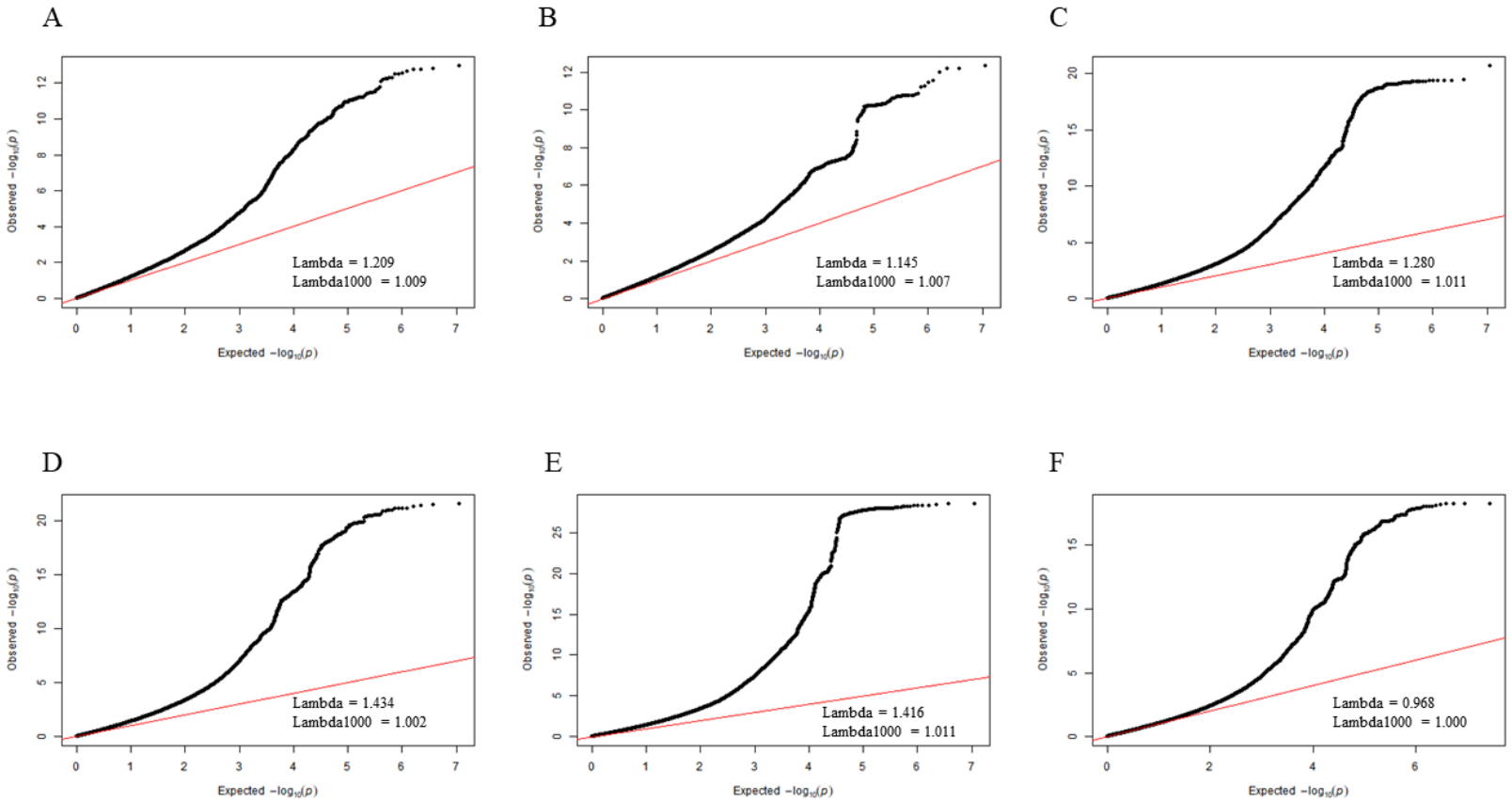
Supplementary material

Supplementary Table 1. The five cohorts of European ancestry for the five neuropsychiatric disorders downloaded from the website of Psychiatric Genomics Consortium (PGC).

Disease	Case	Control	Cohort name	PMID
ADHD	19099	34194	European-Ancestry-GWAS	30478444
ASD	18381	27969	ASD iPSYCH – PGC GWAS – 2017 (publ. 2019)	30804558
BIP	20352	31358	BIP 2018	31043756
MDD	170756	329443	2019 PGC UKB Depression Genome-wide	30718901
SCZ	33640	43456	EUR	31740837

Disease= each neuropsychiatric disorder in the study, ADHD= attention deficit hyperactivity disorder, ASD= autism spectrum disorder, BIP= bipolar disorder, MDD= major depressive disorder, SCZ= schizophrenia; Case= the number of cases in each study; Control= the number of controls in each study; Cohort name= the name of the link to the GWAS cohort on PGC website; PMID= PubMed Unique Identifier of the original publication of each cohort.

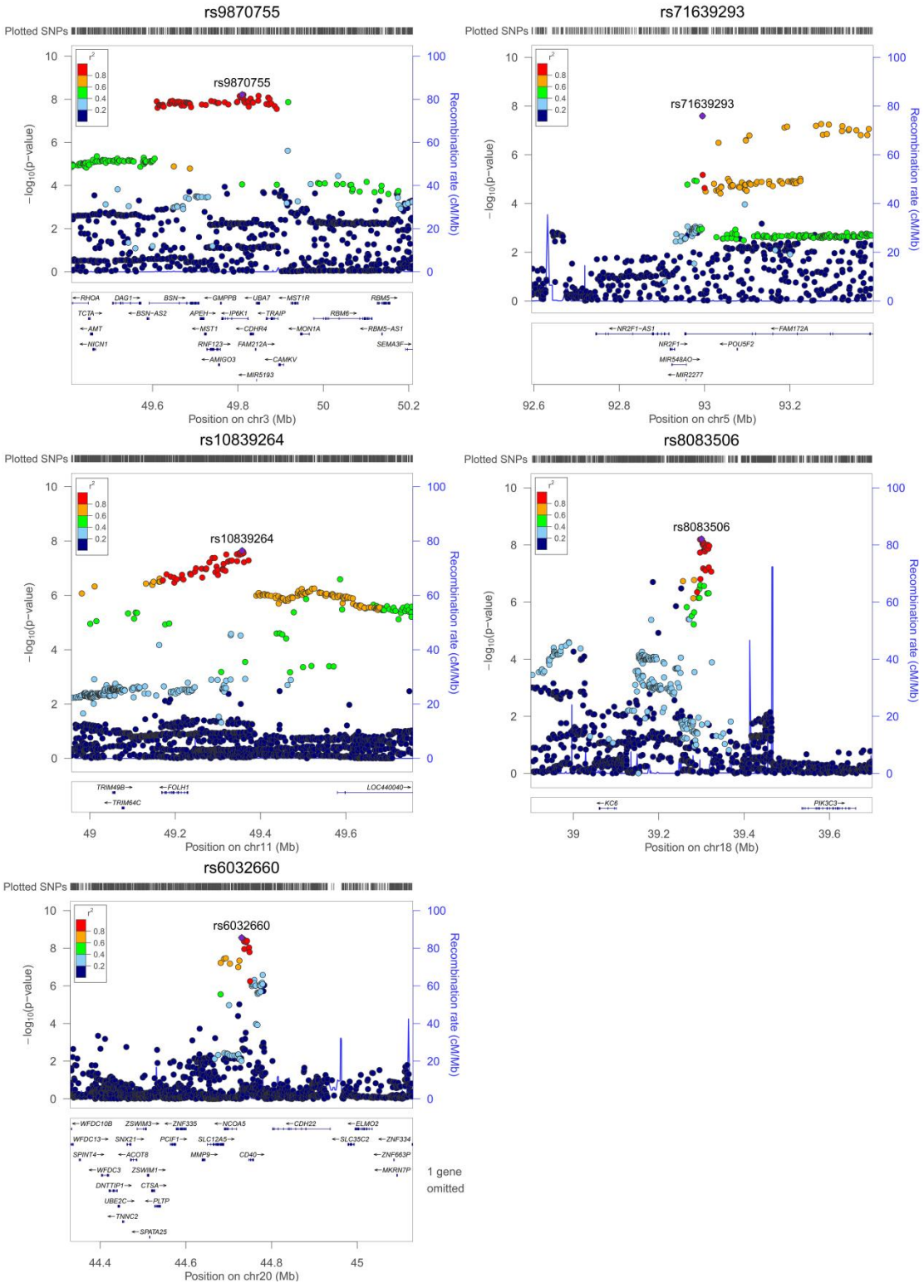
Supplementary Figure 1. Quantile-quantile (QQ) plot of summary statistics for multi-trait joint analysis and meta-analysis of five neuropsychiatric diseases: MTAG analysis of ADHD (**A**), ASD (**B**), BIP (**C**), MDD (**D**), SCZ (**E**), and METAL analysis of five disorders (**F**). The standardized genomic inflation factor of each analysis was indicated in the figure.



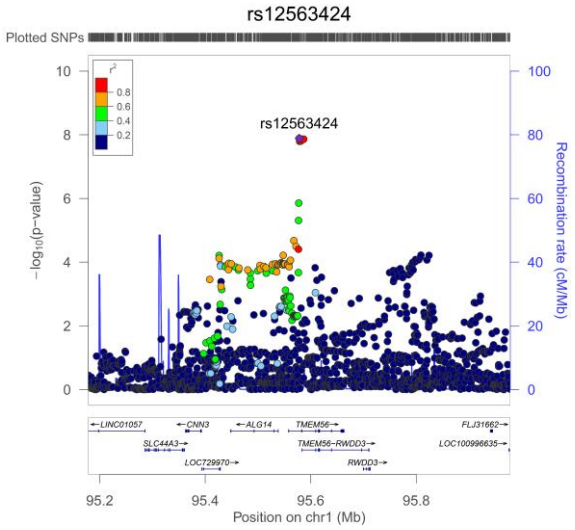
Supplementary Figure 2. Regional association plots of novel significant loci from multi-trait joint analyses.

Regional association plots showing the novel significant loci identified from multi-trait joint analyses of ADHD (**A**), BIP (**B**) and MDD (**C**). The genomic position of each SNP is shown on the X-axis and the $-\log_{10}$ (P-values) are shown on the Y-axis. The most significant SNP is indicated in purple color and the rest of the SNPs are shown in different colors corresponding to the linkage disequilibrium with the top associated SNP. The blue vertical line indicates the recombination rate based on the HapMap project.

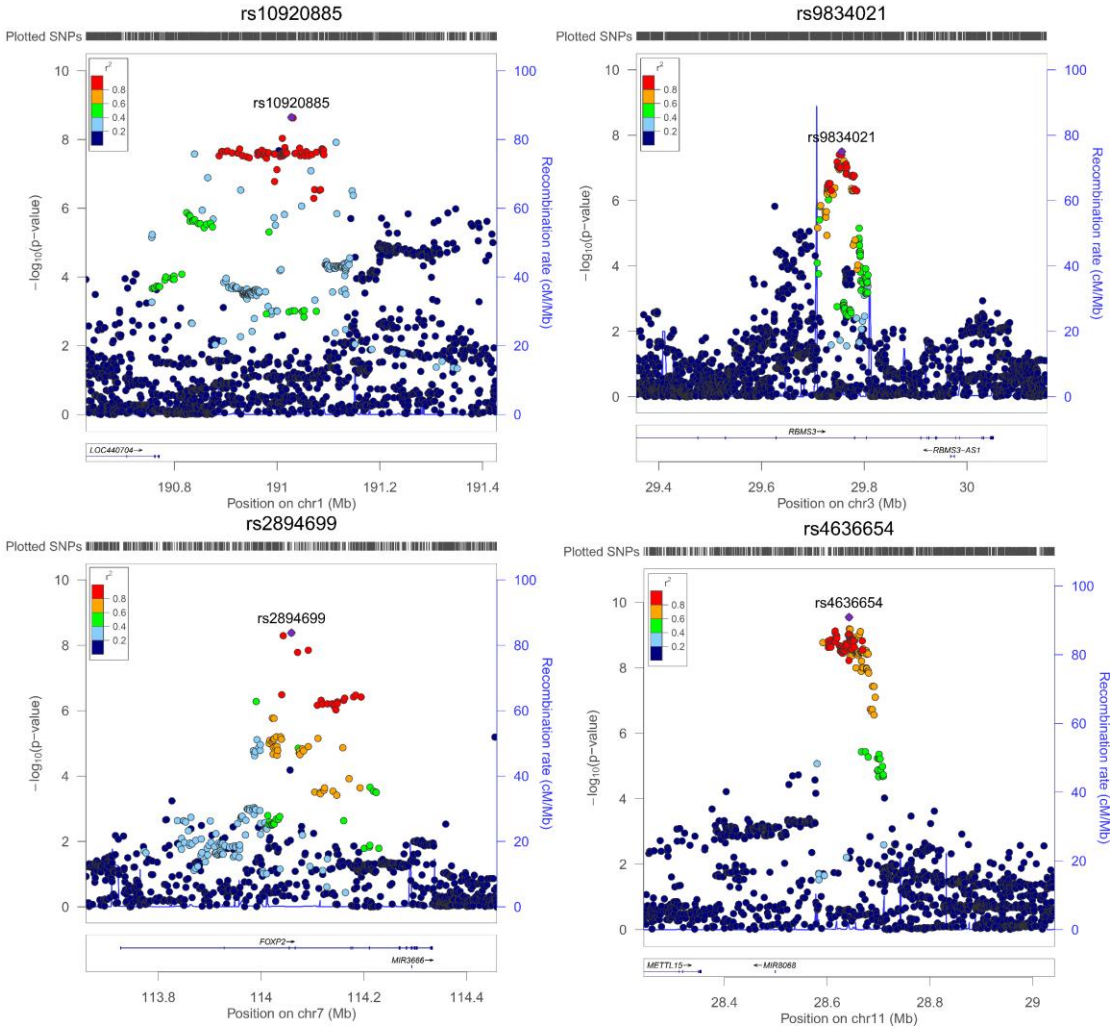
A

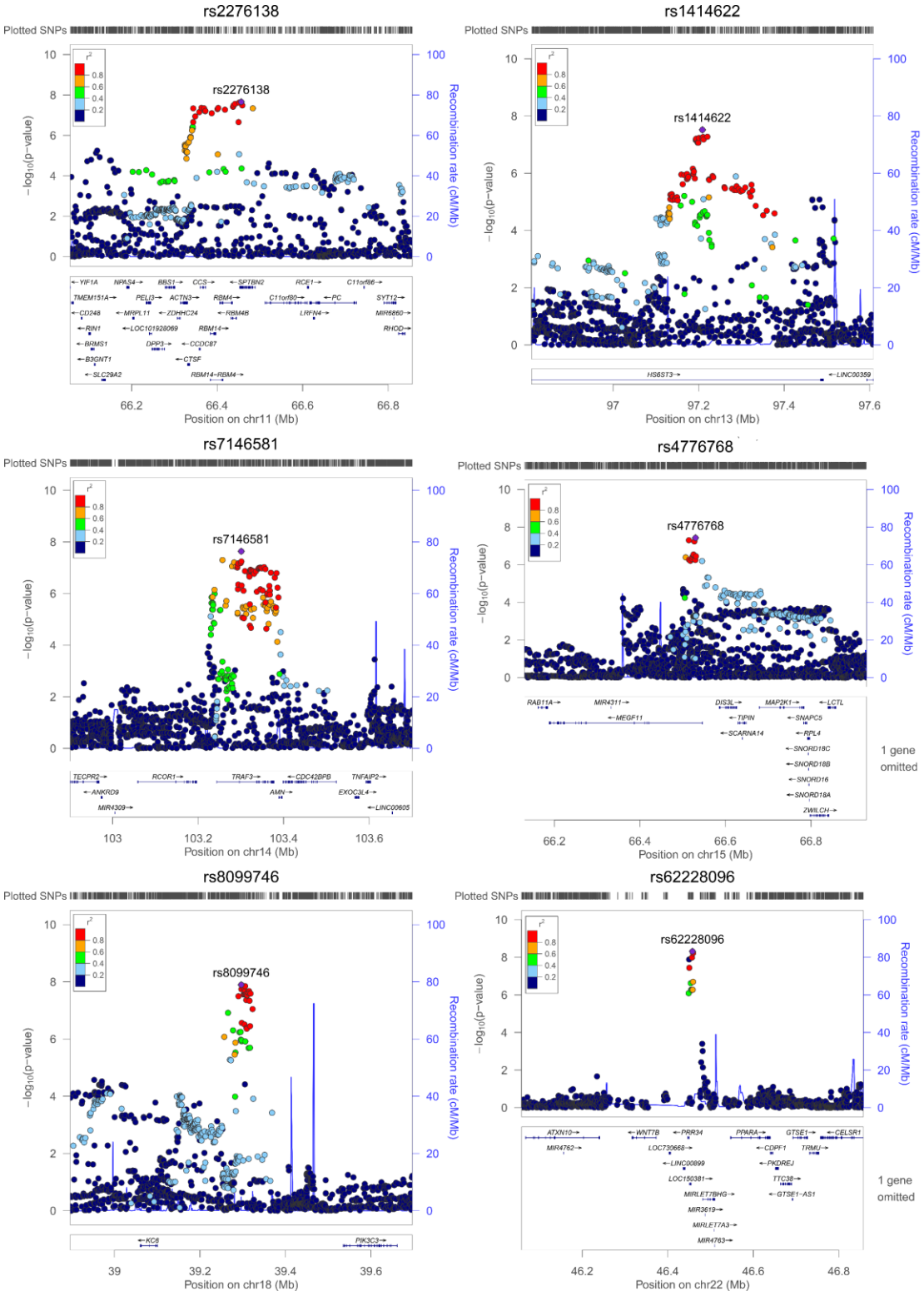

rs9870755
Plotted SNPs
rs9870755
−log10(p-value)
Recombination rate (cM/Mb)
Position on chr3 (Mb)
rs71639293
rs71639293
Position on chr5 (Mb)
rs10839264
rs10839264
Position on chr11 (Mb)
rs8083506
rs8083506
Position on chr18 (Mb)
rs6032660
rs6032660
Position on chr20 (Mb)
1 gene omitted

B


rs12563424
Plotted SNPs
rs12563424
Recombination rate (cM/Mb)
Position on chr1 (Mb)

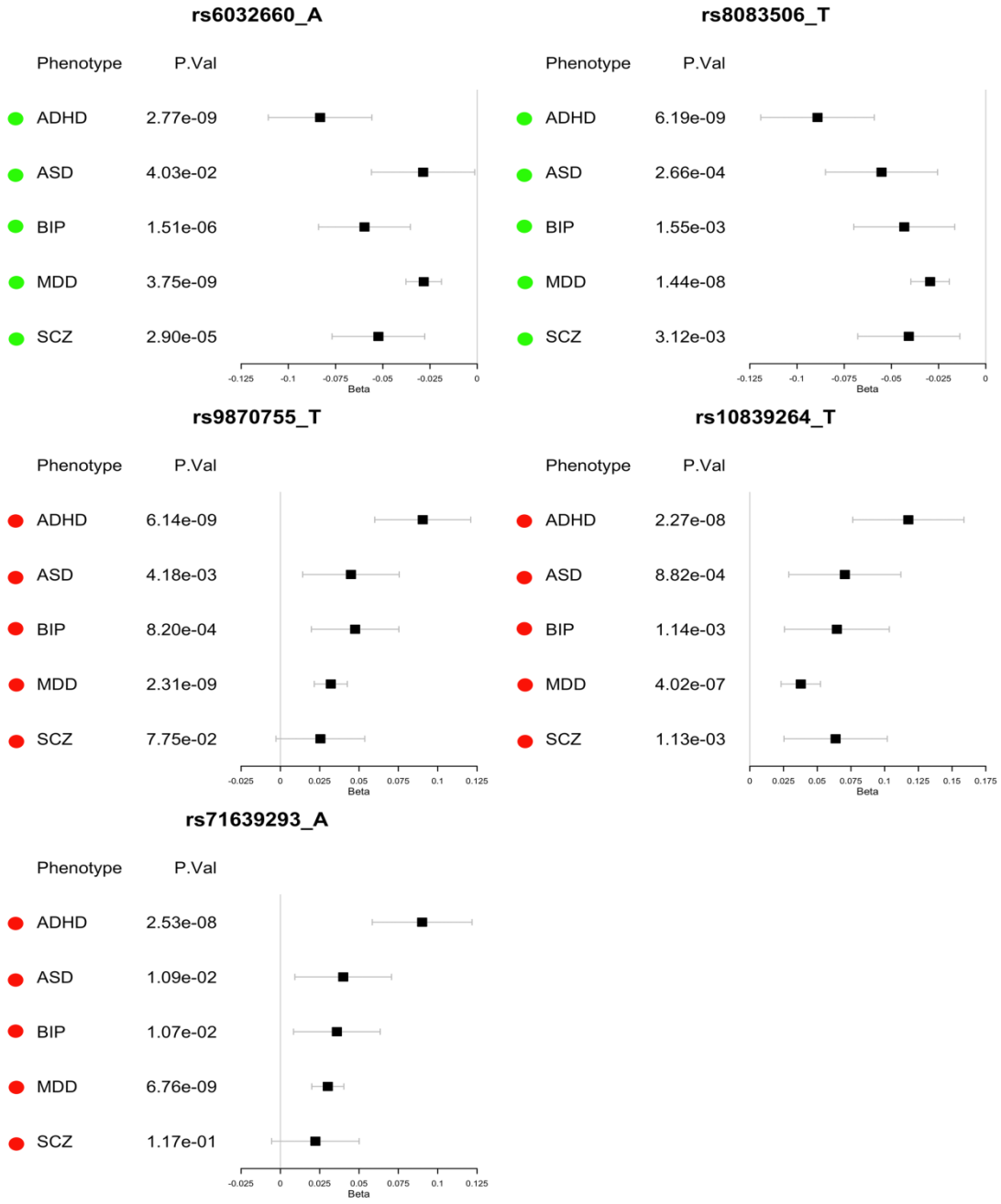
C


rs10920885
rs9834021
rs2894699
rs4636654
Plotted SNPs
Recombination rate (cM/Mb)
Position on chr1 (Mb)
Position on chr3 (Mb)
Position on chr7 (Mb)
Position on chr11 (Mb)

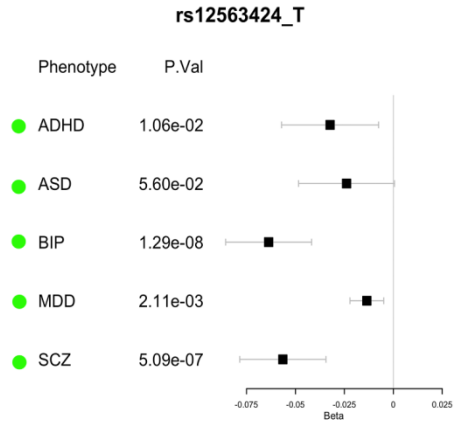

rs2276138
Plotted SNPs
rs2276138
−log10(p−value)
Recombination rate (cM/Mb)
Position on chr11 (Mb)
rs1414622
Plotted SNPs
rs1414622
−log10(p−value)
Recombination rate (cM/Mb)
Position on chr13 (Mb)
rs7146581
Plotted SNPs
rs7146581
−log10(p−value)
Recombination rate (cM/Mb)
Position on chr14 (Mb)
rs4776768
Plotted SNPs
rs4776768
−log10(p−value)
Recombination rate (cM/Mb)
1 gene omitted
Position on chr15 (Mb)
rs8099746
Plotted SNPs
rs8099746
−log10(p−value)
Recombination rate (cM/Mb)
Position on chr18 (Mb)
rs62228096
Plotted SNPs
rs62228096
−log10(p−value)
Recombination rate (cM/Mb)
1 gene omitted
Position on chr22 (Mb)

Supplementary Figure 3. The forest plots of index SNP at each novel locus demonstrating the P value, log odds ratio (beta) and standard error for each SNP in each disease specific association testing. (**A**) ADHD; (**B**) BIP; (**C**) MDD.

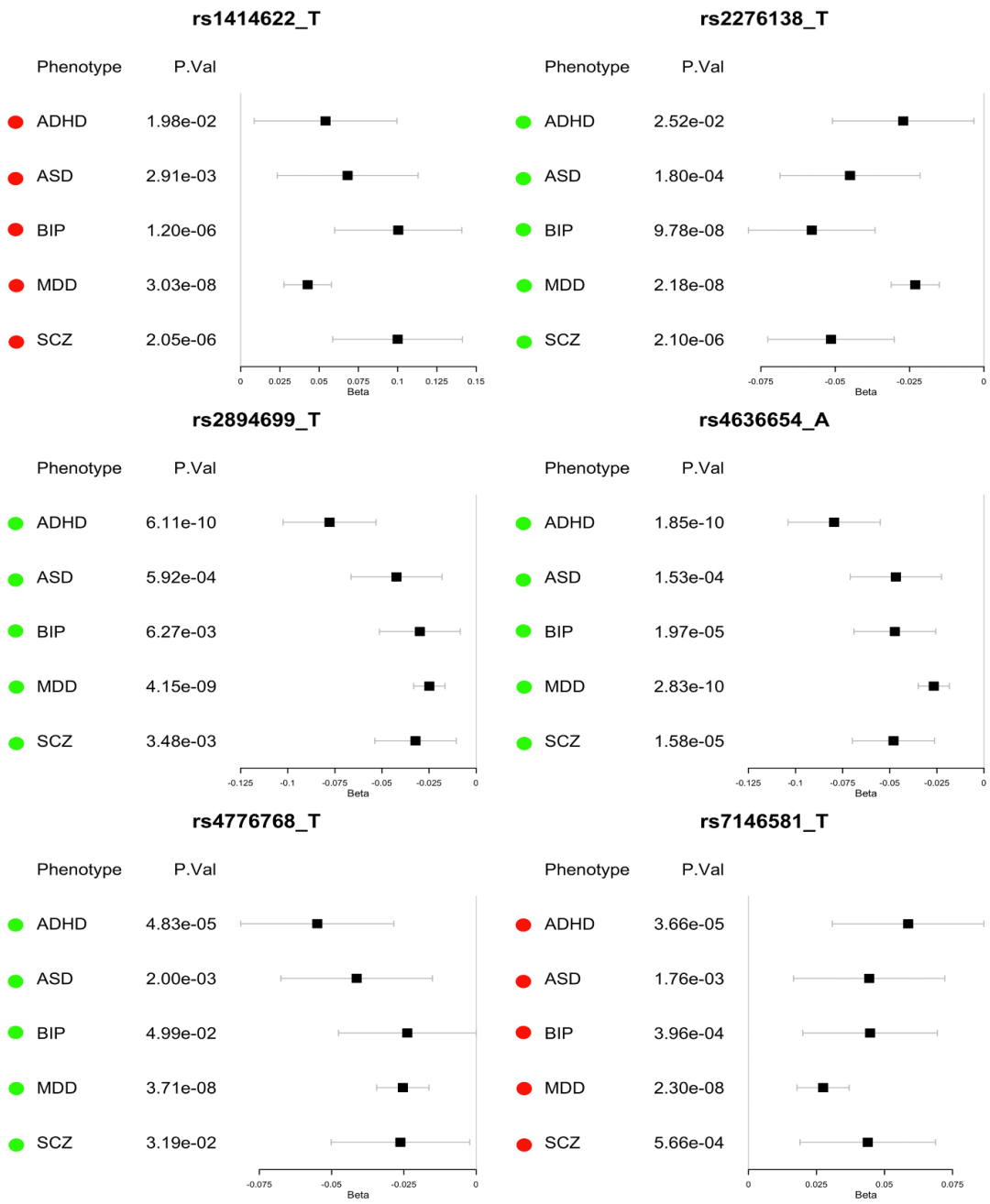
A



B


rs12563424_T
Phenotype
P.Val
ADHD
1.06e-02
ASD
5.60e-02
BIP
1.29e-08
MDD
2.11e-03
SCZ
5.09e-07
-0.075
-0.05
-0.025
0
0.025
Beta

C


rs1414622_T
Phenotype
P.Val
ADHD
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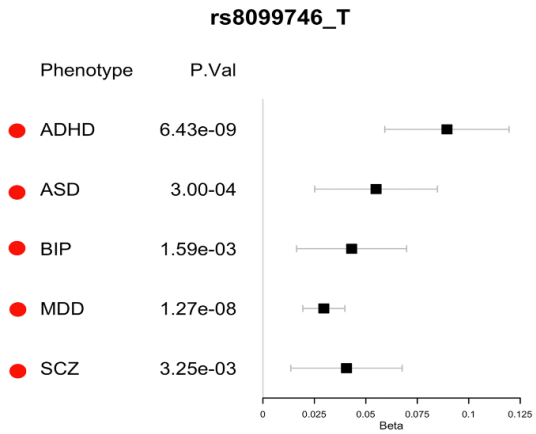
ASD
2.91e-03
BIP
1.20e-06
MDD
3.03e-08
SCZ
2.05e-06
0
0.025
0.05
0.075
0.1
0.125
0.15
Beta
rs2276138_T
Phenotype
P.Val
ADHD
2.52e-02
ASD
1.80e-04
BIP
9.78e-08
MDD
2.18e-08
SCZ
2.10e-06
-0.075
-0.05
-0.025
0
Beta
rs2894699_T
Phenotype
P.Val
ADHD
6.11e-10
ASD
5.92e-04
BIP
6.27e-03
MDD
4.15e-09
SCZ
3.48e-03
-0.125
-0.1
-0.075
-0.05
-0.025
0
Beta
rs4636654_A
Phenotype
P.Val
ADHD
1.85e-10
ASD
1.53e-04
BIP
1.97e-05
MDD
2.83e-10
SCZ
1.58e-05
-0.125
-0.1
-0.075
-0.05
-0.025
0
Beta
rs4776768_T
Phenotype
P.Val
ADHD
4.83e-05
ASD
2.00e-03
BIP
4.99e-02
MDD
3.71e-08
SCZ
3.19e-02
-0.075
-0.05
-0.025
0
Beta
rs7146581_T
Phenotype
P.Val
ADHD
3.66e-05
ASD
1.76e-03
BIP
3.96e-04
MDD
2.30e-08
SCZ
5.66e-04
0
0.025
0.05
0.075
Beta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Phenotype
P.Val
ADHD
6.43e-09
ASD
3.00-04
BIP
1.59e-03
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SCZ
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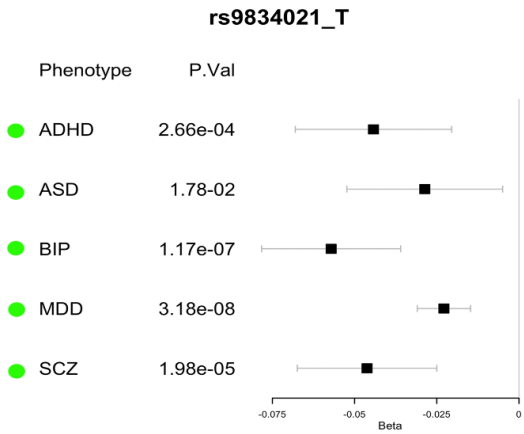
0
0.025
0.05
0.075
0.1
0.125
Beta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Phenotype
P.Val
ADHD
2.66e-04
ASD
1.78-02
BIP
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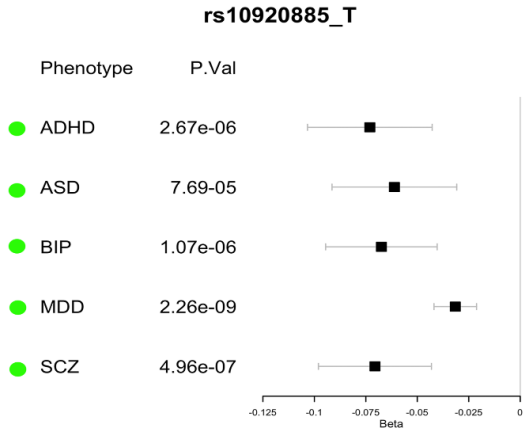
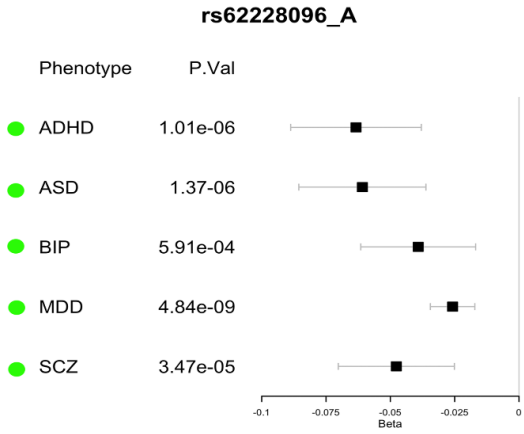
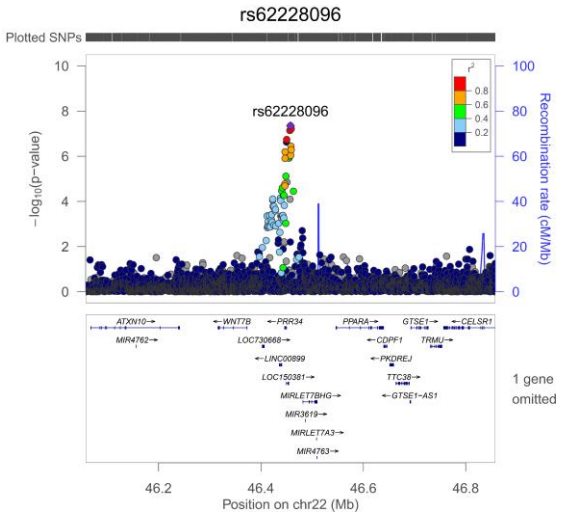
MDD
3.18e-08
SCZ
1.98e-05
-0.075
-0.05
-0.025
0
Beta


rs10920885_T
Phenotype
P.Val
ADHD
2.67e-06
ASD
7.69-05
BIP
1.07e-06
MDD
2.26e-09
SCZ
4.96e-07
-0.125
-0.1
-0.075
-0.05
-0.025
0
Beta


rs62228096_A
Phenotype
P.Val
ADHD
1.01e-06
ASD
1.37-06
BIP
5.91e-04
MDD
4.84e-09
SCZ
3.47e-05
-0.1
-0.075
-0.05
-0.025
0
Beta

Supplementary Figure 4. Regional association plot of the novel significant locus on chromosome 22 in the meta-analysis of five neuropsychiatric disorders.

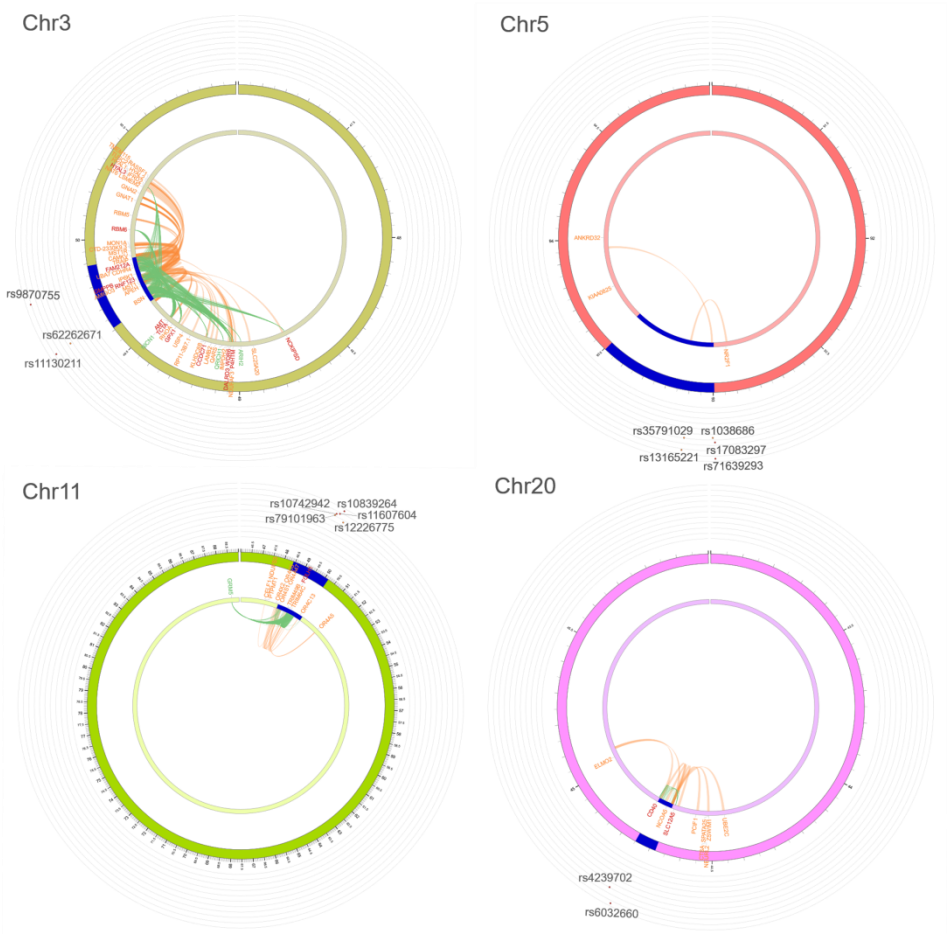
The regional association plot was generated using the LocusZoom software. The genomic coordinates are plotted on the axis, and the –log10 P-values of SNPs are shown on the Y-axis. The most significant SNP is indicated in purple and the remaining SNPs are shown in different colors based on linkage disequilibrium with top associated SNP (the color coding legend is indicated in the upper corner of each plot). The blue vertical line indicates the recombination rate based on the HapMap project.



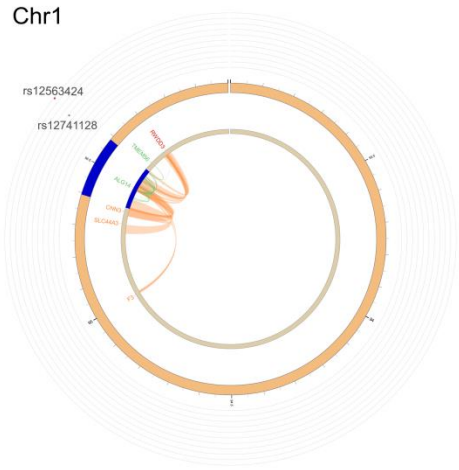
Supplementary Figure 5. Circos plots showing chromatin interactions between causal variants and distant genes.

Each causal variant is indicated on the most outer layer. Y-axis are ranged between 0 to the maximum -log10(P-value) of the SNPs. The further the SNP is from the center of the circle, the smaller the MTAG P-value is. The dark blue regions on the chromosome ring of the second layer and that of the third layer display the genomic locus where each causal variant is located at. The mapped genes by either chromatin interaction and/or eQTLs are shown on the chromosome ring of the third layer and the links display the chromatin interactions. Genes mapped only by chromatin interactions or only by eQTLs are colored orange or green, respectively. When the gene is mapped by both, it is colored red. (**A**) ADHD; (**B**) BIP; (**C**) MDD.

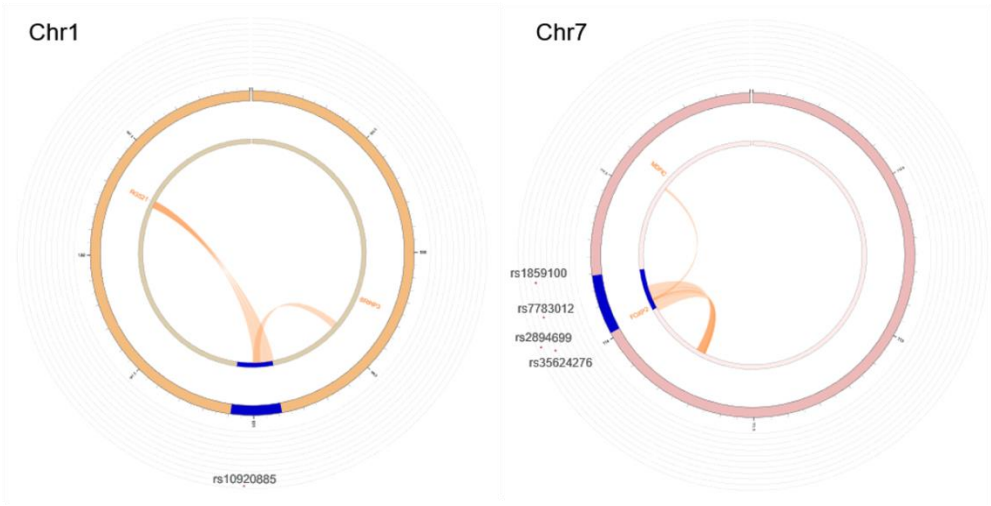
A

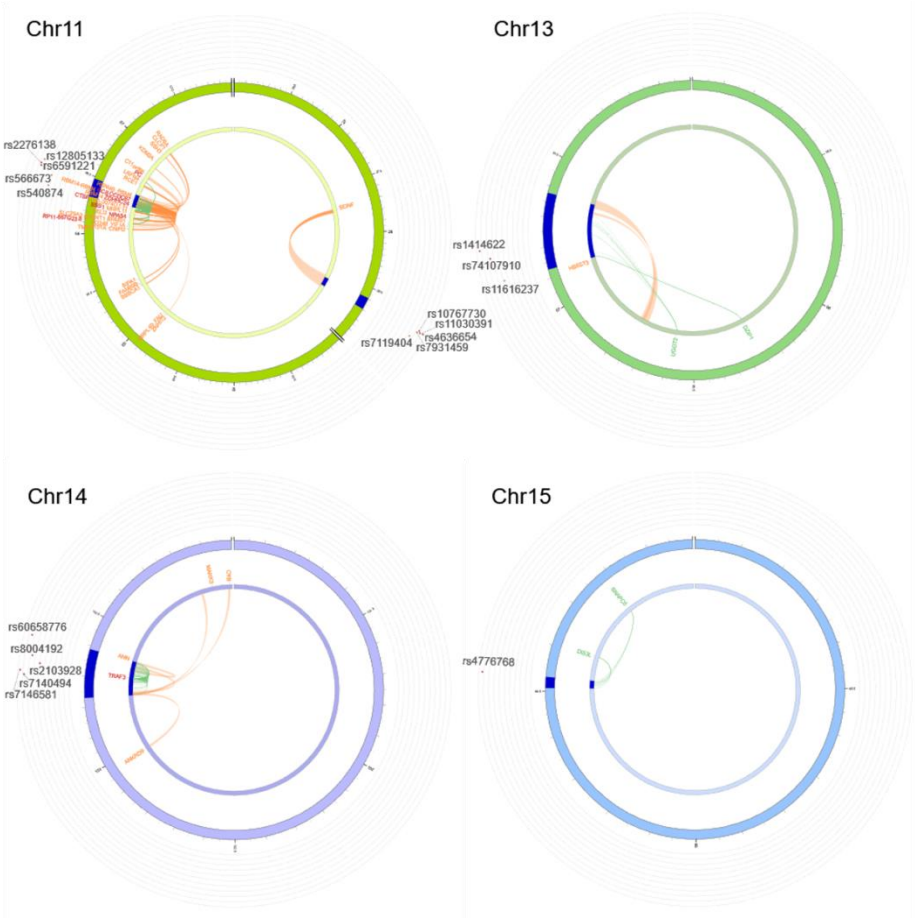


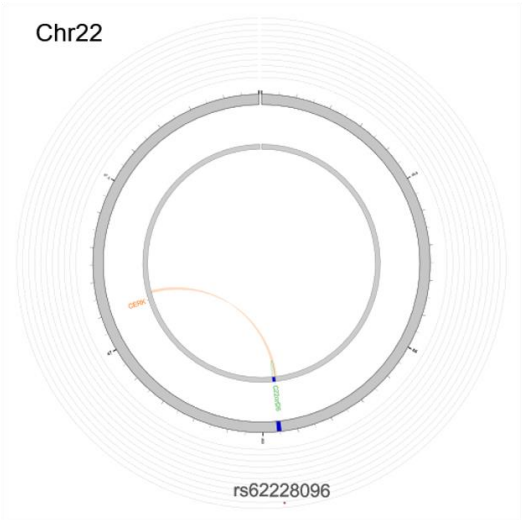
B


Chr1
rs12563424
rs12741128

C

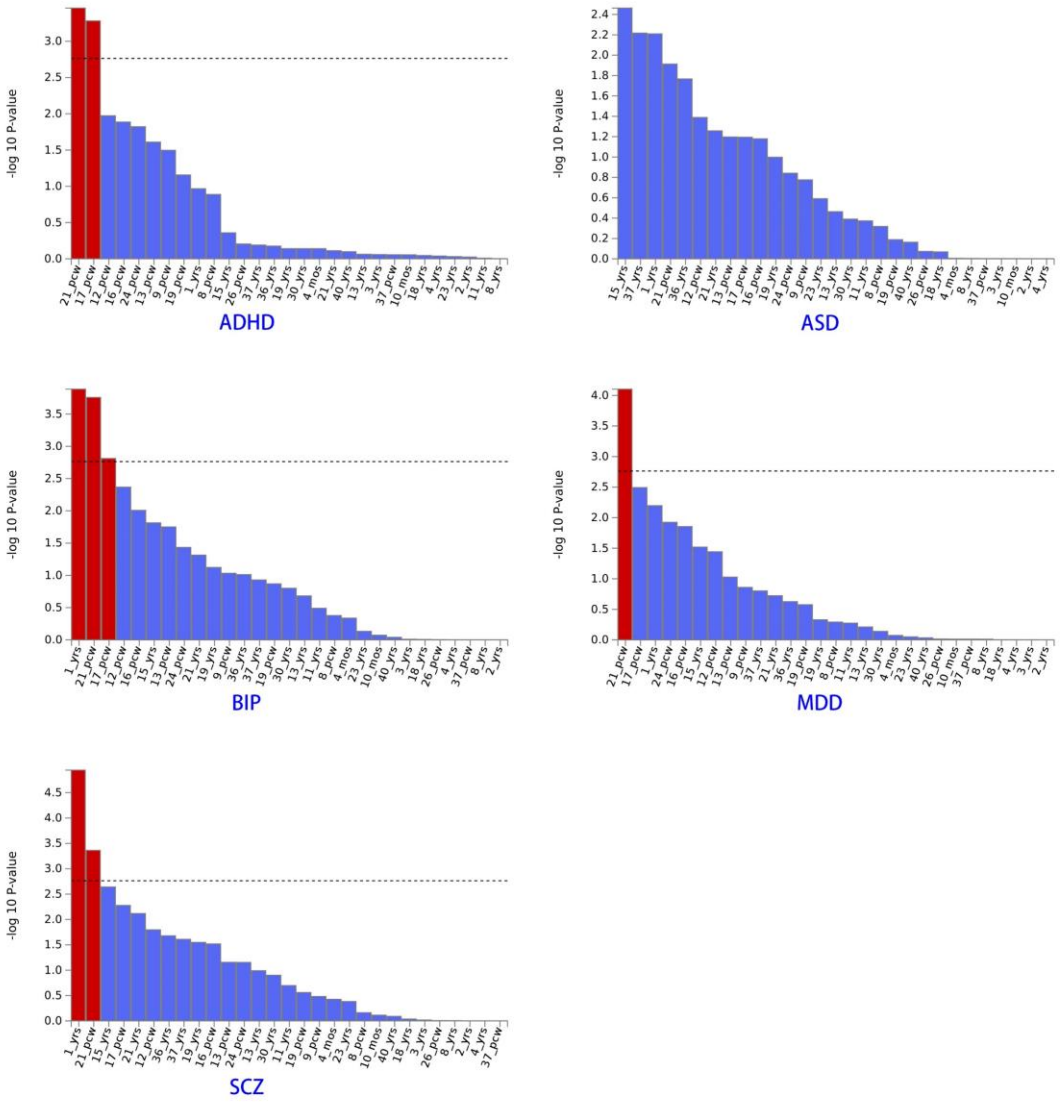

Chr1
rs10920885
Chr7
rs1859100
rs7783012
rs2894699
rs35624276


Chr11
rs2276138
rs12805133
rs6591221
rs566673
rs540874
rs7119404
rs10767730
rs11030391
rs4636654
rs7931459
Chr13
rs1414622
rs74107910
rs11616237
Chr14
rs60658776
rs8004192
rs2103928
rs7140494
rs7146581
Chr15
rs4776768

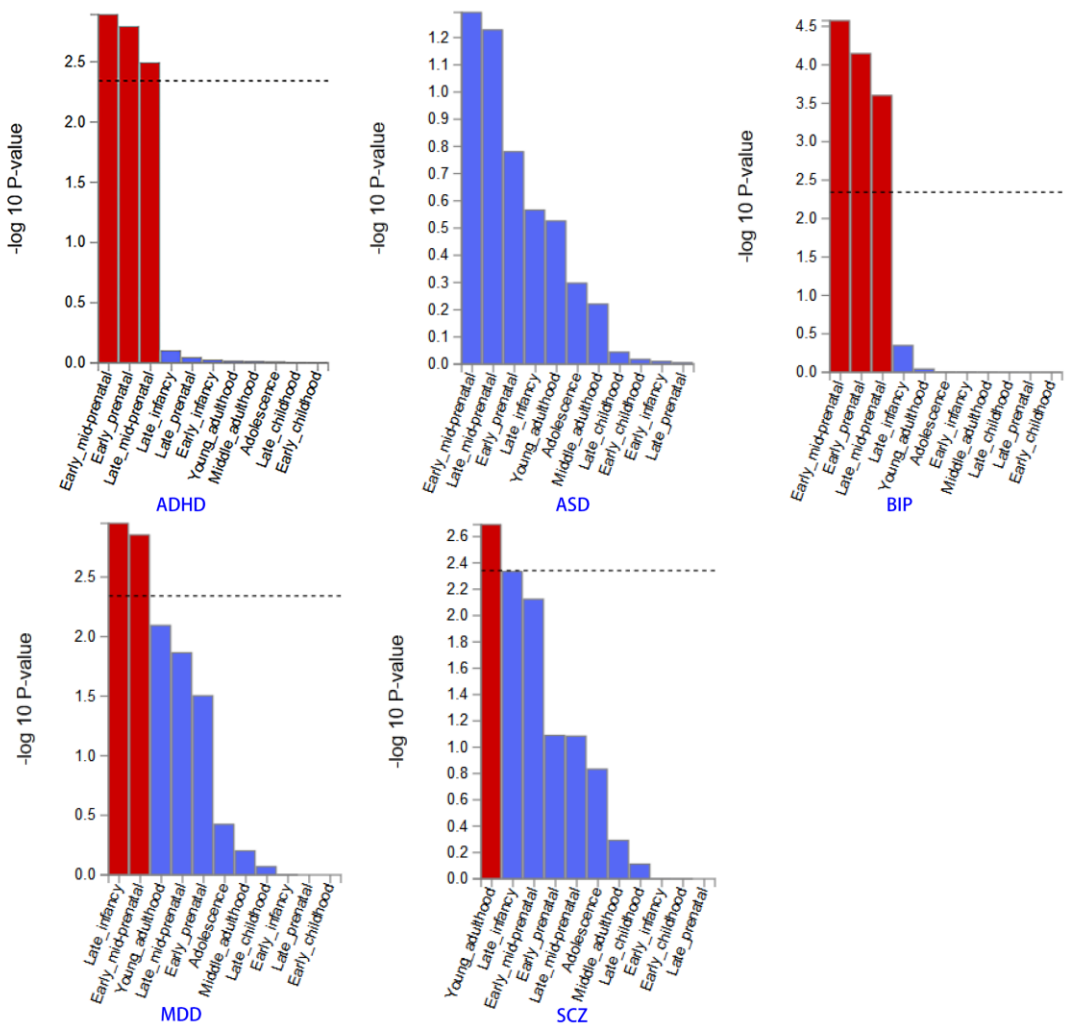

Chr22
rs62228096

Supplementary Figure 6. MAGMA gene expression profile analysis of genes at novel loci identified in MTAG analyses of neuropsychiatric disorders. MAGMA is a generalized gene-set analysis approach, here showing the differentially expressed gene sets **A**) at 29 different ages of human brain samples from BrainSpan.; **B**) at 11 general developmental stages of brain samples from BrainSpan. The ages or developmental stages with significant enrichment of differentially expressed gene sets were colored red. yrs = years; pcw = post conception weeks.

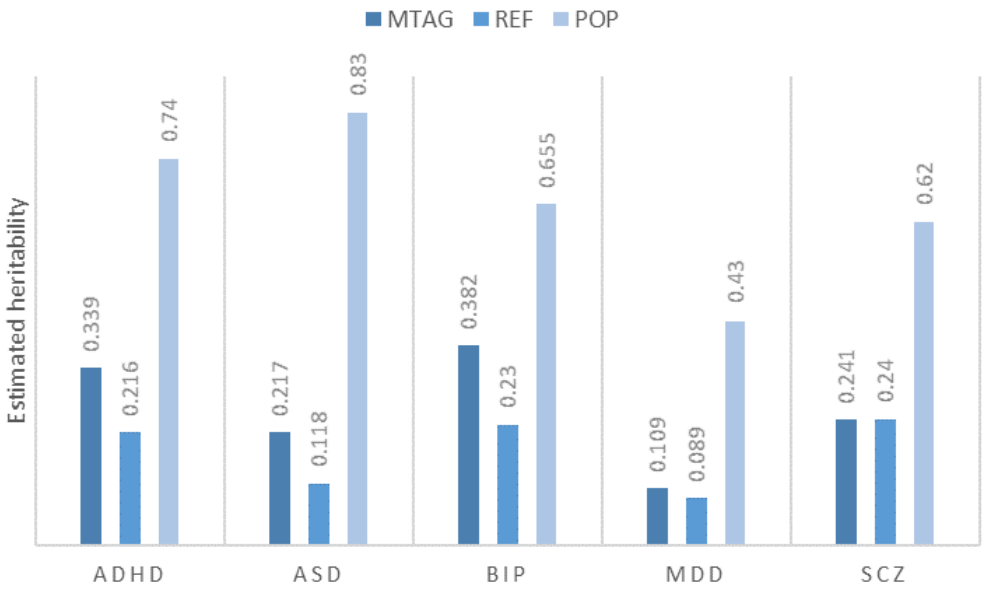
A



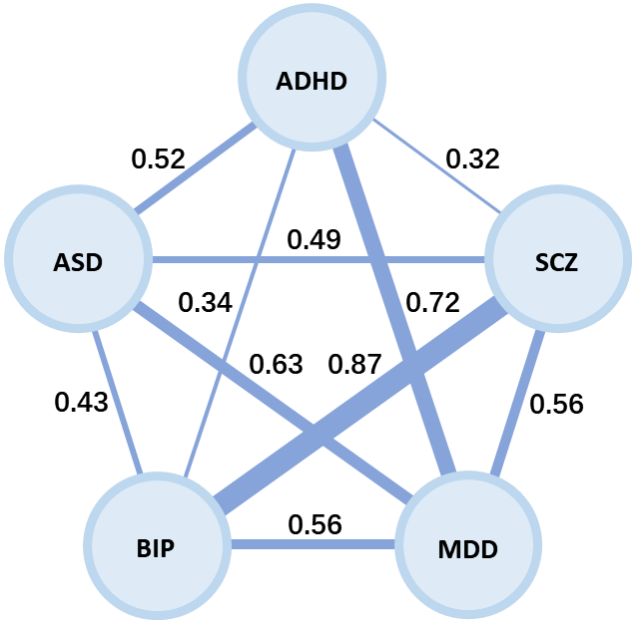
B


-log 10 P-value
Early_mid-prenatal
Early_prenatal
Late_mid-prenatal
Late_infancy
Late_prenatal
Early_infancy
Young_adulthood
Middle_adulthood
Adolescence
Late_childhood
Early_childhood
ADHD
ASD
BIP
MDD
SCZ

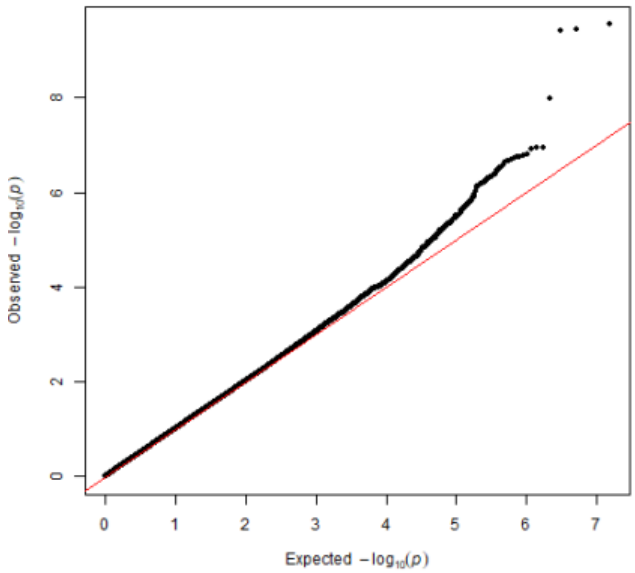
Supplementary Figure 7. Estimated heritability of five neuropsychiatric diseases. The liability scale SNP heritability based on MTAG results (MTAG) were compared with estimates from the original GWAS of each cohort (REF) and those from population studies reported in literature (POP). The population prevalence of each disease used in the heritability estimations is ADHD=0.05, ASD= 0.012, BIP=0.02, MDD= 0.302, SCZ= 0.01, which are the same as that in their original GWAS. The population heritability referred to the median value of heritability reported in prior studies in literature (**Supplementary Table 12**).



Supplementary Figure 8. Genetic correlation between the five neuropsychiatric disorders. The circles representing the five neuropsychiatric disorders, and the width of the line between the circles represents the strength of the pairwise genetic relationships in a positive correlation. All genetic correlations displayed in the schematic diagram were significant (P <0.05).



Supplementary Figure 9. The QQ-plot of the pediatric replication cohort.



λ=1.013

Supplementary Figure 10. Regression plot showing test for correlation of effect size estimates at genome-wide significant loci from ADHD MTAG analysis of 19099 cases and 34194 controls after adjustment for winner's curse and those from the pediatric replication cohort of 2726 ADHD cases and 16321 controls. The effect size estimates from the ADHD MTAG analysis are shown on the X-axis and those from the pediatric replication cohort are indicated on the Y-axis. The blue vertical lines indicate the standard error of the effect size estimates. The color of each dot represents its -log10(p) from the ADHD MTAG analysis. The dashed purple line indicates the observed slope of the linear regression between the effect size estimates from the two studies.