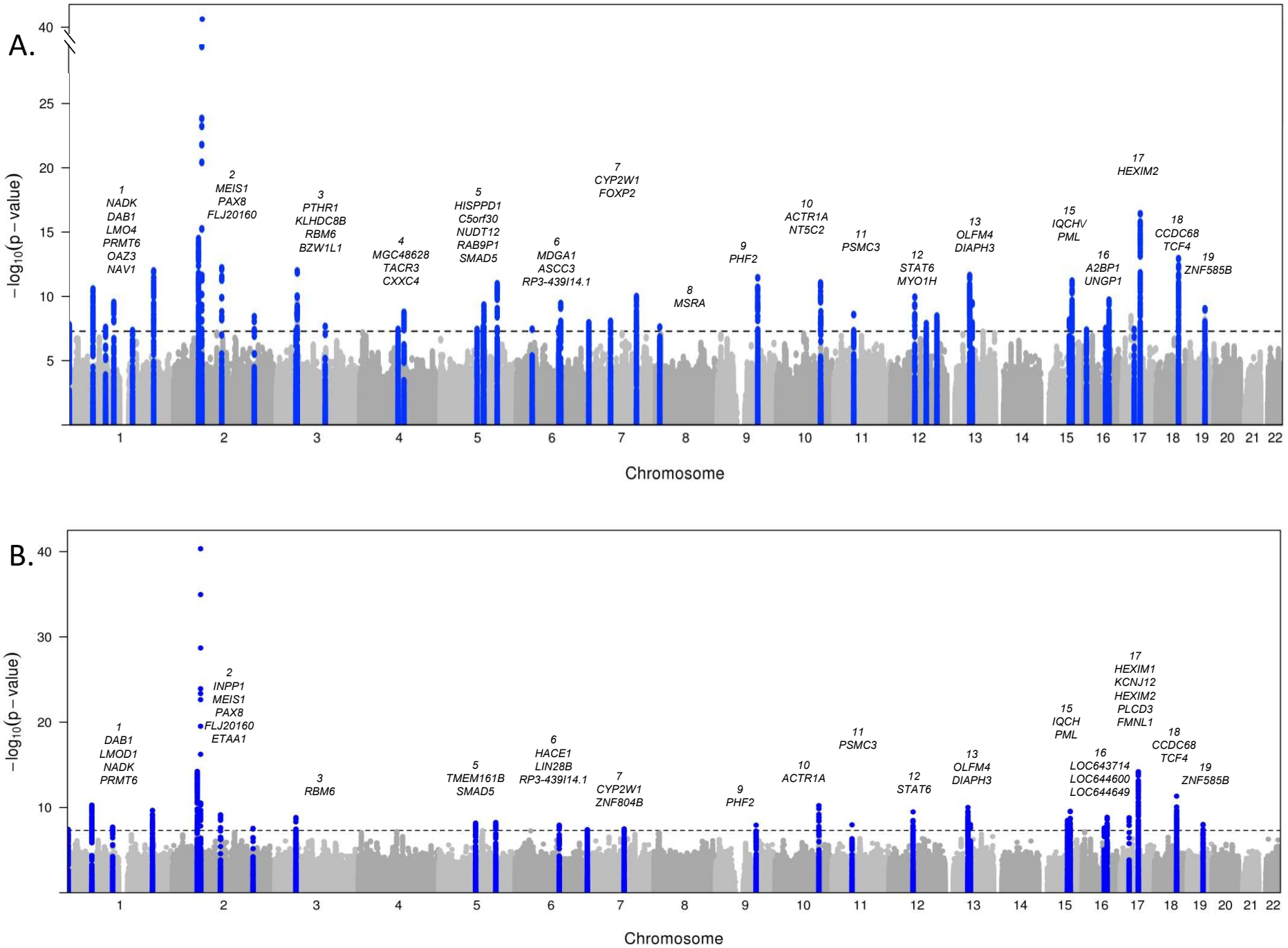
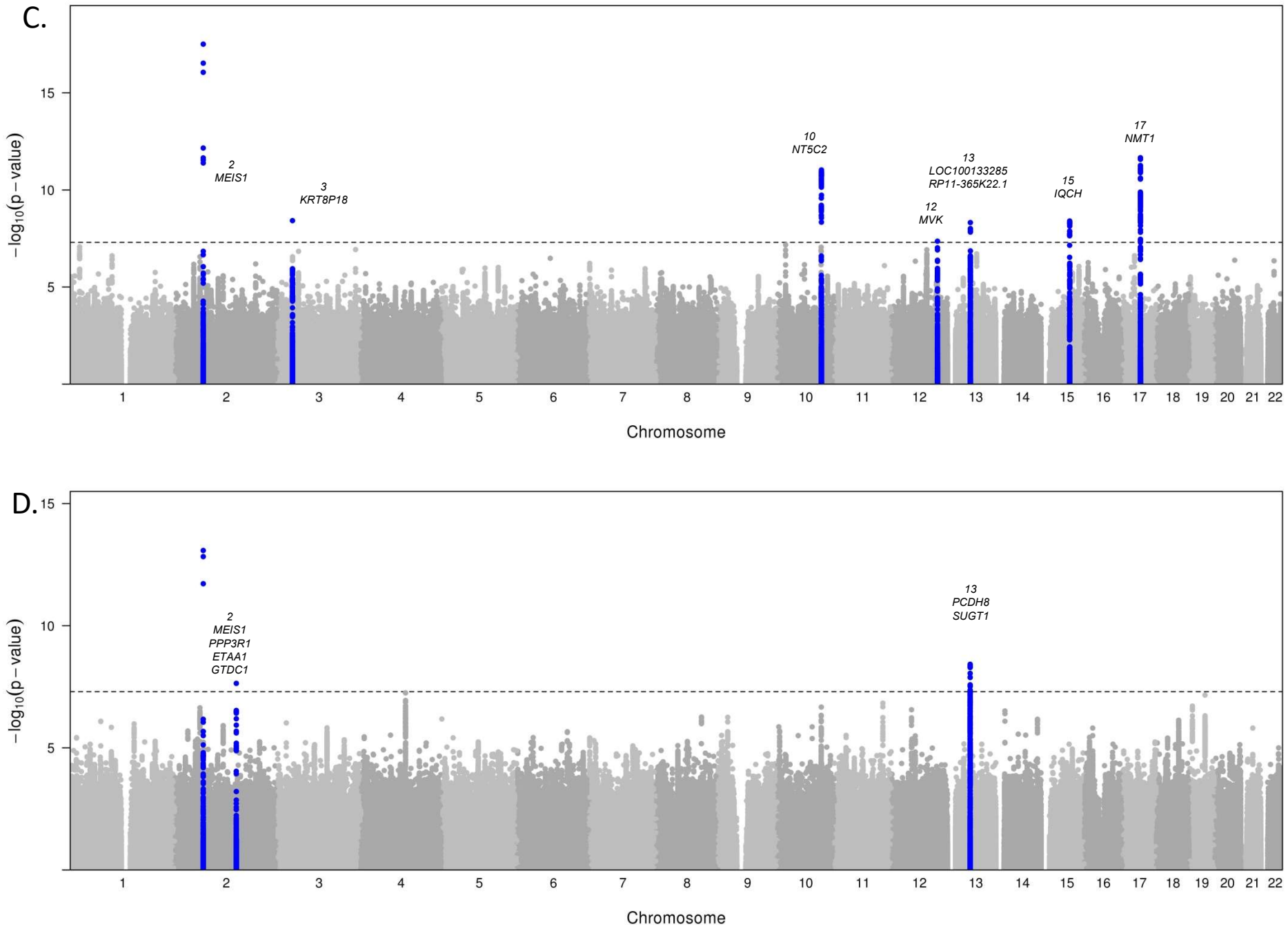
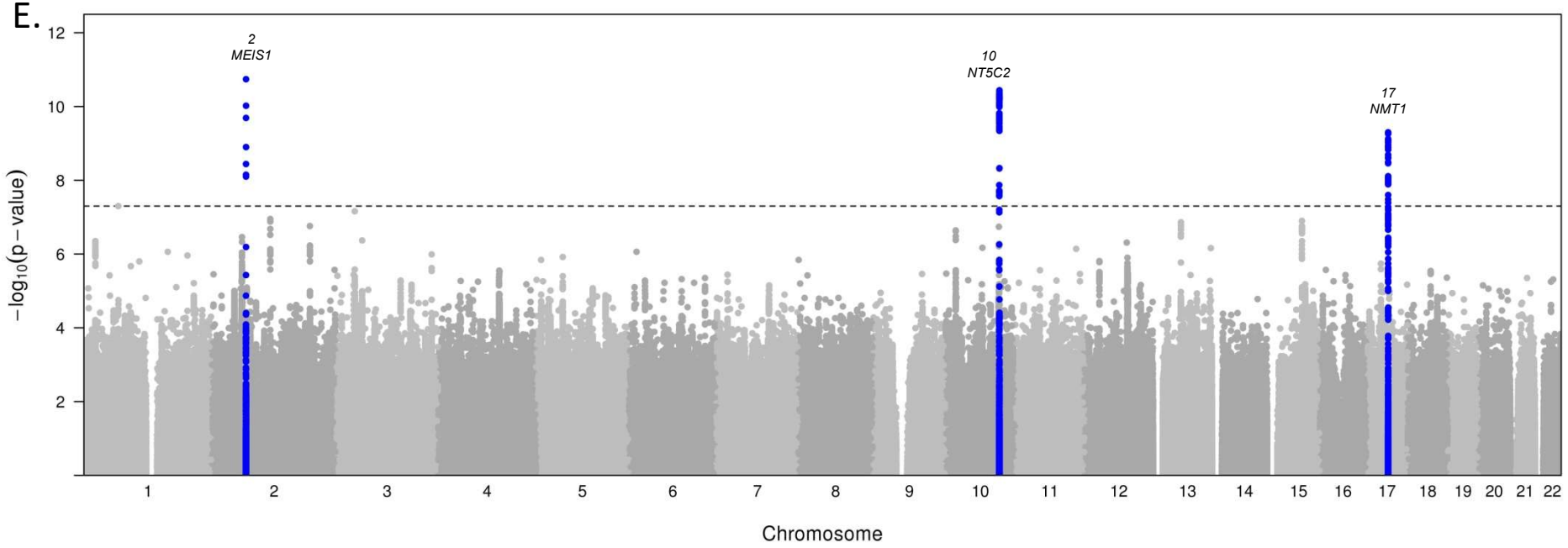

A.
−log10(p−value)
40
25
20
15
10
5
1
NADK
DAB1
LMO4
PRMT6
OAZ3
NAV1
2
MEIS1
PAX8
FLJ20160
3
PTHR1
KLHDC8B
RBM6
BZW1L1
4
MGC48628
TACR3
CXXC4
5
HISPPD1
C5orf30
NUDT12
RAB9P1
SMAD5
6
MDGA1
ASCC3
RP3-439I14.1
7
CYP2W1
FOXP2
8
MSRA
9
PHF2
10
ACTR1A
NT5C2
11
PSMC3
12
STAT6
MYO1H
13
OLFM4
DIAPH3
15
IQCHV
PML
16
A2BP1
UNGP1
17
HEXIM2
18
CCDC68
TCF4
19
ZNF585B
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Chromosome
B.
−log10(p−value)
40
30
20
10
1
DAB1
LMOD1
NADK
PRMT6
2
INPP1
MEIS1
PAX8
FLJ20160
ETAA1
3
RBM6
5
TMEM161B
SMAD5
6
HACE1
LIN28B
RP3-439I14.1
7
CYP2W1
ZNF804B
9
PHF2
10
ACTR1A
11
PSMC3
12
STAT6
13
OLFM4
DIAPH3
15
IQCH
PML
16
LOC643714
LOC644600
LOC644649
17
HEXIM1
KCNJ12
HEXIM2
PLCD3
FMNL1
18
CCDC68
TCF4
19
ZNF585B
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Chromosome


C.
−log10(p − value)
15
10
5
2
MEIS1
3
KRT8P18
10
NT5C2
12
MVK
13
LOC100133285
RP11-365K22.1
15
IQCH
17
NMT1
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Chromosome
D.
−log10(p − value)
15
10
5
2
MEIS1
PPP3R1
ETAA1
GTDC1
13
PCDH8
SUGT1
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Chromosome

E.


2
MEIS1
10
NT5C2
17
NMT1
−log10(p−value)
Chromosome

F.

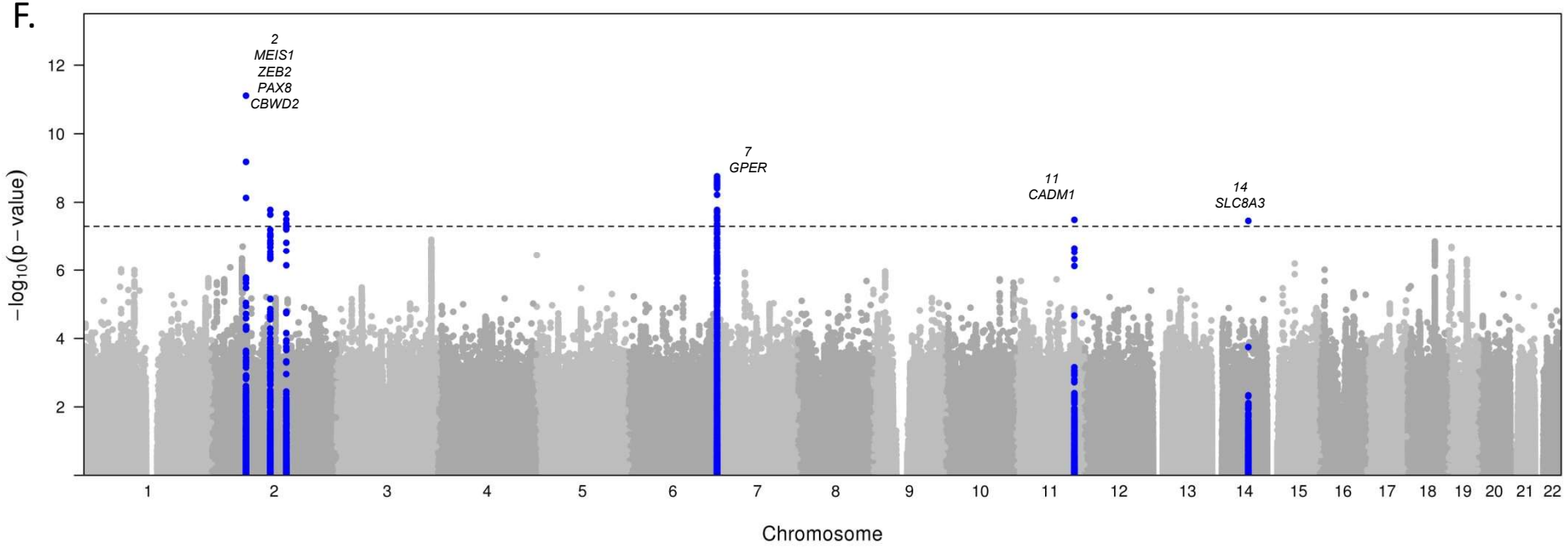

2
MEIS1
ZEB2
PAX8
CBWD2
7
GPER
11
CADM1
14
SLC8A3
−log10(p−value)
Chromosome

Fig. S1. Manhattan plots for genome-wide association analysis of frequent insomnia symptoms (A), frequent insomnia symptoms with exclusions (B), frequent insomnia symptoms stratified by sex, females (C), males (D), any insomnia symptoms stratified by sex, females (E), males (F) . Dotted line is genome-wide significant ($5x10^{-8}$). Heritability estimates were calculated using BOLT-REML. Chromosomes are annotated with the nearest gene to each association signal.

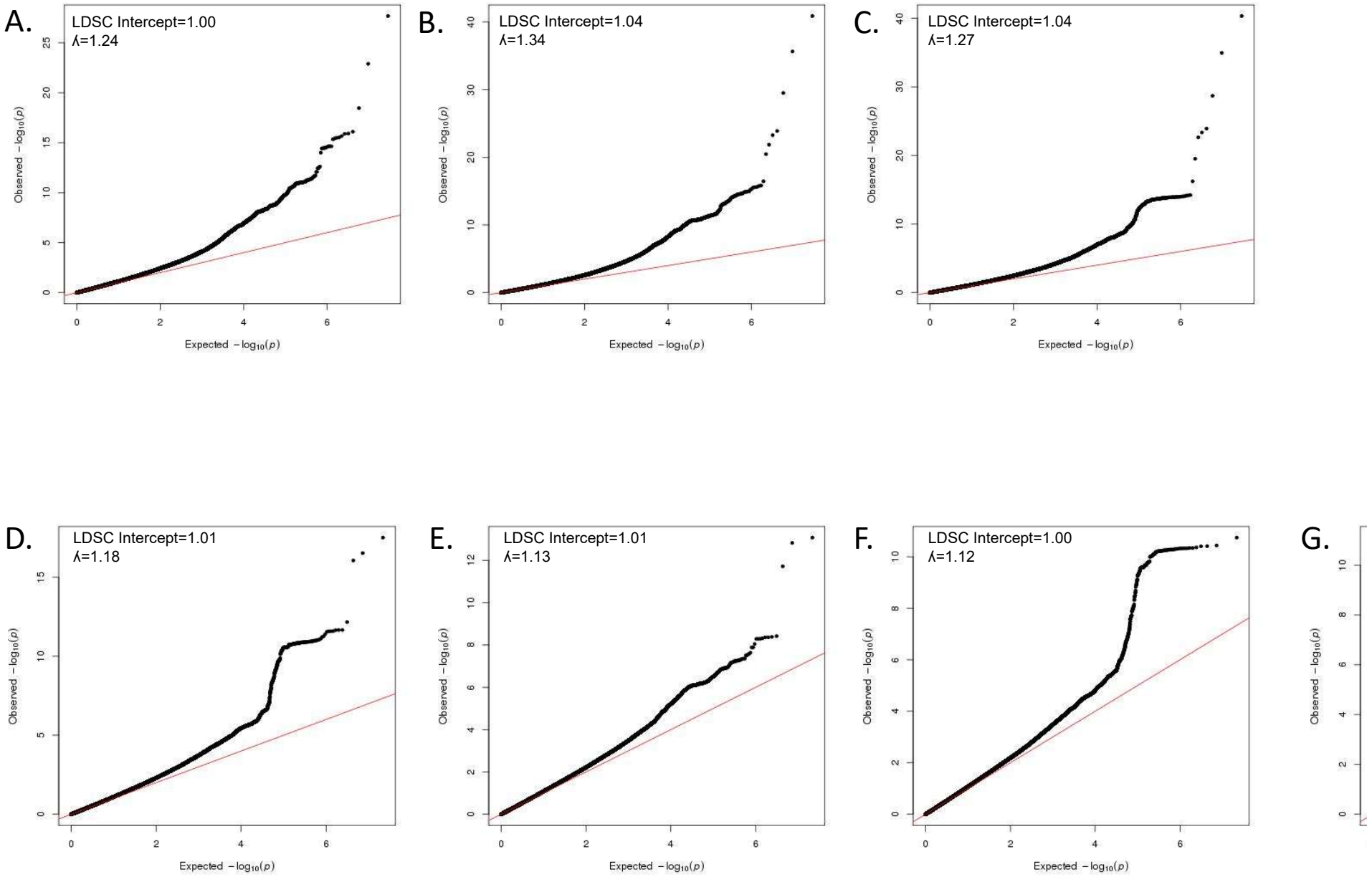
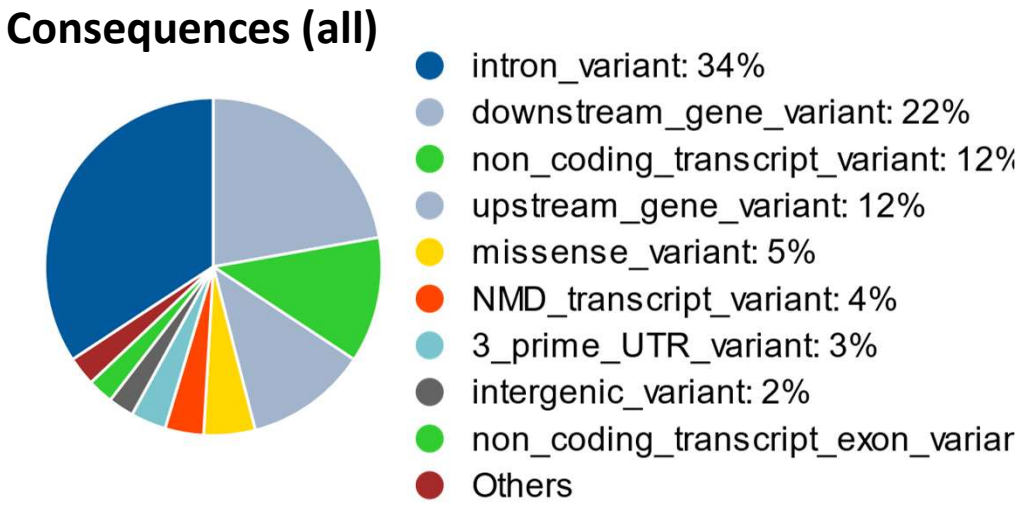

A.
LDSC Intercept=1.00
λ=1.24
B.
LDSC Intercept=1.04
λ=1.34
C.
LDSC Intercept=1.04
λ=1.27
D.
LDSC Intercept=1.01
λ=1.18
E.
LDSC Intercept=1.01
λ=1.13
F.
LDSC Intercept=1.00
λ=1.12
G.
Observed −log10(p)
Expected −log10(p)

Fig. S2. QQ plot for genome-wide association analysis of insomnia symptoms. Plots A-G show the expected verses observed P values from our association analysis of any insomnia symptoms (A), frequent insomnia symptoms (B), frequent insomnia symptoms with exclusions (C), sex stratified frequent insomnia symptoms, females (D), males (E), sex stratified any insomnia symptoms, females (F), males (G). Lambda inflation values were calculated using GenABEL in R and the intercept using LDSC.

		Frequent Insomnia Symptoms				Any Insomnia Symptoms			
		all	all with exclusions	male	female	all	all with exclusions	male	female
Frequent Insomnia Symptoms	all	1							
	all with exclusions	1.028	1						
	male	0.943	0.971	1					
	female	0.957	0.981	0.807	1				
Any Insomnia Symptoms	all	0.977	1.018	0.924	0.933	1			
	all with exclusions	0.966	0.931	0.877	0.951	1.016	1		
	male	0.916	0.953	0.962	0.792	0.952	0.932	1	
	female	0.937	0.978	0.787	0.984	0.945	1.001	0.802	1

Fig. S3. Genetic correlation between the reported insomnia symptoms GWAS shown, as measured by LDSC. Color scale represents the strength of the correlation.



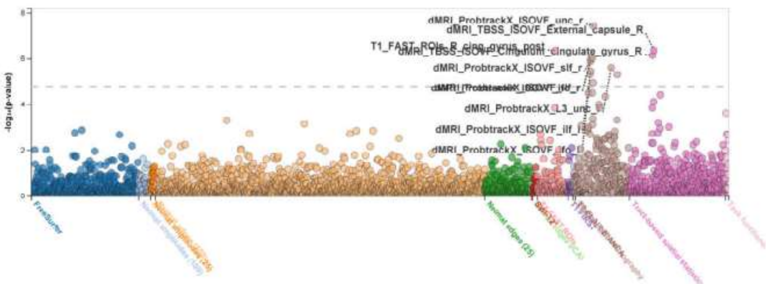
Variant Effect Predictor results for all PICS variants >=.2

Fig. S4. Summary of variant annotation. Variants within the credible set for each locus were mapped based on functional annotation of each SNP. NMD=nonsense mediated decay, UTR=untranslated region.

16 : 51,484,837 T / C (rs1544637)

Nearest gene: *SALL1*
MAF ranges from 4.8e-1 to 4.8e-1
View on UCSC (http://genome.ucsc.edu/cgi-bin/hgTracks?db=hg19&highlight=hg19.chr16%3A{ variant.pos }}-51484837&position=chr16%3A51284837-51684837) , GWAS Catalog (https://www.ebi.ac.uk/gwas/search?query=rs1544637) , dbSNP (http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?searchType=adhoc_search&type=rs&rs=rs1544637)

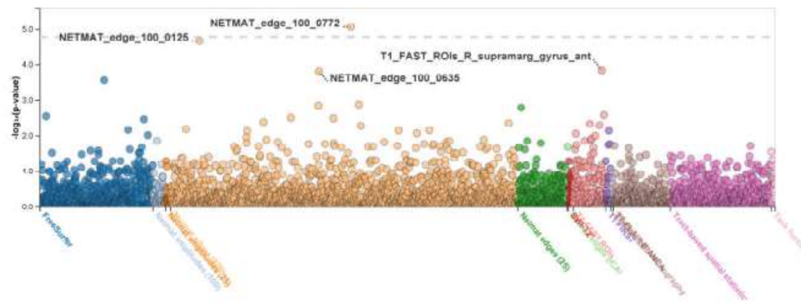
Download Image



3 : 49,980,596 C / T (rs4688760)

Nearest gene: *RBM6*
MAF ranges from 3.0e-1 to 3.0e-1
View on UCSC (http://genome.ucsc.edu/cgi-bin/hgTracks?db=hg19&highlight=hg19.chr3%3A{ variant.pos }}-49980596&position=chr3%3A49780596-50180596) , GWAS Catalog (https://www.ebi.ac.uk/gwas/search?query=rs4688760) , dbSNP (http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?searchType=adhoc_search&type=rs&rs=rs4688760)

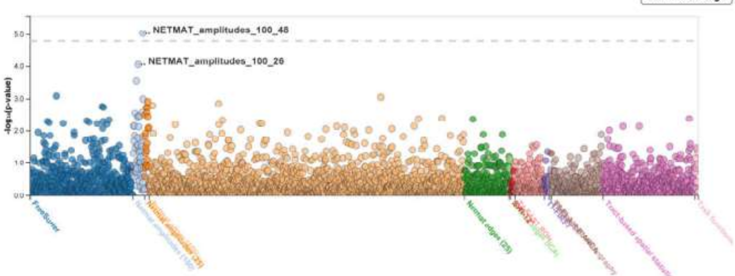
Download Image



15 : 74,340,336 G / C (rs4886860)

Nearest gene: *PML*
MAF ranges from 2.3e-1 to 2.3e-1
View on UCSC (http://genome.ucsc.edu/cgi-bin/hgTracks?db=hg19&highlight=hg19.chr15%3A{ variant.pos }}-74340336&position=chr15%3A74140336-74540336) , GWAS Catalog (https://www.ebi.ac.uk/gwas/search?query=rs4886860) , dbSNP (http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?searchType=adhoc_search&type=rs&rs=rs4886860)

Download Image



2 : 114,082,175 A / G (rs62158170)

Nearest gene: *PAX8*
MAF ranges from 2.0e-1 to 2.0e-1
View on UCSC (http://genome.ucsc.edu/cgi-bin/hgTracks?db=hg19&highlight=hg19.chr2%3A{ variant.pos }}-114082175&position=chr2%3A113882175-114282175) , GWAS Catalog (https://www.ebi.ac.uk/gwas/search?query=rs62158170) , dbSNP (http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?searchType=adhoc_search&type=rs&rs=rs62158170)

iAycHgsIDJweDsgc3Ryb2tlLXdpZHRoOiAycHg7IiB4MT0iMTY3LjM2MSIgeTE9IjIzLjI3MjcilHgyPSIxNzguNzI3IiB5Mj0iMjMuMjcyNyIgLz48L2c+PGcgY2xhc3M9Imx6LWRhdGFfbGF5ZXIIc2NhdHRlci1sYWJlbCI+P)

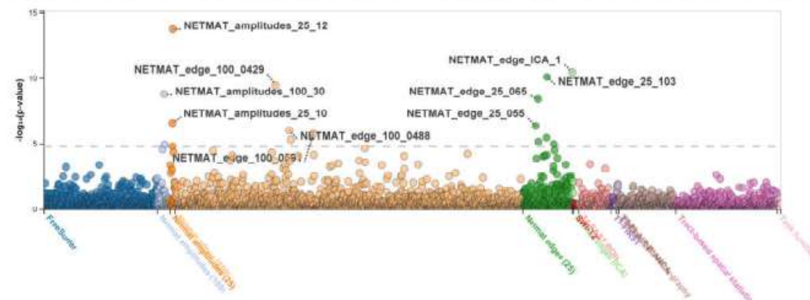


Fig. S5. Association of frequent insomnia symptom loci with brain imaging phenotypes in the UK Biobank (images from http://big.stats.ox.ac.uk/).

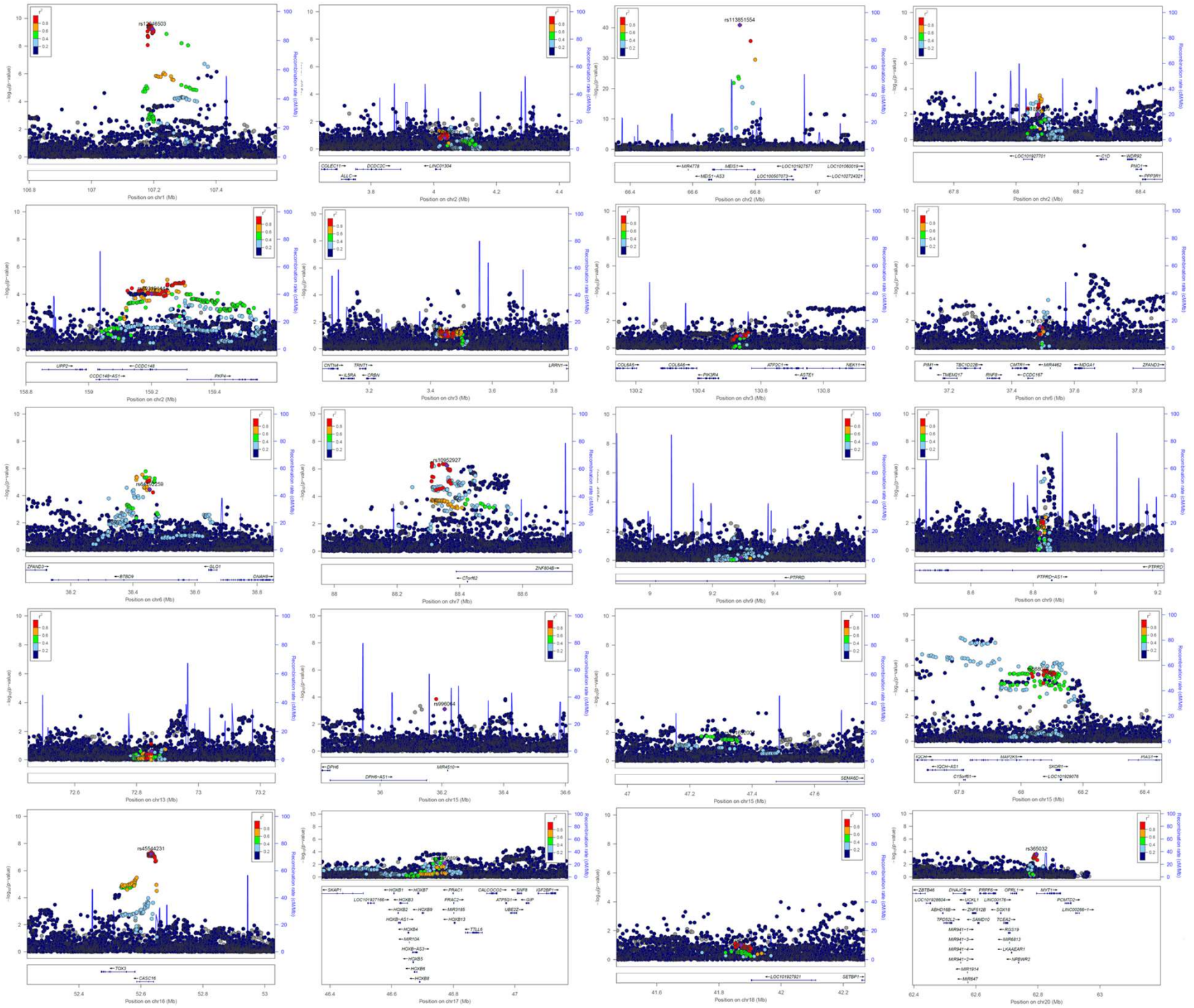

rs12446503
rs113851554
rs10952927
rs9960064
rs45544231
rs365032
Position on chr1 (Mb)
Position on chr2 (Mb)
Position on chr3 (Mb)
Position on chr6 (Mb)
Position on chr7 (Mb)
Position on chr9 (Mb)
Position on chr13 (Mb)
Position on chr15 (Mb)
Position on chr16 (Mb)
Position on chr17 (Mb)
Position on chr18 (Mb)
Position on chr20 (Mb)
Recombination rate (cM/Mb)

Fig. S6. Regional association plots for RLS loci in insomnia symptoms GWAS. Panels highlight loci previously identified to associate with RLS. Genes within the region are shown in the lower panel. The blue line indicates the recombination rate. Filled circles show the log10 P value for each SNP, with the RLS SNP shown in purple. Additional SNPs in the locus are colored according to correlation (r^2) with the RLS SNP (estimated by LocusZoom based on the CEU HapMap haplotypes).

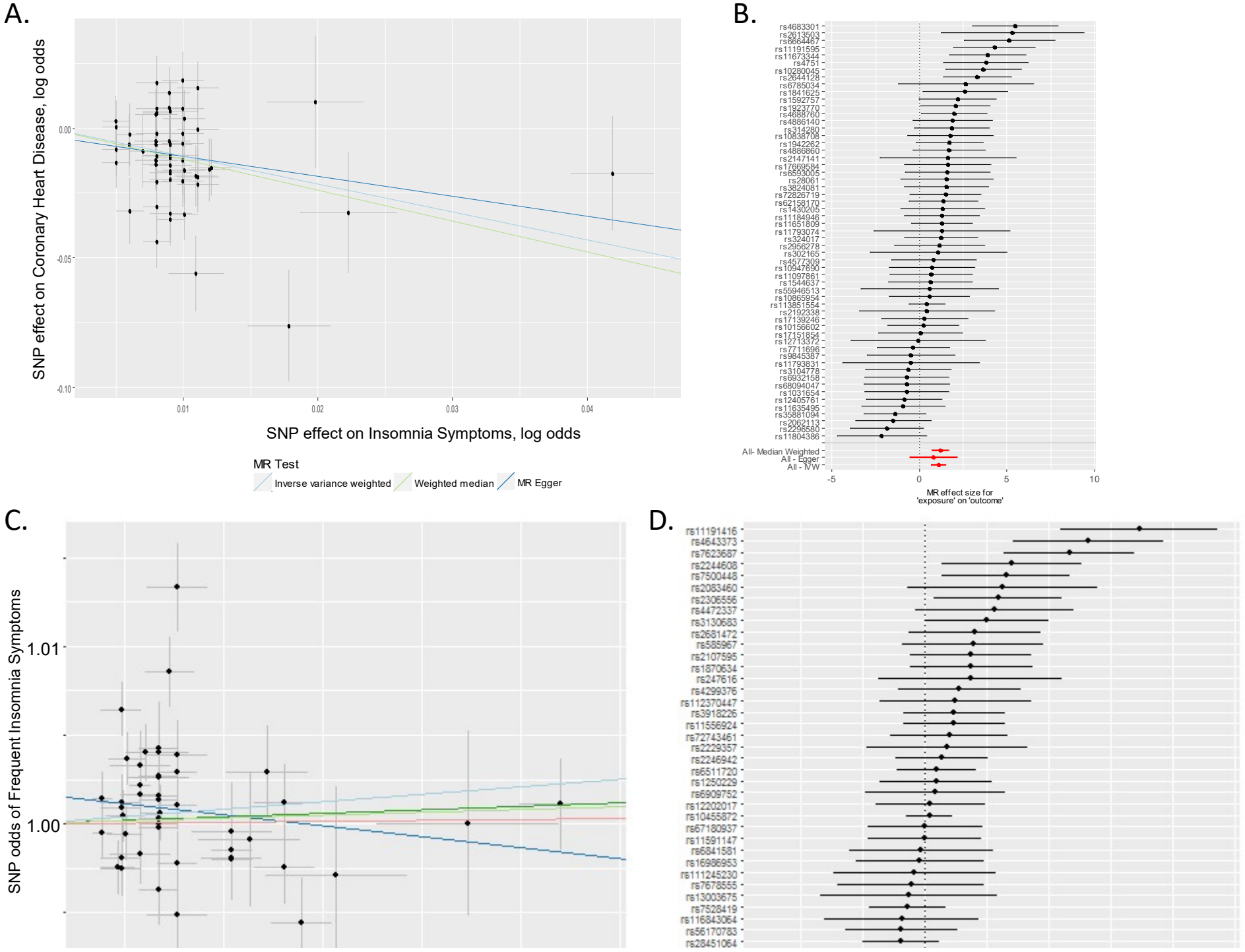

A.
SNP effect on Coronary Heart Disease, log odds
0.00
-0.05
-0.10
0.01
0.02
0.03
0.04
SNP effect on Insomnia Symptoms, log odds
MR Test
Inverse variance weighted
Weighted median
MR Egger
B.
rs4683301
rs2613503
rs6664467
rs11191595
rs11673344
rs4751
rs10280045
rs2644128
rs6785034
rs1841625
rs1592757
rs1923770
rs4688760
rs4886140
rs314280
rs10838708
rs1942262
rs4886860
rs2147141
rs17669584
rs6593005
rs28061
rs3824081
rs72826719
rs62158170
rs1430205
rs11184946
rs11651809
rs11793074
rs324017
rs2956278
rs302165
rs4577309
rs10947690
rs11097861
rs1544637
rs55946513
rs10865954
rs113851554
rs2192338
rs17139246
rs10156602
rs17151854
rs12713372
rs7711696
rs9845387
rs11793831
rs3104778
rs6932158
rs68094047
rs1031654
rs12405761
rs11635495
rs35881094
rs2062113
rs2296580
rs11804386
All- Median Weighted
All - Egger
All - IVW
-5
0
5
10
MR effect size for
'exposure' on 'outcome'
C.
SNP odds of Frequent Insomnia Symptoms
1.01
1.00
D.
rs111191416
rs4643373
rs7623687
rs2244608
rs7500448
rs2083460
rs2306556
rs4472337
rs3130683
rs2681472
rs586967
rs2107595
rs1870634
rs247616
rs4299376
rs112370447
rs3918226
rs11556924
rs72743461
rs2229357
rs2246942
rs6511720
rs1250229
rs6909752
rs12202017
rs10455872
rs67180937
rs11591147
rs6841581
rs16986953
rs111245230
rs7678555
rs13003675
rs7528419
rs116843064
rs56170783
rs28451064

Fig. S7. Causal relationship of insomnia symptoms with CAD in the UK Biobank. Association between single nucleotide polymorphisms associated with frequent insomnia symptoms and CAD (A) and forest plot shows the estimate of the effect of genetically increased insomnia risk on CAD (B). Association between single nucleotide polymorphisms associated with CAD and insomnia symptoms (C) and forest plot shows the estimate of the effect of genetically increased CAD risk on insomnia symptoms (D). Results are shown for multiple MR association tests. Forest plots show each SNP with the 95% confidence interval (gray line segment) of the estimate and the Inverse Variance MR, MR-Egger, and Weighted Median MR results in red.