSH-GODD discovery cohort. UKHLS – Controls from the UKHLS cohort.

a)



b)

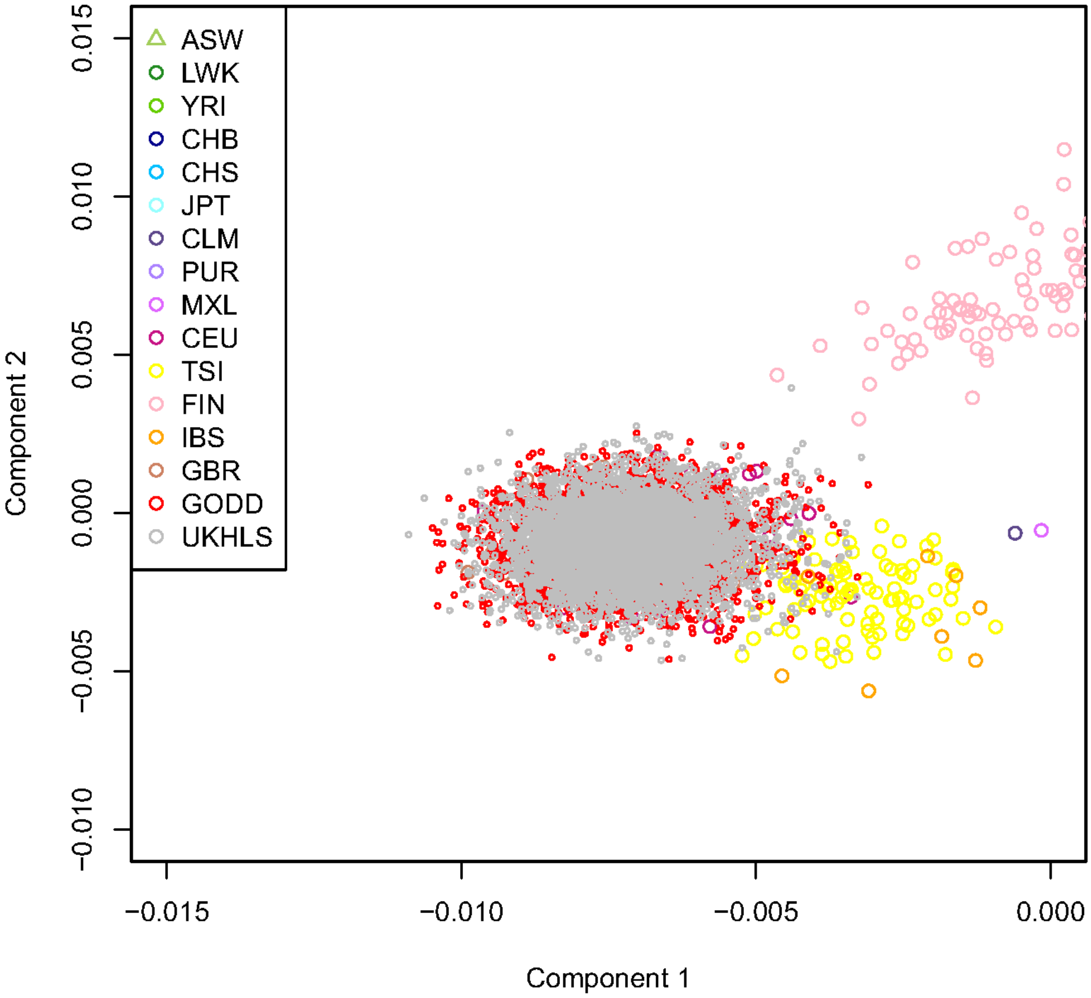

Component 2
Component 1
0.015
0.010
0.005
0.000
−0.005
−0.010
−0.015
−0.010
−0.005
0.000
ASW
LWK
YRI
CHB
CHS
JPT
CLM
PUR
MXL
CEU
TSI
FIN
IBS
GBR
GODD
UKHLS

Figure S3. Q-Q plot. Observed versus expected p-values of association in the discovery cohort. The unadjusted genomic control inflation factor (λ_{GC}) was 1.104. The genomic control inflation factor adjusted to a case control sample size of 1000 (λ_{1000}) [2] was 1.025

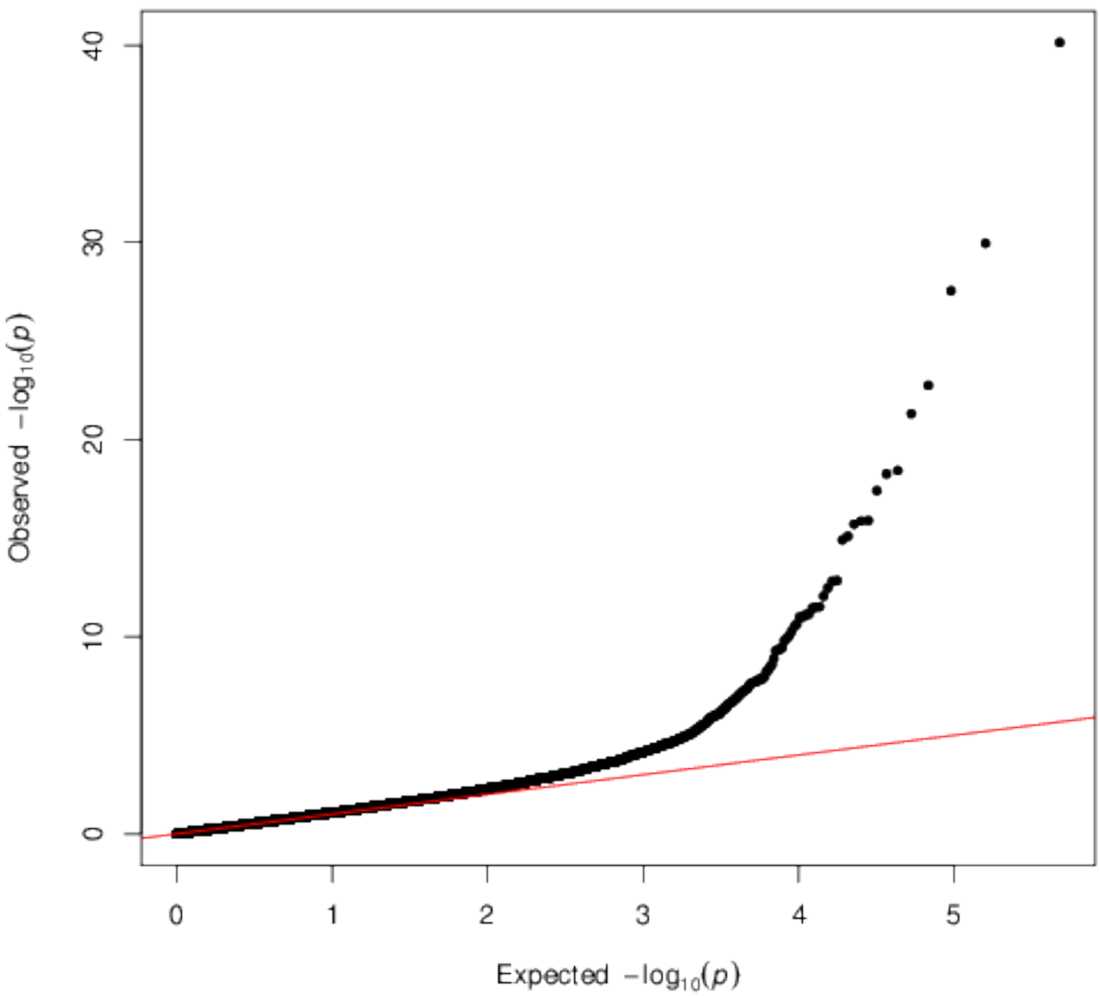
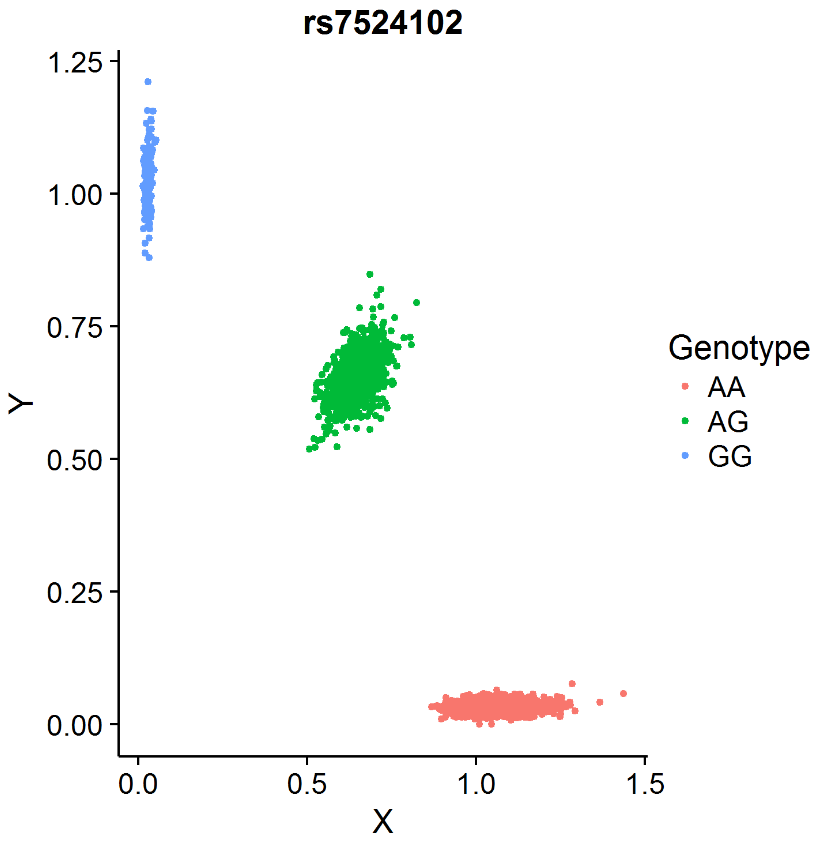
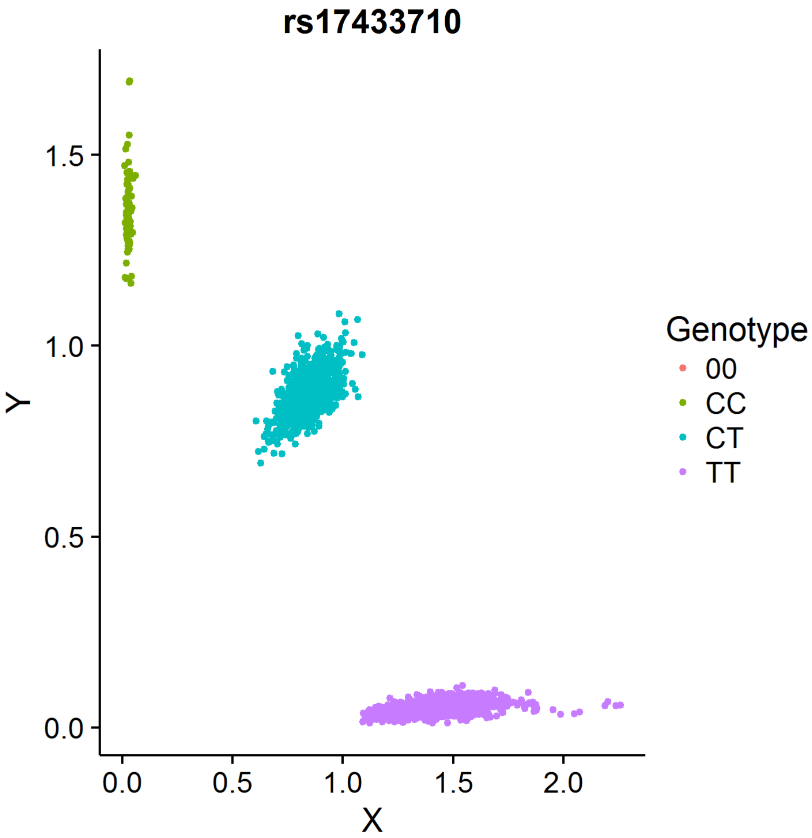


Figure S4. Raw intensity scatter plots of all genome wide significant associated variants generated using R. 00 denotes missing genotype.

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Y
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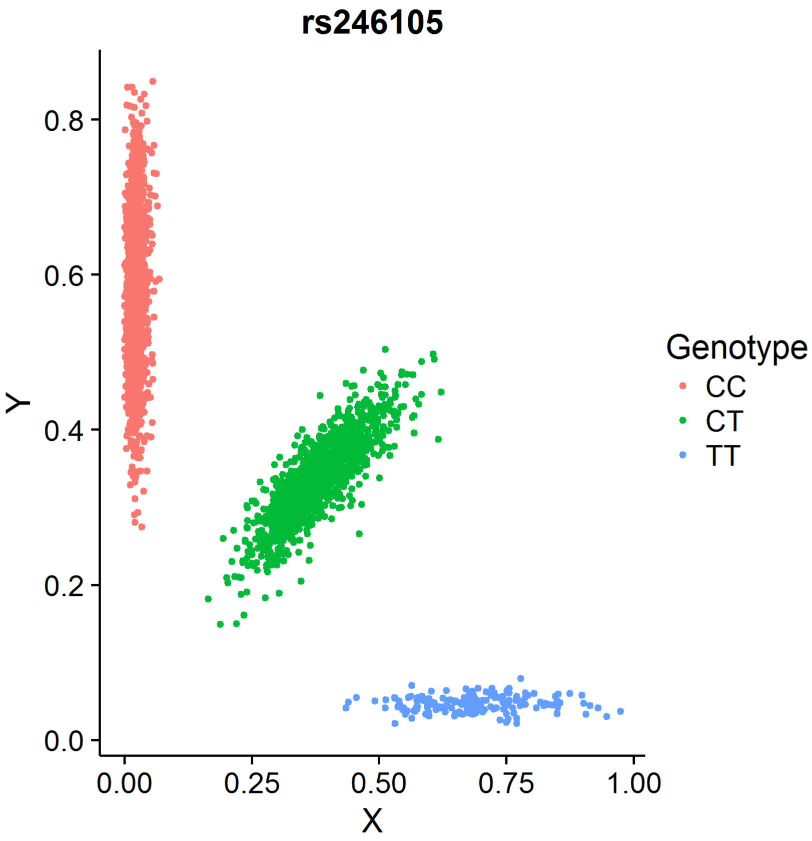
1.0
0.5
0.0
X
0.0
0.5
1.0
1.5
2.0
Genotype
00
CC
CT
TT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0.4
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0.0
X
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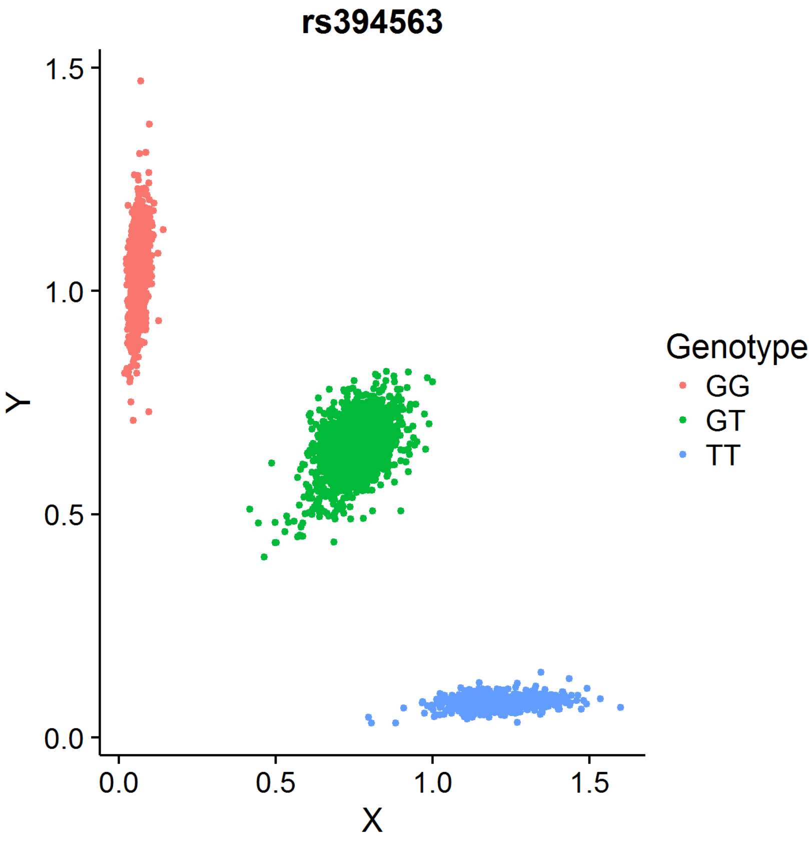
0.50
0.75
1.00
Genotype
CC
CT
TT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Y
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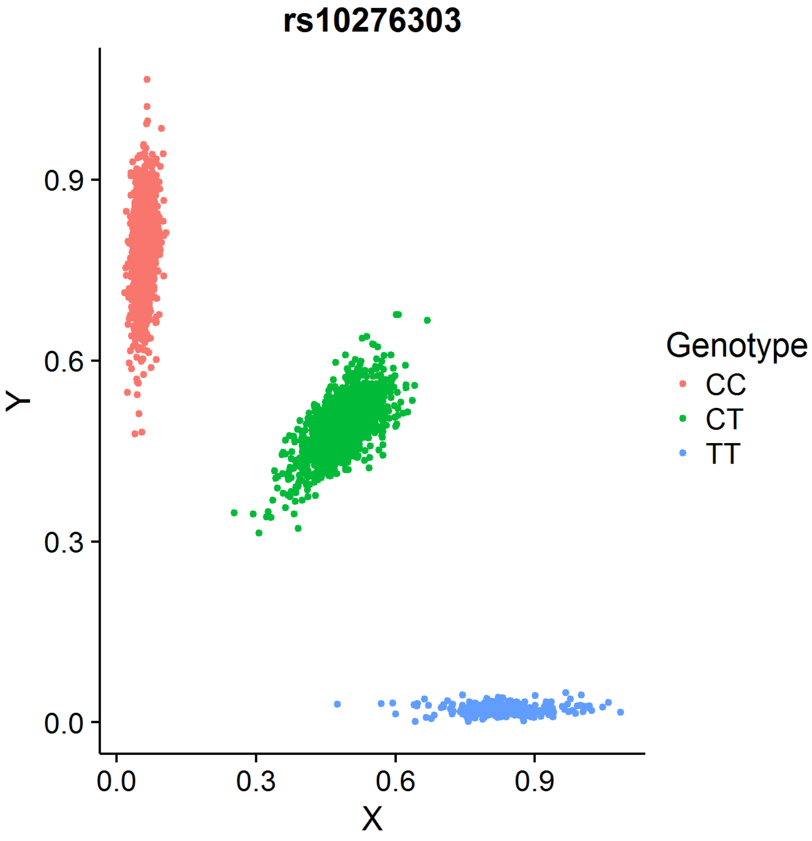
0.5
1.0
1.5
X
Genotype
GG
GT
TT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0.3
0.0
Y
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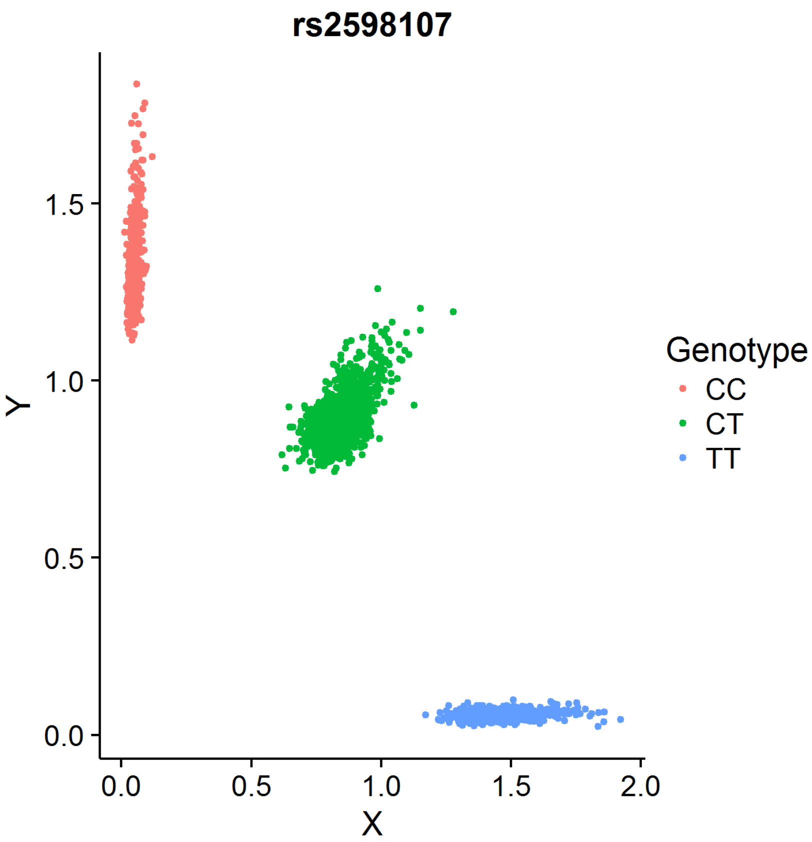
0.3
0.6
0.9
X
Genotype
CC
CT
TT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0.0
X
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0.5
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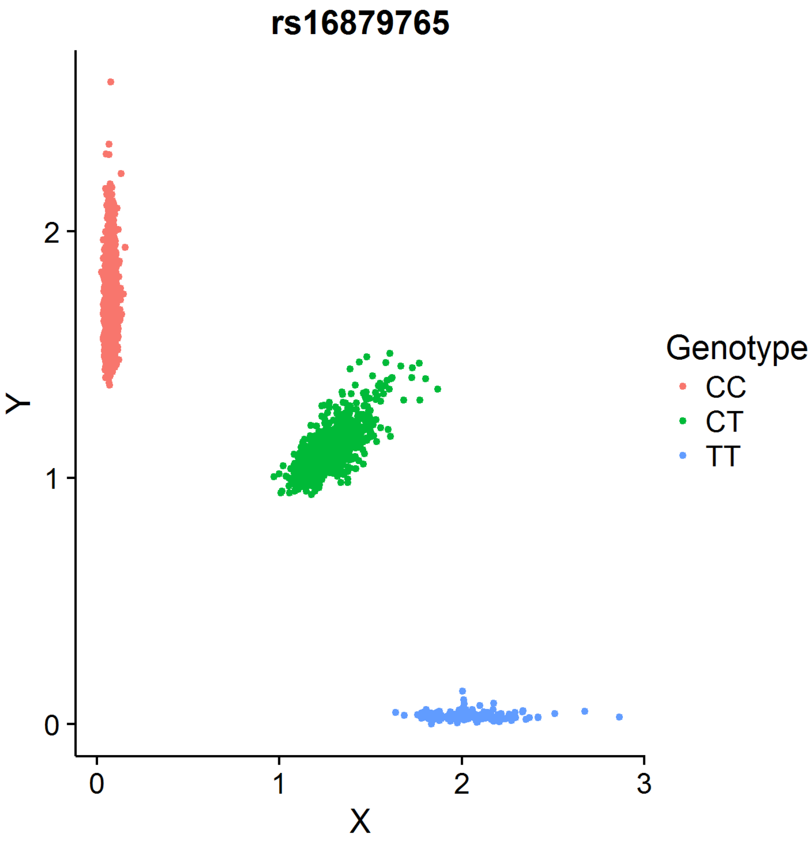
1.5
2.0
Genotype
CC
CT
TT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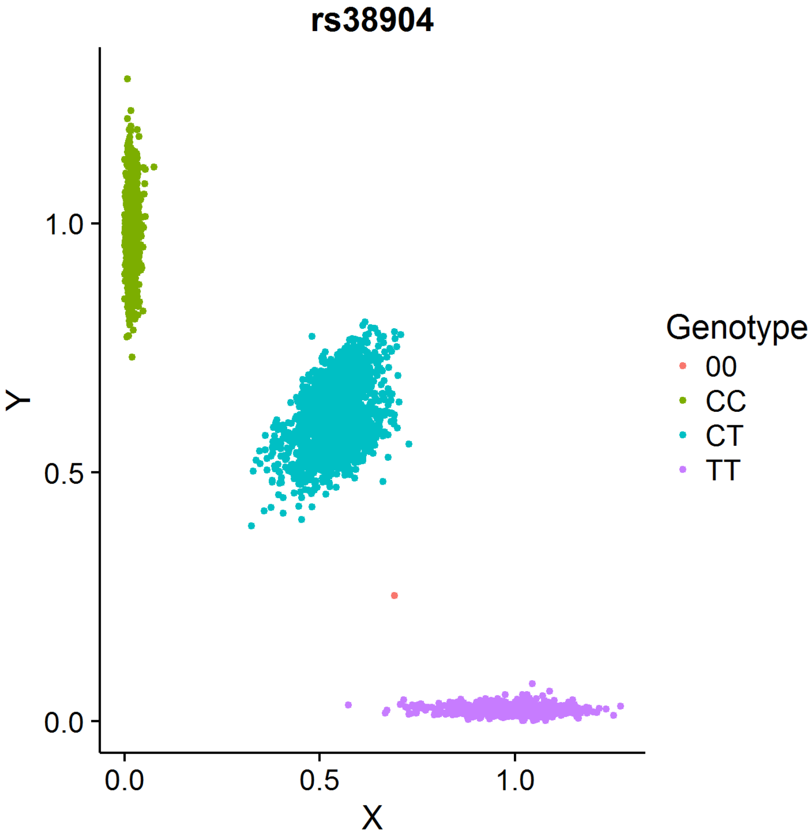
Y
2
1
0
X
0
1
2
3
Genotype
CC
CT
TT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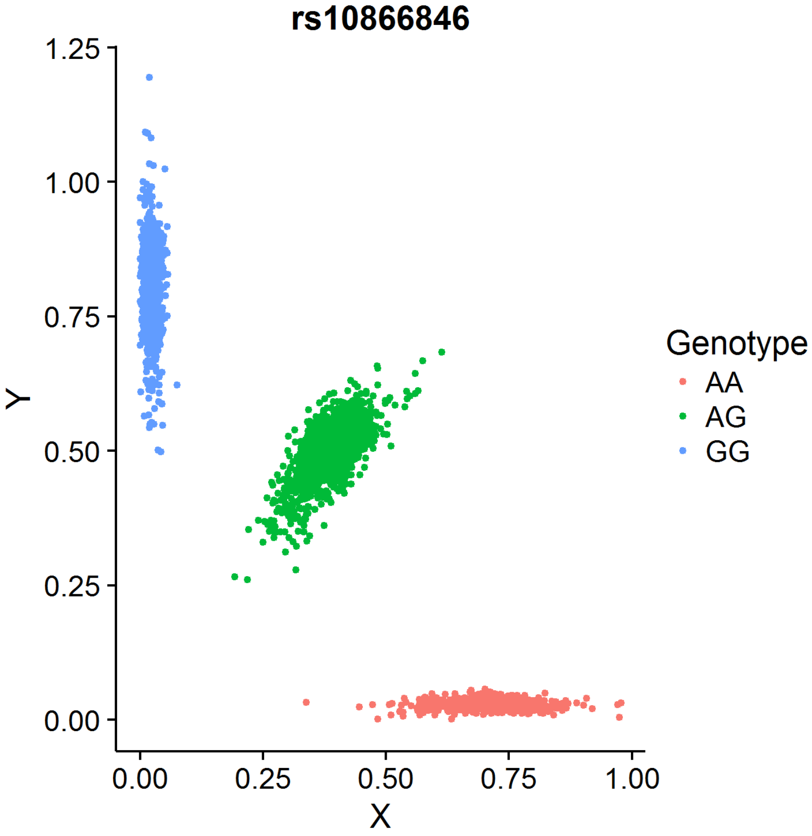
1.0
X
Genotype
00
CC
CT
TT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1.00
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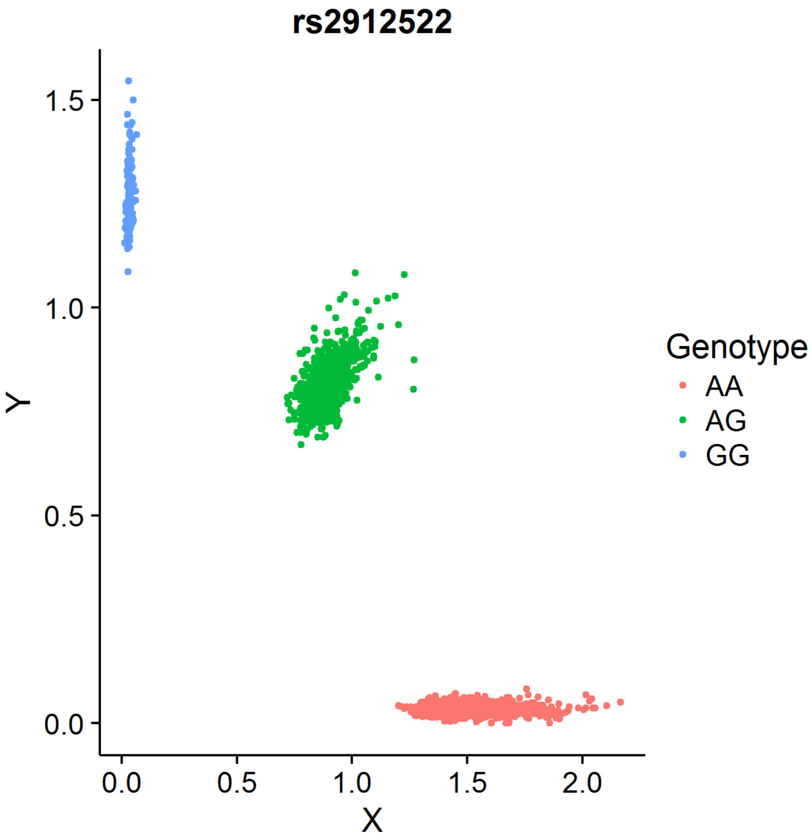
0.25
0.00
0.00
0.25
0.50
0.75
1.00
X
Genotype
AA
AG
GG


rs2912522
Y
1.5
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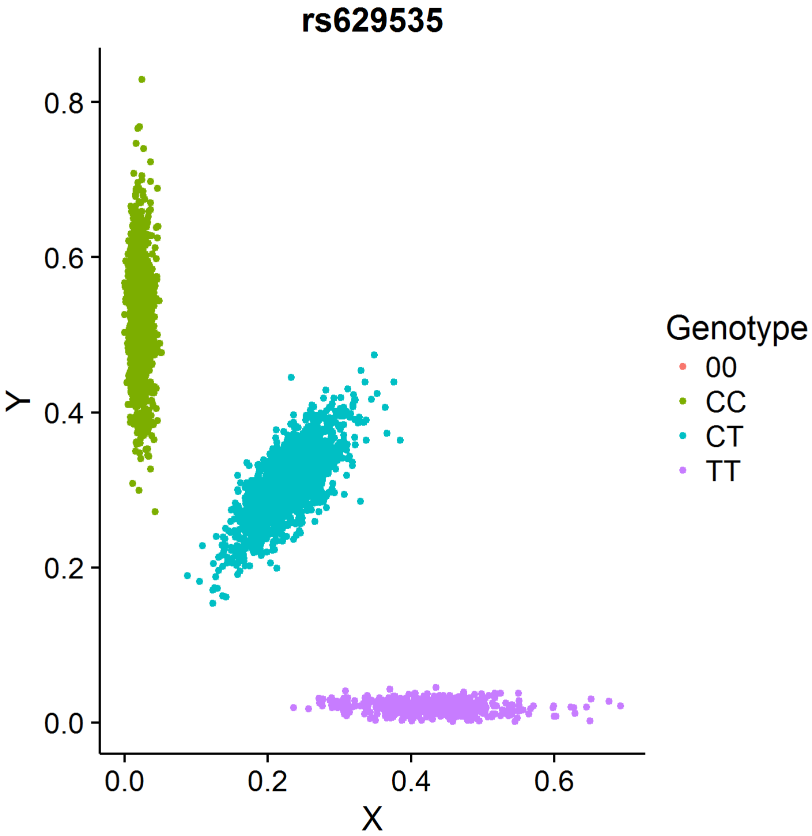
0.5
0.0
X
0.0
0.5
1.0
1.5
2.0
Genotype
● AA
● AG
● GG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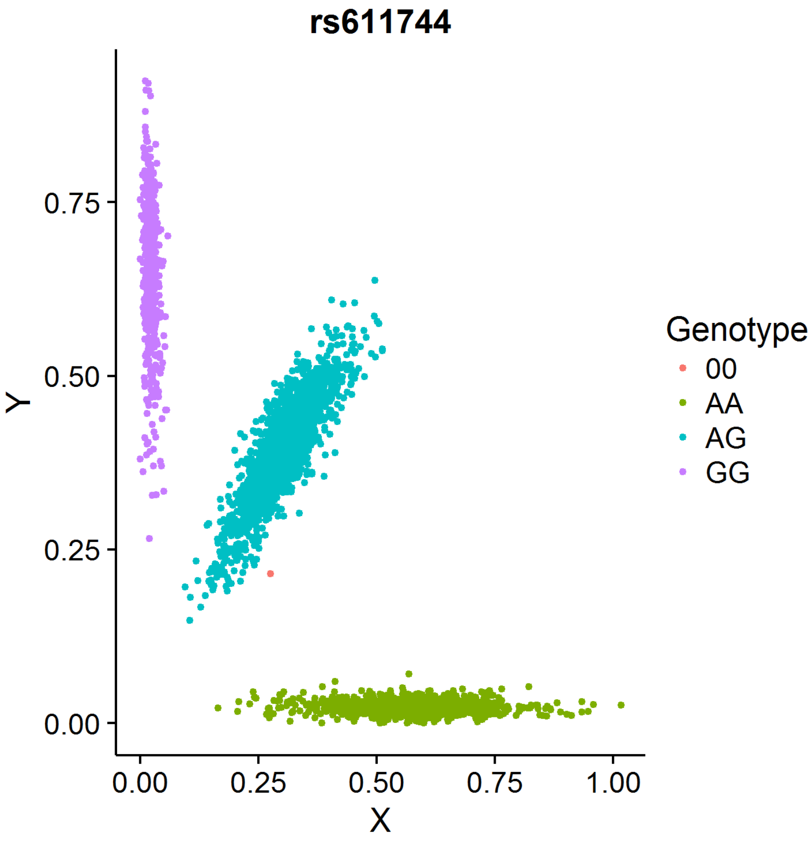
0.4
0.2
0.0
X
0.0
0.2
0.4
0.6
Genotype
● 00
● CC
● CT
● TT



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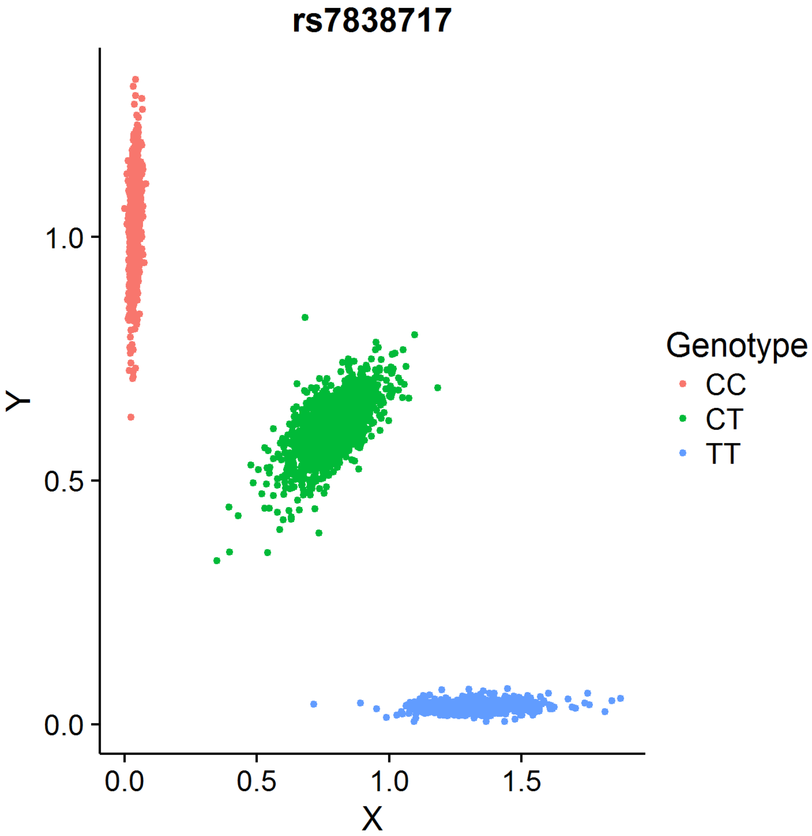

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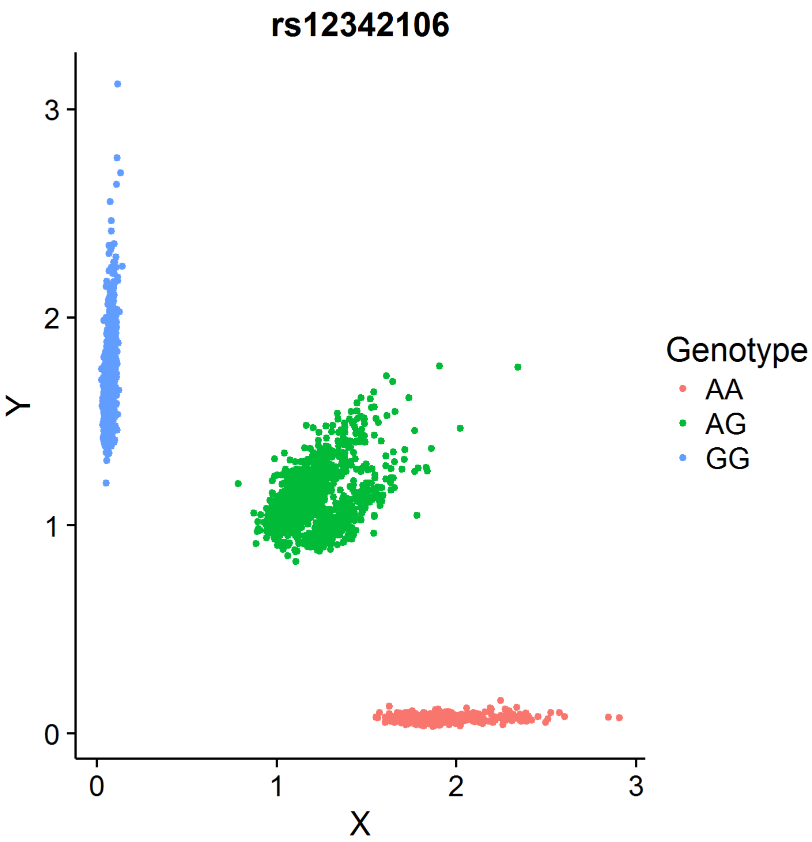
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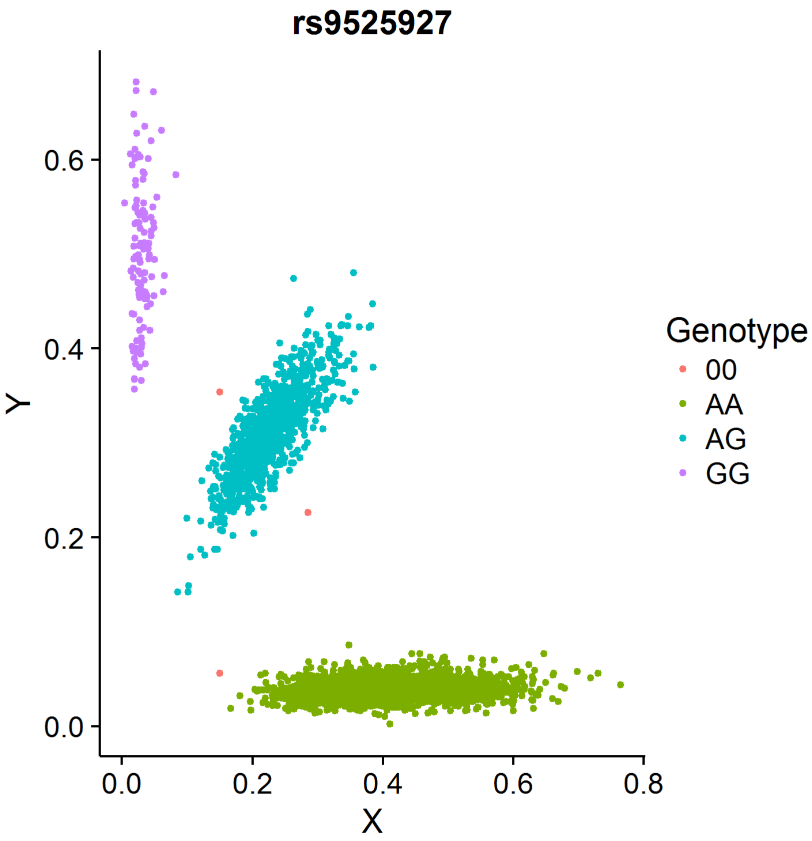
3
2
1
0
X
0
1
2
3
Genotype
AA
AG
GG


rs9525927
Y
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0.4
0.2
0.0
X
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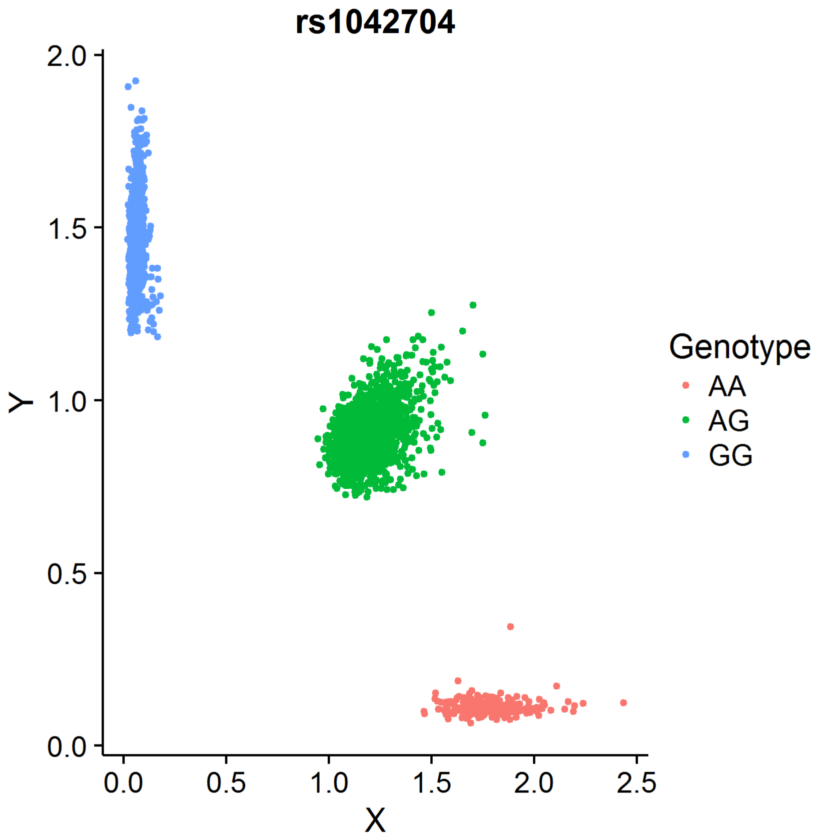
0.2
0.4
0.6
0.8
Genotype
00
AA
AG
GG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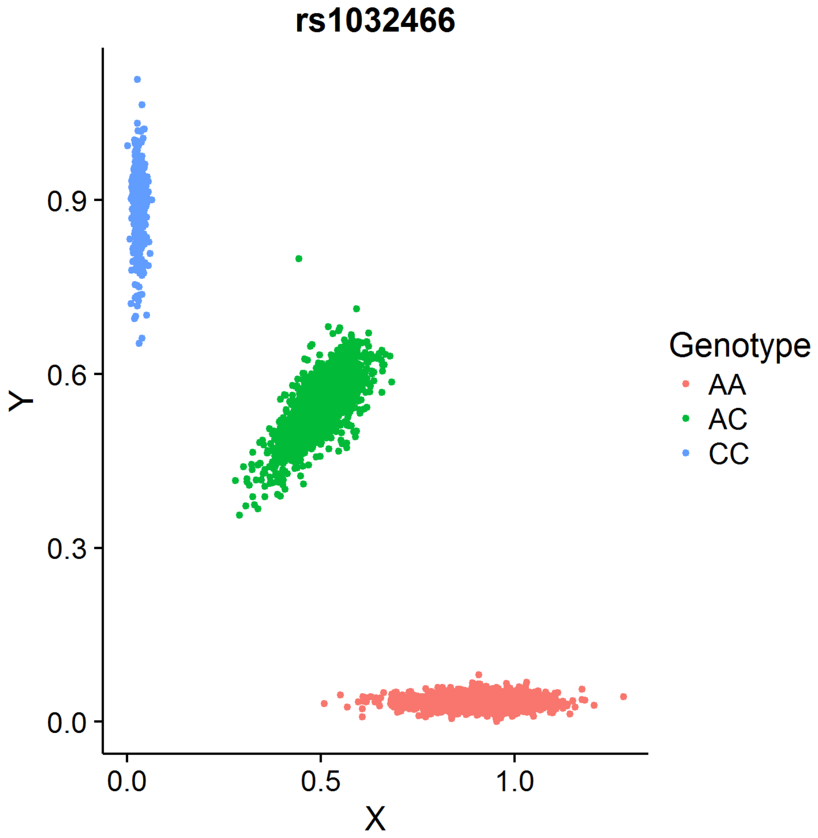
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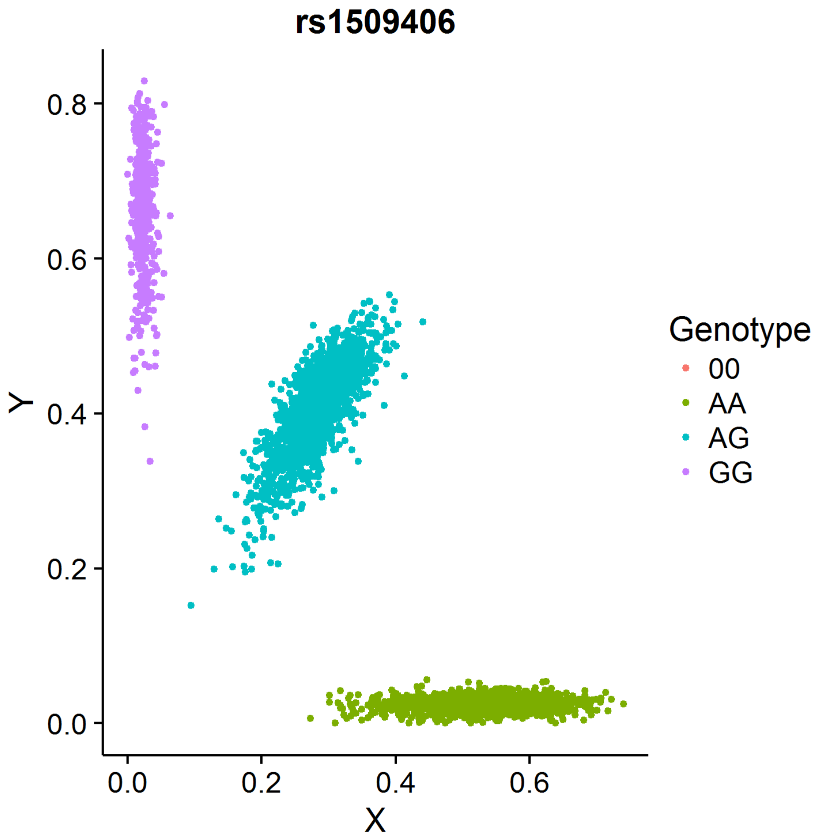
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0.4
0.6
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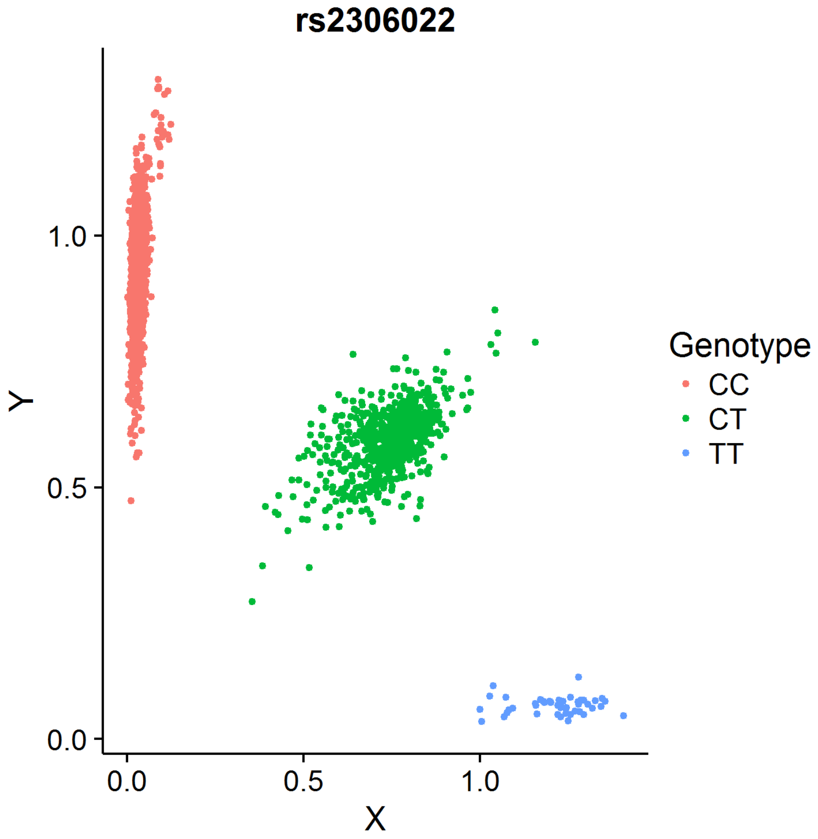
● 00
● AA
● AG
● GG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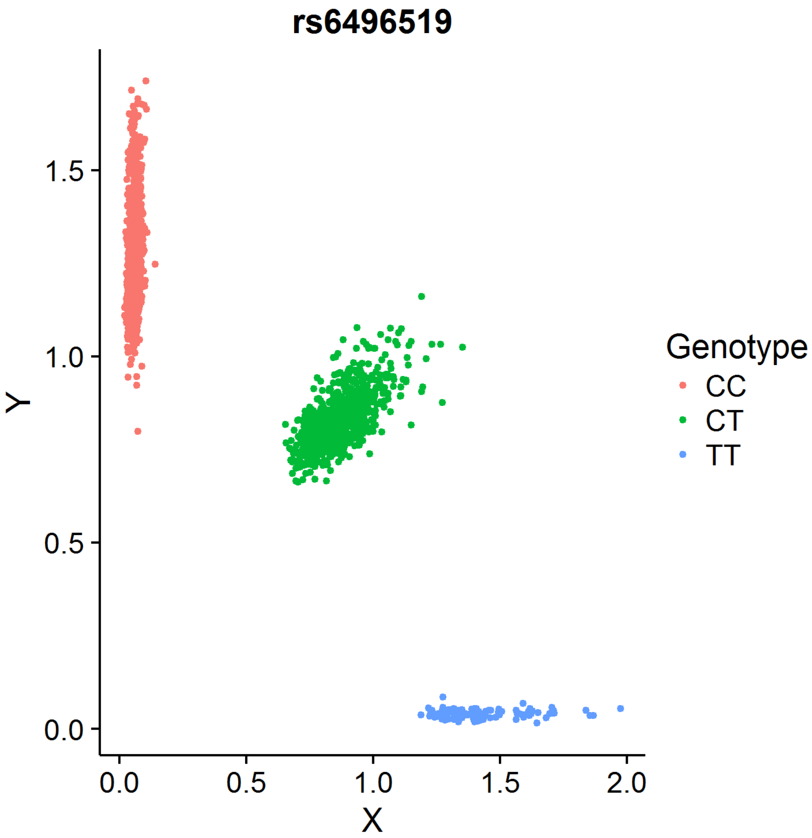
1.0
X
Genotype
● CC
● CT
● TT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0.0
X
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0.5
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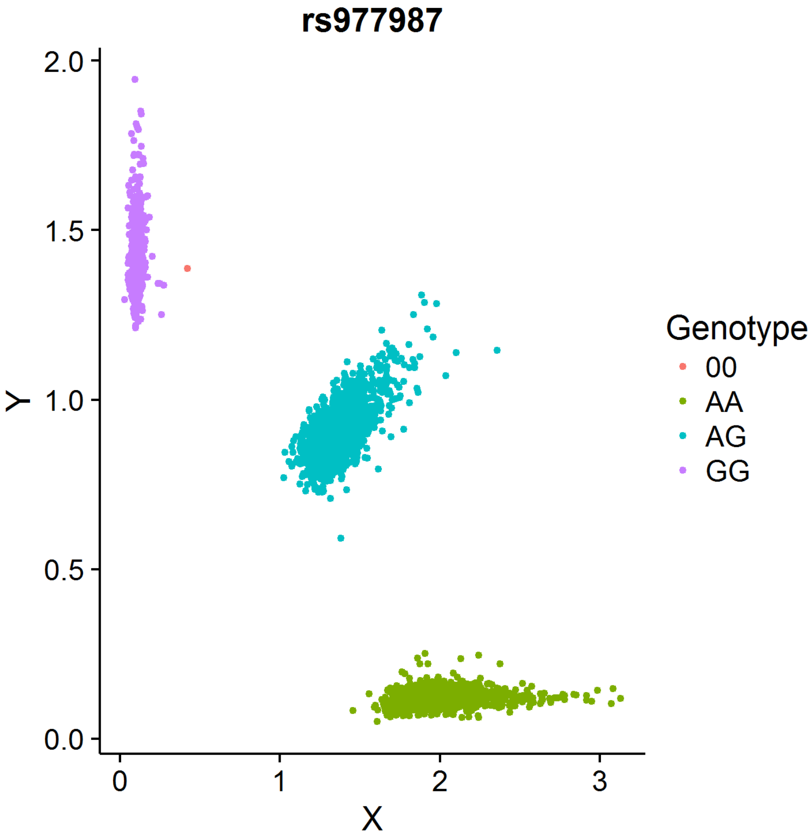
1.5
2.0
Genotype
CC
CT
TT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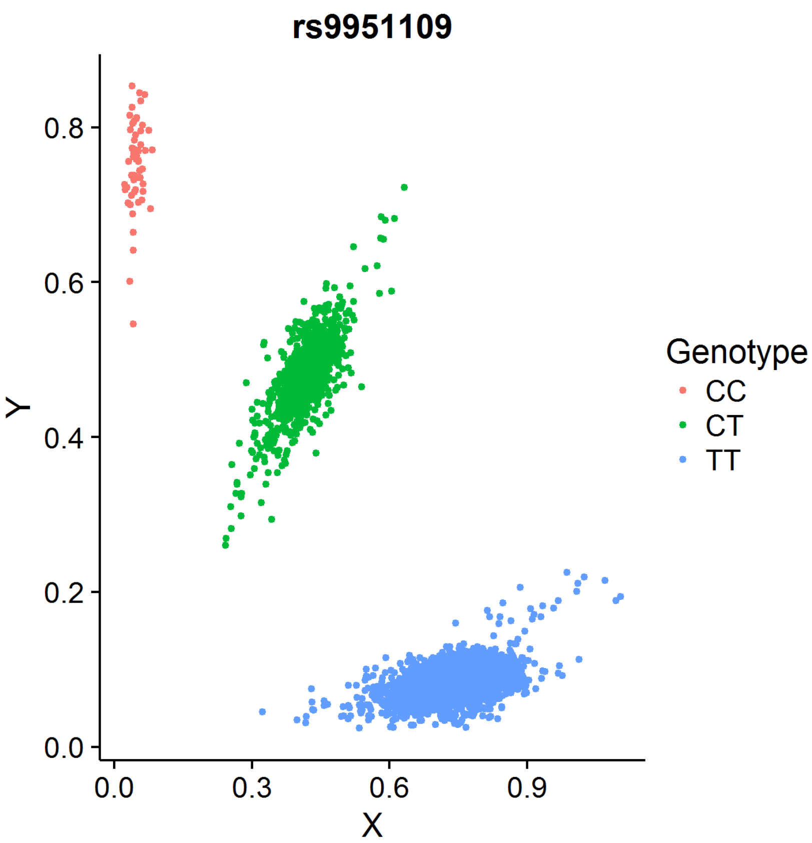
0.0
X
0
1
2
3
Genotype
00
AA
AG
GG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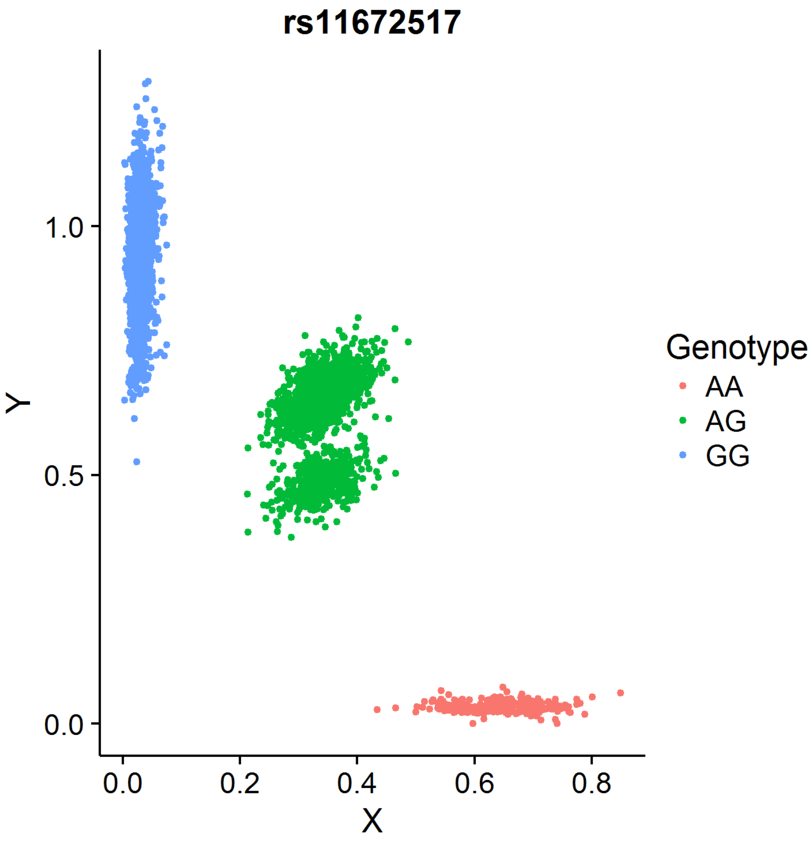
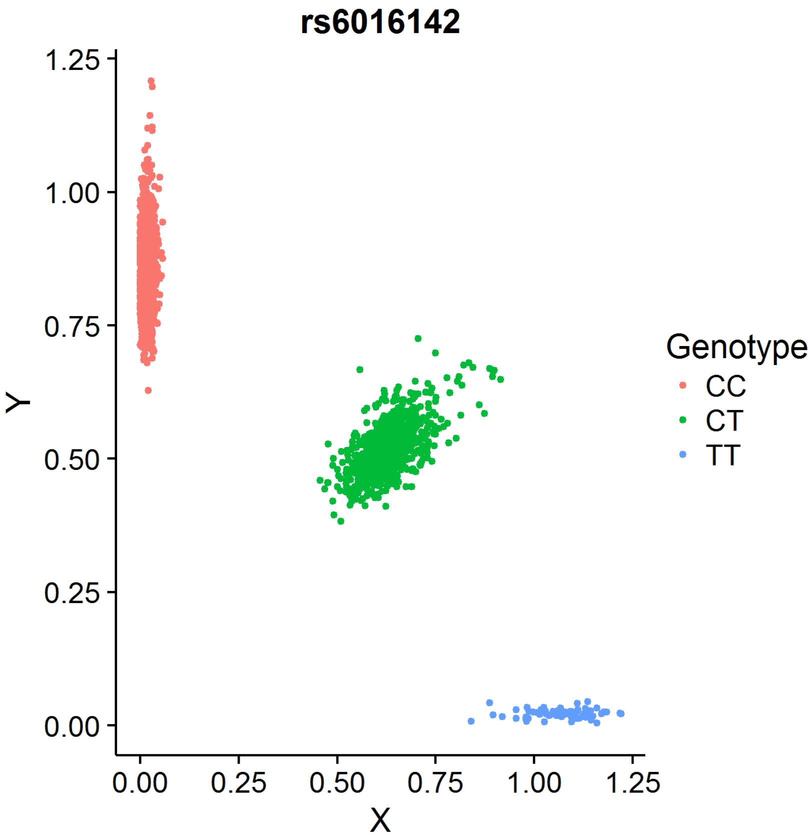

rs11672517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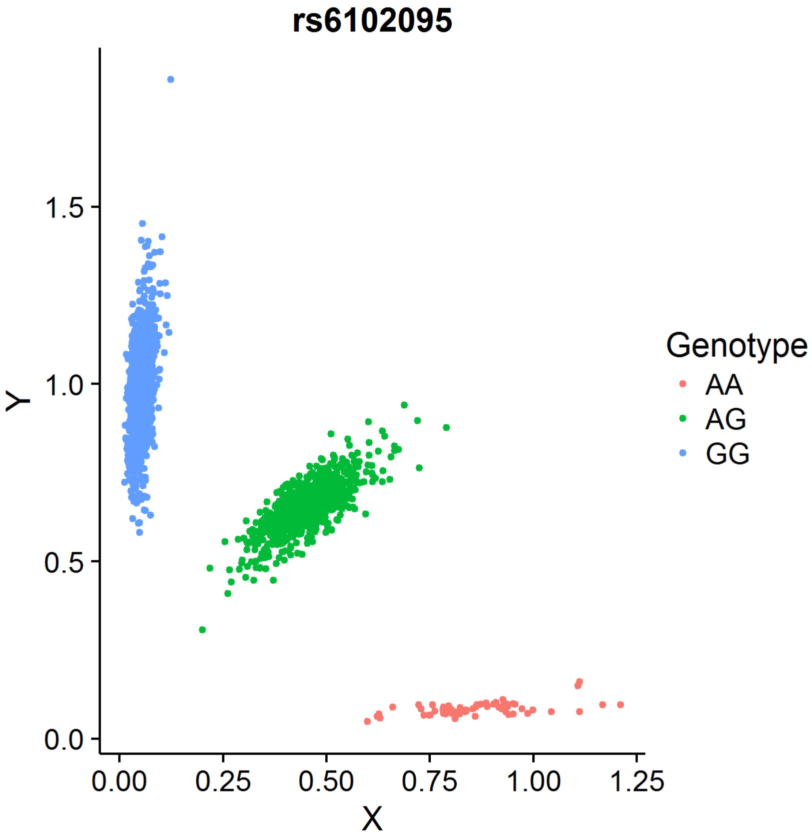
1.00
0.75
0.50
0.25
0.00
Y
0.00
0.25
0.50
0.75
1.00
1.25
X
Genotype
CC
CT
TT


rs6102095
1.5
1.0
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0.0
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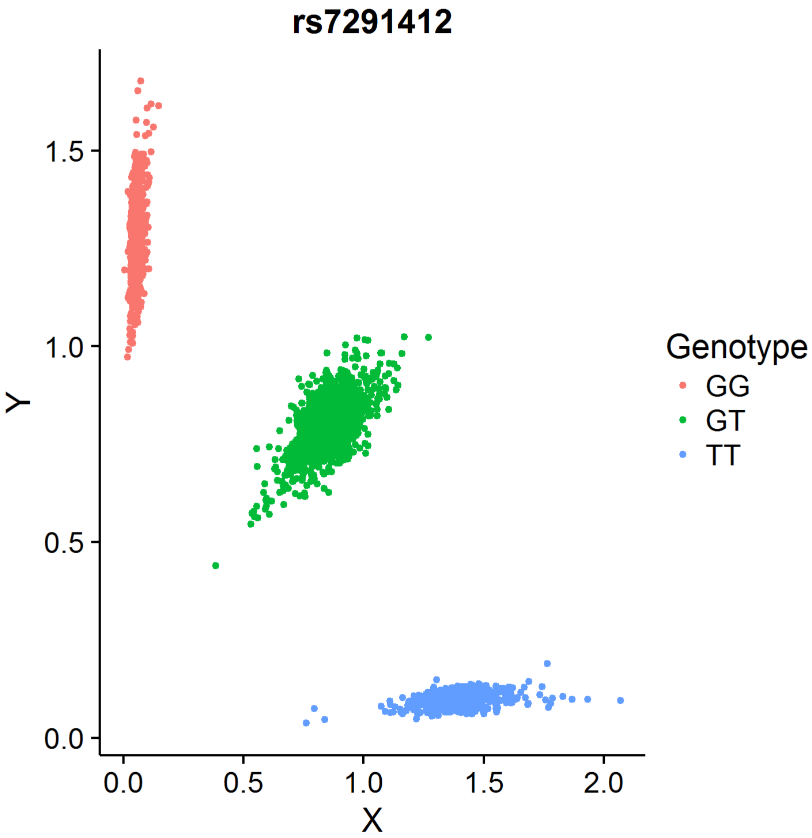
0.50
0.75
1.00
1.25
X
Genotype
AA
AG
GG


rs7291412
Y
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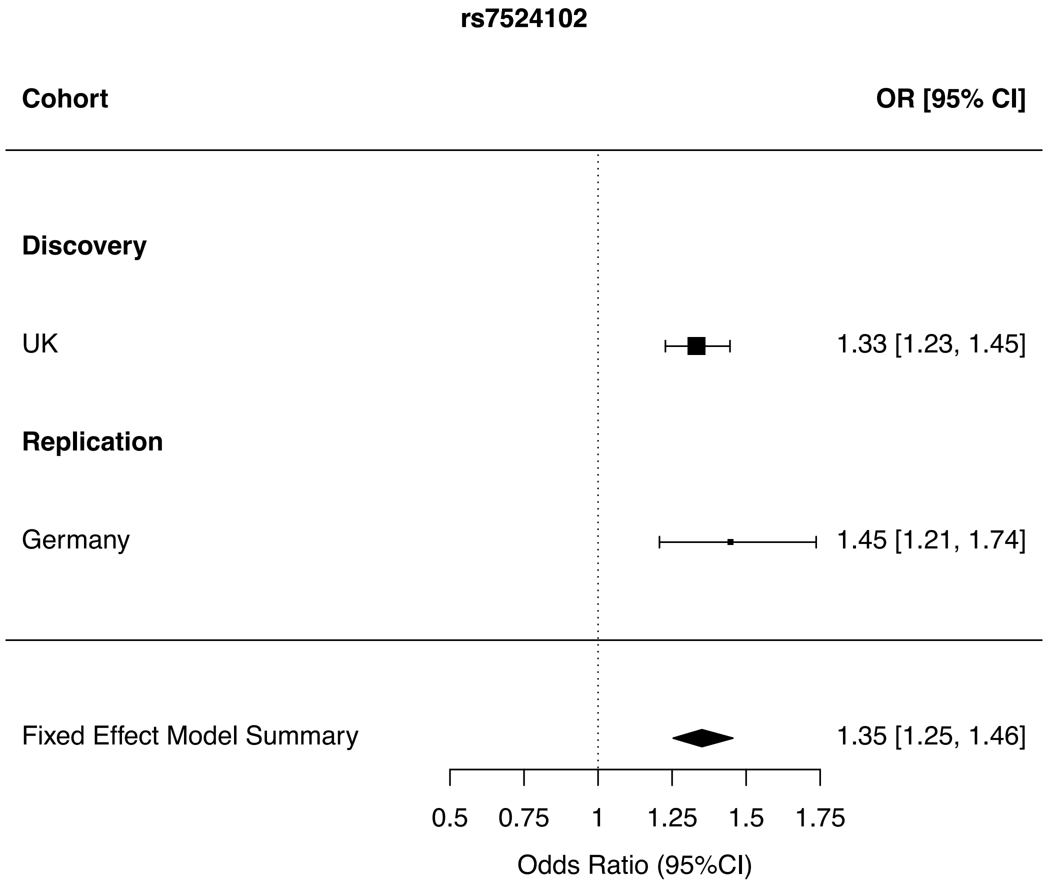
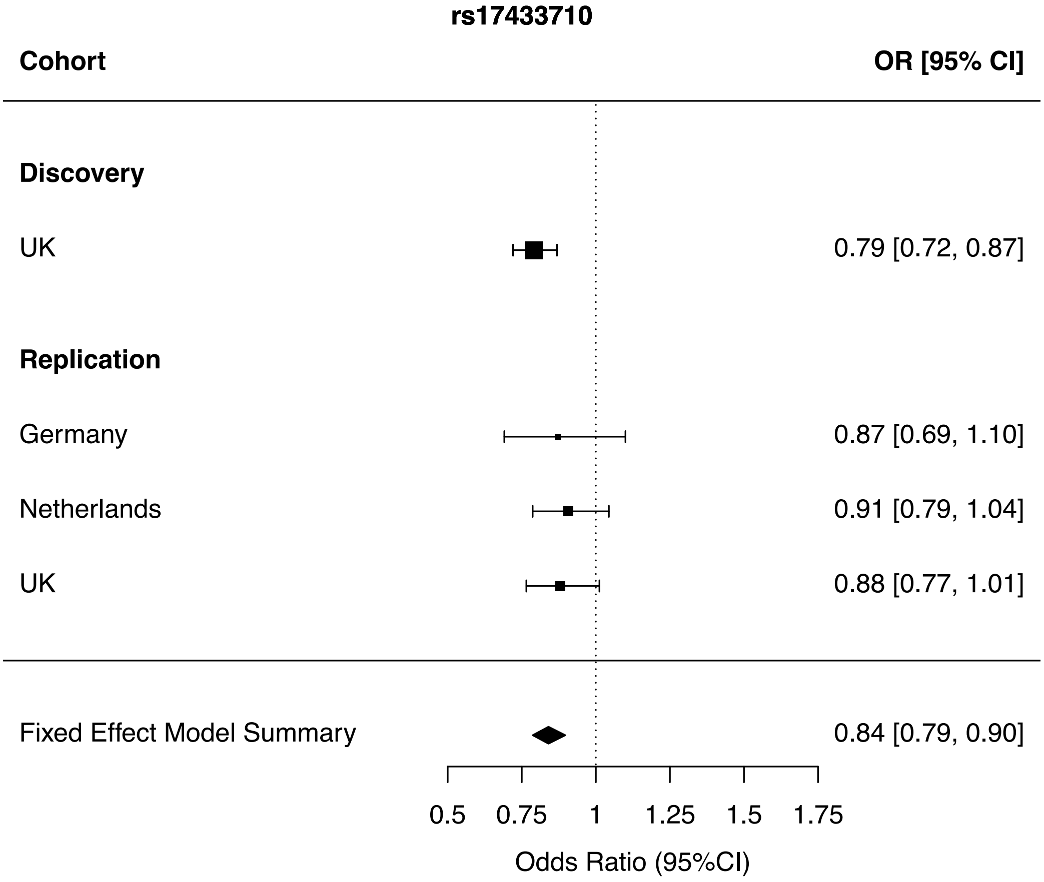
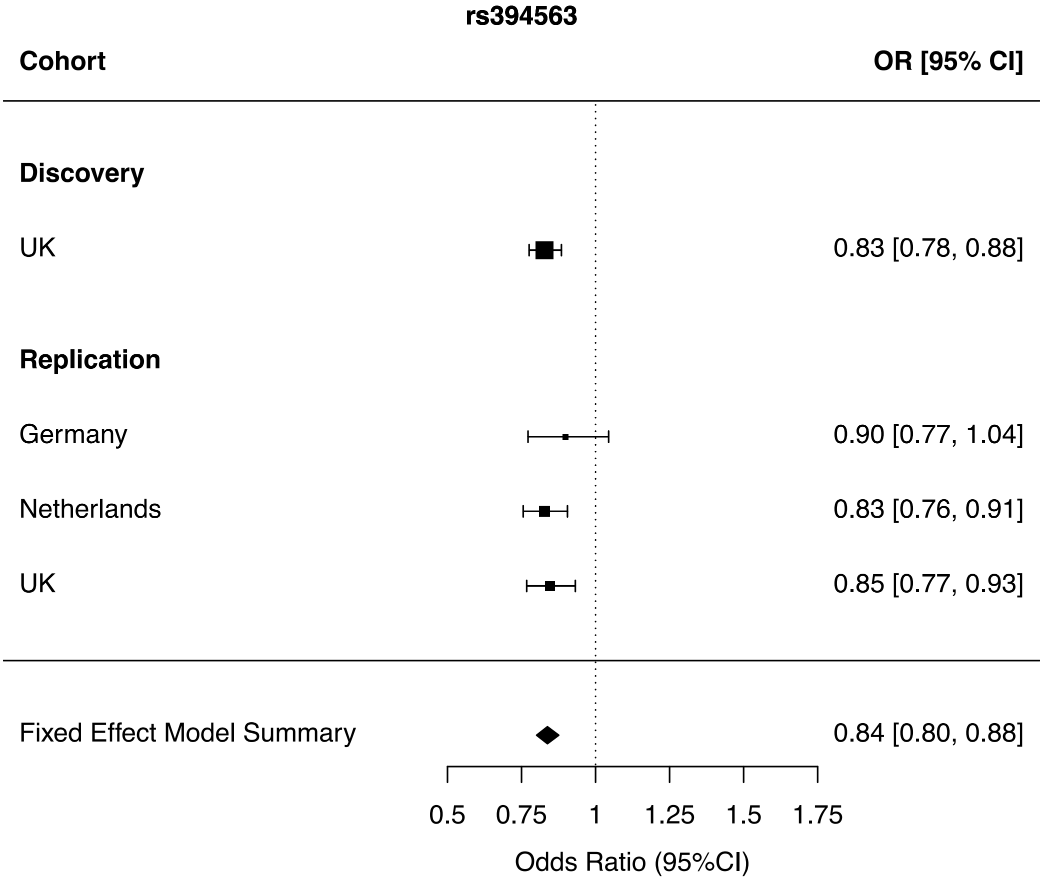
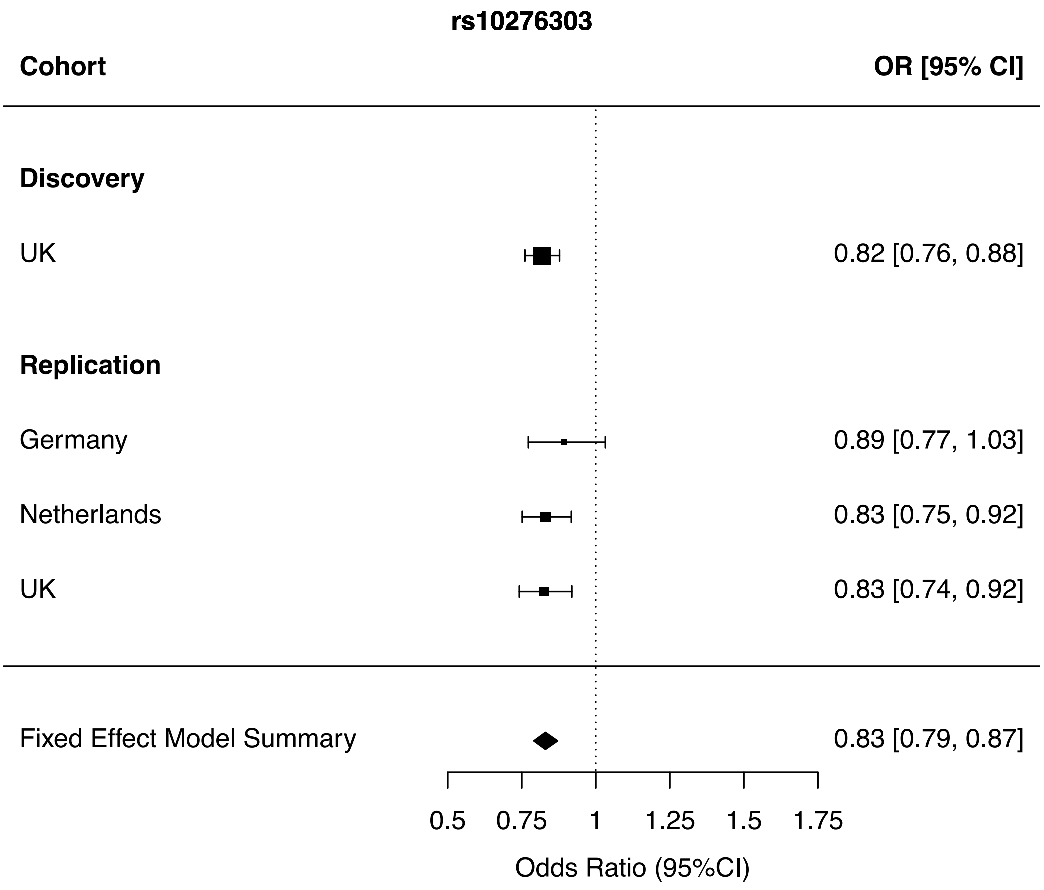
1.0
0.5
0.0
0.0
0.5
1.0
1.5
2.0
X
Genotype
GG
GT
TT

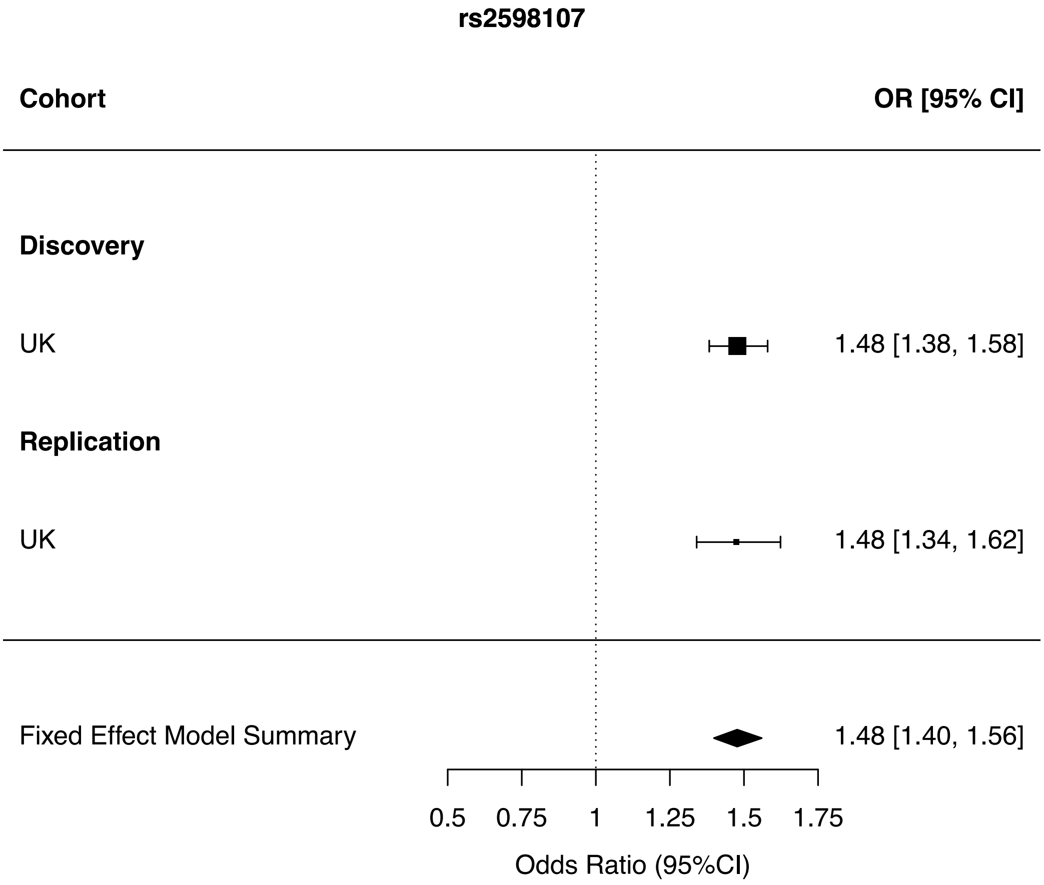
Figure S5. Forest plots showing the magnitude and direction of odds ratio for the risk allele at all associated loci, across the different cohorts in which it was genotyped. The size of the box is proportional to the weight (size) of the dataset in the fixed-effects meta-analysis. The whiskers represent the 95% confidence intervals.




rs17433710
Cohort
OR [95% CI]
Discovery
UK
0.79 [0.72, 0.87]
Replication
Germany
0.87 [0.69, 1.10]
Netherlands
0.91 [0.79, 1.04]
UK
0.88 [0.77, 1.01]
Fixed Effect Model Summary
0.84 [0.79, 0.90]
0.5
0.75
1
1.25
1.5
1.75
Odds Ratio (95%CI)


rs394563
Cohort
OR [95% CI]
Discovery
UK
0.83 [0.78, 0.88]
Replication
Germany
0.90 [0.77, 1.04]
Netherlands
0.83 [0.76, 0.91]
UK
0.85 [0.77, 0.93]
Fixed Effect Model Summary
0.84 [0.80, 0.88]
0.5
0.75
1
1.25
1.5
1.75
Odds Ratio (95%CI)


rs10276303
Cohort
OR [95% CI]
Discovery
UK
0.82 [0.76, 0.88]
Replication
Germany
0.89 [0.77, 1.03]
Netherlands
0.83 [0.75, 0.92]
UK
0.83 [0.74, 0.92]
Fixed Effect Model Summary
0.83 [0.79, 0.87]
0.5
0.75
1
1.25
1.5
1.75
Odds Ratio (95%CI)


rs2598107
Cohort
OR [95% CI]
Discovery
UK
1.48 [1.38, 1.58]
Replication
UK
1.48 [1.34, 1.62]
Fixed Effect Model Summary
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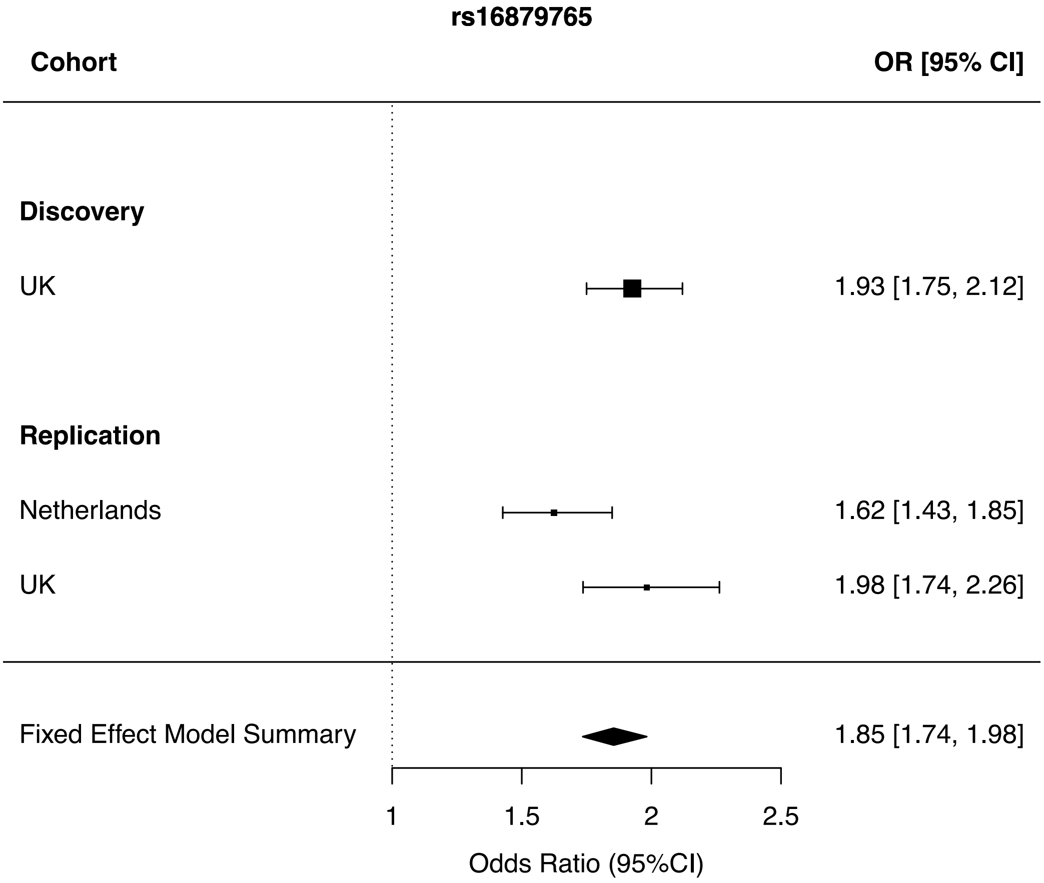
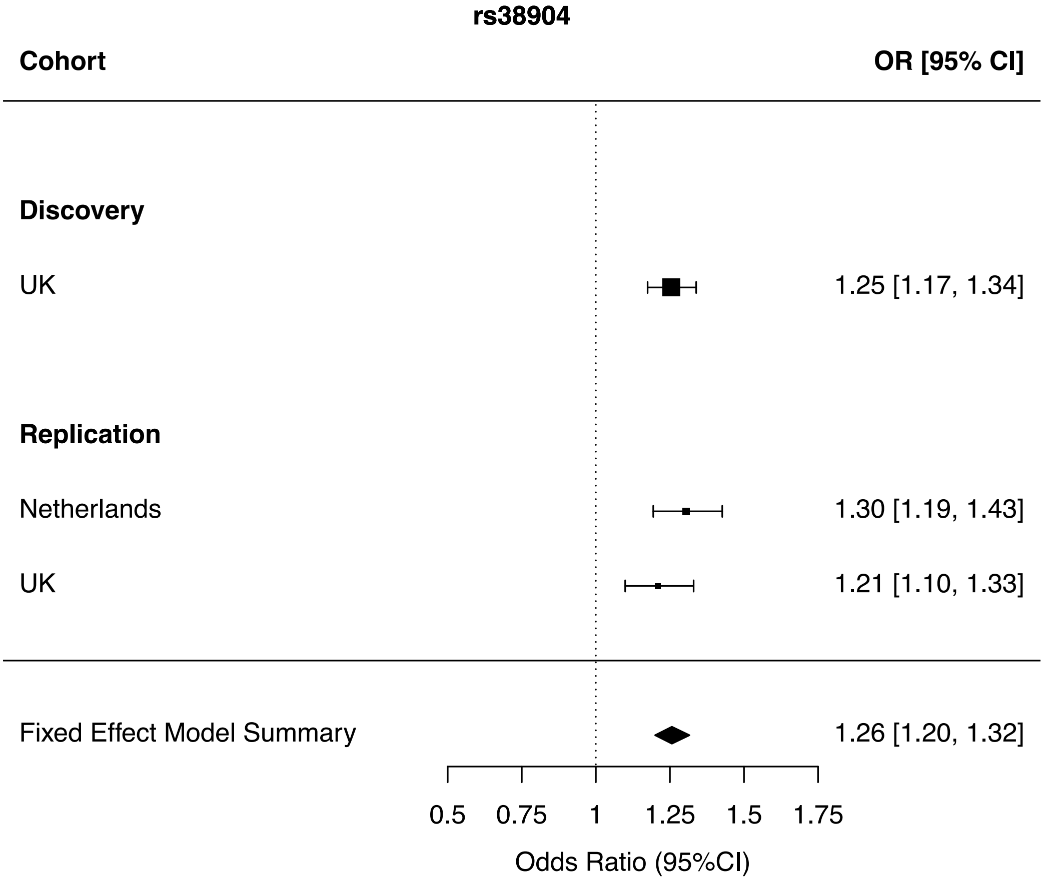
0.5
0.75
1
1.25
1.5
1.75
Odds Ratio (95%CI)


rs16879765
Cohort
OR [95% CI]
Discovery
UK
1.93 [1.75, 2.12]
Replication
Netherlands
1.62 [1.43, 1.85]
UK
1.98 [1.74, 2.26]
Fixed Effect Model Summary
1.85 [1.74, 1.98]
1
1.5
2
2.5
Odds Ratio (95%CI)


rs38904
Cohort
OR [95% CI]
Discovery
UK
1.25 [1.17, 1.34]
Replication
Netherlands
1.30 [1.19, 1.43]
UK
1.21 [1.10, 1.33]
Fixed Effect Model Summary
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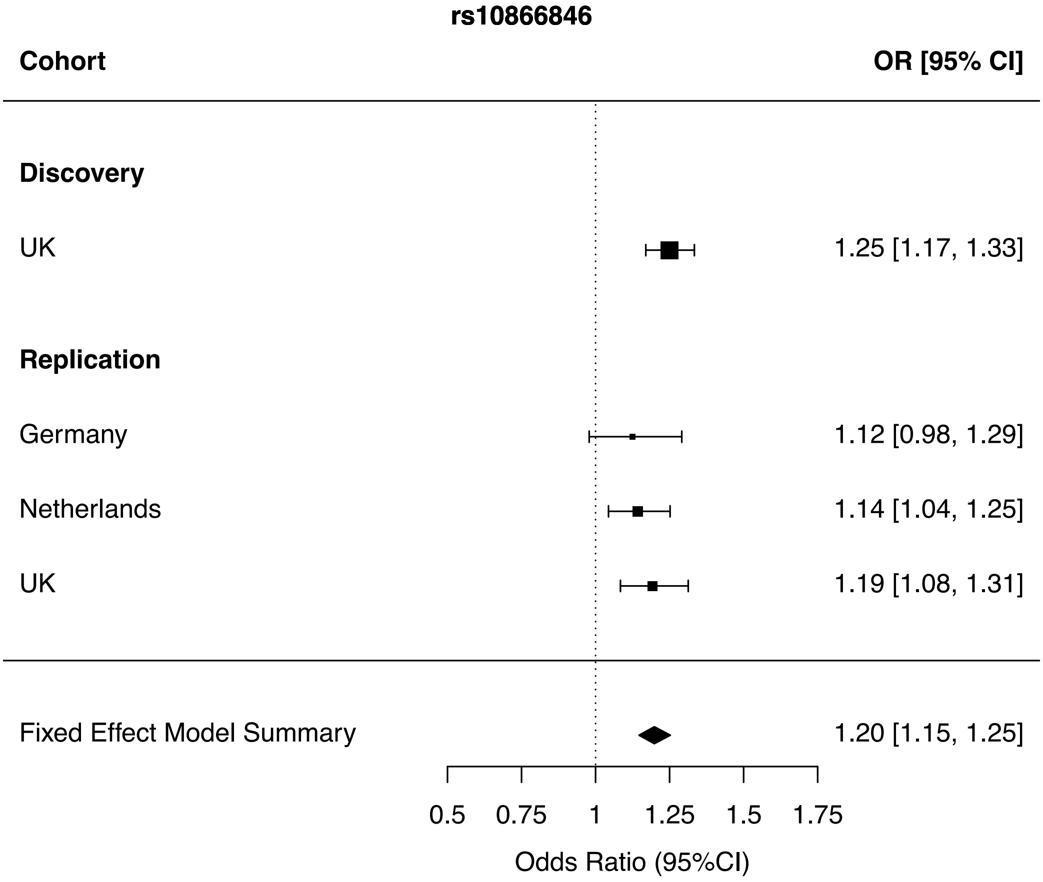
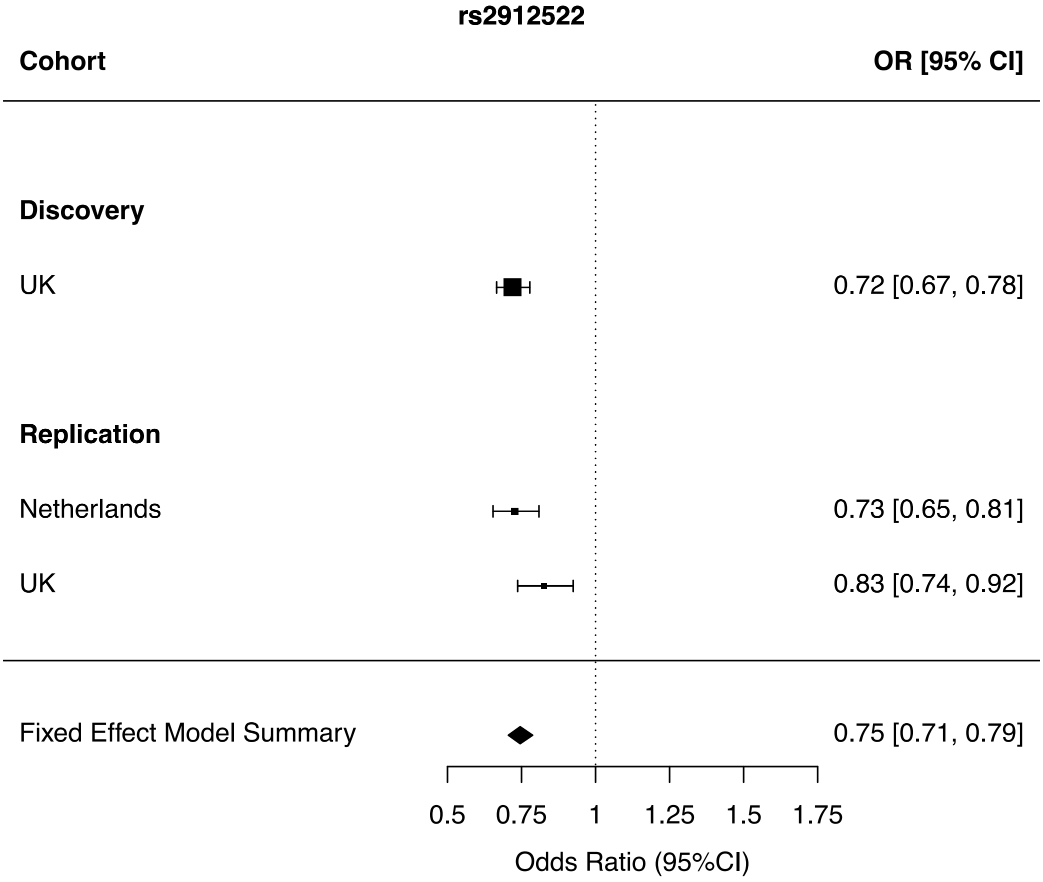
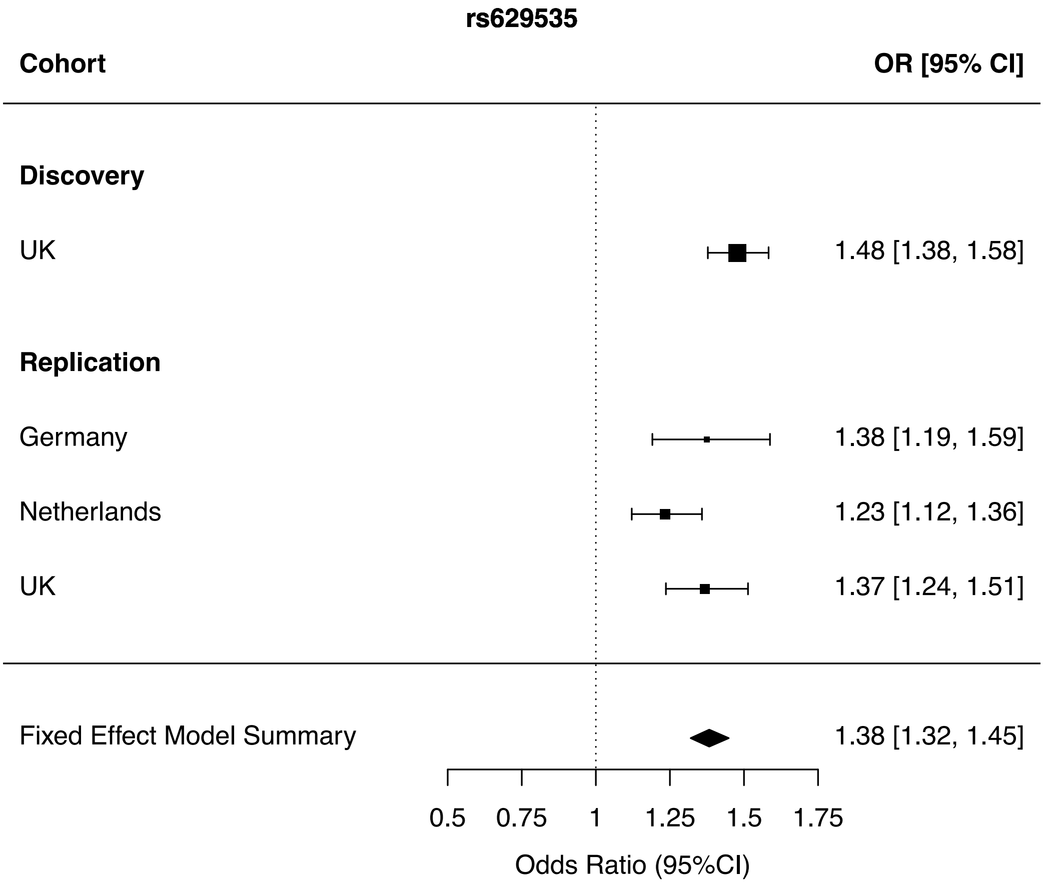
0.5
0.75
1
1.25
1.5
1.75
Odds Ratio (95%CI)


rs10866846
Cohort
OR [95% CI]
Discovery
UK
1.25 [1.17, 1.33]
Replication
Germany
1.12 [0.98, 1.29]
Netherlands
1.14 [1.04, 1.25]
UK
1.19 [1.08, 1.31]
Fixed Effect Model Summary
1.20 [1.15, 1.25]
0.5
0.75
1
1.25
1.5
1.75
Odds Ratio (95%CI)


rs2912522
Cohort
OR [95% CI]
Discovery
UK
0.72 [0.67, 0.78]
Replication
Netherlands
0.73 [0.65, 0.81]
UK
0.83 [0.74, 0.92]
Fixed Effect Model Summary
0.75 [0.71, 0.79]
0.5
0.75
1
1.25
1.5
1.75
Odds Ratio (95%CI)


rs629535
Cohort
OR [95% CI]
Discovery
UK
1.48 [1.38, 1.58]
Replication
Germany
1.38 [1.19, 1.59]
Netherlands
1.23 [1.12, 1.36]
UK
1.37 [1.24, 1.51]
Fixed Effect Model Summary
1.38 [1.32, 1.45]
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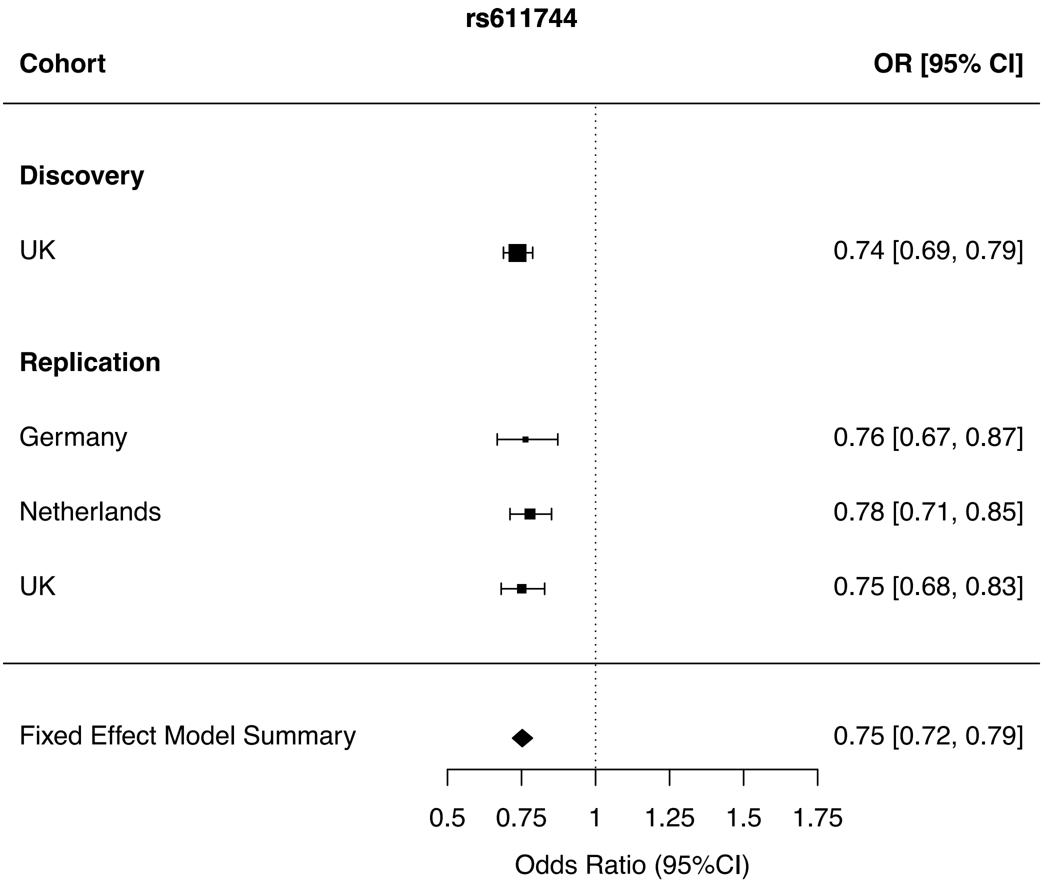
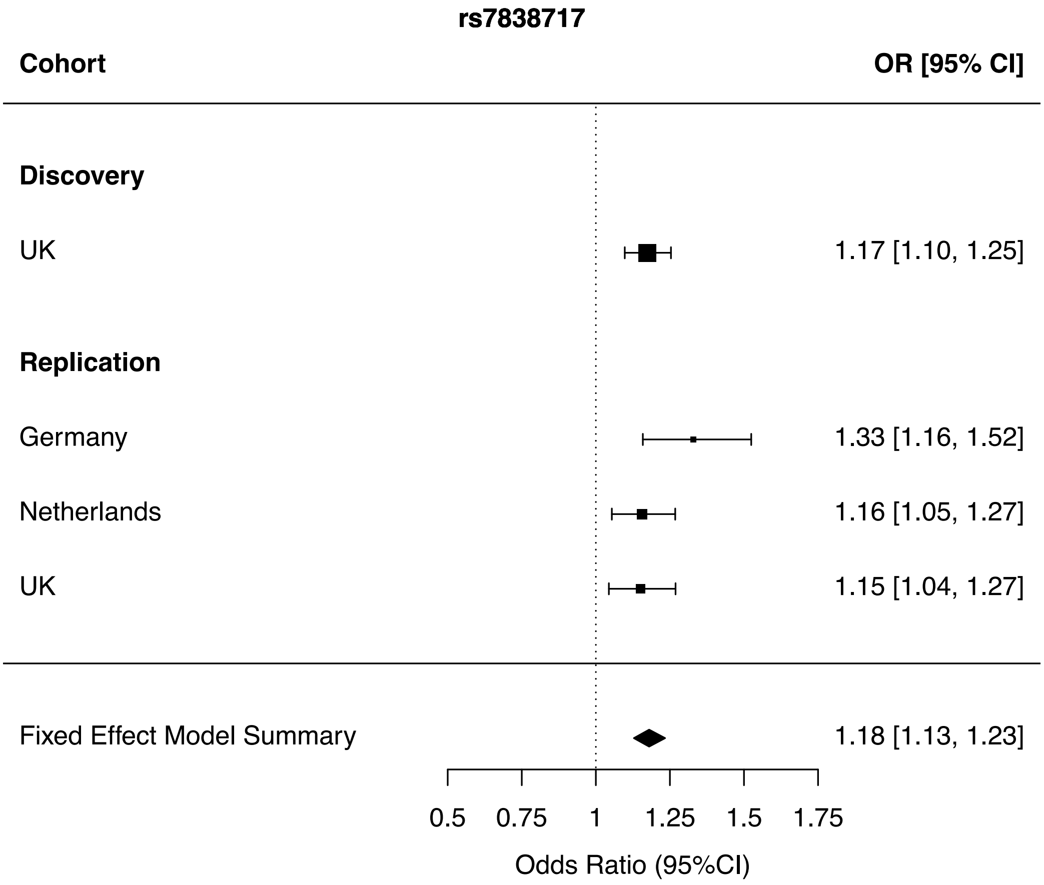
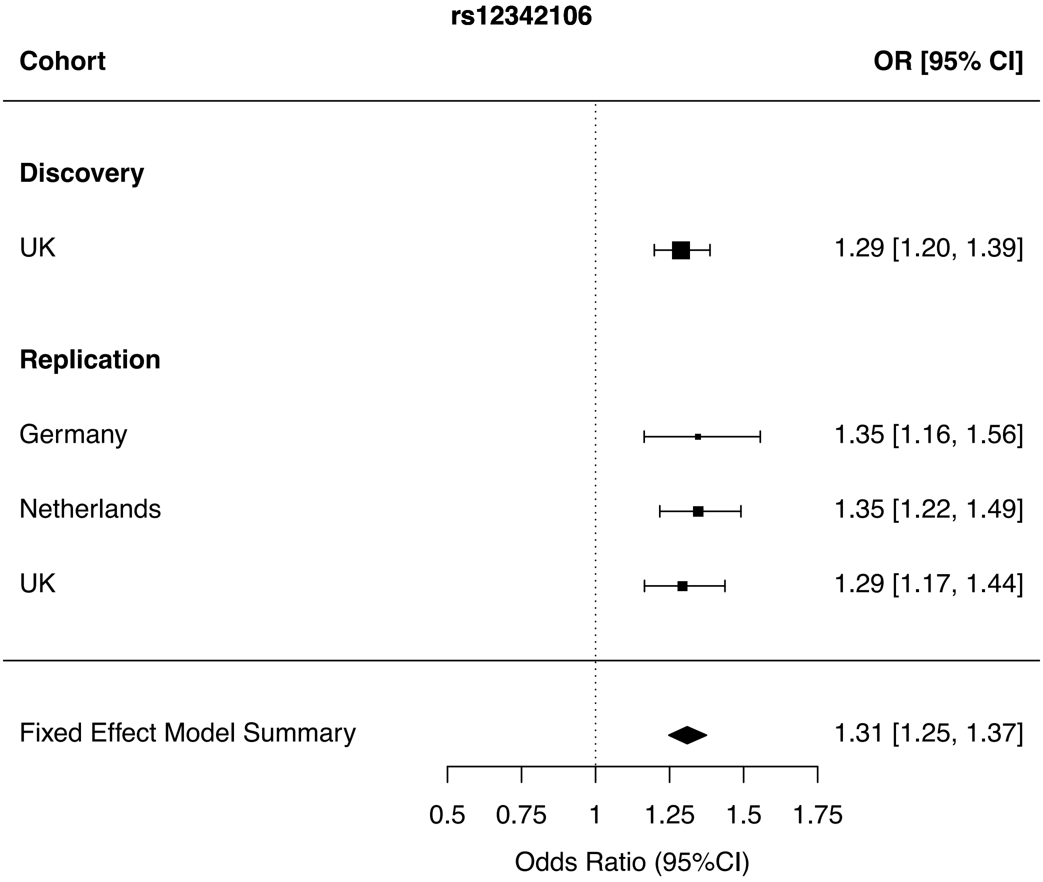
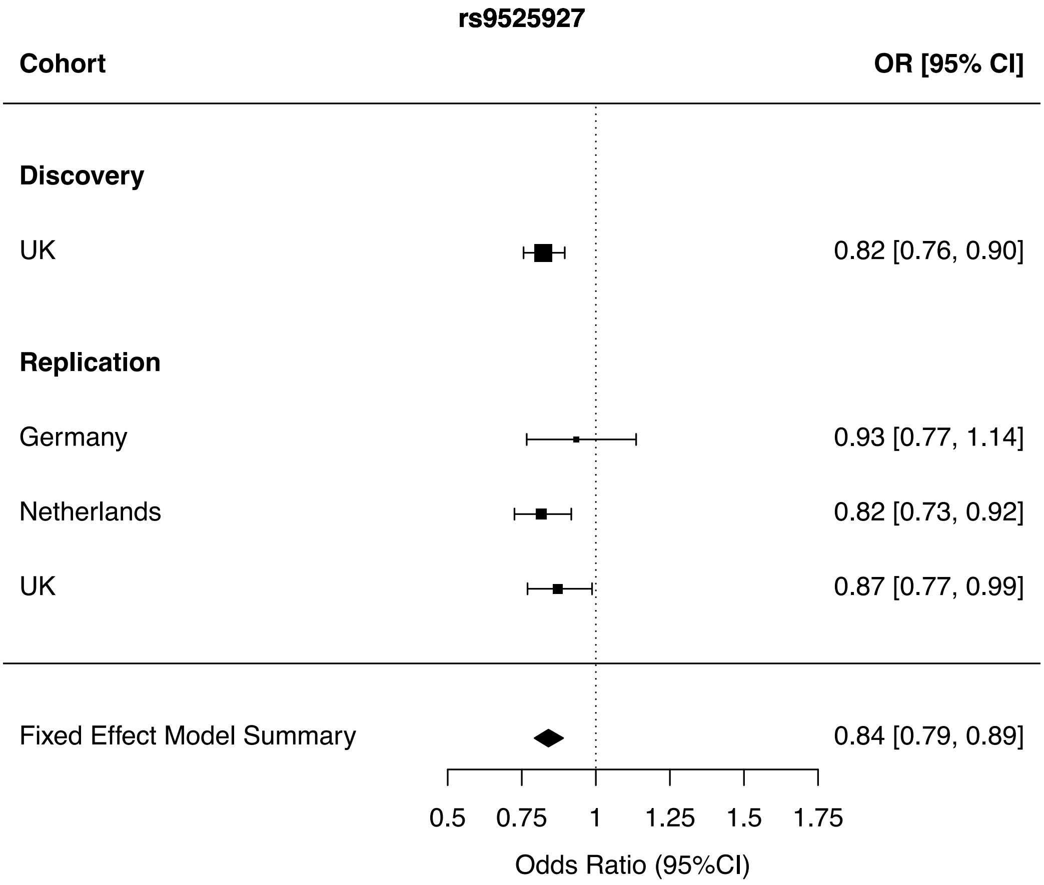
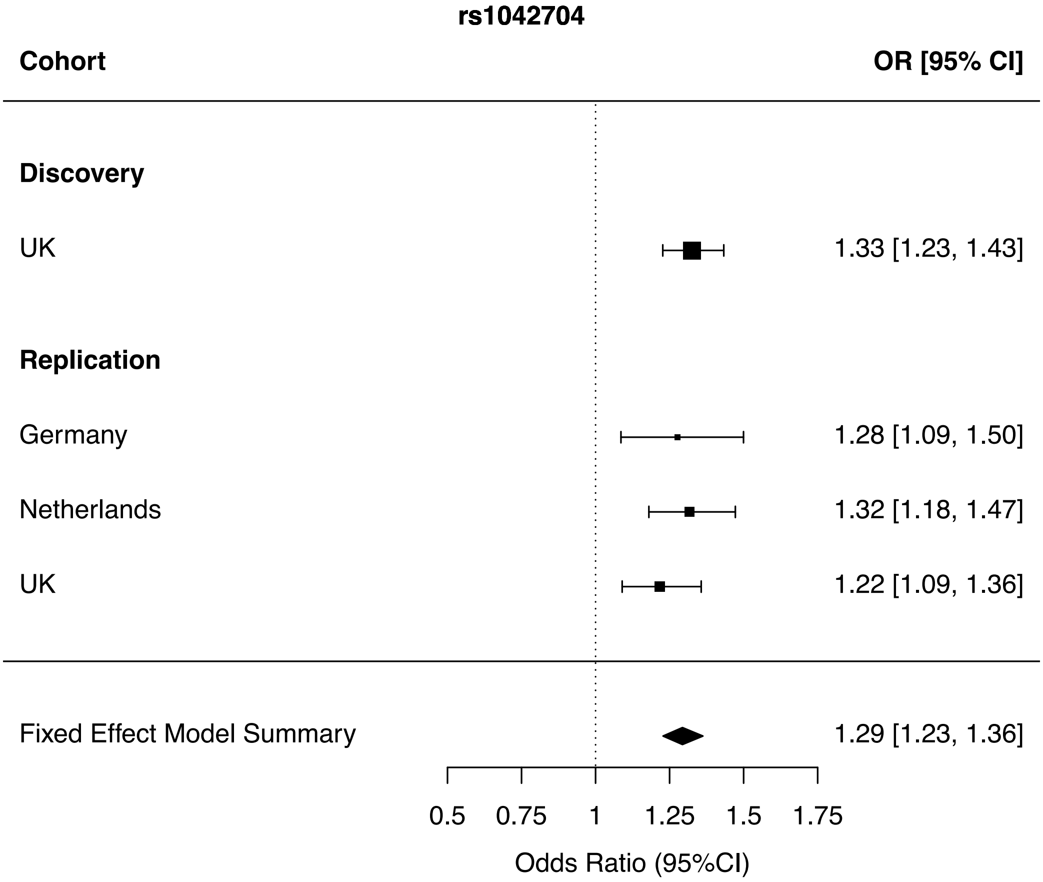
0.75
1
1.25
1.5
1.75
Odds Ratio (95%CI)

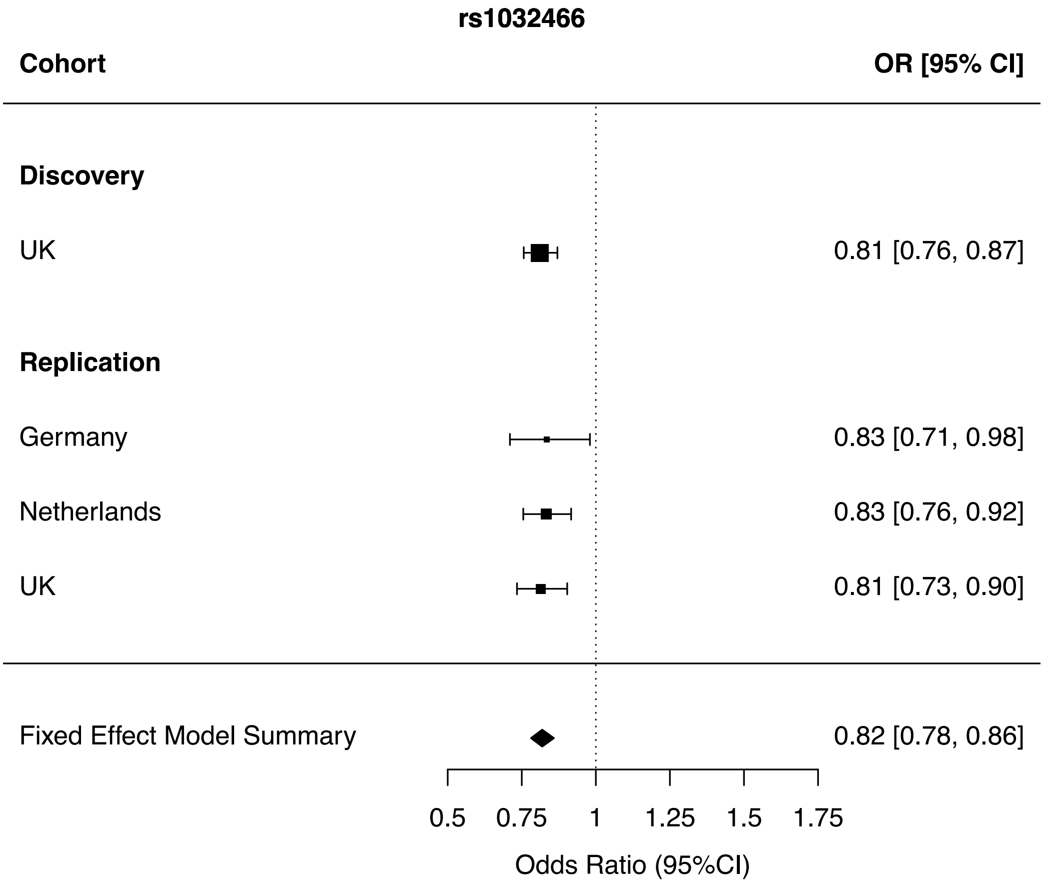

rs611744
Cohort
OR [95% CI]
Discovery
UK
0.74 [0.69, 0.79]
Replication
Germany
0.76 [0.67, 0.87]
Netherlands
0.78 [0.71, 0.85]
UK
0.75 [0.68, 0.83]
Fixed Effect Model Summary
0.75 [0.72, 0.79]
0.5
0.75
1
1.25
1.5
1.75
Odds Ratio (95%CI)

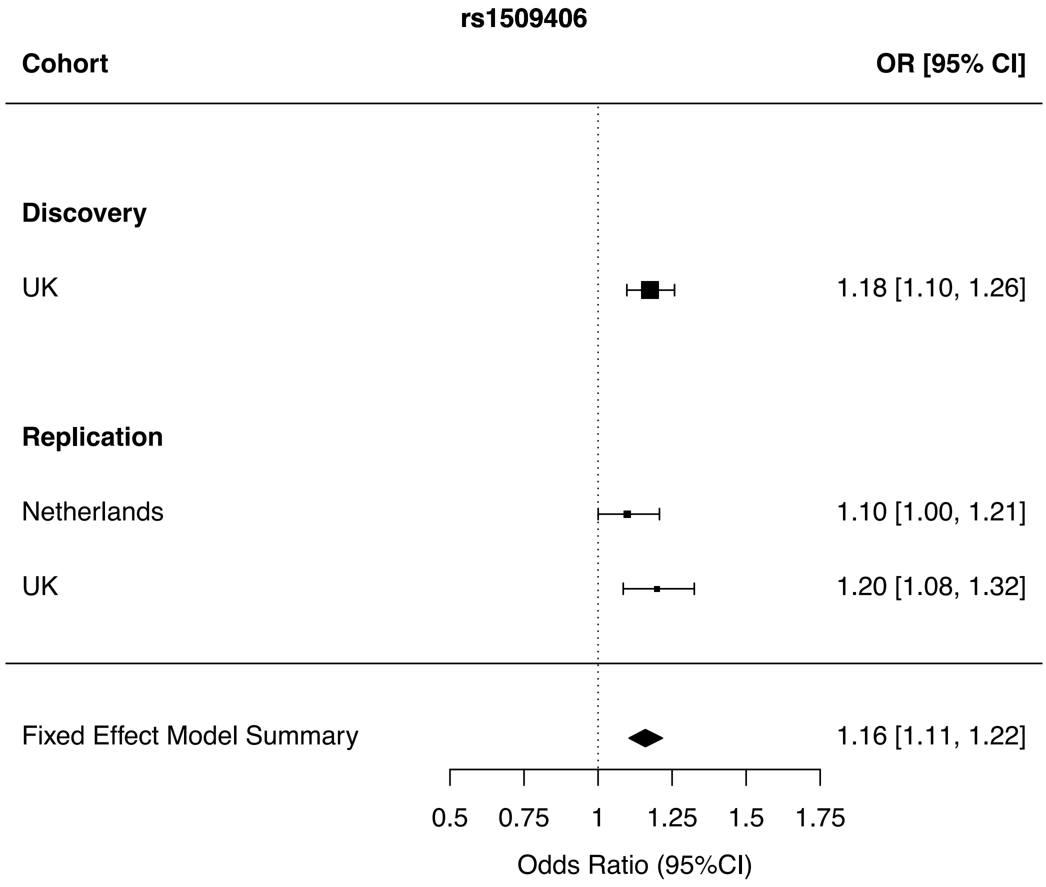

rs7838717
Cohort
OR [95% CI]
Discovery
UK
1.17 [1.10, 1.25]
Replication
Germany
1.33 [1.16, 1.52]
Netherlands
1.16 [1.05, 1.27]
UK
1.15 [1.04, 1.27]
Fixed Effect Model Summary
1.18 [1.13, 1.23]
0.5
0.75
1
1.25
1.5
1.75
Odds Ratio (95%CI)

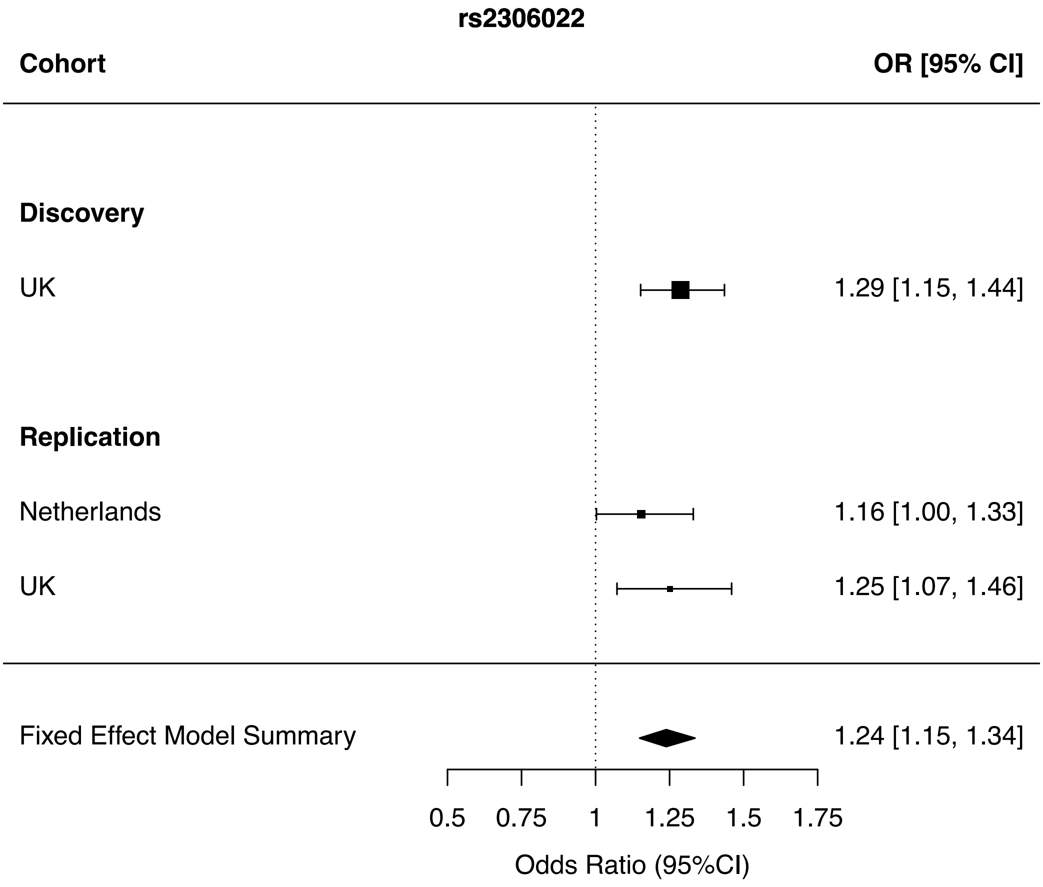

rs12342106
Cohort
OR [95% CI]
Discovery
UK
1.29 [1.20, 1.39]
Replication
Germany
1.35 [1.16, 1.56]
Netherlands
1.35 [1.22, 1.49]
UK
1.29 [1.17, 1.44]
Fixed Effect Model Summary
1.31 [1.25, 1.37]
0.5
0.75
1
1.25
1.5
1.75
Odds Ratio (95%CI)

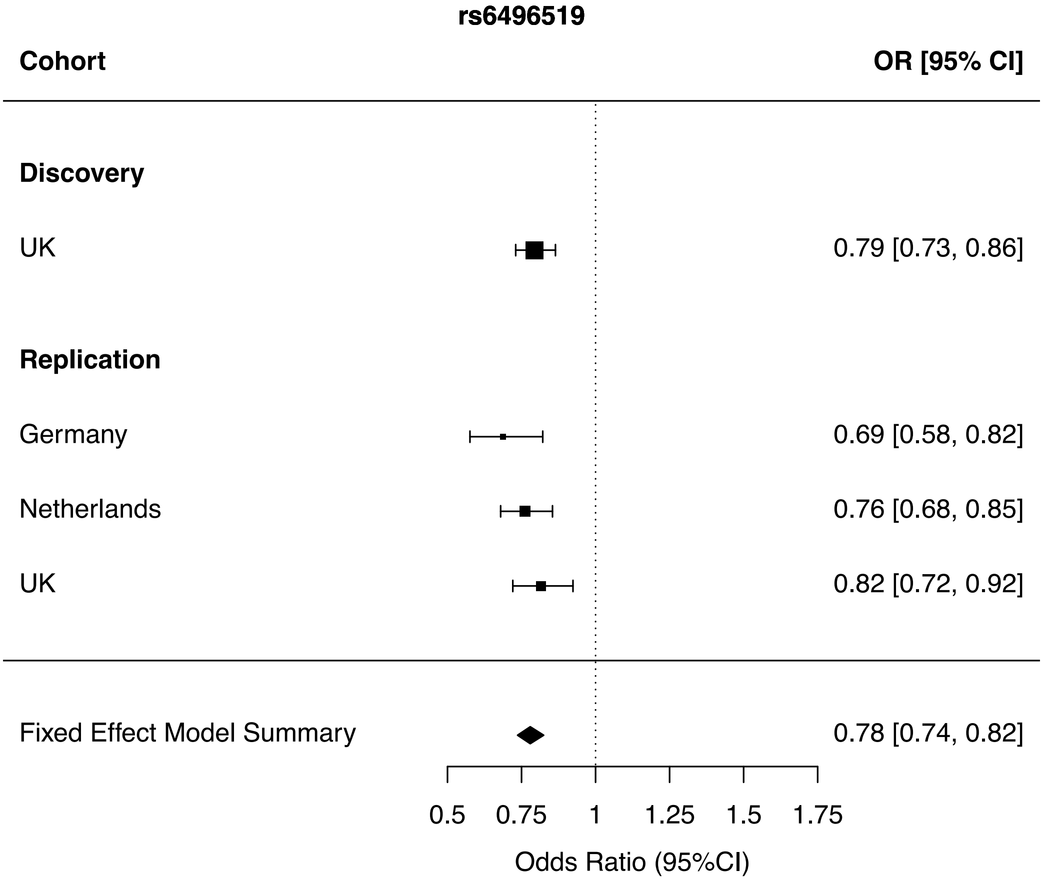

rs9525927
Cohort
OR [95% CI]
Discovery
UK
0.82 [0.76, 0.90]
Replication
Germany
0.93 [0.77, 1.14]
Netherlands
0.82 [0.73, 0.92]
UK
0.87 [0.77, 0.99]
Fixed Effect Model Summary
0.84 [0.79, 0.89]
0.5
0.75
1
1.25
1.5
1.75
Odds Ratio (95%CI)

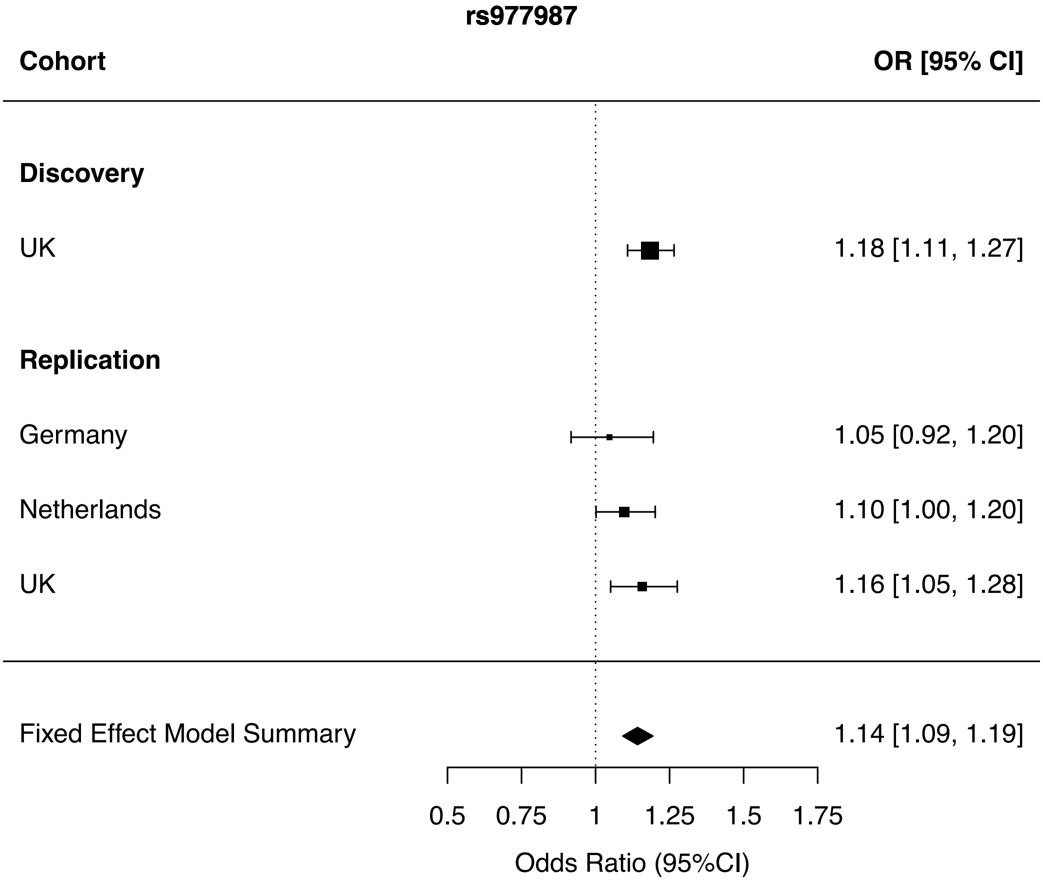

rs1042704
Cohort
OR [95% CI]
Discovery
UK
1.33 [1.23, 1.43]
Replication
Germany
1.28 [1.09, 1.50]
Netherlands
1.32 [1.18, 1.47]
UK
1.22 [1.09, 1.36]
Fixed Effect Model Summary
1.29 [1.23, 1.36]
0.5
0.75
1
1.25
1.5
1.75
Odds Ratio (95%CI)

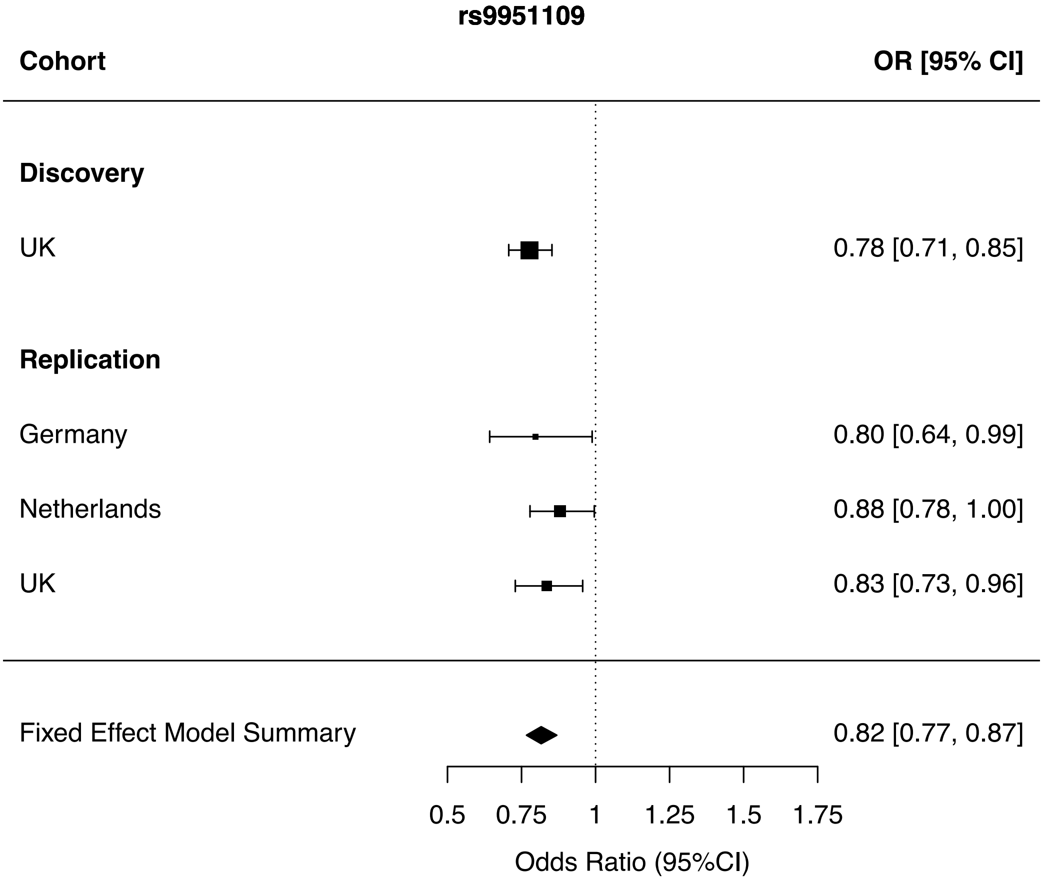

rs1032466
Cohort
OR [95% CI]
Discovery
UK
0.81 [0.76, 0.87]
Replication
Germany
0.83 [0.71, 0.98]
Netherlands
0.83 [0.76, 0.92]
UK
0.81 [0.73, 0.90]
Fixed Effect Model Summary
0.82 [0.78, 0.86]
0.5
0.75
1
1.25
1.5
1.75
Odds Ratio (95%CI)

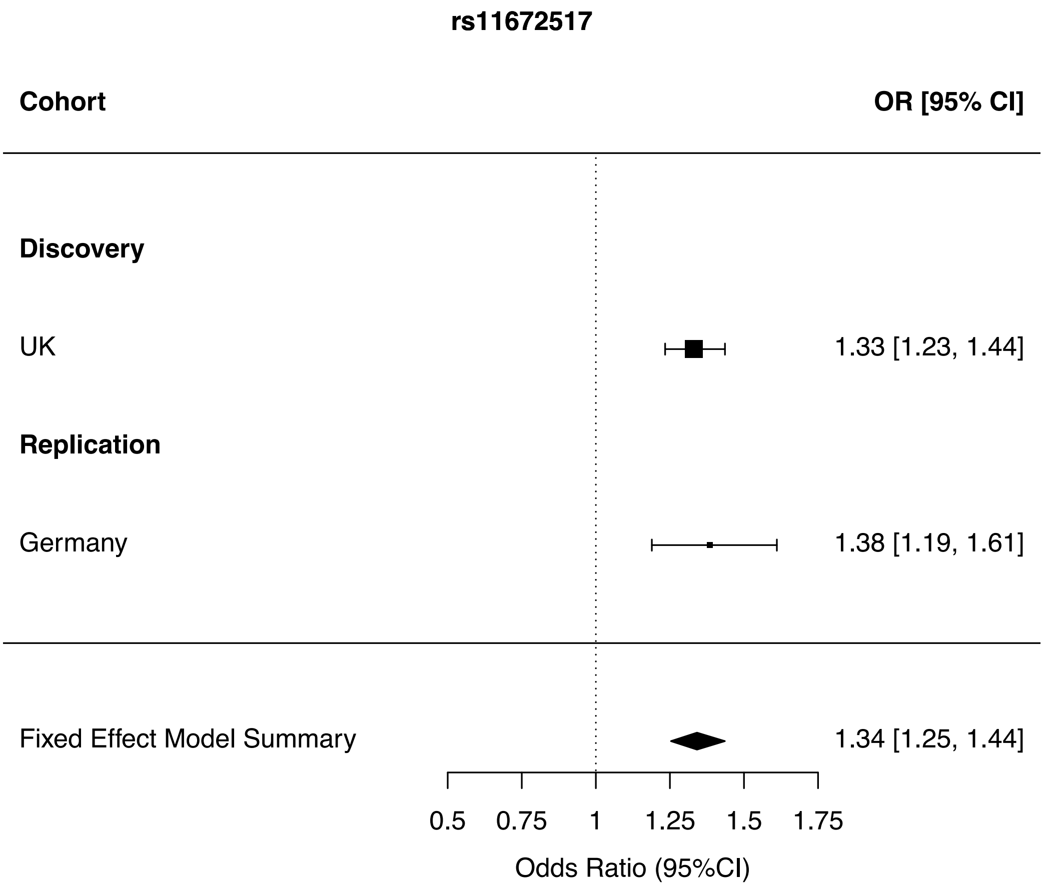

rs1509406
Cohort
OR [95% CI]
Discovery
UK
1.18 [1.10, 1.26]
Replication
Netherlands
1.10 [1.00, 1.21]
UK
1.20 [1.08, 1.32]
Fixed Effect Model Summary
1.16 [1.11, 1.22]
0.5
0.75
1
1.25
1.5
1.75
Odds Ratio (95%CI)

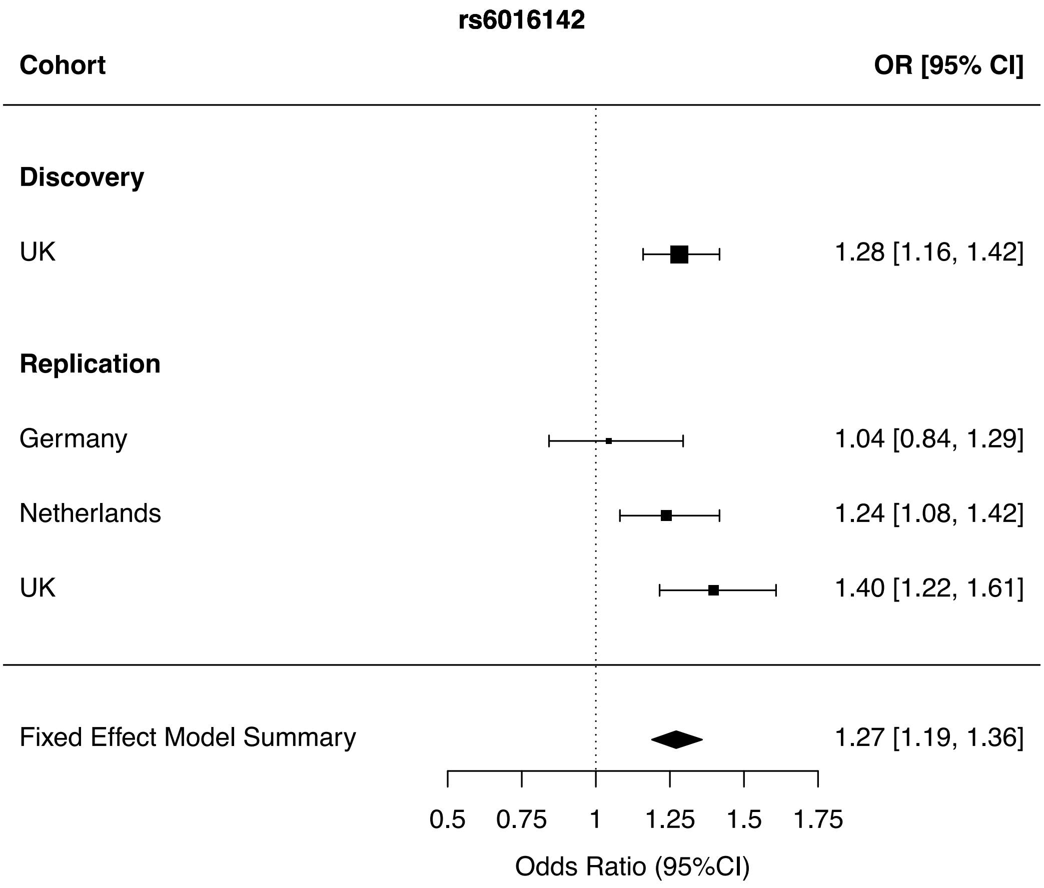

rs2306022
Cohort
OR [95% CI]
Discovery
UK
1.29 [1.15, 1.44]
Replication
Netherlands
1.16 [1.00, 1.33]
UK
1.25 [1.07, 1.46]
Fixed Effect Model Summary
1.24 [1.15, 1.34]
0.5
0.75
1
1.25
1.5
1.75
Odds Ratio (95%CI)

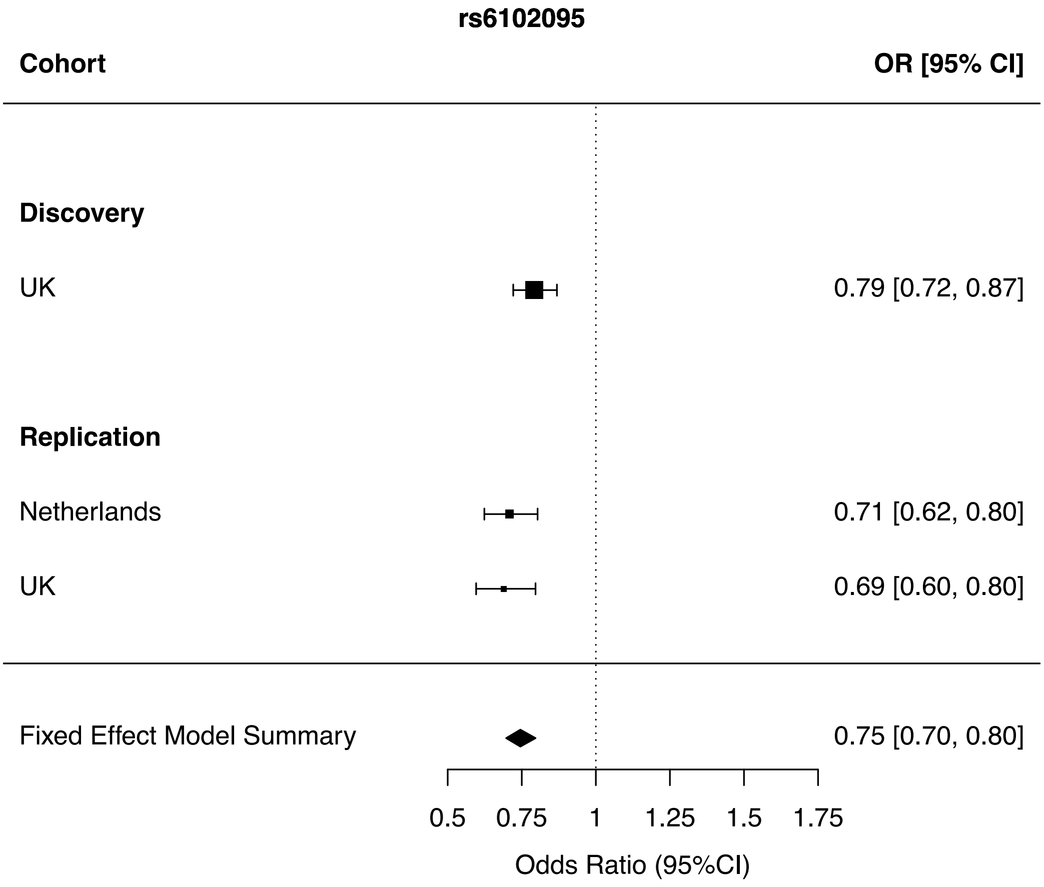

rs6496519
Cohort
OR [95% CI]
Discovery
UK
0.79 [0.73, 0.86]
Replication
Germany
0.69 [0.58, 0.82]
Netherlands
0.76 [0.68, 0.85]
UK
0.82 [0.72, 0.92]
Fixed Effect Model Summary
0.78 [0.74, 0.82]
0.5
0.75
1
1.25
1.5
1.75
Odds Ratio (95%CI)


rs977987
Cohort
OR [95% CI]
Discovery
UK
1.18 [1.11, 1.27]
Replication
Germany
1.05 [0.92, 1.20]
Netherlands
1.10 [1.00, 1.20]
UK
1.16 [1.05, 1.28]
Fixed Effect Model Summary
1.14 [1.09, 1.19]
0.5
0.75
1
1.25
1.5
1.75
Odds Ratio (95%CI)


rs9951109
Cohort
OR [95% CI]
Discovery
UK
0.78 [0.71, 0.85]
Replication
Germany
0.80 [0.64, 0.99]
Netherlands
0.88 [0.78, 1.00]
UK
0.83 [0.73, 0.96]
Fixed Effect Model Summary
0.82 [0.77, 0.87]
0.5
0.75
1
1.25
1.5
1.75
Odds Ratio (95%CI)


rs11672517
Cohort
OR [95% CI]
Discovery
UK
1.33 [1.23, 1.44]
Replication
Germany
1.38 [1.19, 1.61]
Fixed Effect Model Summary
1.34 [1.25, 1.44]
0.5
0.75
1
1.25
1.5
1.75
Odds Ratio (95%CI)


rs6016142
Cohort
OR [95% CI]
Discovery
UK
1.28 [1.16, 1.42]
Replication
Germany
1.04 [0.84, 1.29]
Netherlands
1.24 [1.08, 1.42]
UK
1.40 [1.22, 1.61]
Fixed Effect Model Summary
1.27 [1.19, 1.36]
0.5
0.75
1
1.25
1.5
1.75
Odds Ratio (95%CI)


rs6102095
Cohort
OR [95% CI]
Discovery
UK
0.79 [0.72, 0.87]
Replication
Netherlands
0.71 [0.62, 0.80]
UK
0.69 [0.60, 0.80]
Fixed Effect Model Summary
0.75 [0.70, 0.80]
0.5
0.75
1
1.25
1.5
1.75
Odds Ratio (95%CI)

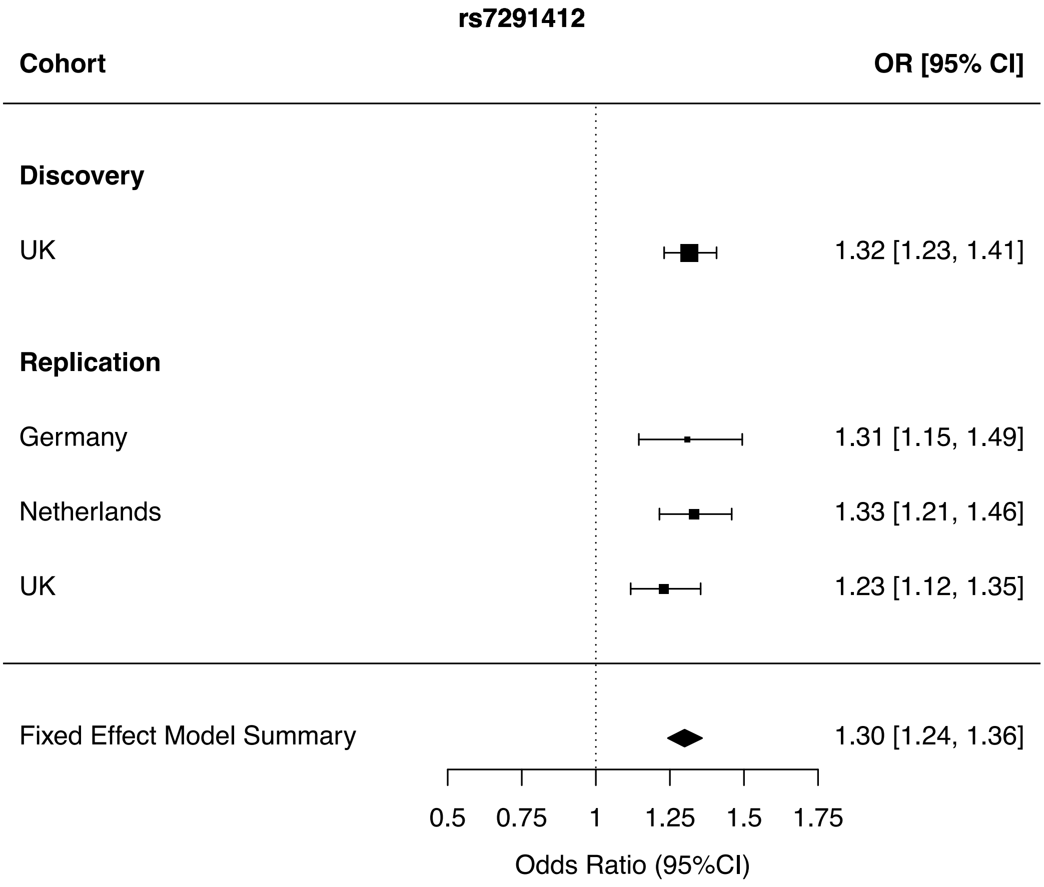
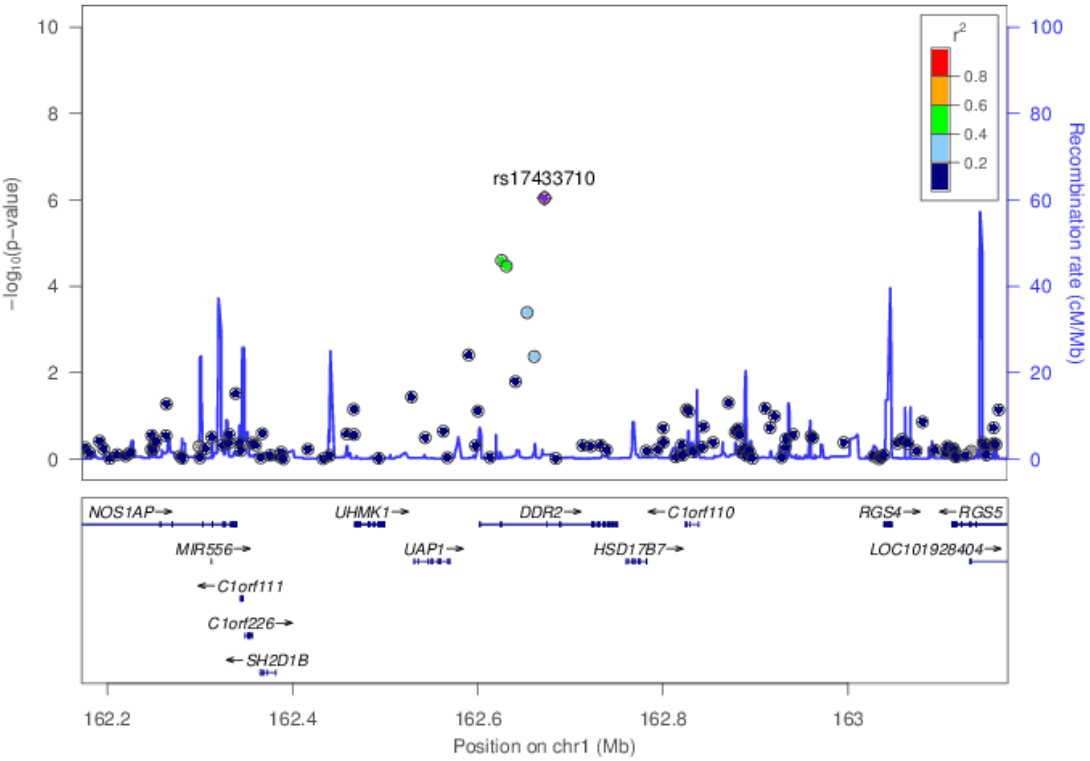
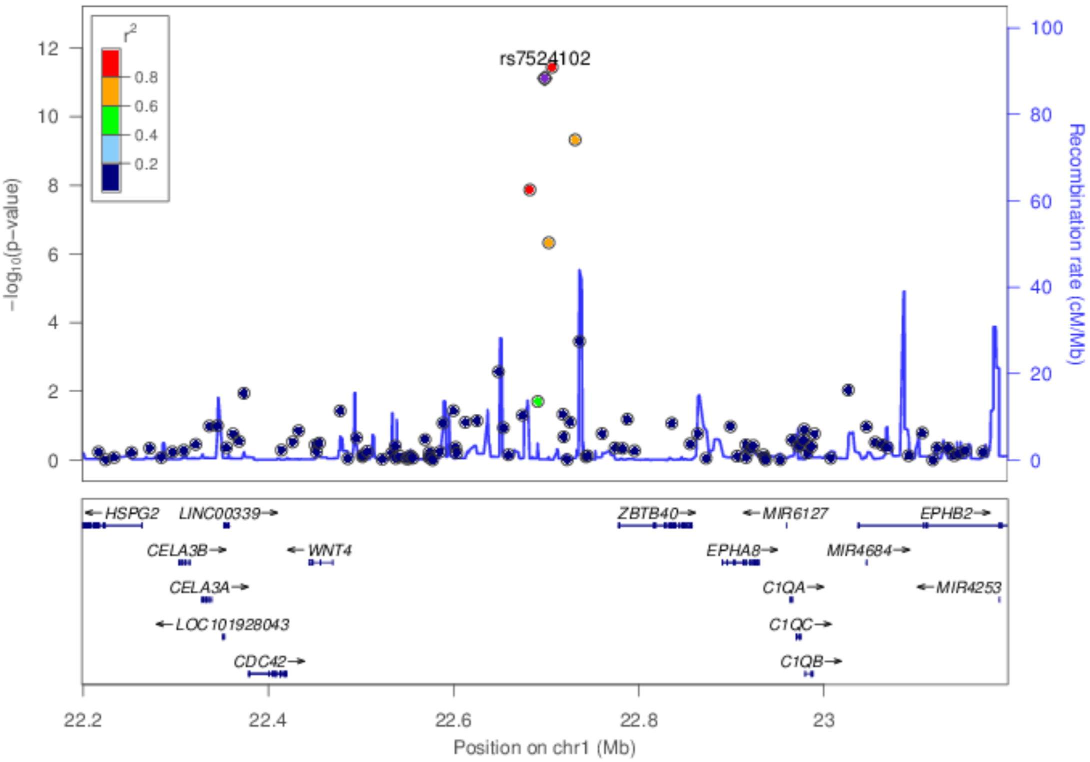
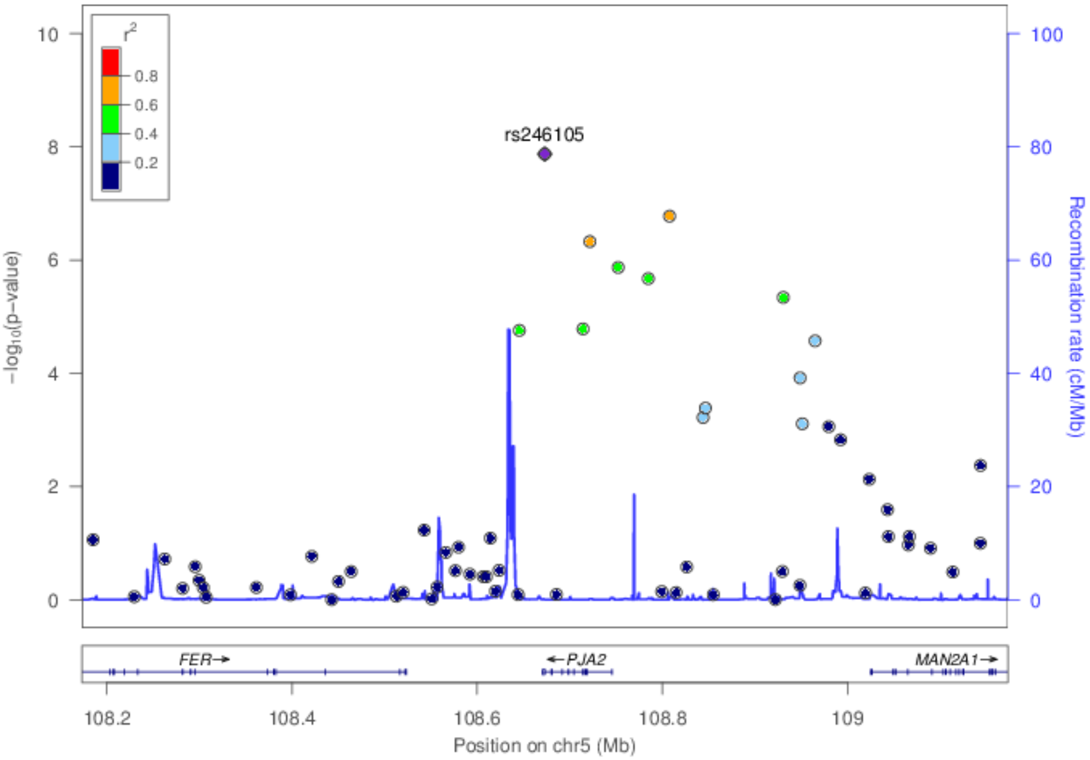
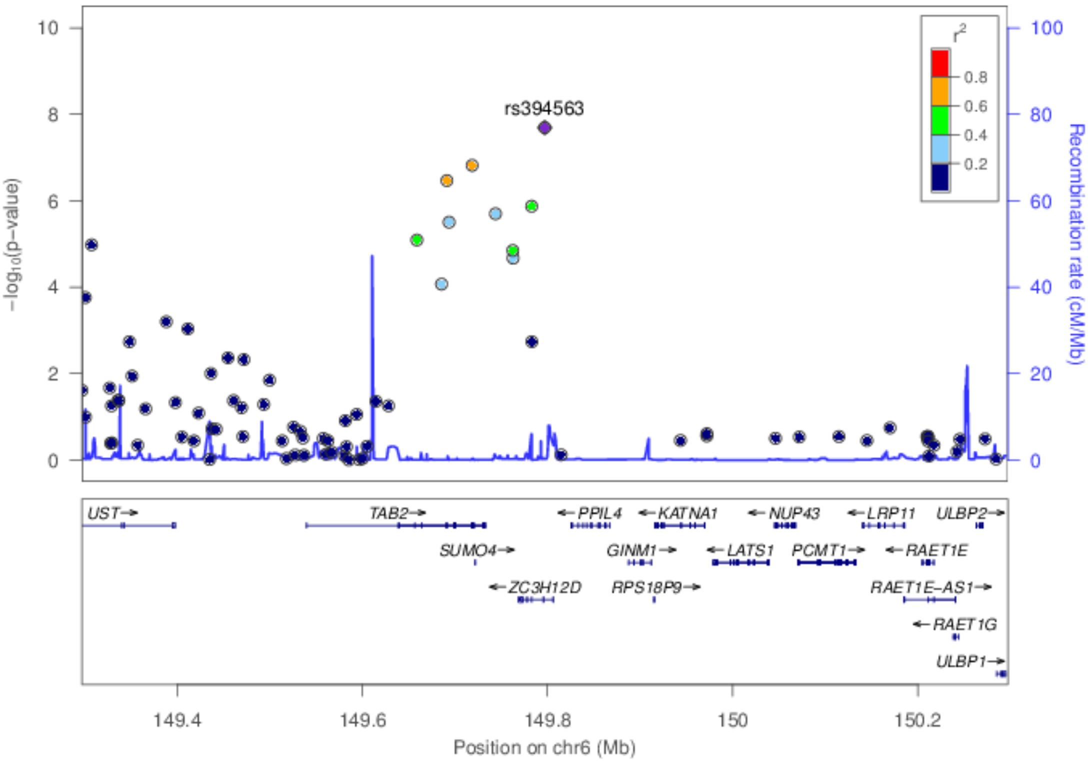

rs7291412
Cohort
OR [95% CI]
Discovery
UK
1.32 [1.23, 1.41]
Replication
Germany
1.31 [1.15, 1.49]
Netherlands
1.33 [1.21, 1.46]
UK
1.23 [1.12, 1.35]
Fixed Effect Model Summary
1.30 [1.24, 1.36]
0.5
0.75
1
1.25
1.5
1.75
Odds Ratio (95%CI)

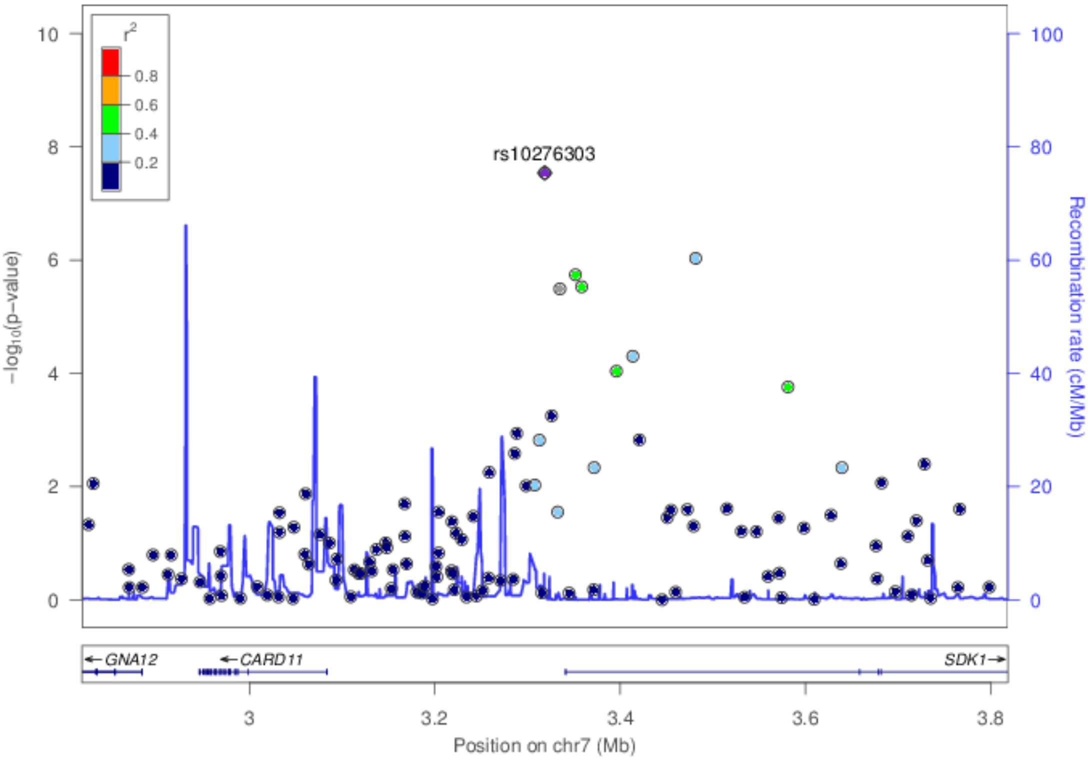
Figure S6. Annotated regional association plots for all 26 variants significantly associated with Dupuytren's disease ($p \leq 5x10^{-8}$) after meta-analysis of discovery and replication cohorts, plotted with LocusZoom [1]. Recombination rate was calculated within the software using data from HapMap genotypes. In the lower panel of each figure, genes within 500kb of the index SNP are shown. The position on each chromosome is shown in relation to Human Genome build hg19.

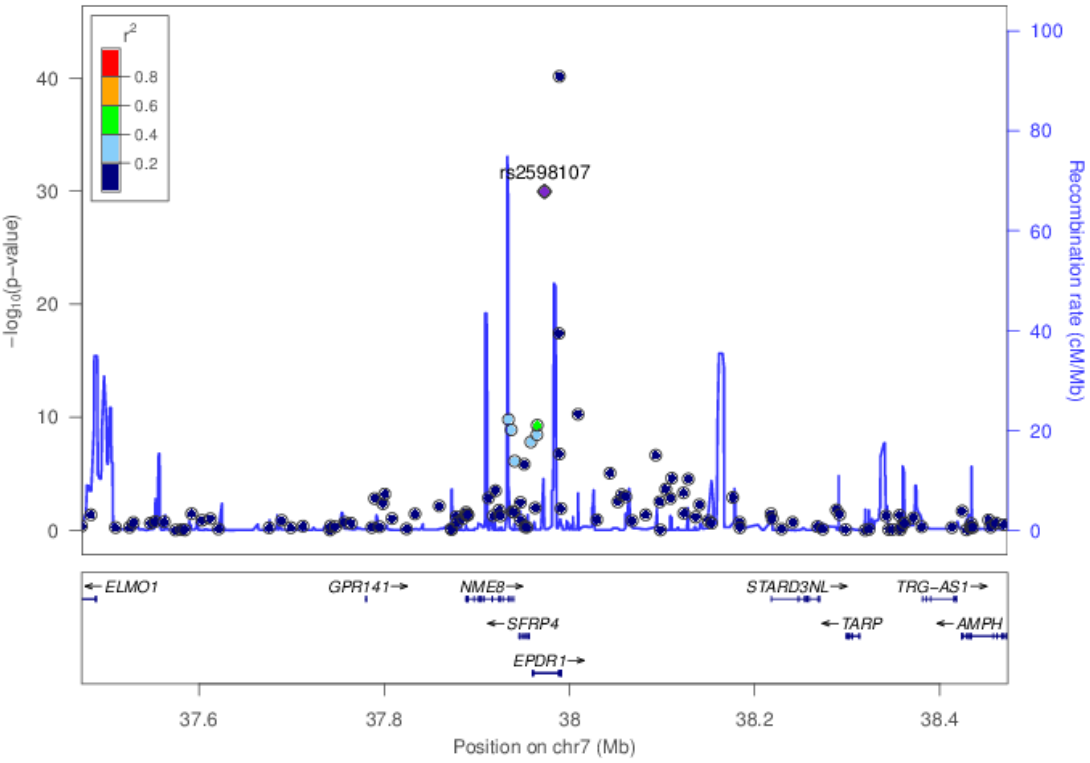


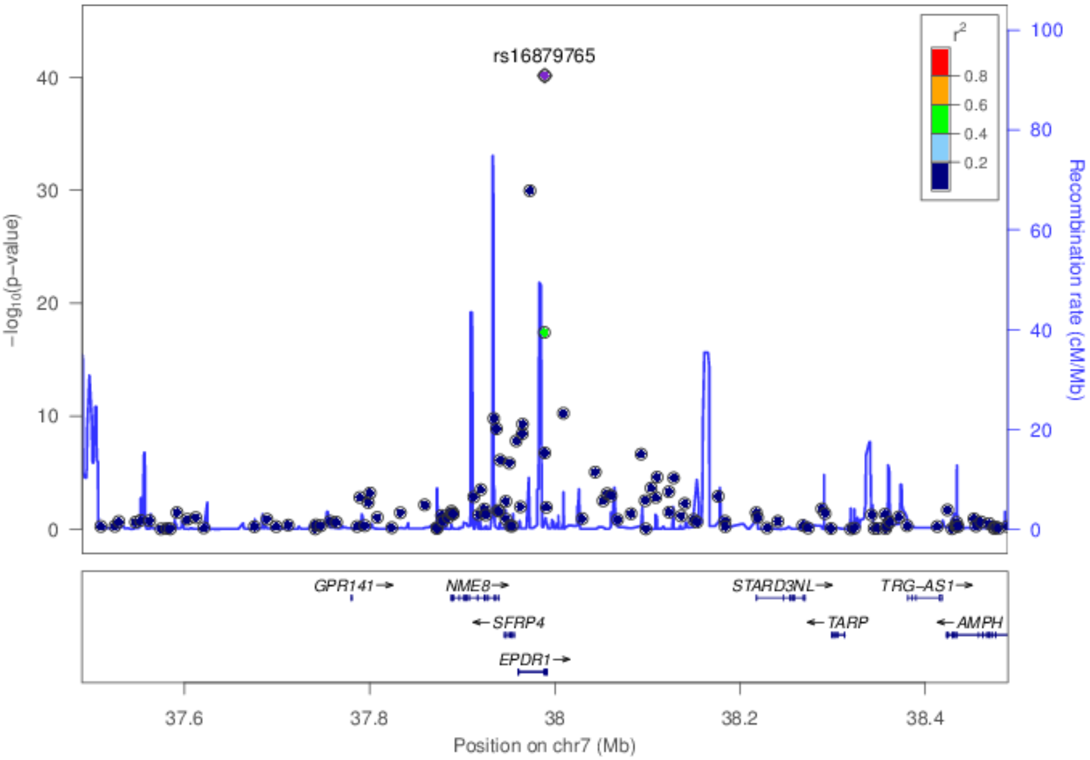

r²
0.8
0.6
0.4
0.2
rs7524102
−log₁₀(p−value)
0
2
4
6
8
10
12
Recombination rate (cM/Mb)
0
20
40
60
80
100
HSPG2
LINC00339
CELA3B
WNT4
CELA3A
LOC101928043
CDC42
ZBTB40
MIR6127
EPHB2
EPHA8
MIR4684
C1QA
MIR4253
C1QC
C1QB
22.2
22.4
22.6
22.8
23
Position on chr1 (Mb)

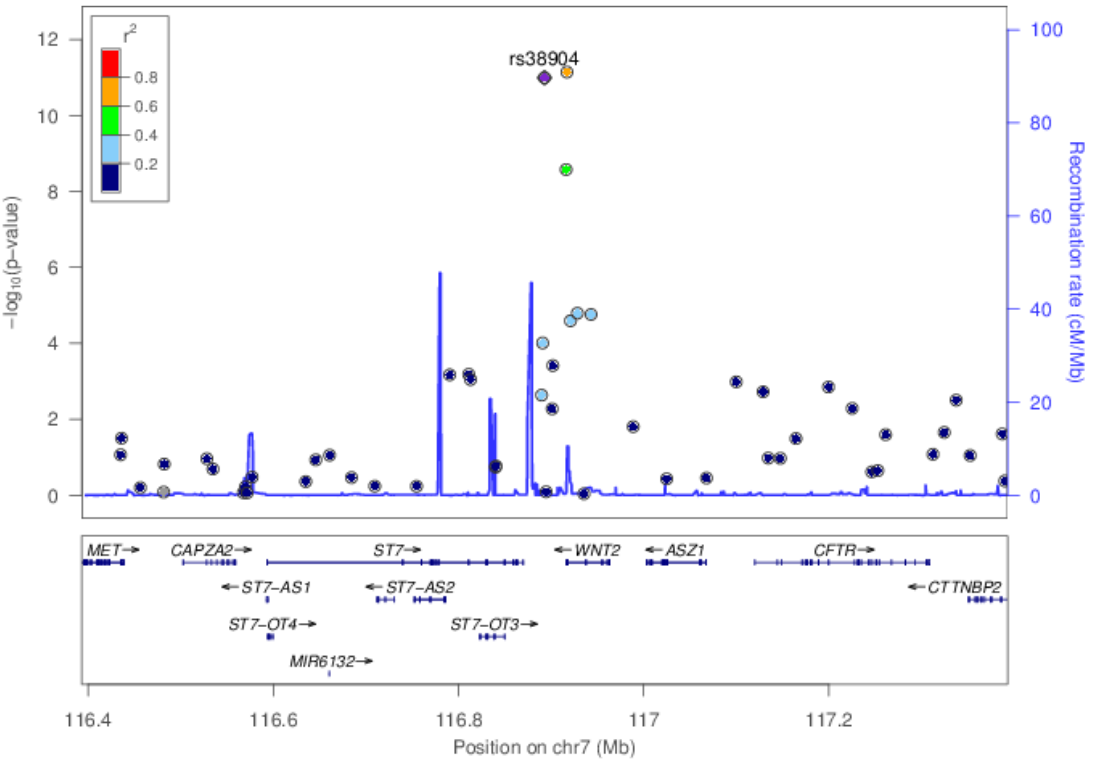

r²
0.8
0.6
0.4
0.2
rs246105
−log₁₀(p−value)
0
2
4
6
8
10
Recombination rate (cM/Mb)
0
20
40
60
80
100
FER
PJA2
MAN2A1
108.2
108.4
108.6
108.8
109
Position on chr5 (Mb)

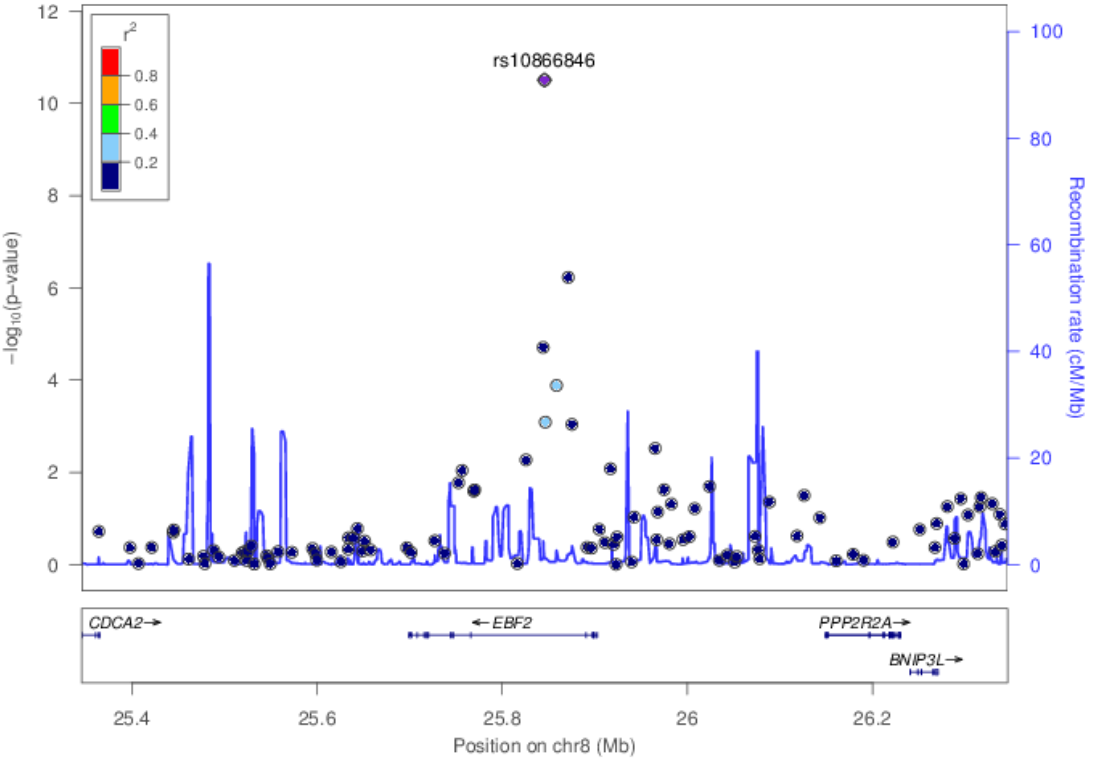

rs394563
r2
0.8
0.6
0.4
0.2
−log10(p−value)
10
8
6
4
2
0
100
80
60
40
20
0
Recombination rate (cM/Mb)
UST→
TAB2→
←PPIL4
←KATNA1
←NUP43
←LRP11
ULBP2→
SUMO4→
GINM1→
←LATS1
PCMT1→
←RAET1E
←ZC3H12D
RPS18P9→
RAET1E−AS1→
←RAET1G
ULBP1→
149.4
149.6
149.8
150
150.2
Position on chr6 (Mb)

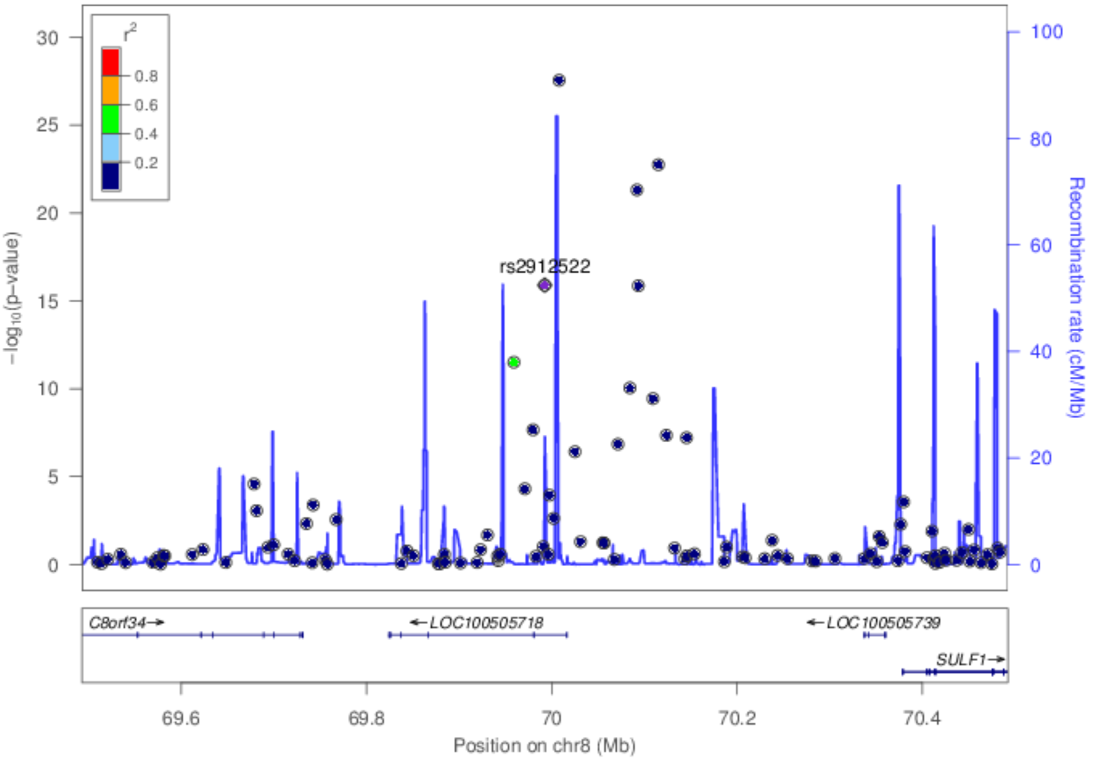

rs10276303
r2
0.8
0.6
0.4
0.2
−log10(p−value)
10
8
6
4
2
0
100
80
60
40
20
0
Recombination rate (cM/Mb)
←GNA12
←CARD11
SDK1→
3
3.2
3.4
3.6
3.8
Position on chr7 (Mb)


r²
0.8
0.6
0.4
0.2
rs2598107
−log₁₀(p−value)
0
10
20
30
40
Recombination rate (cM/Mb)
0
20
40
60
80
100
ELMO1
GPR141
NME8
SFRP4
EPDR1
STARD3NL
TARP
TRG−AS1
AMPH
37.6
37.8
38
38.2
38.4
Position on chr7 (Mb)

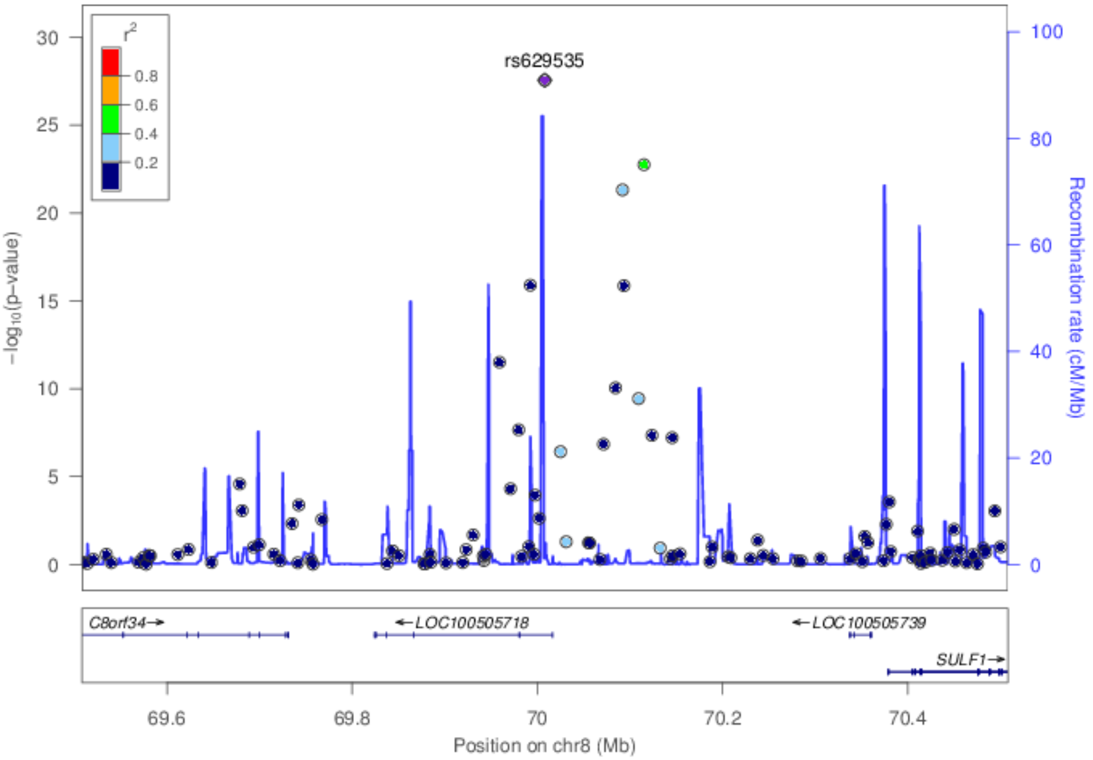

r²
0.8
0.6
0.4
0.2
rs16879765
−log₁₀(p−value)
0
10
20
30
40
Recombination rate (cM/Mb)
0
20
40
60
80
100
GPR141
NME8
SFRP4
EPDR1
STARD3NL
TARP
TRG−AS1
AMPH
37.6
37.8
38
38.2
38.4
Position on chr7 (Mb)


rs38904
r2
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
12
10
8
6
4
2
0
100
80
60
40
20
0
MET→
CAPZA2→
ST7→
←WNT2
←ASZ1
CFTR→
←ST7−AS1
←ST7−AS2
←CTTNBP2
ST7−OT4→
ST7−OT3→
MIR6132→
116.4
116.6
116.8
117
117.2
Position on chr7 (Mb)

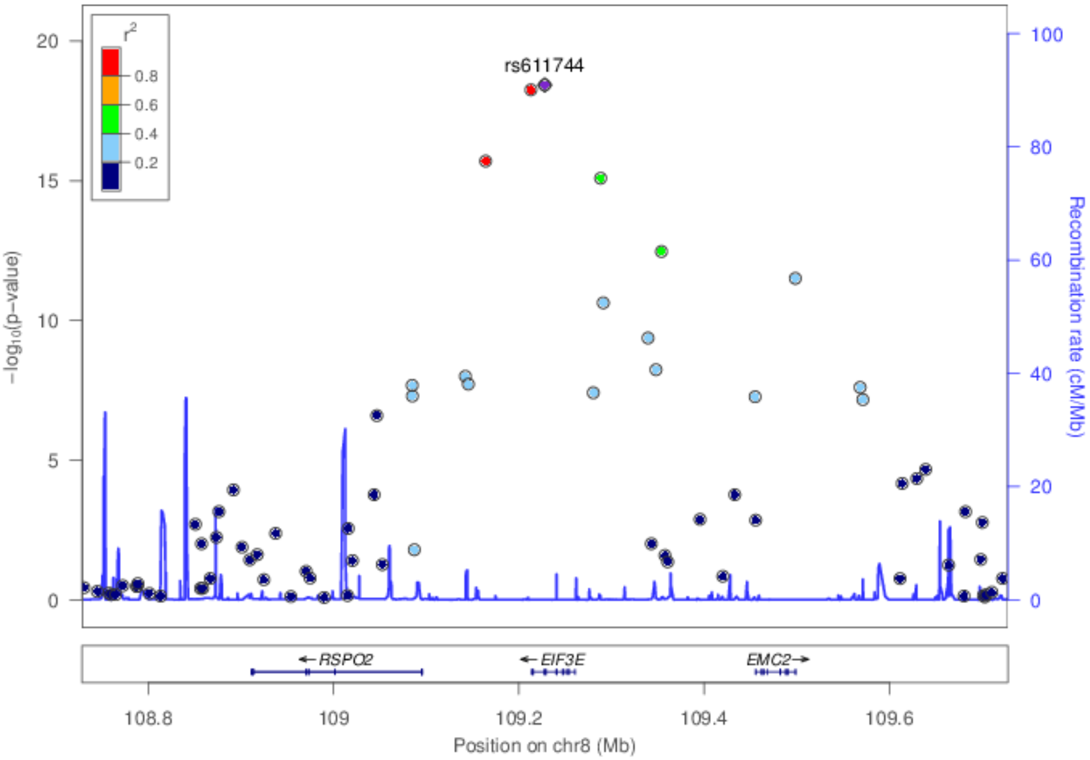

rs10866846
r2
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
12
10
8
6
4
2
0
100
80
60
40
20
0
CDCA2→
←EBF2
PPP2R2A→
BNIP3L→
25.4
25.6
25.8
26
26.2
Position on chr8 (Mb)

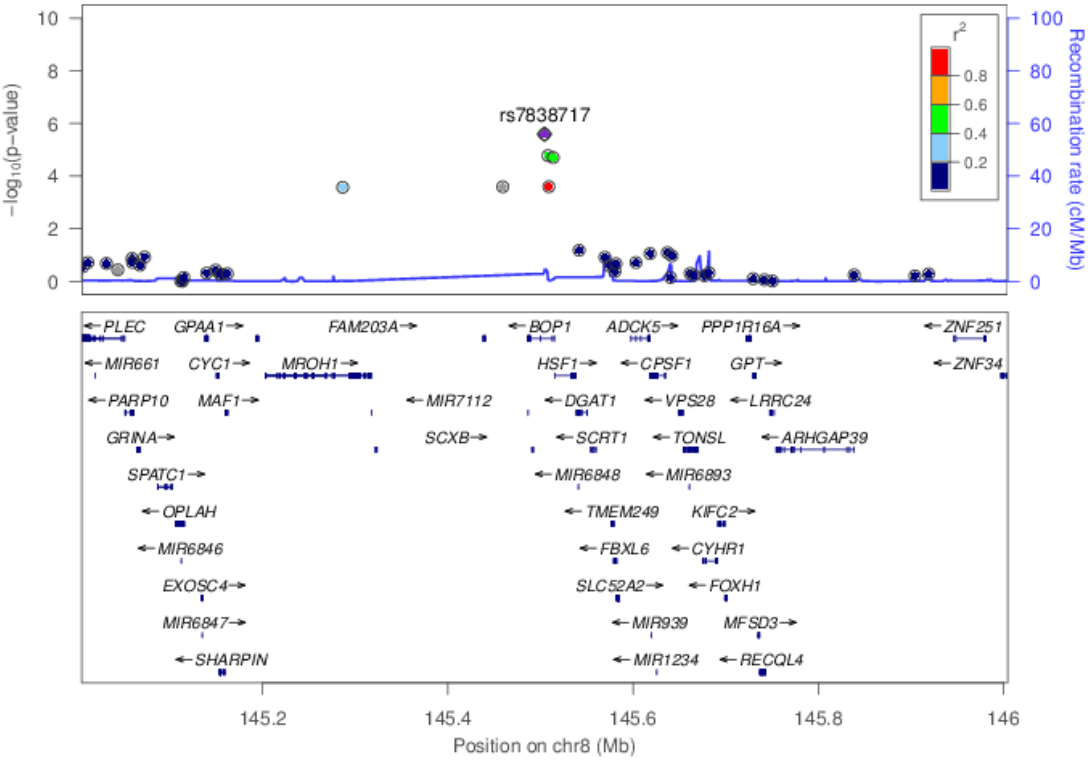


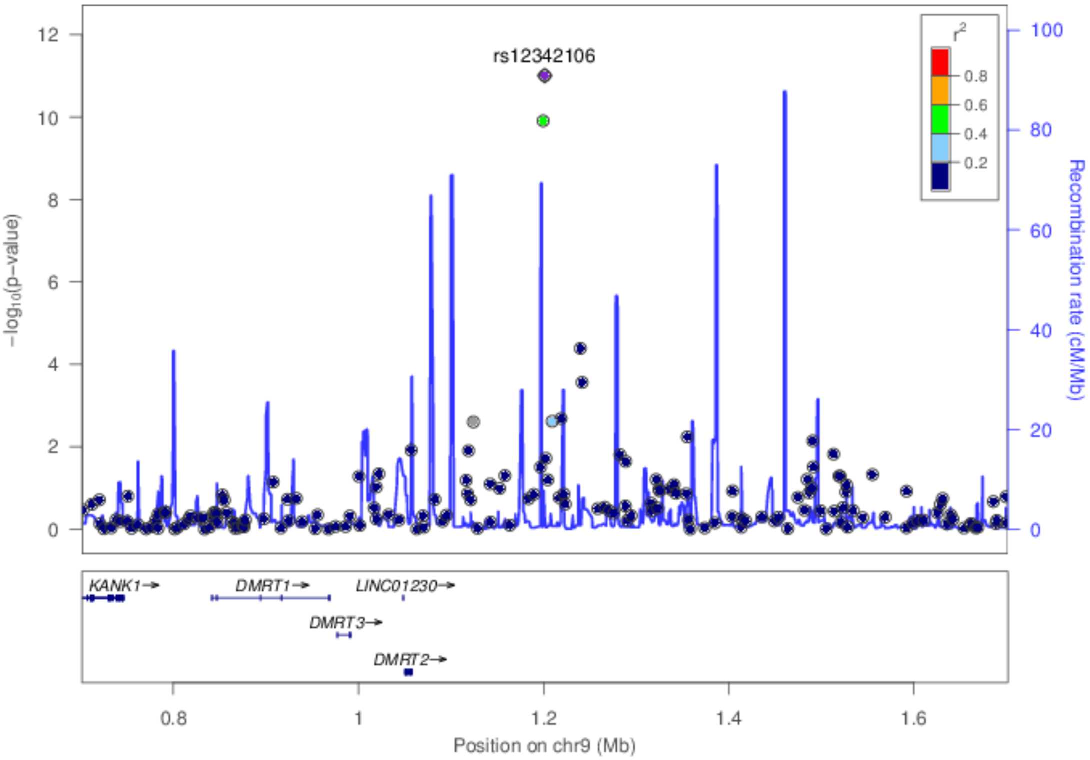
r^2
0.8
0.6
0.4
0.2
rs2912522
−log10(p−value)
Recombination rate (cM/Mb)
0
5
10
15
20
25
30
0
20
40
60
80
100
C8orf34→
←LOC100505718
←LOC100505739
SULF1→
69.6
69.8
70
70.2
70.4
Position on chr8 (Mb)

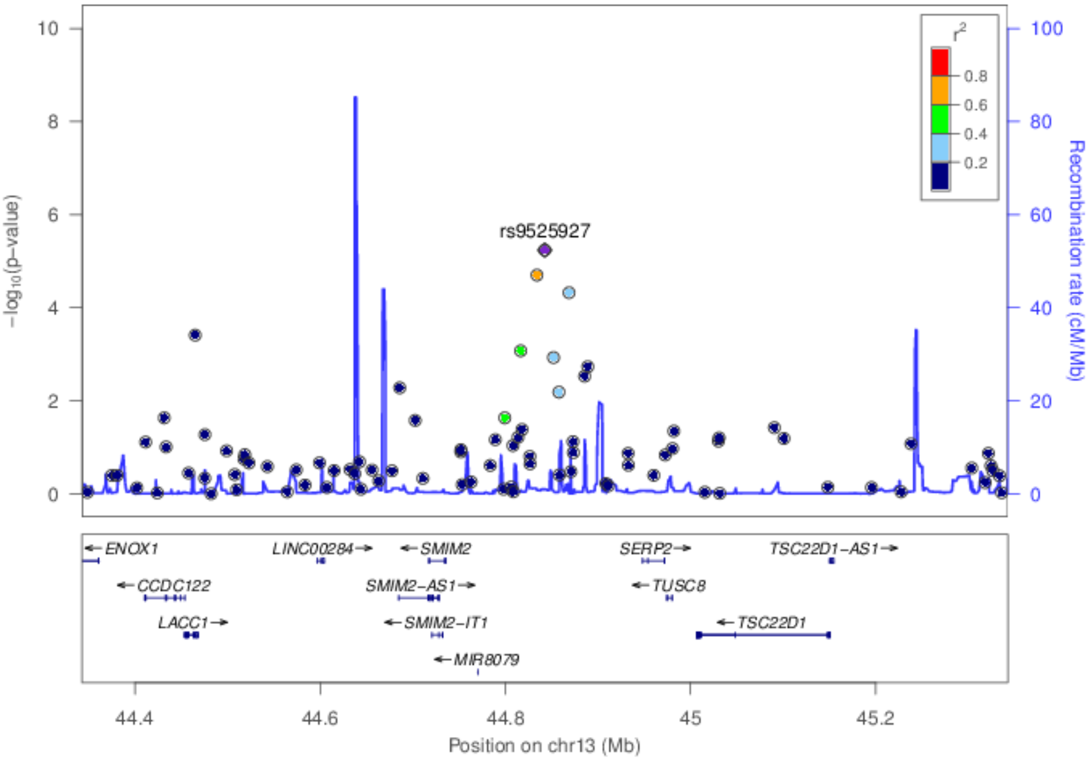


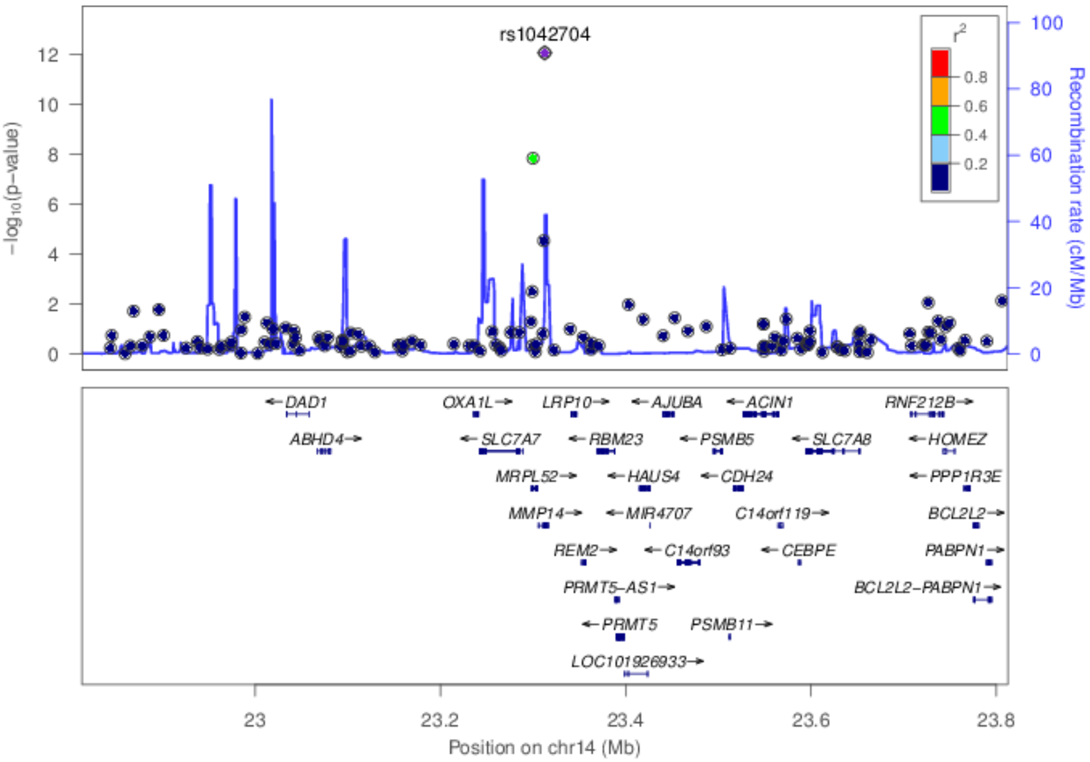
r^2
0.8
0.6
0.4
0.2
rs629535
−log10(p−value)
Recombination rate (cM/Mb)
0
5
10
15
20
25
30
0
20
40
60
80
100
C8orf34→
←LOC100505718
←LOC100505739
SULF1→
69.6
69.8
70
70.2
70.4
Position on chr8 (Mb)

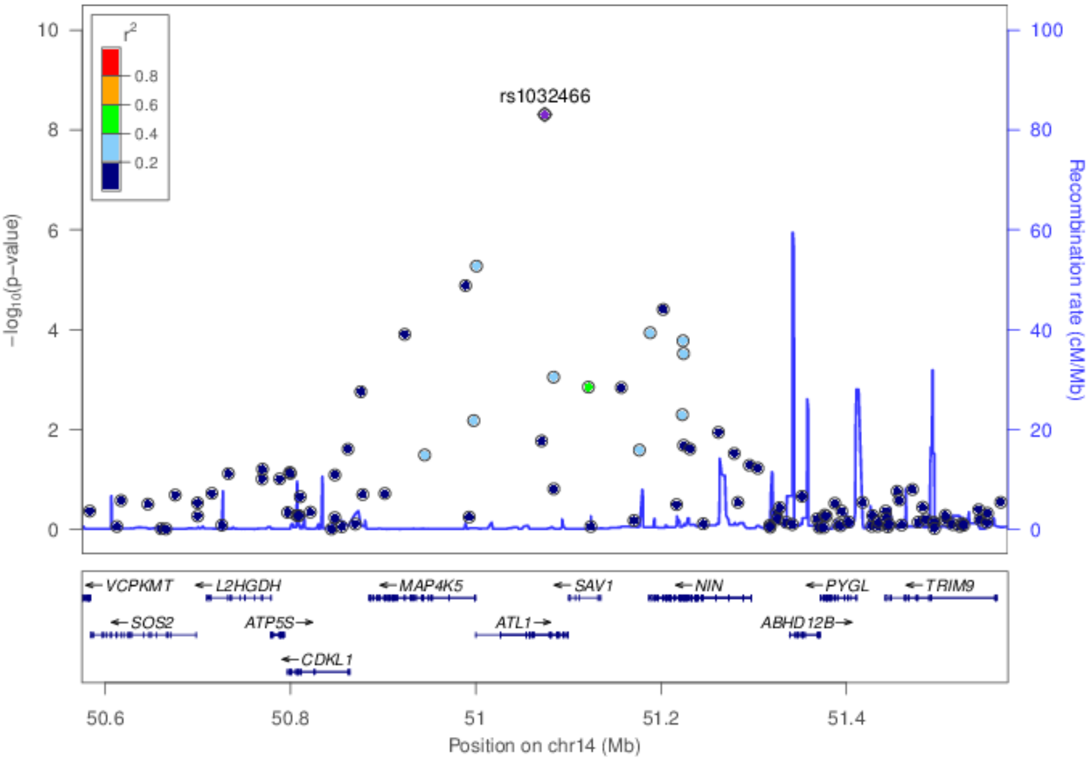

r²
0.8
0.6
0.4
0.2
rs611744
20
15
10
5
0
−log₁₀(p−value)
100
80
60
40
20
0
Recombination rate (cM/Mb)
← RSPO2
← EIF3E
EMC2 →
108.8
109
109.2
109.4
109.6
Position on chr8 (Mb)

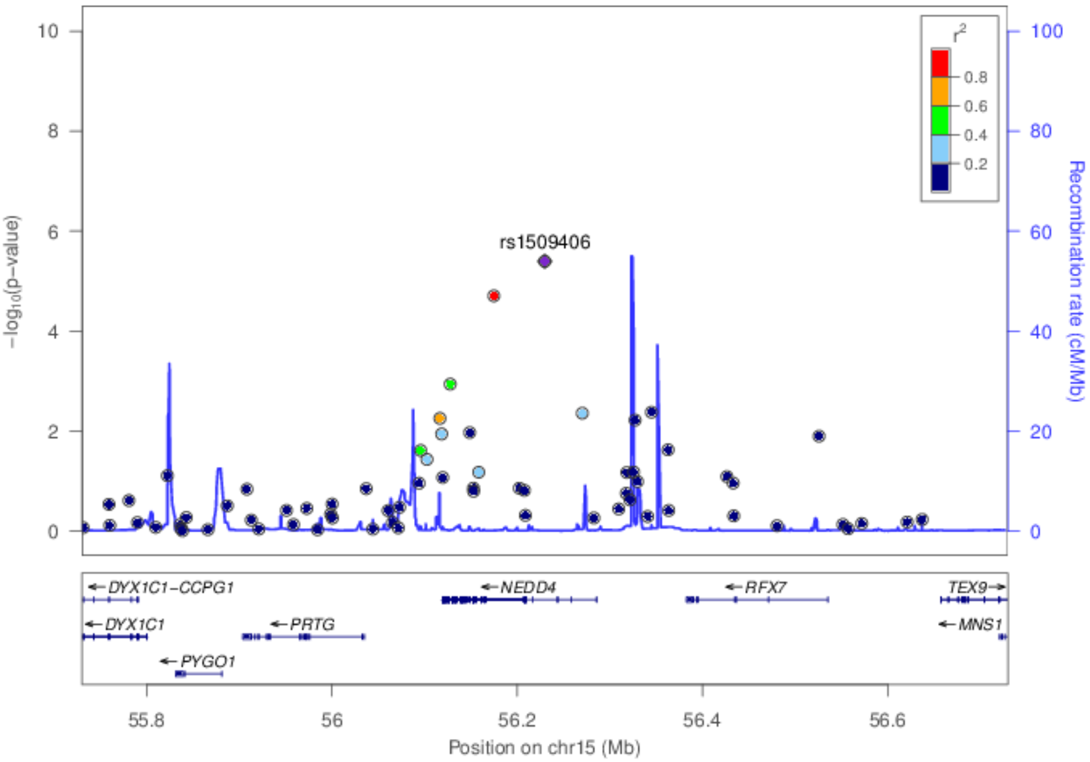

r²
0.8
0.6
0.4
0.2
rs7838717
10
8
6
4
2
0
−log₁₀(p−value)
100
80
60
40
20
0
Recombination rate (cM/Mb)
← PLEC
GPAA1 →
FAM203A →
← BOP1
ADCK5 →
PPP1R16A →
← ZNF251
← MIR661
CYC1 →
MROH1 →
HSF1 →
← CPSF1
GPT →
← ZNF34
← PARP10
MAF1 →
← MIR7112
← DGAT1
← VPS28
← LRRC24
GRINA →
SCXB →
← SCRT1
← TONSL
← ARHGAP39
SPATC1 →
← MIR6848
← MIR6893
← OPLAH
← TMEM249
KIFC2 →
← MIR6846
← FBXL6
← CYHR1
EXOSC4 →
SLC52A2 →
← FOXH1
MIR6847 →
← MIR939
MFSD3 →
← SHARPIN
← MIR1234
← RECQL4
145.2
145.4
145.6
145.8
146
Position on chr8 (Mb)

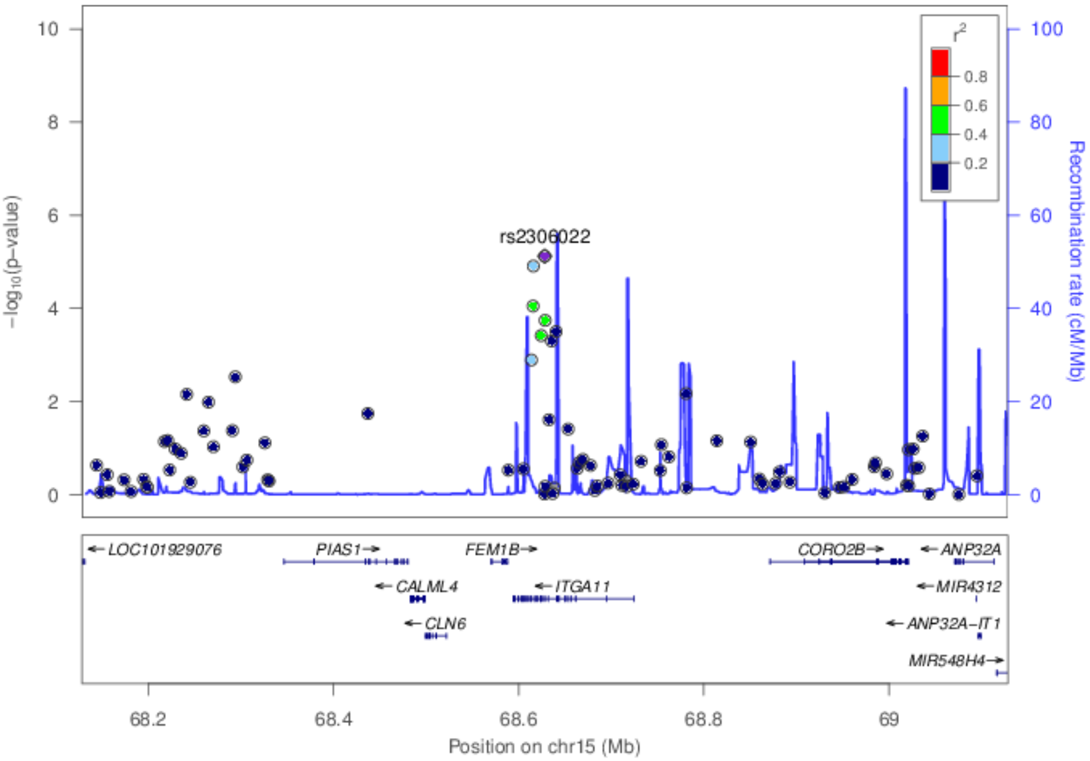

rs12342106
r²
0.8
0.6
0.4
0.2
−log₁₀(p−value)
0
2
4
6
8
10
12
Recombination rate (cM/Mb)
0
20
40
60
80
100
KANK1→
DMRT1→
LINC01230→
DMRT3→
DMRT2→
0.8
1
1.2
1.4
1.6
Position on chr9 (Mb)

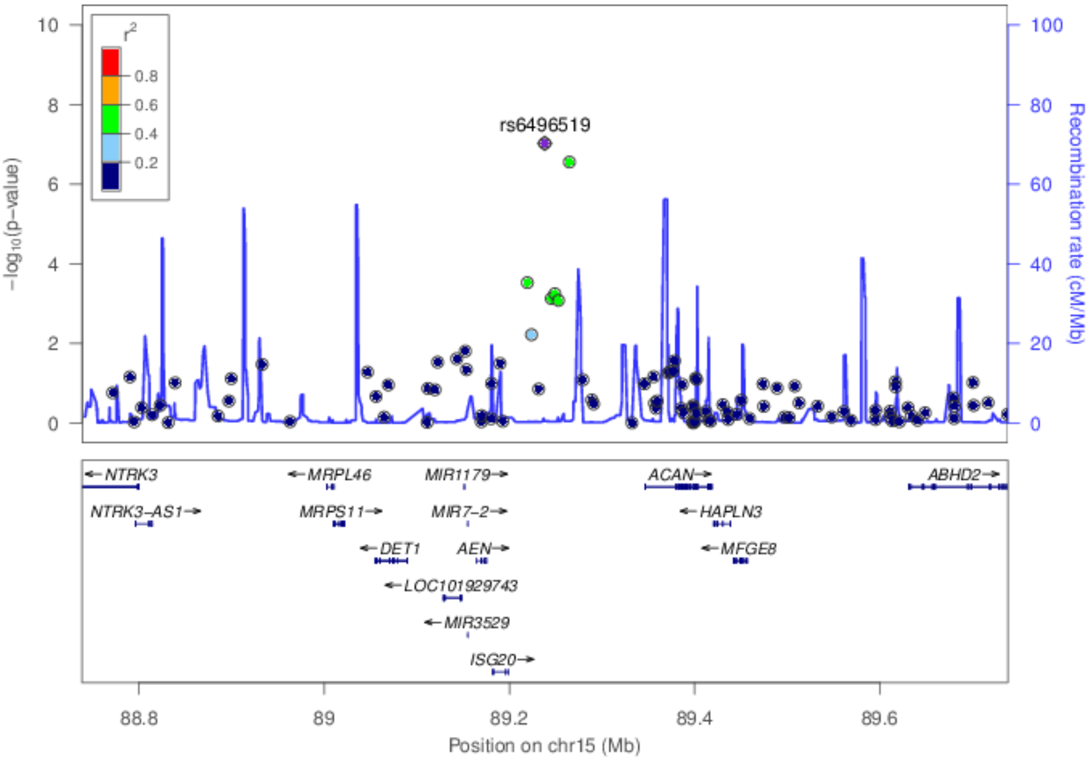

rs9525927
r²
0.8
0.6
0.4
0.2
−log₁₀(p−value)
0
2
4
6
8
10
Recombination rate (cM/Mb)
0
20
40
60
80
100
←ENOX1
←CCDC122
LACC1→
LINC00284→
←SMIM2
SMIM2−AS1→
←SMIM2−IT1
←MIR8079
SERP2→
←TUSC8
TSC22D1−AS1→
←TSC22D1
44.4
44.6
44.8
45
45.2
Position on chr13 (Mb)

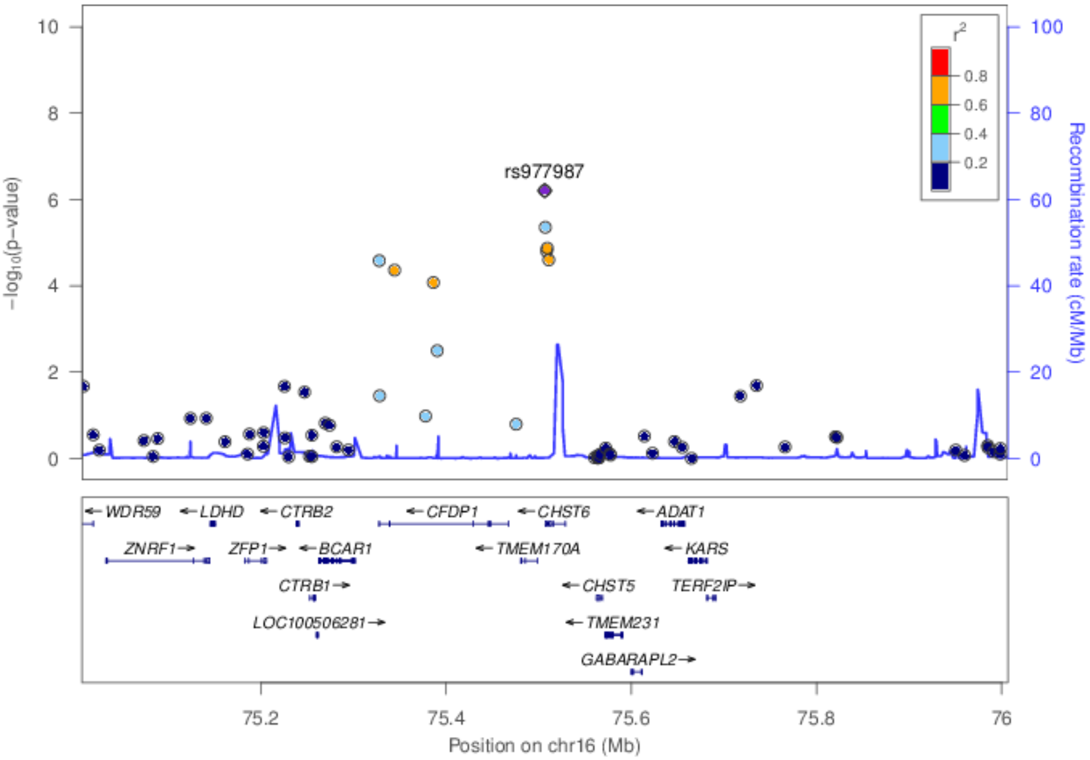

rs1042704
−log10(p−value)
Recombination rate (cM/Mb)
r2
0.8
0.6
0.4
0.2
12
10
8
6
4
2
0
100
80
60
40
20
0
←DAD1
ABHD4→
OXA1L→
←SLC7A7
MRPL52→
MMP14→
REM2→
PRMT5−AS1→
←PRMT5
LOC101926933→
LRP10→
←RBM23
←HAUS4
←MIR4707
←C14orf93
PSMB11→
←AJUBA
←PSMB5
←CDH24
C14orf119→
←CEBPE
←ACIN1
←SLC7A8
RNF212B→
←HOMEZ
←PPP1R3E
BCL2L2→
PABPN1→
BCL2L2−PABPN1→
23
23.2
23.4
23.6
23.8
Position on chr14 (Mb)

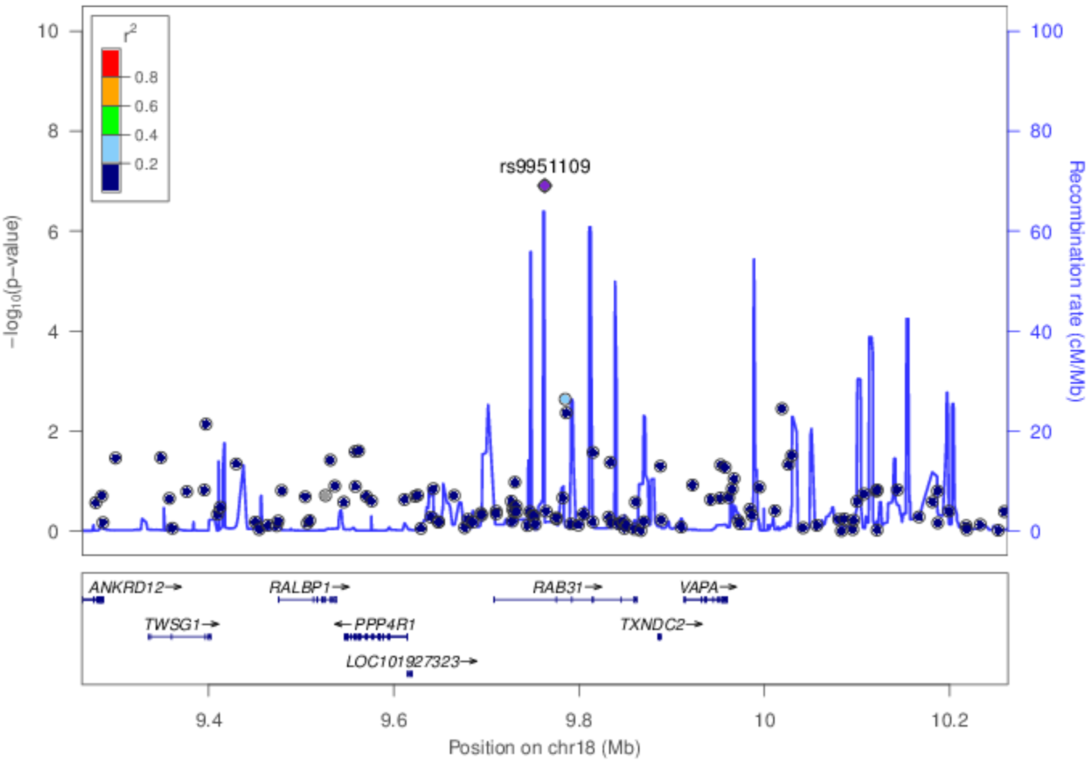

rs1032466
−log10(p−value)
Recombination rate (cM/Mb)
r2
0.8
0.6
0.4
0.2
10
8
6
4
2
0
100
80
60
40
20
0
←VCPKMT
←SOS2
←L2HGDH
ATP5S→
←CDKL1
←MAP4K5
ATL1→
←SAV1
←NIN
←PYGL
ABHD12B→
←TRIM9
50.6
50.8
51
51.2
51.4
Position on chr14 (Mb)

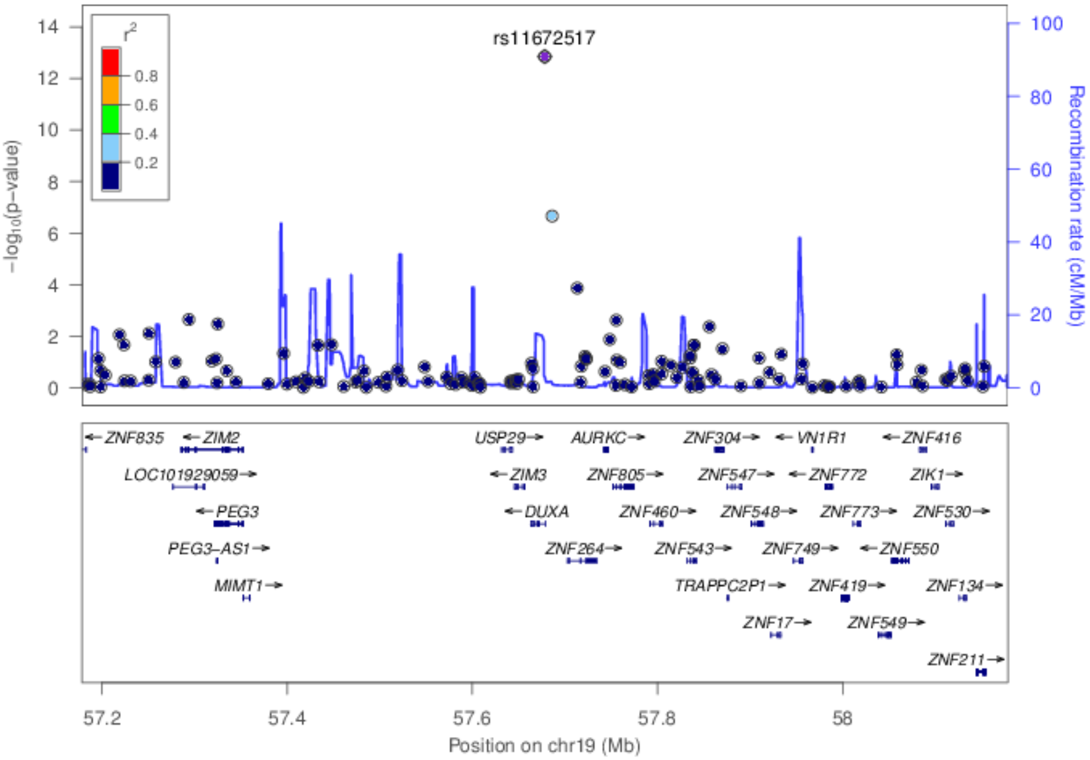

rs1509406
r^2
0.8
0.6
0.4
0.2
$-\log_{10}$(p−value)
Recombination rate (cM/Mb)
0
2
4
6
8
10
0
20
40
60
80
100
DYX1C1−CCPG1
DYX1C1
PYGO1
PRTG
NEDD4
RFX7
TEX9
MNS1
55.8
56
56.2
56.4
56.6
Position on chr15 (Mb)

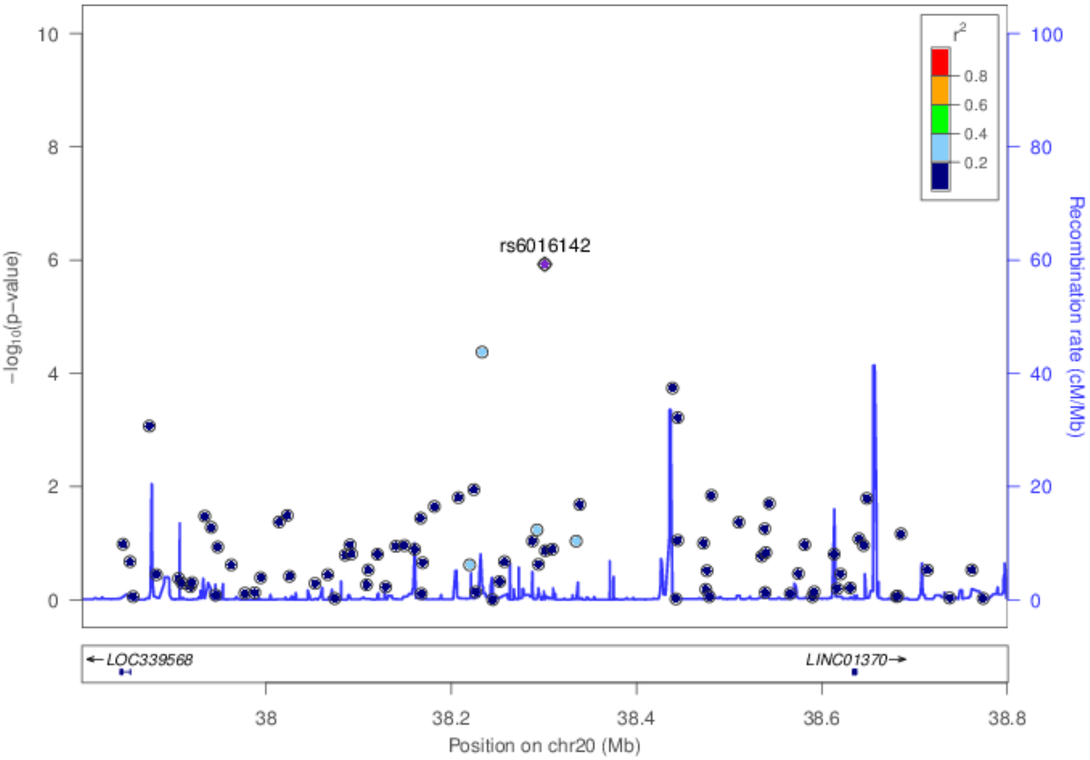

rs2306022
r^2
0.8
0.6
0.4
0.2
$-\log_{10}$(p−value)
Recombination rate (cM/Mb)
0
2
4
6
8
10
0
20
40
60
80
100
LOC101929076
PIAS1
CALML4
CLN6
FEM1B
ITGA11
CORO2B
ANP32A
MIR4312
ANP32A−IT1
MIR548H4
68.2
68.4
68.6
68.8
69
Position on chr15 (Mb)

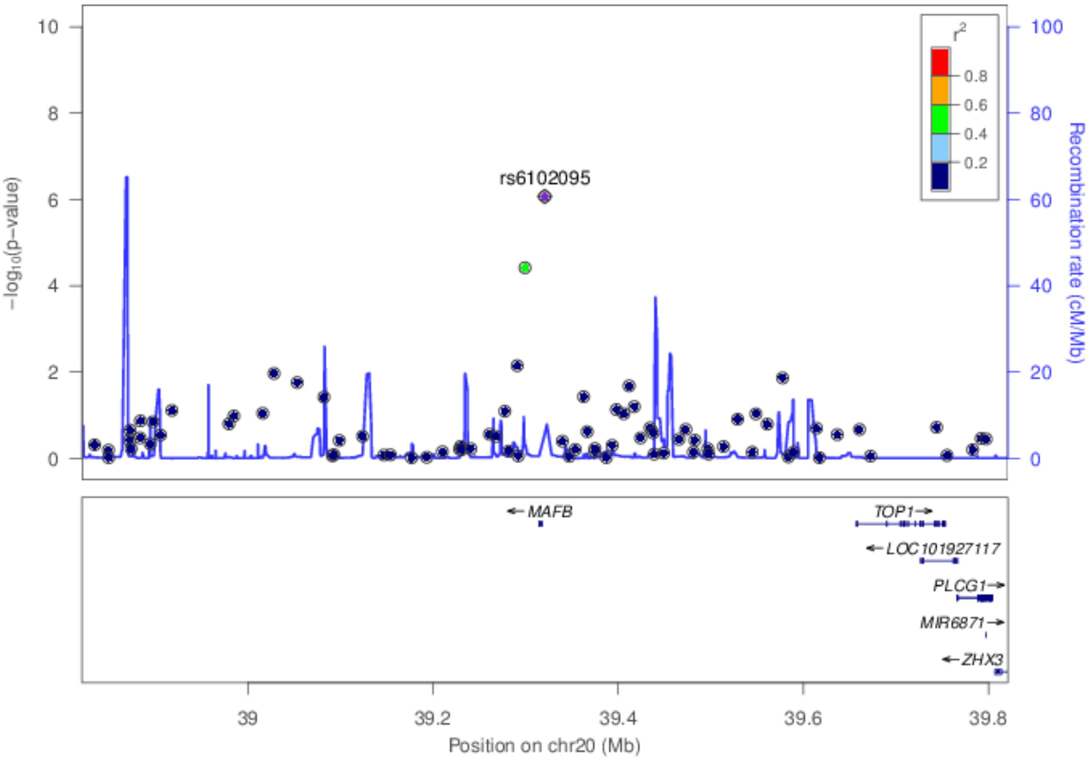

rs6496519
r2
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
10
8
6
4
2
0
100
80
60
40
20
0
NTRK3
NTRK3−AS1
MRPL46
MRPS11
DET1
LOC101929743
MIR1179
MIR7−2
AEN
MIR3529
ISG20
ACAN
HAPLN3
MFGE8
ABHD2
88.8
89
89.2
89.4
89.6
Position on chr15 (Mb)


rs977987
r2
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
10
8
6
4
2
0
100
80
60
40
20
0
WDR59
LDHD
CTRB2
CFDP1
CHST6
ADAT1
ZNRF1
ZFP1
BCAR1
TMEM170A
KARS
CTRB1
CHST5
TERF2IP
LOC100506281
TMEM231
GABARAPL2
75.2
75.4
75.6
75.8
76
Position on chr16 (Mb)


rs9951109
r2
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
0
2
4
6
8
10
0
20
40
60
80
100
ANKRD12→
TWSG1→
RALBP1→
←PPP4R1
LOC101927323→
RAB31→
TXNDC2→
VAPA→
9.4
9.6
9.8
10
10.2
Position on chr18 (Mb)


rs11672517
r2
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
0
2
4
6
8
10
12
14
0
20
40
60
80
100
←ZNF835
←ZIM2
LOC101929059→
←PEG3
PEG3−AS1→
MIMT1→
USP29→
←ZIM3
←DUXA
AURKC→
ZNF805→
ZNF264→
ZNF460→
ZNF543→
ZNF304→
ZNF547→
ZNF548→
TRAPPC2P1→
ZNF17→
←VN1R1
←ZNF772
ZNF749→
ZNF773→
ZNF419→
ZNF549→
←ZNF416
ZIK1→
ZNF530→
←ZNF550
ZNF134→
ZNF211→
57.2
57.4
57.6
57.8
58
Position on chr19 (Mb)


rs6016142
−log10(p−value)
Recombination rate (cM/Mb)
r2
0.8
0.6
0.4
0.2
0
2
4
6
8
10
0
20
40
60
80
100
LOC339568
LINC01370
38
38.2
38.4
38.6
38.8
Position on chr20 (Mb)


rs6102095
−log10(p−value)
Recombination rate (cM/Mb)
r2
0.8
0.6
0.4
0.2
0
2
4
6
8
10
0
20
40
60
80
100
MAFB
TOP1
LOC101927117
PLCG1
MIR6871
ZHX3
39
39.2
39.4
39.6
39.8
Position on chr20 (Mb)

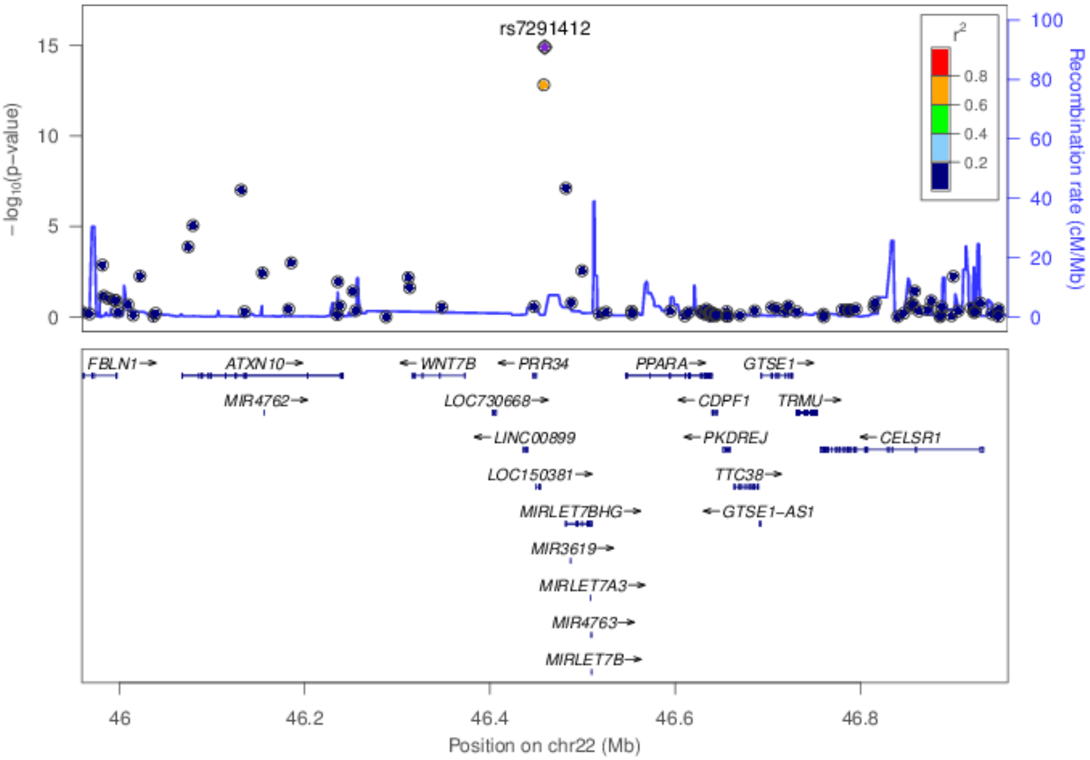
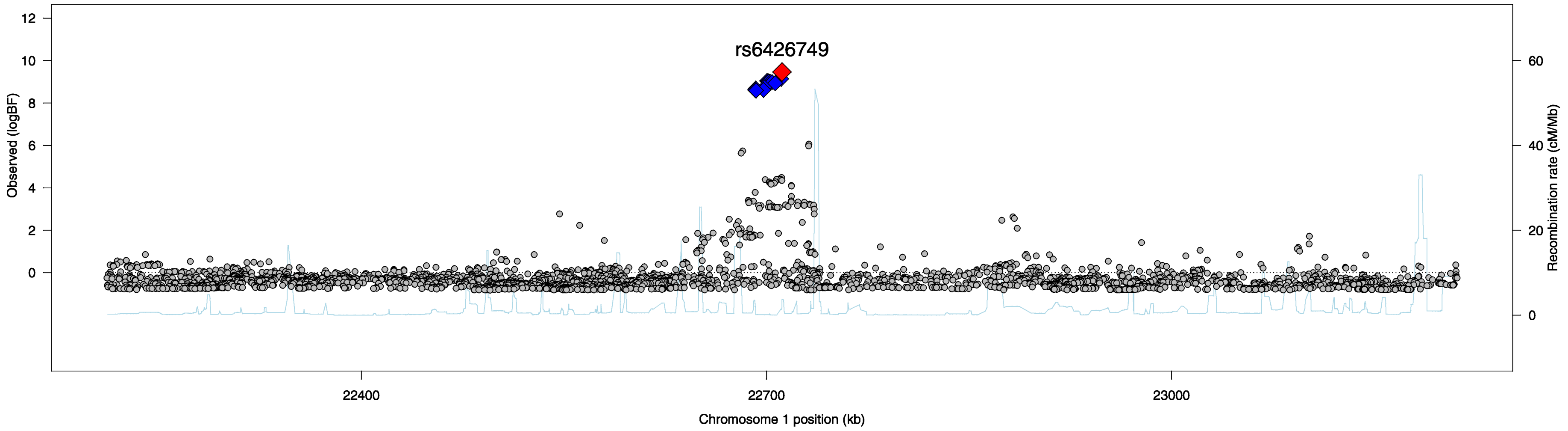
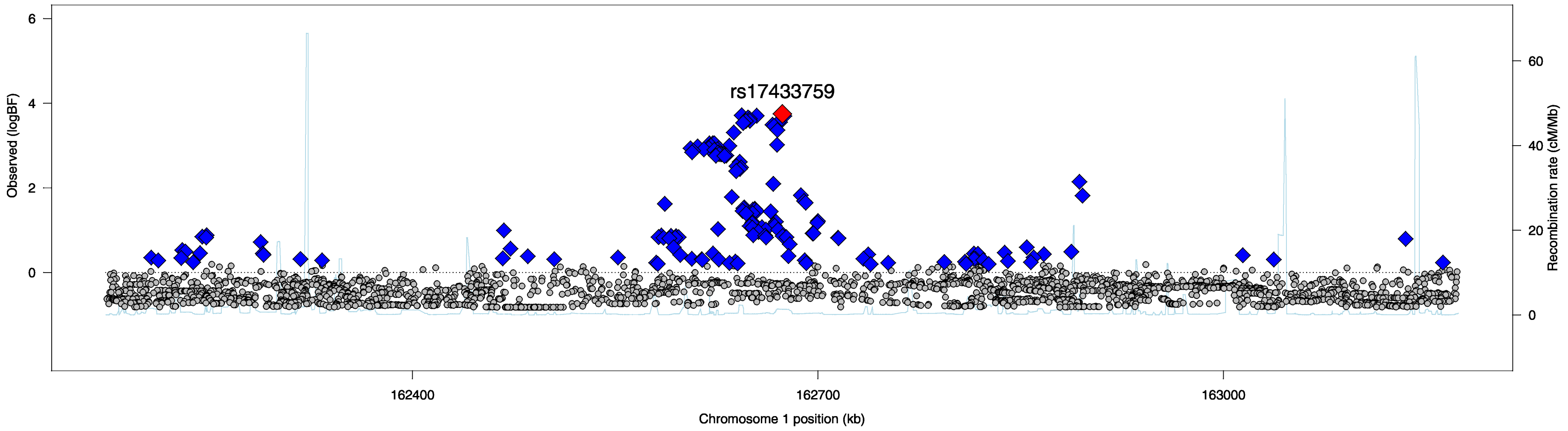
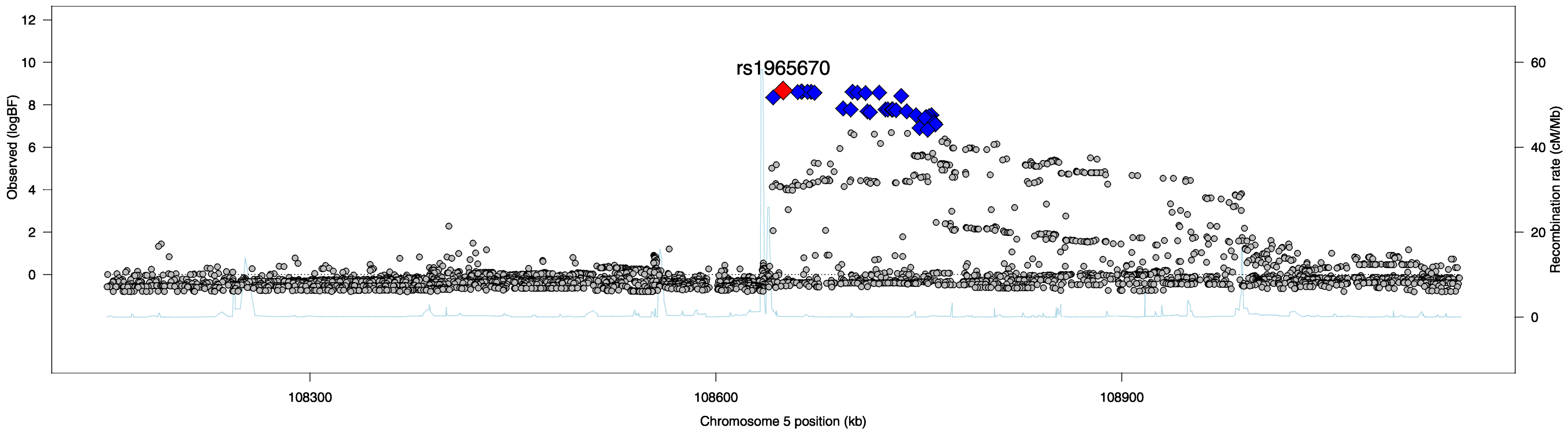
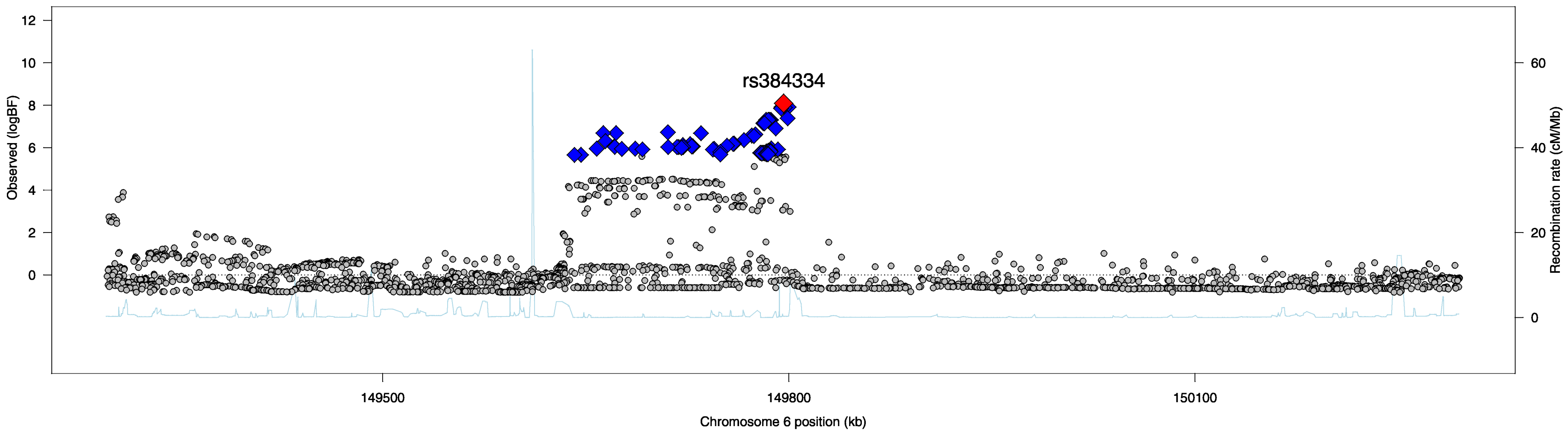

rs7291412
−log10(p−value)
15
10
5
0
Recombination rate (cM/Mb)
100
80
60
40
20
0
r2
0.8
0.6
0.4
0.2
FBLN1→
ATXN10→
←WNT7B
←PRR34
PPARA→
GTSE1→
MIR4762→
LOC730668→
←CDPF1
TRMU→
←LINC00899
←PKDREJ
←CELSR1
LOC150381→
TTC38→
MIRLET7BHG→
←GTSE1−AS1
MIR3619→
MIRLET7A3→
MIR4763→
MIRLET7B→
46
46.2
46.4
46.6
46.8
Position on chr22 (Mb)

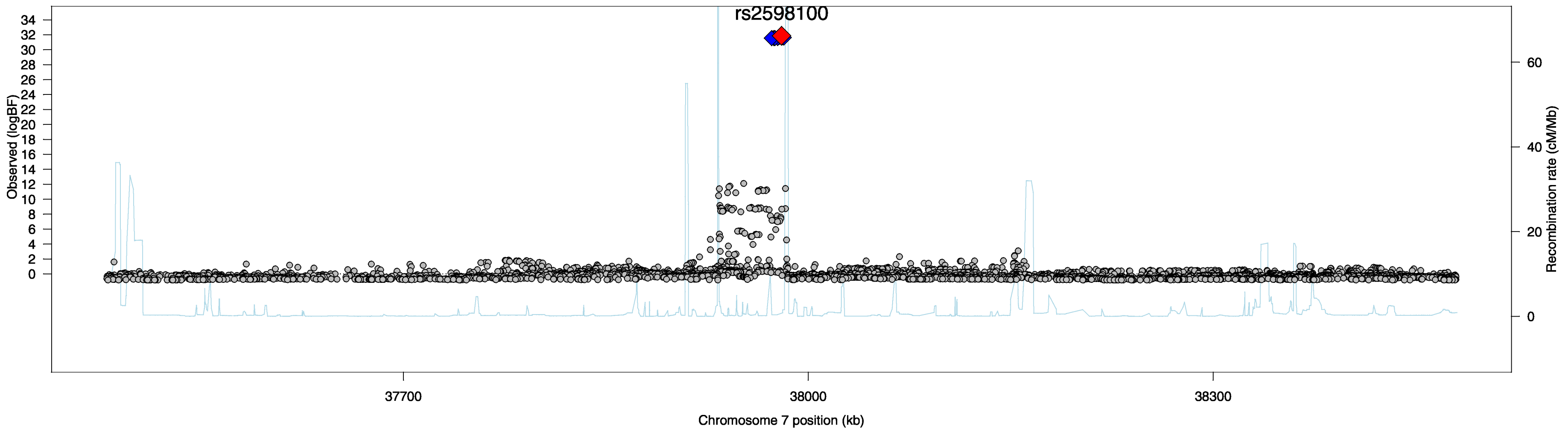
Figure S7. Graphical illustration of the 99% credible sets for all 26 associated regions. For each regional plot, the SNP with the highest posterior probability of association is labeled and depicted with a red diamond. Other SNPs that make up the 99% credible set (Table S2) are depicted with blue diamonds. Imputed SNPs that do not form part of the 99% credible set are depicted with grey circles. Recombination peaks are depicted in light blue and are calculated from HapMap genotypes. The position on each chromosome is shown in relation to Human Genome build hg19.

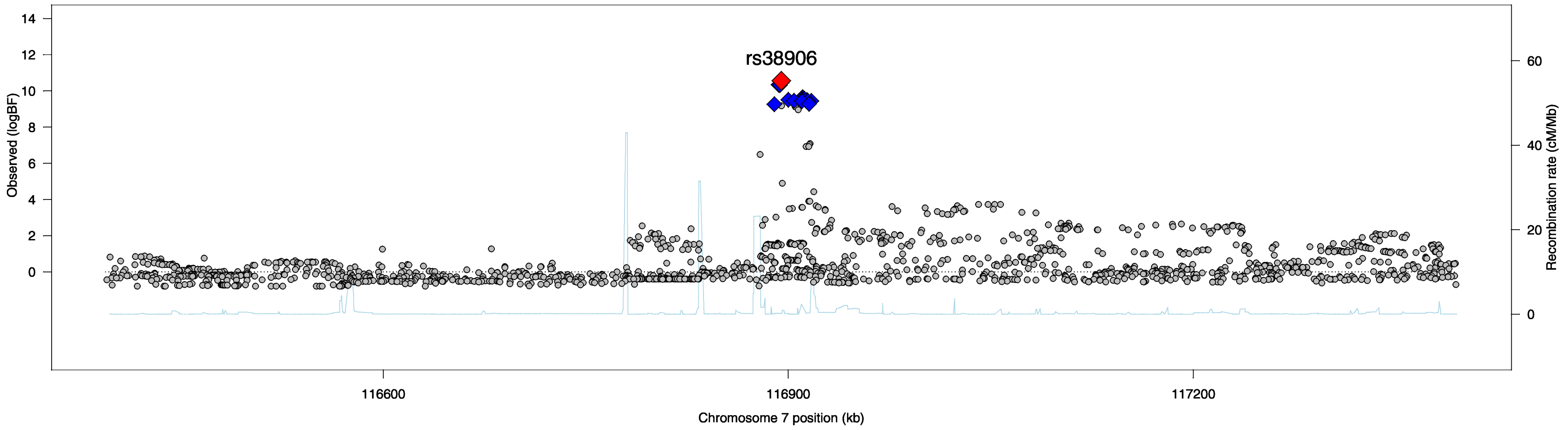

rs6426749
Observed (logBF)
12
10
8
6
4
2
0
Recombination rate (cM/Mb)
60
40
20
0
22400
22700
23000
Chromosome 1 position (kb)

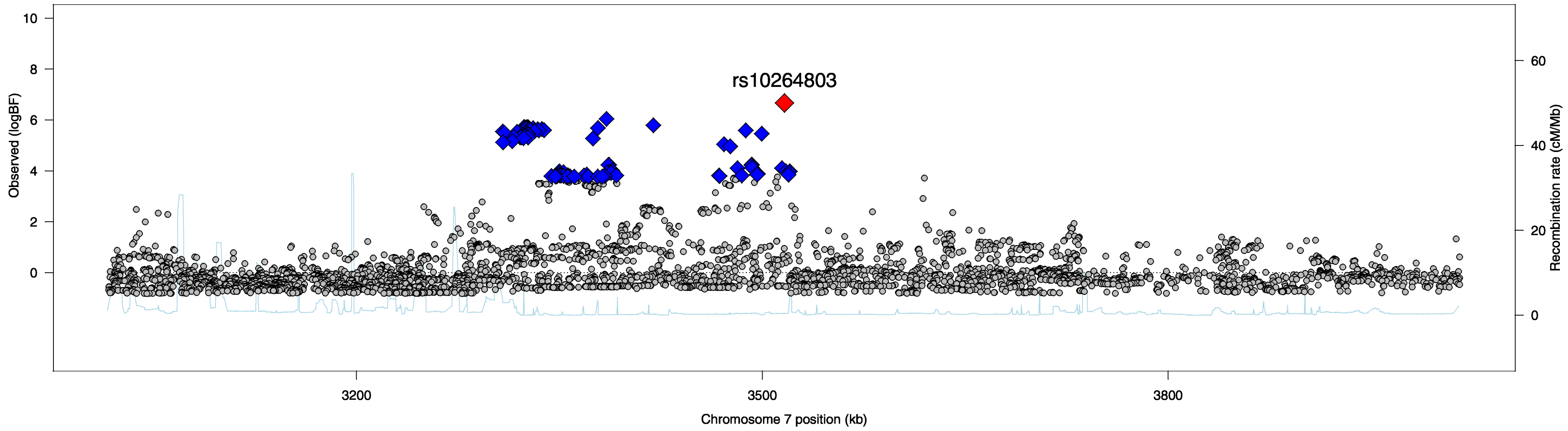

rs17433759
Observed (logBF)
6
4
2
0
Recombination rate (cM/Mb)
60
40
20
0
162400
162700
163000
Chromosome 1 position (kb)


rs1965670
Observed (logBF)
12
10
8
6
4
2
0
Recombination rate (cM/Mb)
60
40
20
0
108300
108600
108900
Chromosome 5 position (kb)

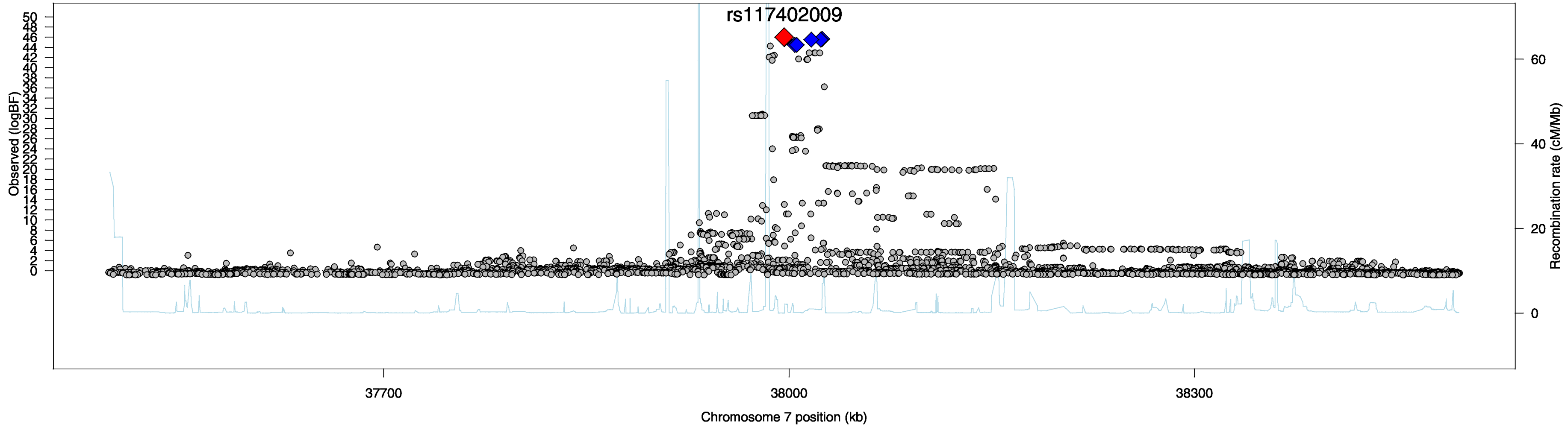

rs384334
Observed (logBF)
12
10
8
6
4
2
0
Recombination rate (cM/Mb)
60
40
20
0
149500
149800
150100
Chromosome 6 position (kb)


rs2598100
Observed (logBF)
34
32
30
28
26
24
22
20
18
16
14
12
10
8
6
4
2
0
Recombination rate (cM/Mb)
60
40
20
0
37700
38000
38300
Chromosome 7 position (kb)

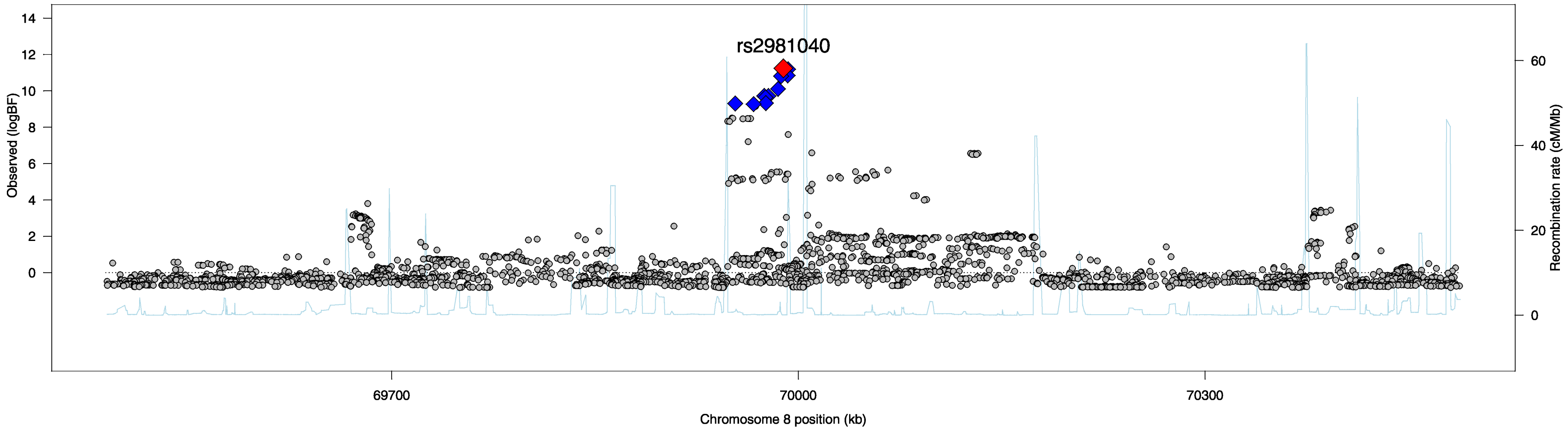

rs38906
Observed (logBF)
14
12
10
8
6
4
2
0
Recombination rate (cM/Mb)
60
40
20
0
116600
116900
117200
Chromosome 7 position (kb)

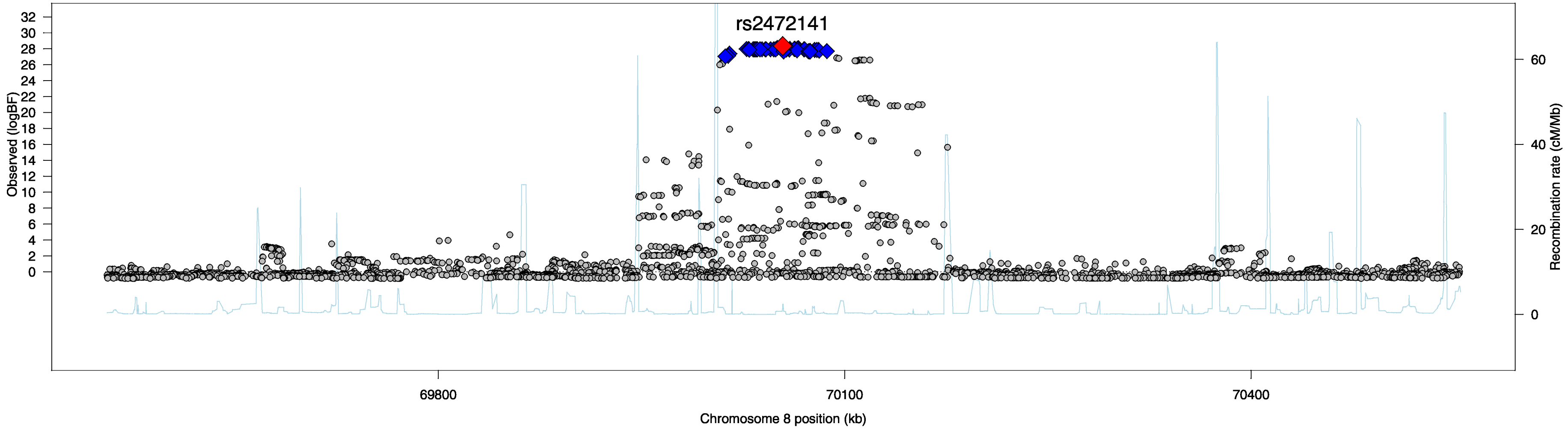


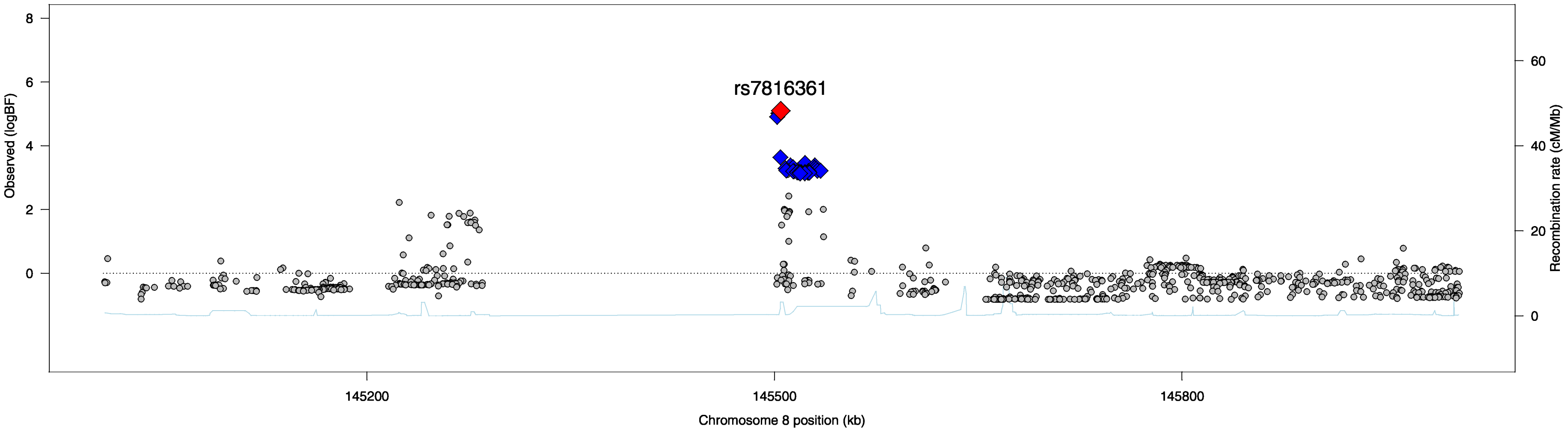
rs10264803
Observed (logBF)
10
8
6
4
2
0
Recombination rate (cM/Mb)
60
40
20
0
3200
3500
3800
Chromosome 7 position (kb)

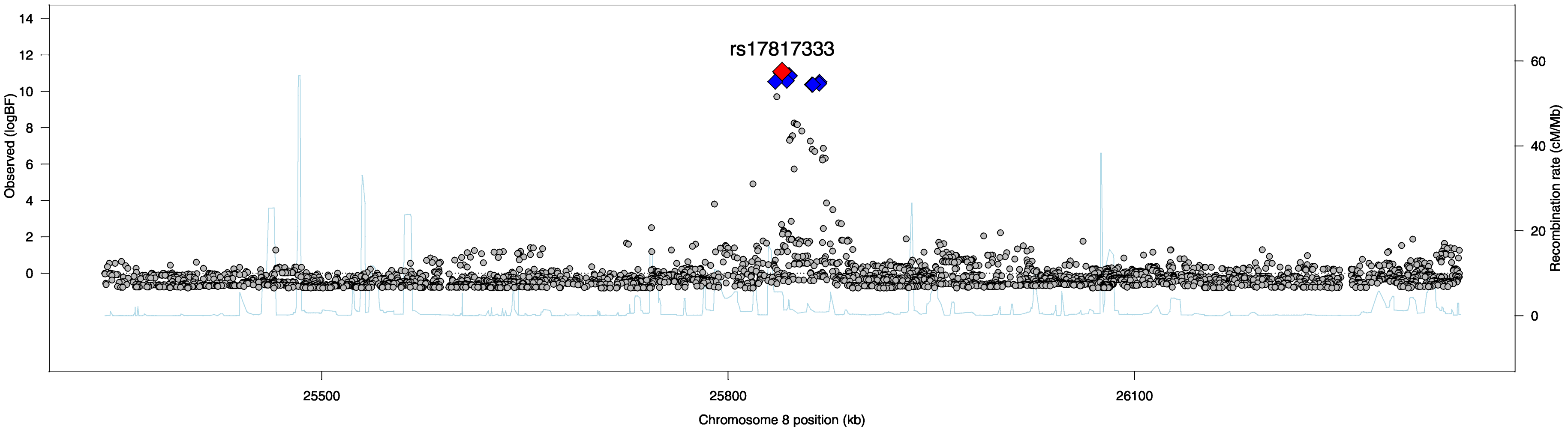


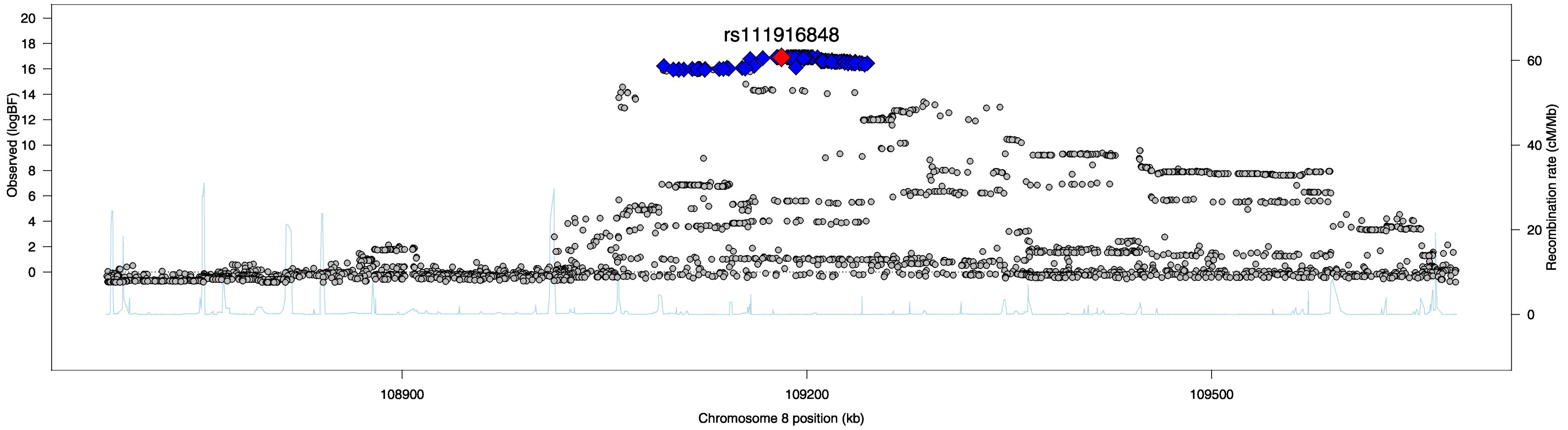
rs117402009
Observed (logBF)
50
48
46
44
42
40
38
36
34
32
30
28
26
24
22
20
18
16
14
12
10
8
6
4
2
0
Recombination rate (cM/Mb)
60
40
20
0
37700
38000
38300
Chromosome 7 position (kb)

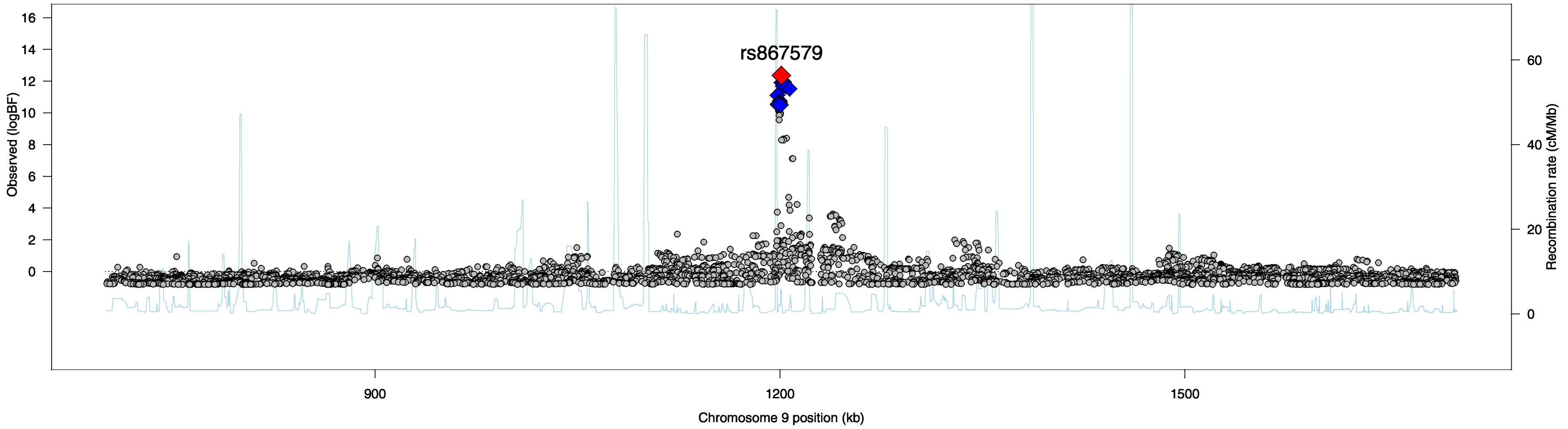

rs2981040
Observed (logBF)
14
12
10
8
6
4
2
0
Recombination rate (cM/Mb)
60
40
20
0
69700
70000
70300
Chromosome 8 position (kb)

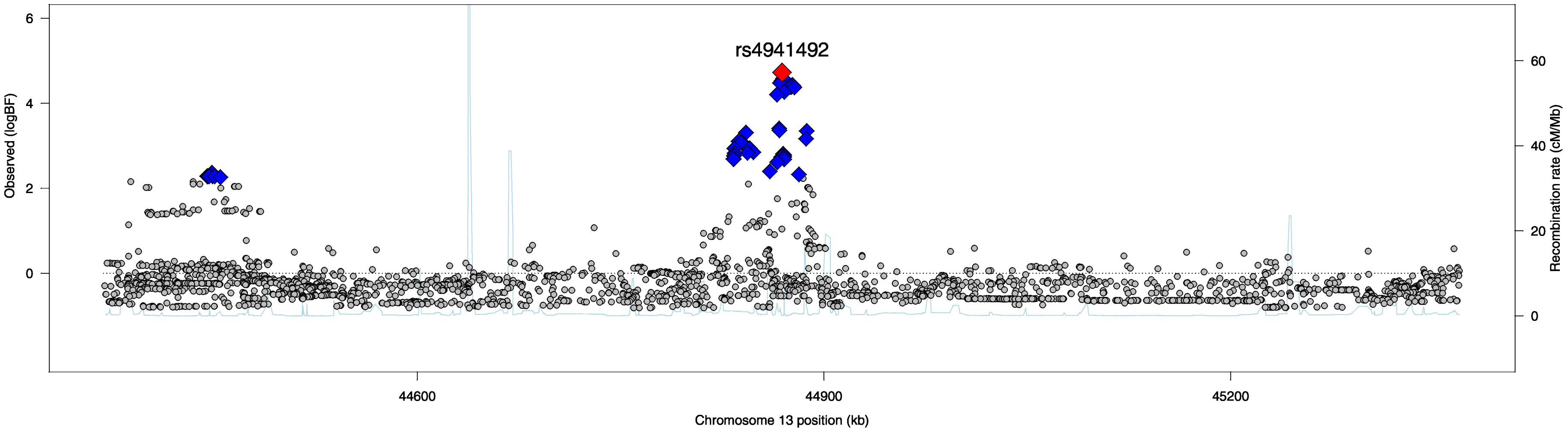

rs2472141
Observed (logBF)
32
30
28
26
24
22
20
18
16
14
12
10
8
6
4
2
0
Recombination rate (cM/Mb)
60
40
20
0
69800
70100
70400
Chromosome 8 position (kb)

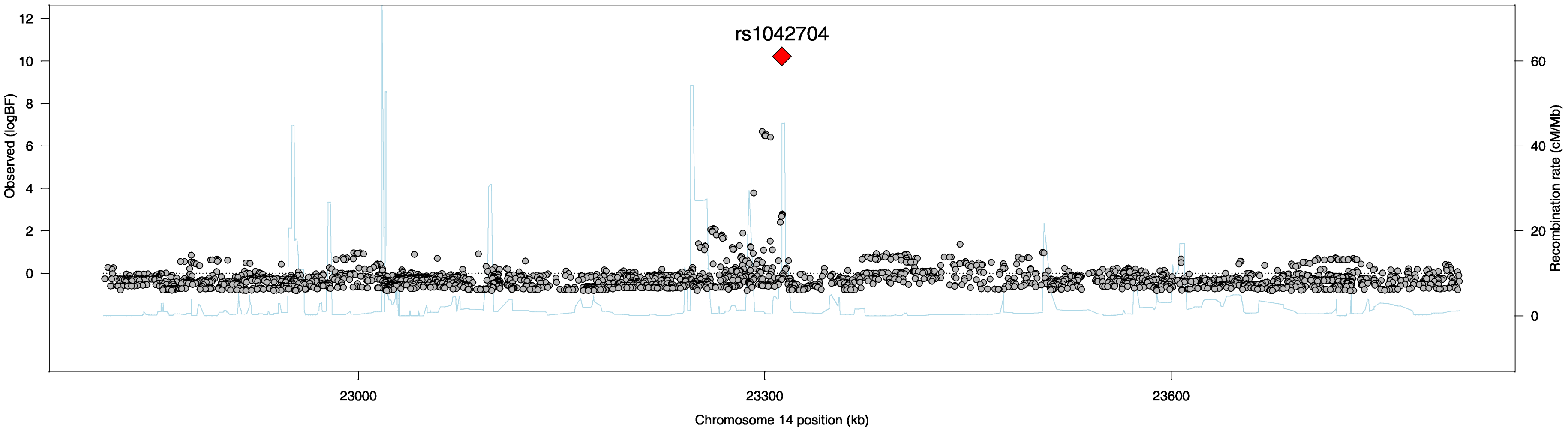

rs7816361
Observed (logBF)
8
6
4
2
0
Recombination rate (cM/Mb)
60
40
20
0
145200
145500
145800
Chromosome 8 position (kb)

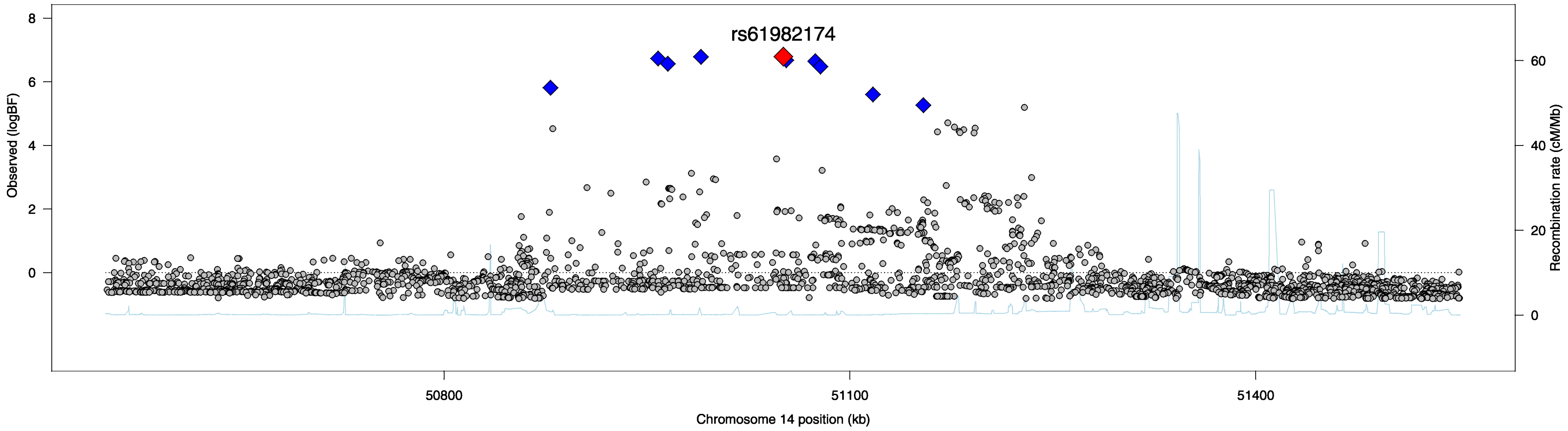

rs17817333
Observed (logBF)
14
12
10
8
6
4
2
0
Recombination rate (cM/Mb)
60
40
20
0
25500
25800
26100
Chromosome 8 position (kb)

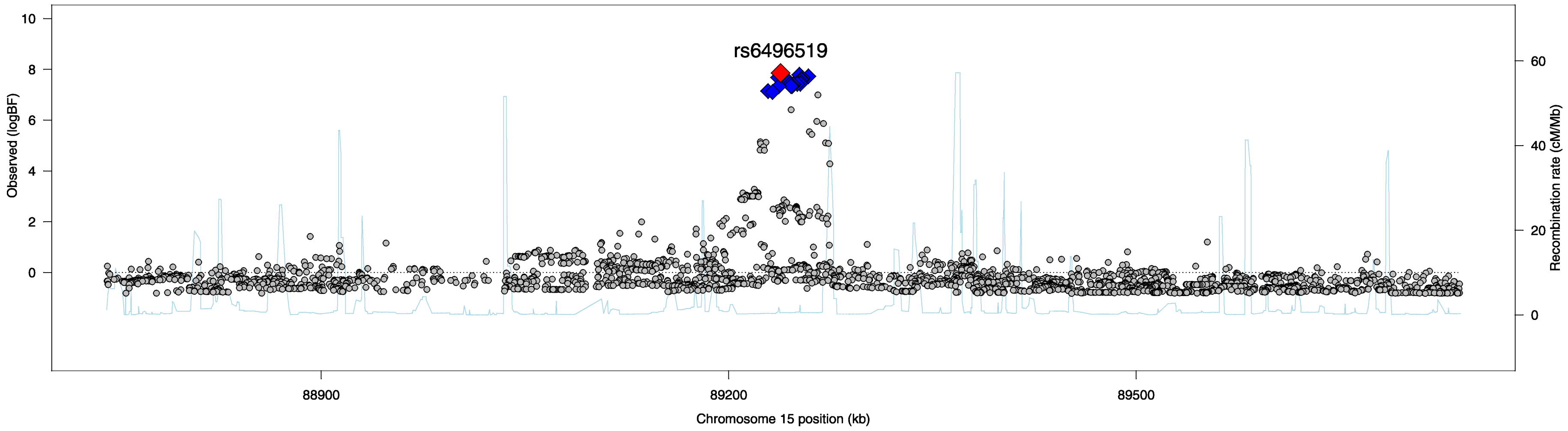

rs111916848
Observed (logBF)
Recombination rate (cM/Mb)
Chromosome 8 position (kb)
20
18
16
14
12
10
8
6
4
2
0
60
40
20
0
108900
109200
109500

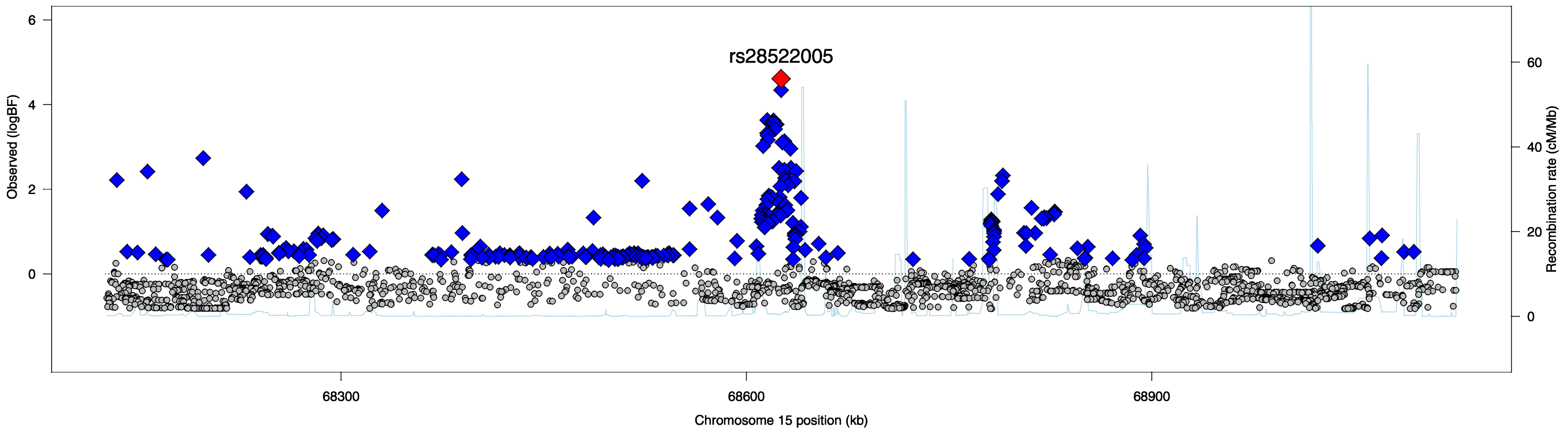

rs867579
Observed (logBF)
Recombination rate (cM/Mb)
Chromosome 9 position (kb)
16
14
12
10
8
6
4
2
0
60
40
20
0
900
1200
1500

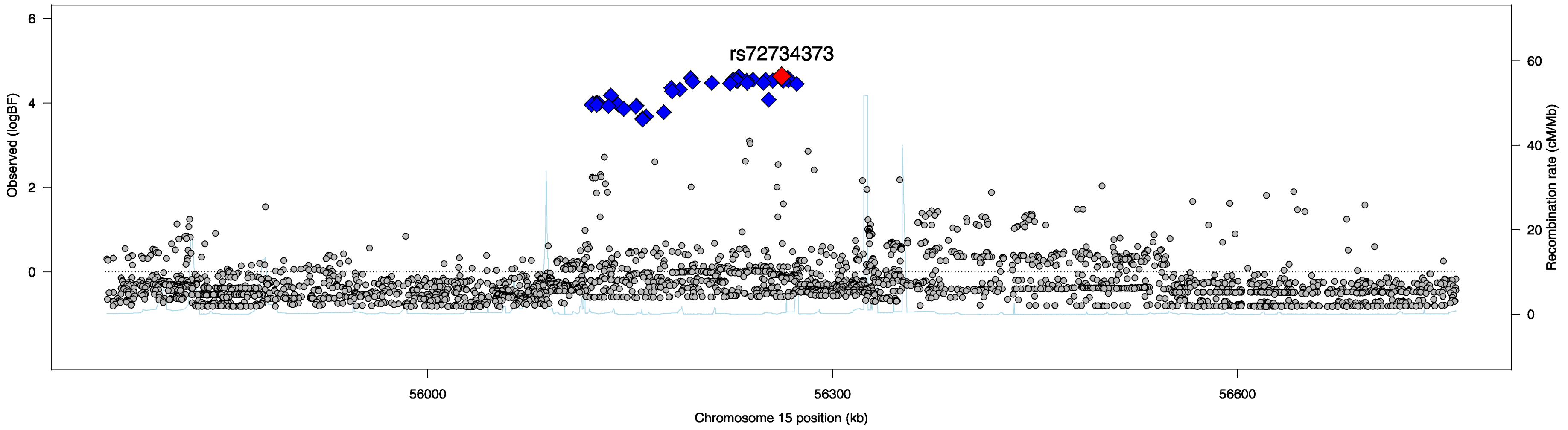

rs4941492
Observed (logBF)
6
4
2
0
Recombination rate (cM/Mb)
60
40
20
0
44600
44900
45200
Chromosome 13 position (kb)

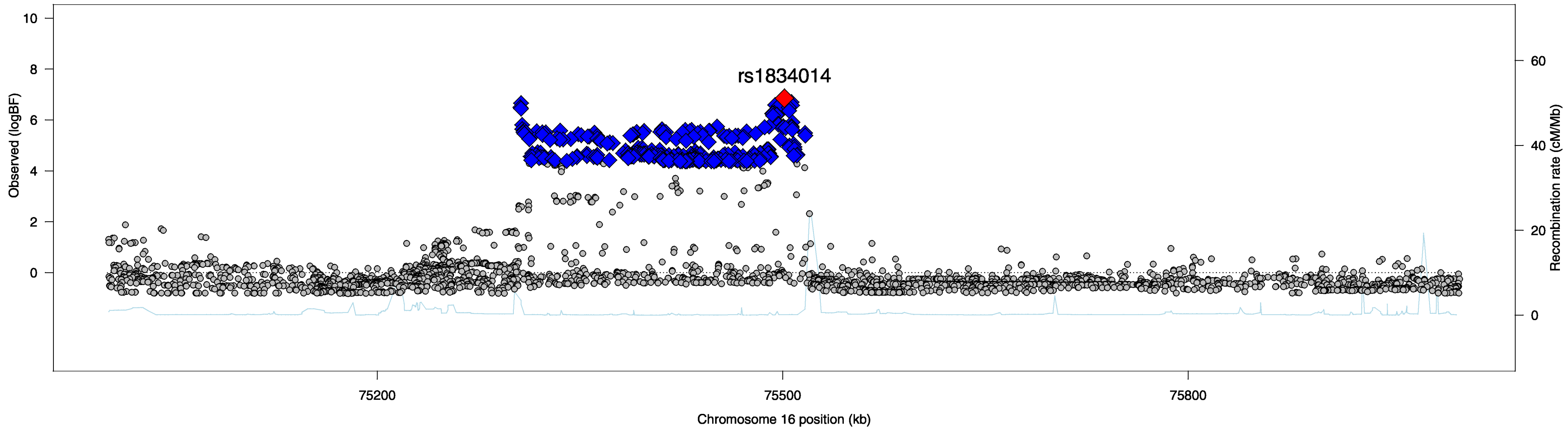

rs1042704
Observed (logBF)
12
10
8
6
4
2
0
Recombination rate (cM/Mb)
60
40
20
0
23000
23300
23600
Chromosome 14 position (kb)

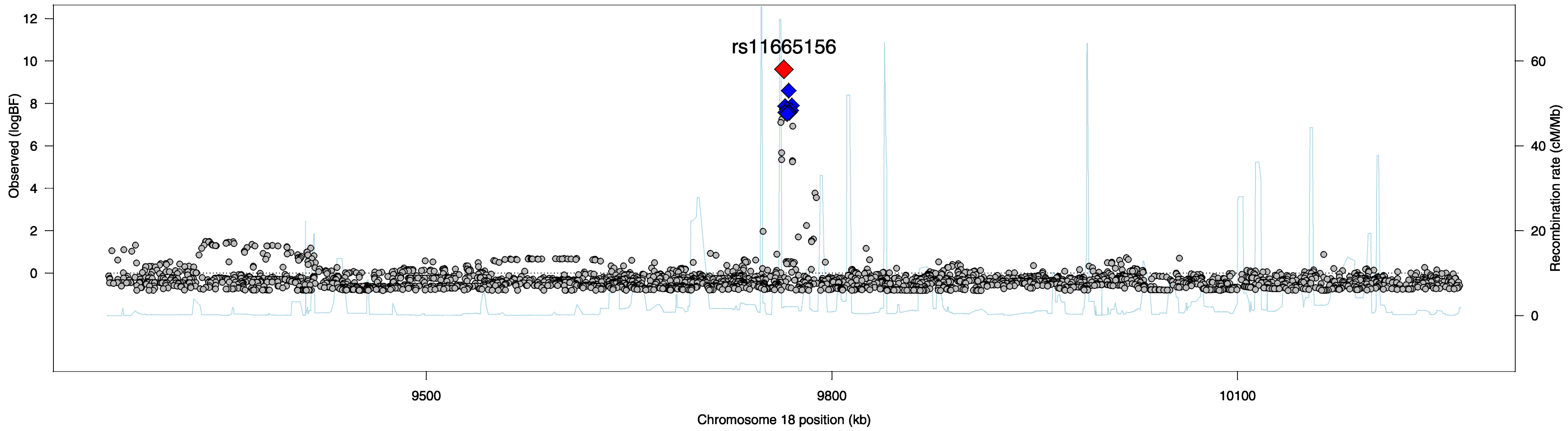

rs61982174
Observed (logBF)
8
6
4
2
0
Recombination rate (cM/Mb)
60
40
20
0
50800
51100
51400
Chromosome 14 position (kb)

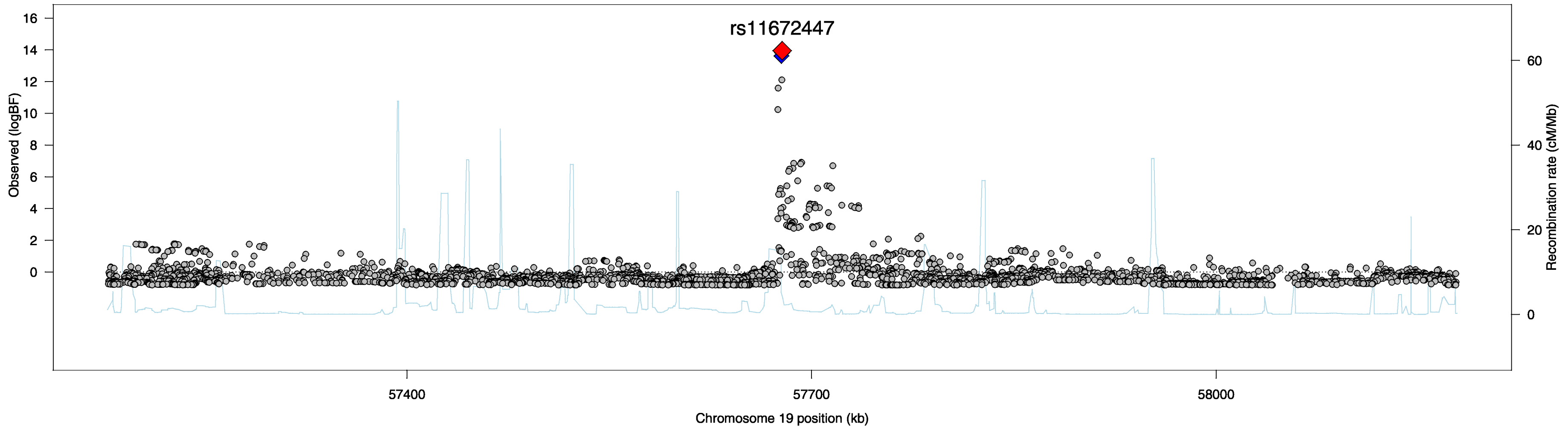

rs6496519
Observed (logBF)
10
8
6
4
2
0
Recombination rate (cM/Mb)
60
40
20
0
88900
89200
89500
Chromosome 15 position (kb)

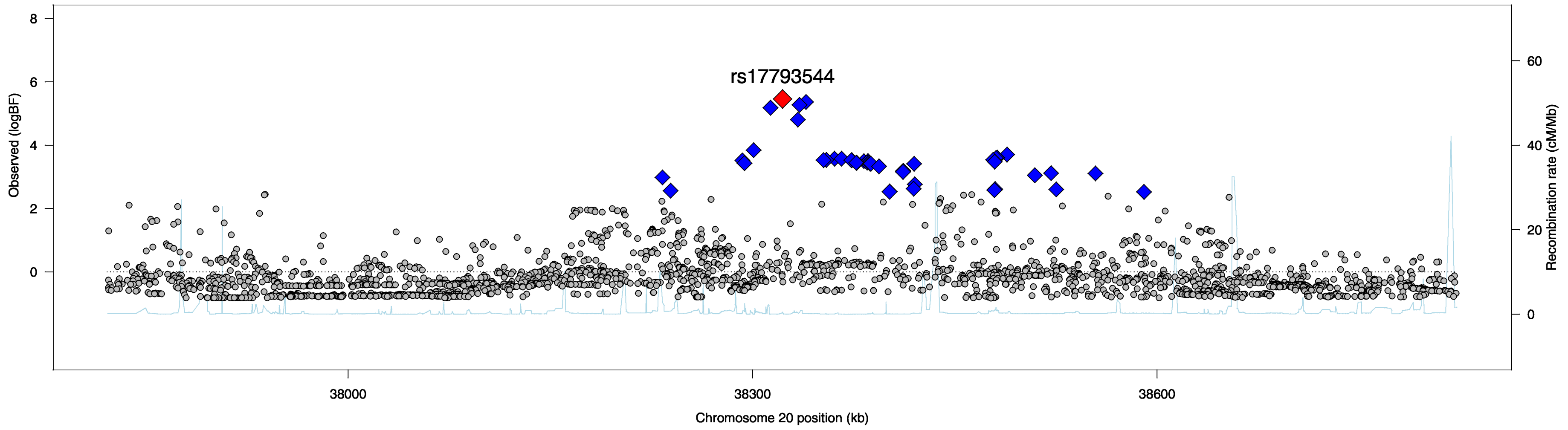

rs28522005
Observed (logBF)
6
4
2
0
Recombination rate (cM/Mb)
60
40
20
0
68300
68600
68900
Chromosome 15 position (kb)

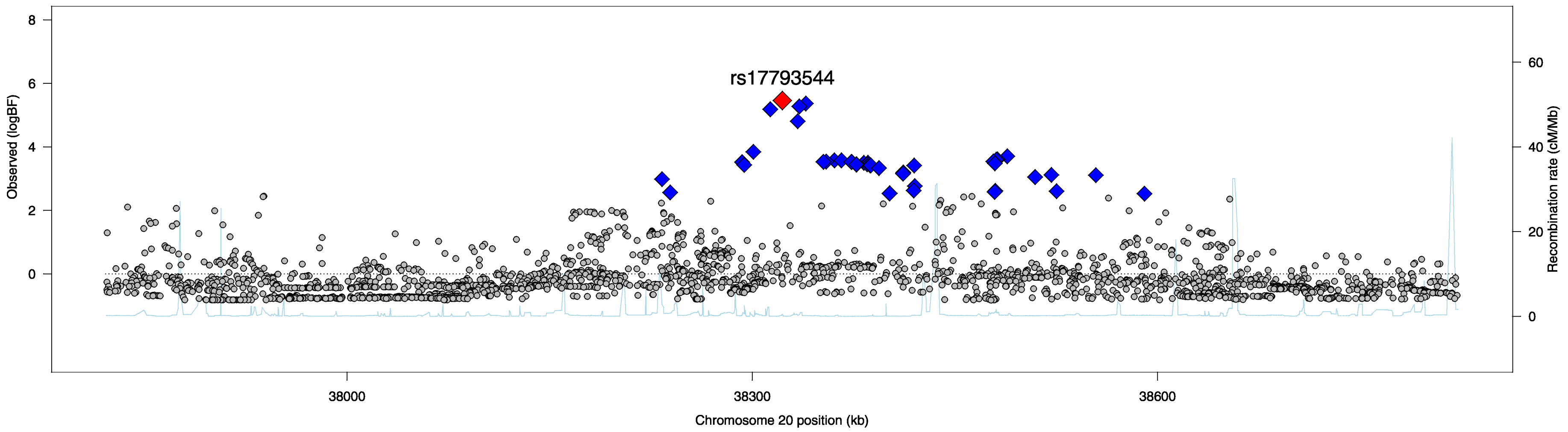

rs72734373
Observed (logBF)
6
4
2
0
Recombination rate (cM/Mb)
60
40
20
0
56000
56300
56600
Chromosome 15 position (kb)

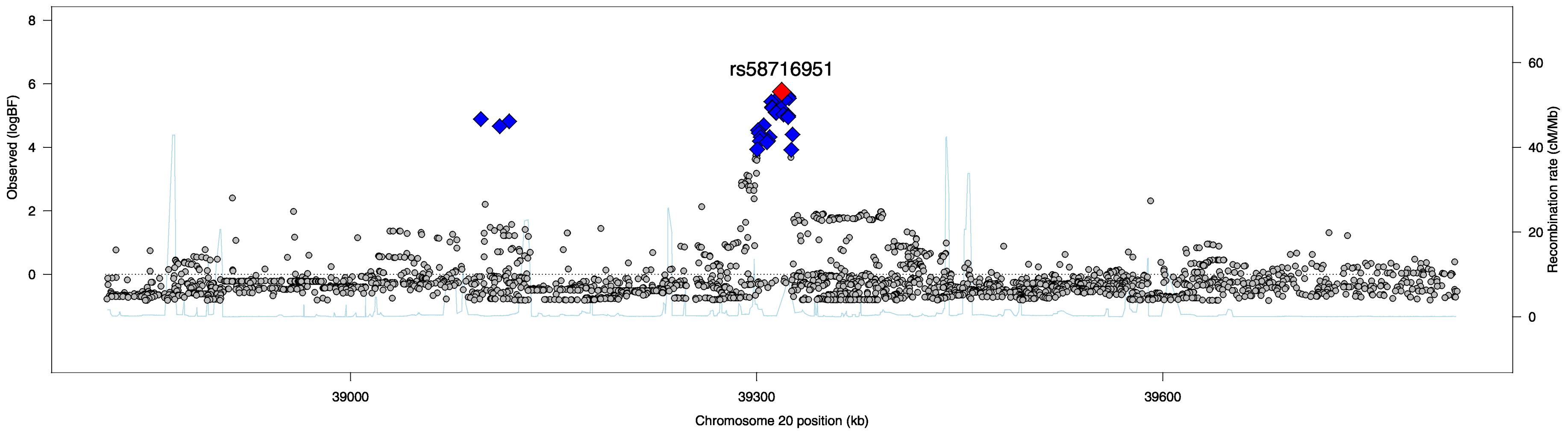

rs1834014
Observed (logBF)
10
8
6
4
2
0
Recombination rate (cM/Mb)
60
40
20
0
75200
75500
75800
Chromosome 16 position (kb)


rs11665156
Observed (logBF)
12
10
8
6
4
2
0
Recombination rate (cM/Mb)
60
40
20
0
9500
9800
10100
Chromosome 18 position (kb)


rs11672447
Observed (logBF)
16
14
12
10
8
6
4
2
0
Recombination rate (cM/Mb)
60
40
20
0
57400
57700
58000
Chromosome 19 position (kb)


rs17793544
Observed (logBF)
8
6
4
2
0
Recombination rate (cM/Mb)
60
40
20
0
38000
38300
38600
Chromosome 20 position (kb)


rs17793544
Observed (logBF)
8
6
4
2
0
Recombination rate (cM/Mb)
60
40
20
0
38000
38300
38600
Chromosome 20 position (kb)


rs58716951
Observed (logBF)
8
6
4
2
0
Recombination rate (cM/Mb)
60
40
20
0
39000
39300
39600
Chromosome 20 position (kb)

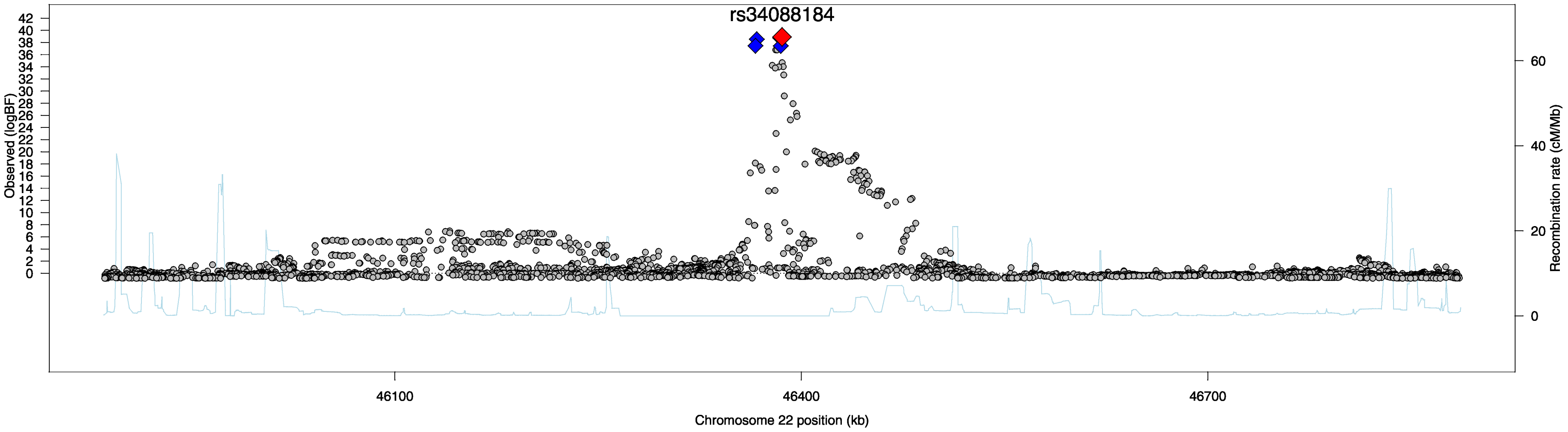

rs34088184
Observed (logBF)
42
40
38
36
34
32
30
28
26
24
22
20
18
16
14
12
10
8
6
4
2
0
Recombination rate (cM/Mb)
60
40
20
0
46100
46400
46700
Chromosome 22 position (kb)

Figure S8. Immunohistochemistry of fixed, surgically resected fibrotic DD tissue confirms WNT3A expression (brown, upper left panel) compared to isotype control (brown, upper right panel), and palm skin (brown, lower left panel). SFRP4 was also not expressed in palm skin (brown, lower right panel). Scale bar = 20µm.

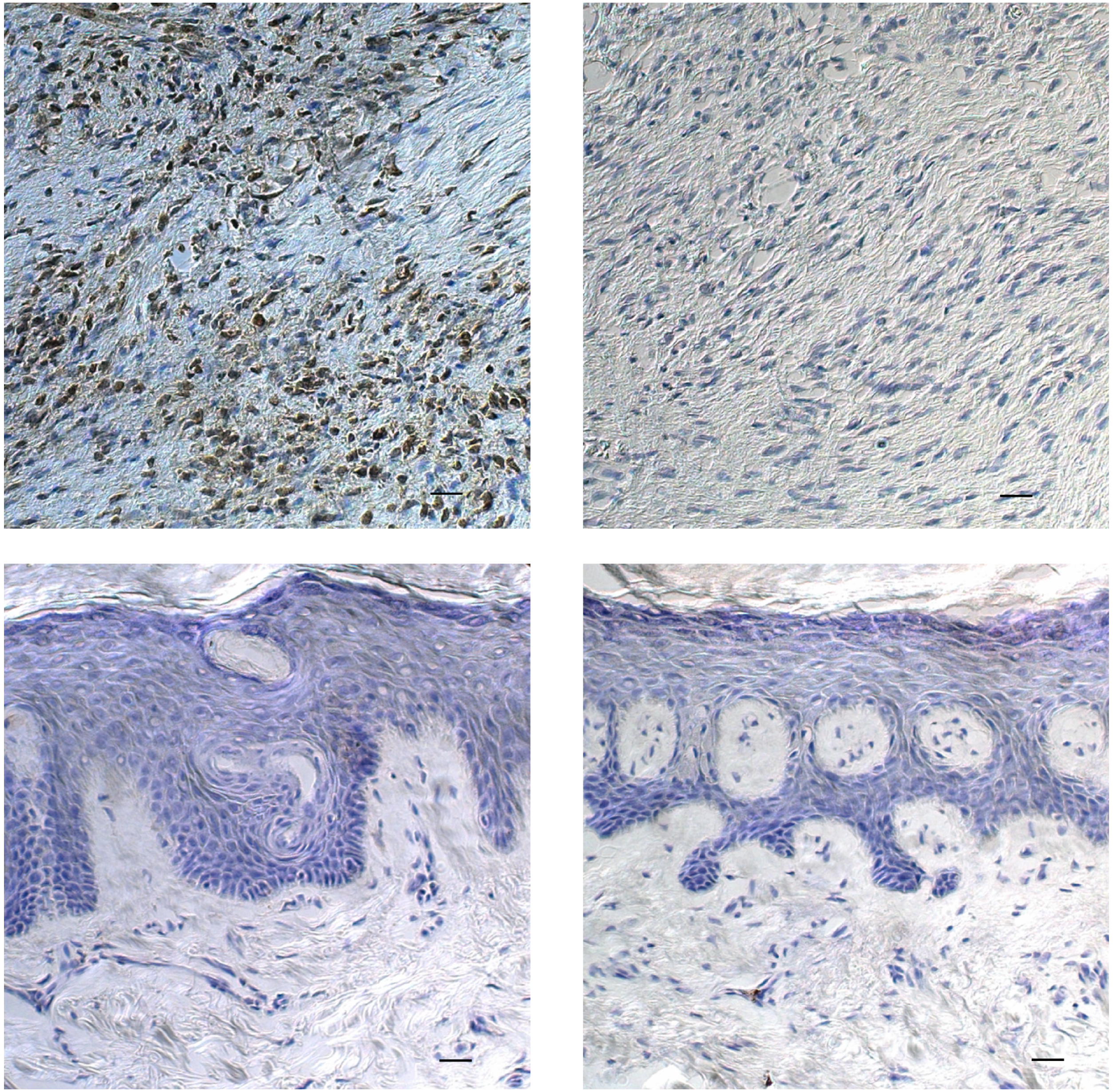
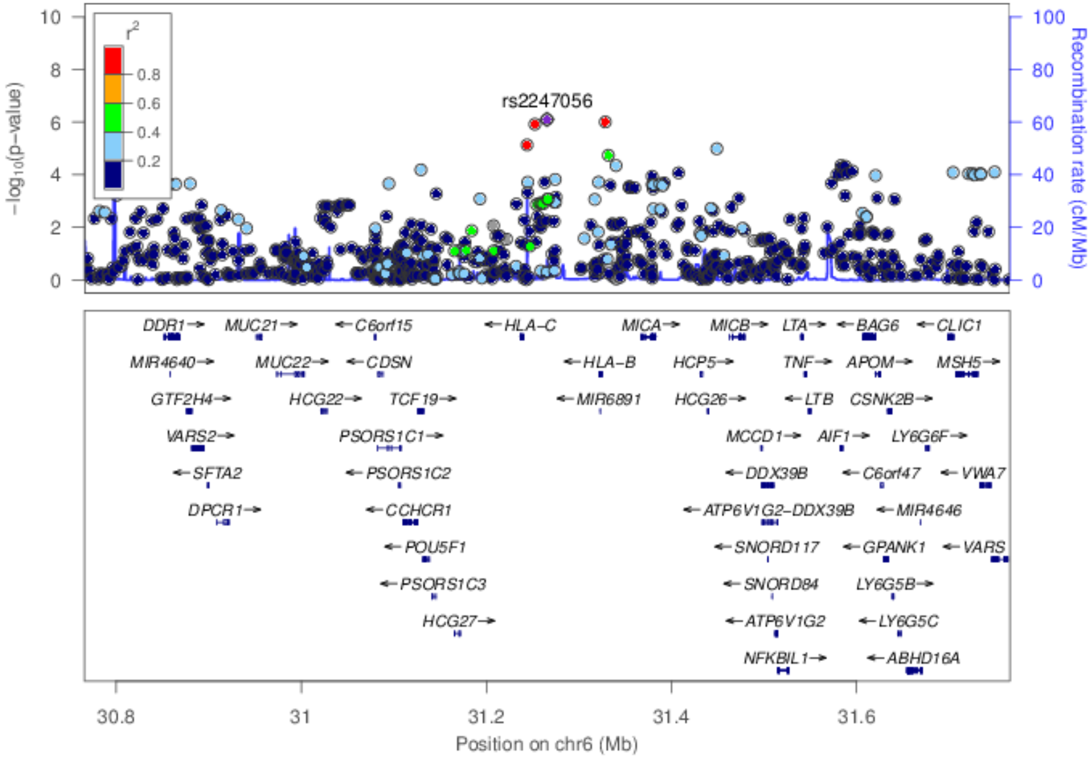


Figure S9. Annotated regional association plots for a) rs12677559 and b) rs2247056 after analysis of the discovery cohort, plotted with LocusZoom [1]. Recombination rate was calculated within the software using data from HapMap. In the lower panel of each figure, genes within 500kb of the index SNP are shown. The position on the chromosomes is shown in relation to Human Genome build hg19.

a)



b)

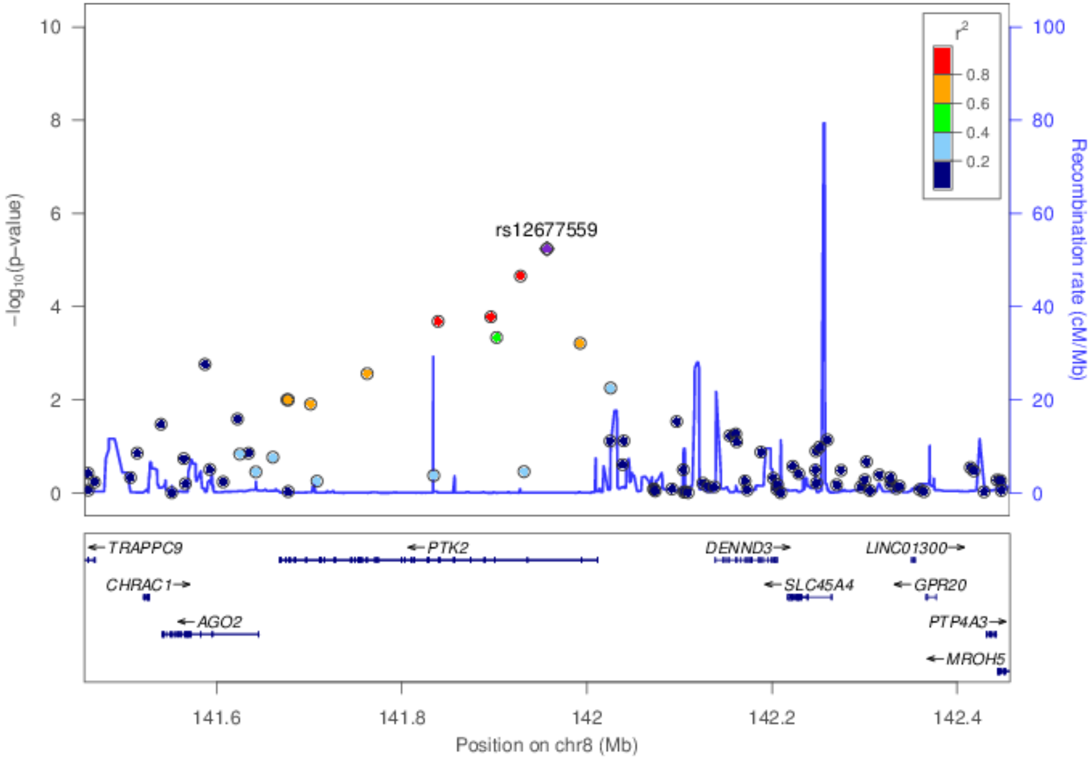

−log10(p−value)
10
8
6
4
2
0
Recombination rate (cM/Mb)
100
80
60
40
20
0
r²
0.8
0.6
0.4
0.2
rs12677559
TRAPPC9
PTK2
DENND3
LINC01300
CHRAC1
SLC45A4
GPR20
AGO2
PTP4A3
MROH5
141.6
141.8
142
142.2
142.4
Position on chr8 (Mb)

Table S1. Samples and genotyping platforms used in the discovery and replication phases

			Pre-QC		Post-QC	
Phase	Geographical Origin	Genotyping Platform	Cases	Controls	Cases	Controls
Discovery	United Kingdom	Illumina HumanCoreExome	4201	4891	3871	4686
Replication	Germany	Taqman Affymetrix 6.0 Illumina Axiom	768	1353	768	1321
	Netherlands	Sequenom Custom array	2195	1983	2104	1860
	United Kingdom	Sequenom Custom array Illumina HumanCoreExome	1207	5070	1169	5070

Table S2. 99% credible sets for associated loci. This table is supplied as an Excel workbook, with a separate worksheet for each individual credible set.

Table S3. Variants carried through to replication phase, if an assay could be designed. Variants that reached genome-wide significance ($p>5x10^{-8}$) on meta-analysis of discovery and replication cohorts are also reported in Table 1 in the main manuscript. This table is supplied as an Excel workbook.