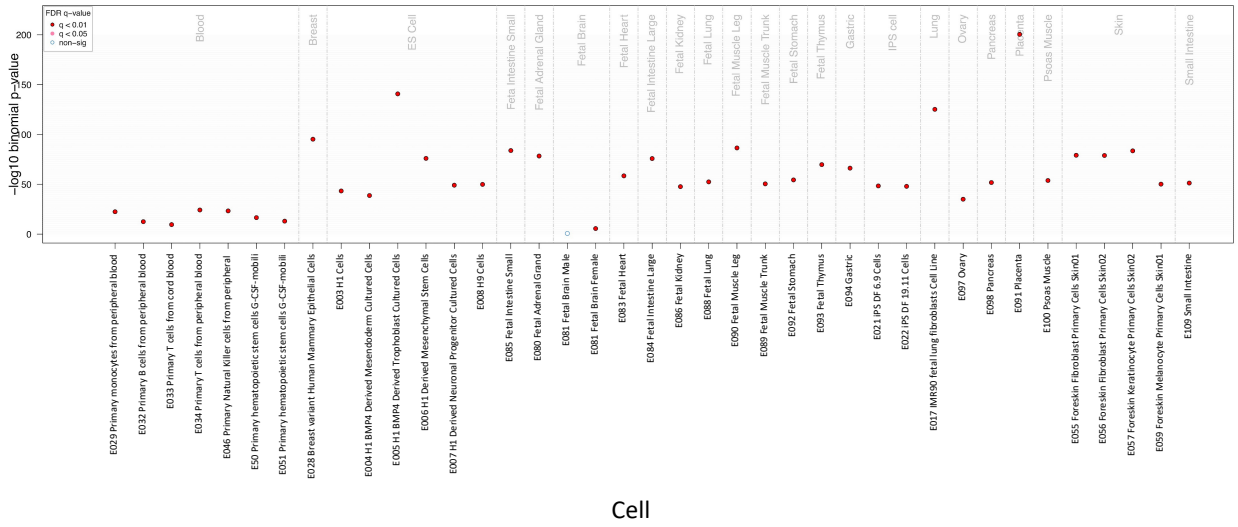
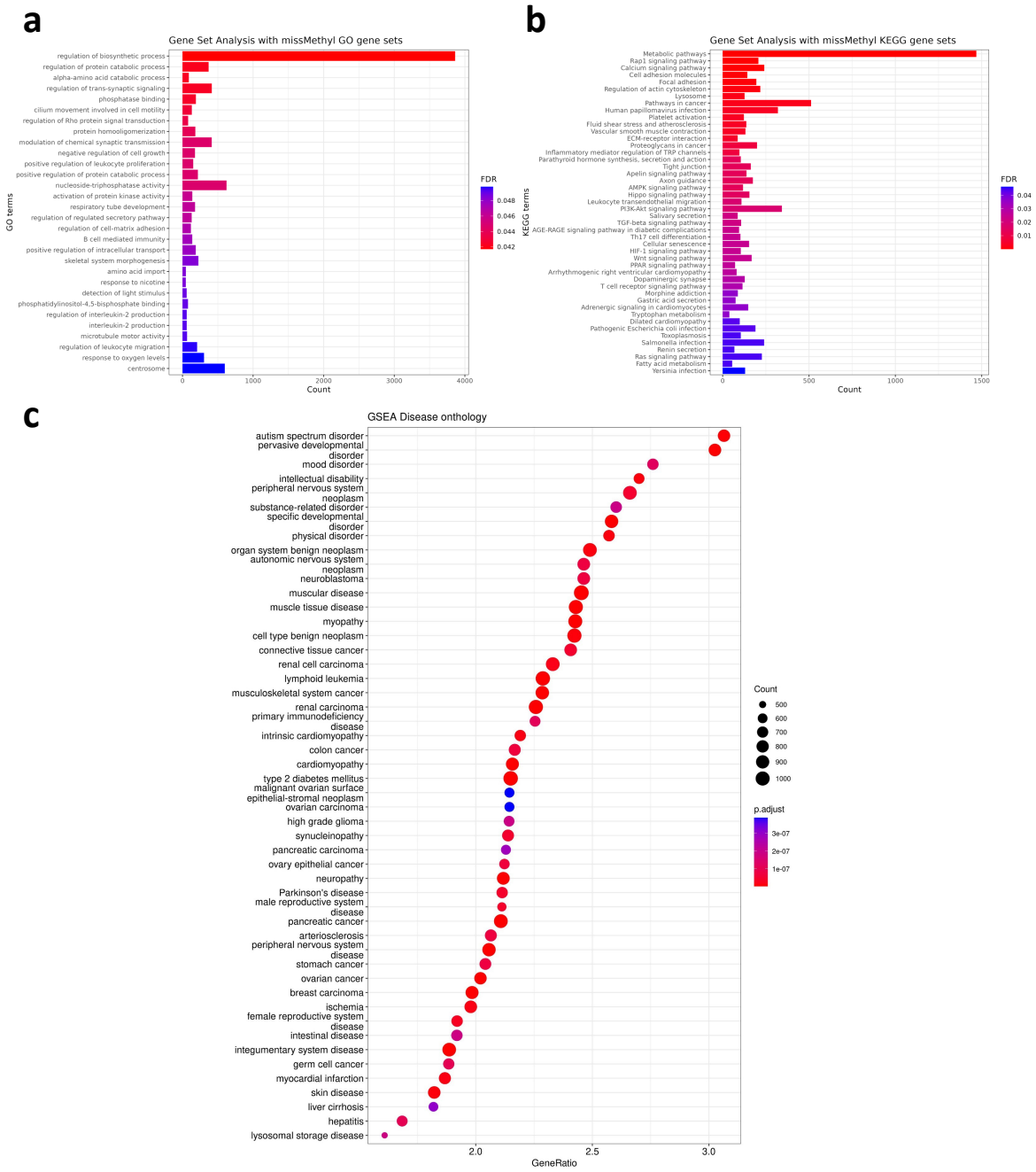
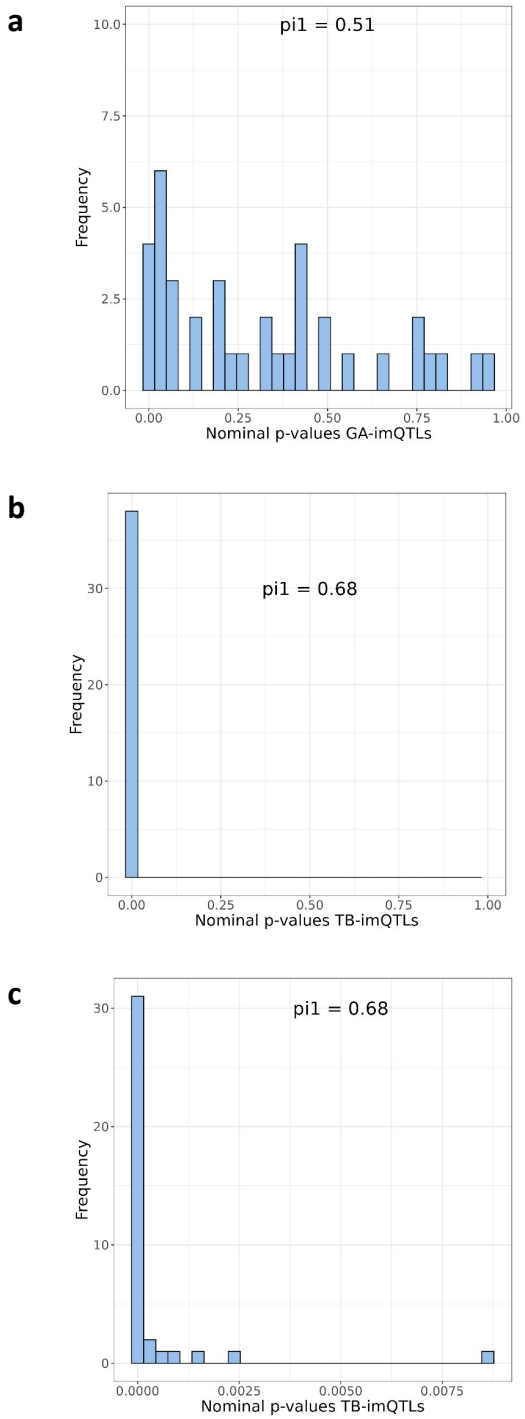


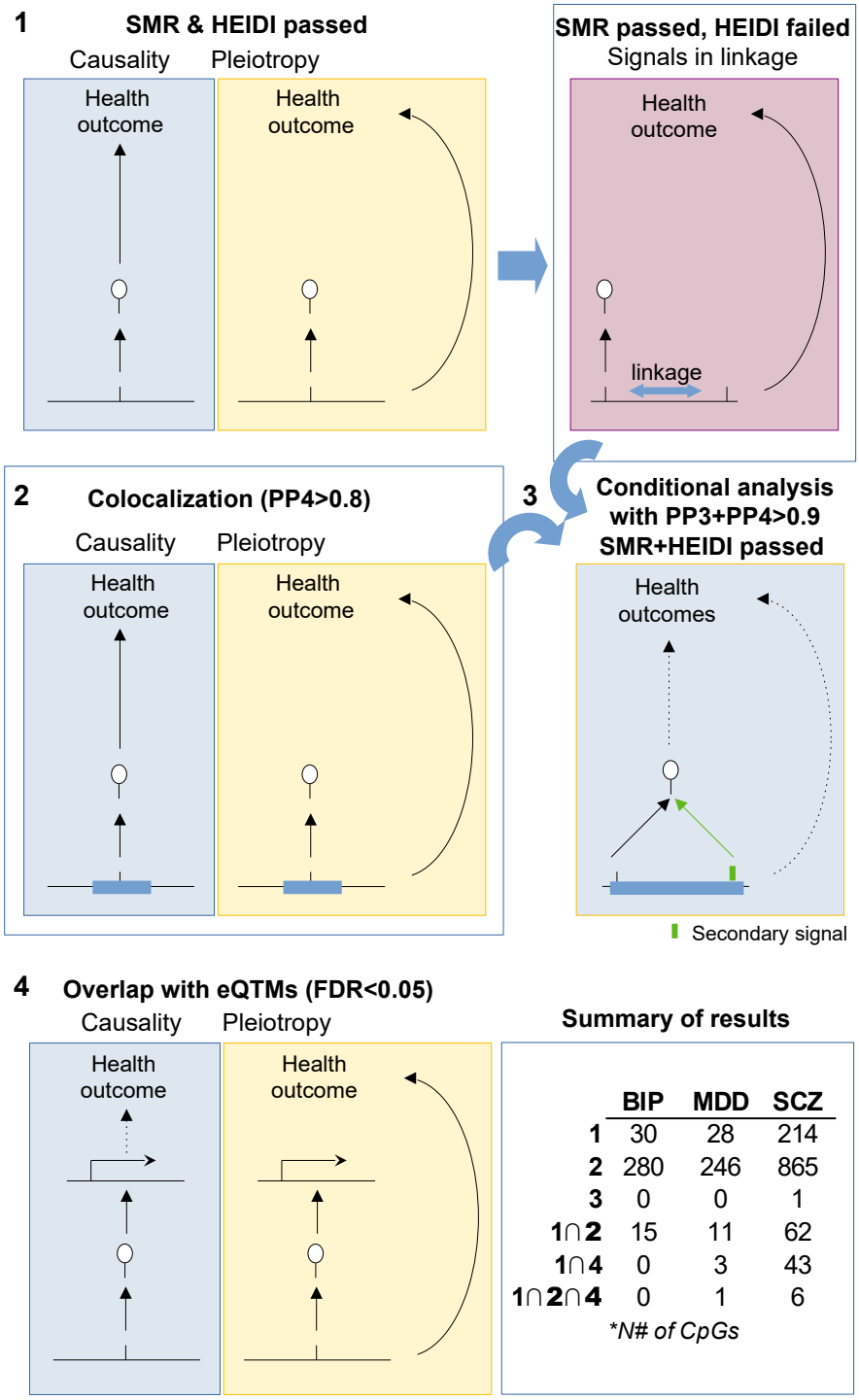
Supplementary Figure 1. Enrichment on fetal placenta-specific H3K4me1 broadPeaks. We performed an enrichment analysis of H3K4me1 broadPeaks on the top 10,000 mSites of the permuted database with eFORGE. The Y-axis represents the -log10 binomial p-value of the enrichment analysis, while different tissues are shown in the X-axis. False Discovery Rate (FDR) corrected q-values below 0.01 and 0.05 are represented by red and pink dots, respectively, while blue dots show q-values > 0.05.



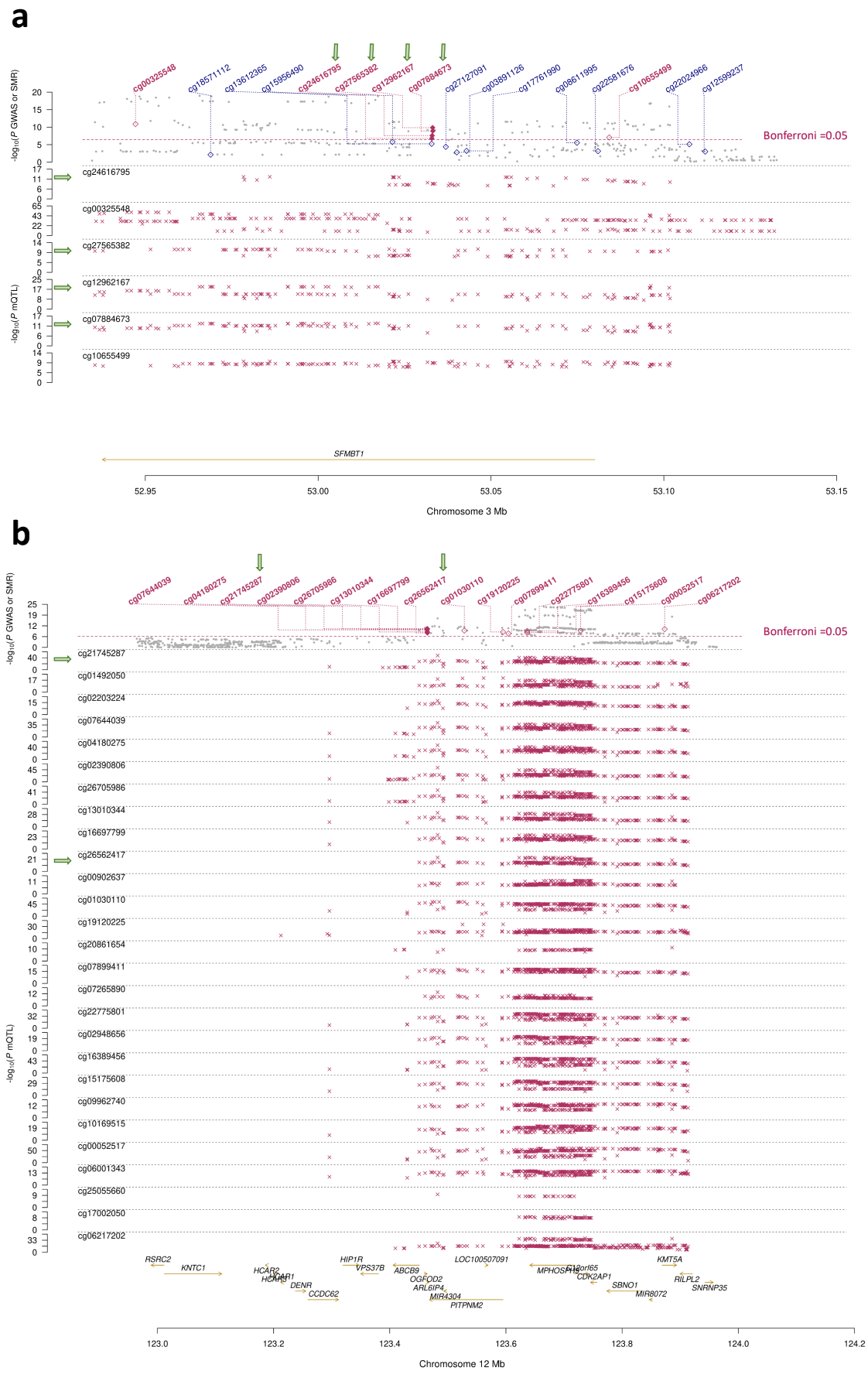
Supplementary Figure 2. Over-representation and gene set enrichment analysis of the mSites from the permuted database. An overrepresentation analysis was performed using MissMethyl R package and Gene Ontology (GO) and Kyoto Encyclopaedia of Genes and Genomes (KEGG) gene sets. Results are plotted in the **a** and **b** barplots, respectively. Additionally, a gene set enrichment analysis was performed with the DOSE R package, using the Disease Ontology (DO) database. DOSE results are shown in **c**. In all three plots, the Y-axis represents the top gene sets enriched, and the adjusted p-value is colour coded. In plots **a** and **b**, the X-axes represent the counts, while in **c**, the counts are reported by the dot size and the X-axis represents the gene ratio.



Supplementary Figure 3. Histograms of Storey's pi1 sharing. a Distribution of the nominal p-values of the GA-imQTLs that were used to compute the Storey's pi1 value of sharing with the significant STB-imQTLs, calculated with the qvalue R function. **b** Distribution of the nominal p-values of the TB-imQTLs that were used to compute the Storey's pi1 value of sharing with the significant STB-imQTLs (X axis 0-1), calculated with the qvalue_trunc function, as suggested by the developers when p values do not follow a 0 to 1 uniform distribution (https://rdrr.io/github/StoreyLab/qvalue/src/R/qvalue_trunc.R). **c** Same distribution as shown in **b**, with the X axis from 0 to the maximum p value.



Supplementary Figure 4. Workflow and results of the main analyses performed. In a first step, we performed the SMR and HEIDI tests, followed by colocalization. Those hits that passed SMR but failed to pass HEIDI and were suggestive of association with both traits according to colocalization were considered for a conditional analysis with a second round of SMR and HEIDI tests, with the aim of discovering secondary associated signals. Finally, those CpGs passing the SMR and HEIDI tests, were interrogated in the eQTMs database of the RICHS cohort. The CpG overlap between the four approaches is summarized in the right-bottom table.


a
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cg03891126
cg17761990
cg08611995
cg22561676
cg10655499
cg22024966
cg12599237
Bonferroni =0.05
-log10(P GWAS or SMR)
-log10(P mQTL)
cg24616795
cg00325548
cg27565382
cg12962167
cg07884673
cg10655499
SFMBT1
52.95
53.00
53.05
53.10
53.15
Chromosome 3 Mb
b
cg07644039
cg04180275
cg21745287
cg02390806
cg26705986
cg13010344
cg16697799
cg26562417
cg01030110
cg19120225
cg07899411
cg22775801
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cg06217202
Bonferroni =0.05
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-log10(P mQTL)
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HCAR3
HCAR1
DENR
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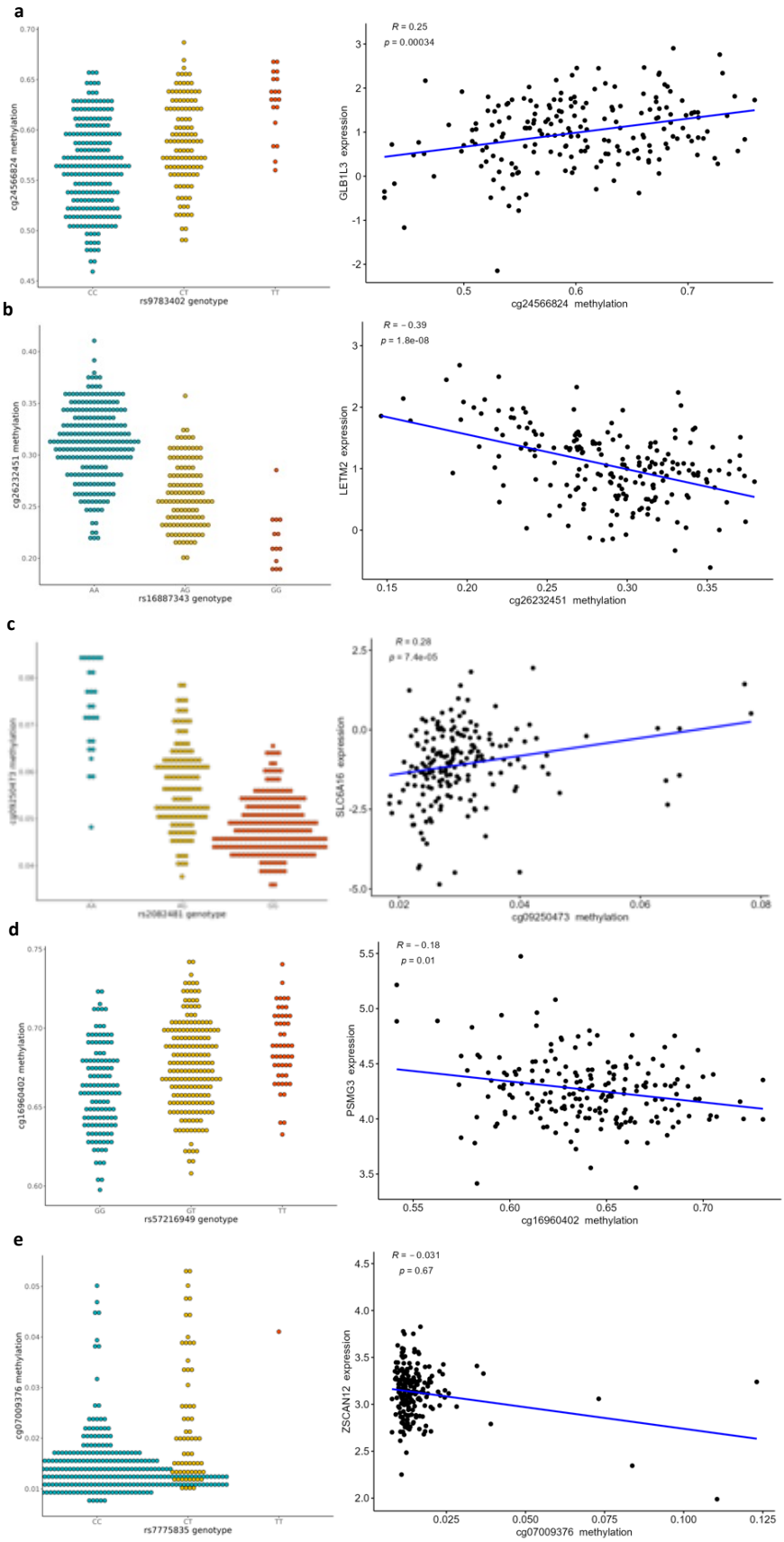
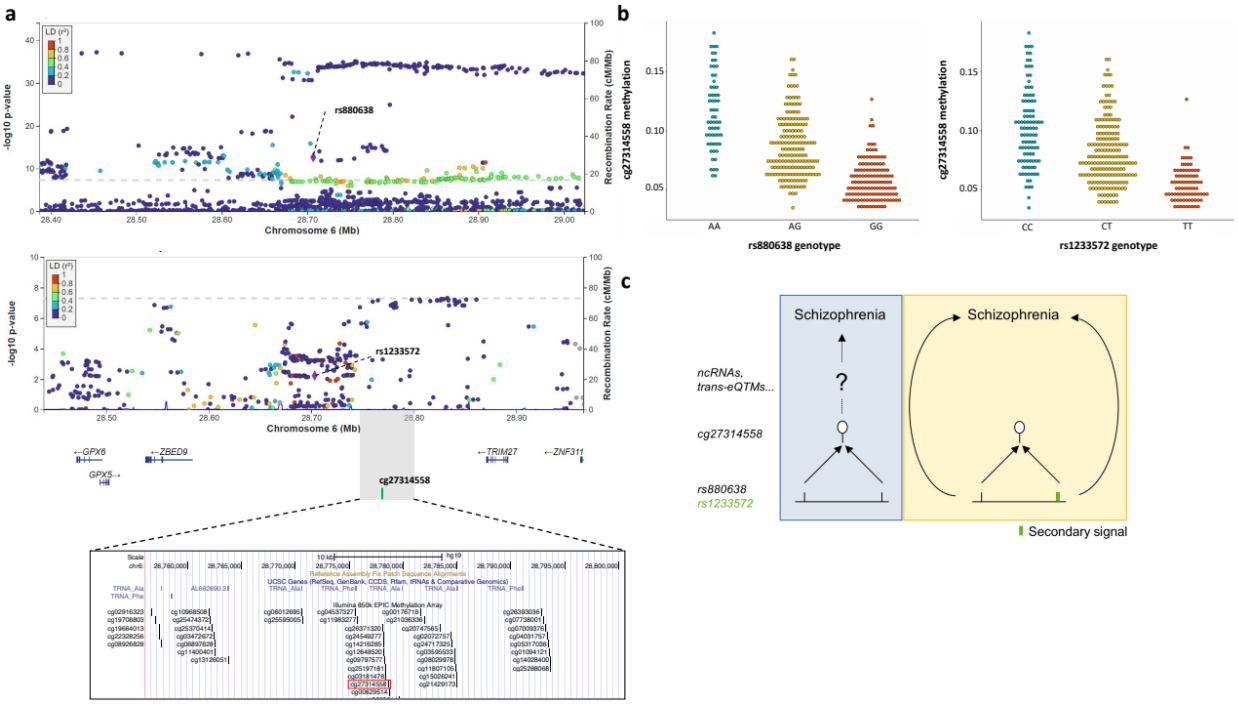
C12orf65
CDK2AP1
KMT5A
SBNO1
MIR8072
RILPL2
SNRNP35
123.0
123.2
123.4
123.6
123.8
124.0
124.2
Chromosome 12 Mb

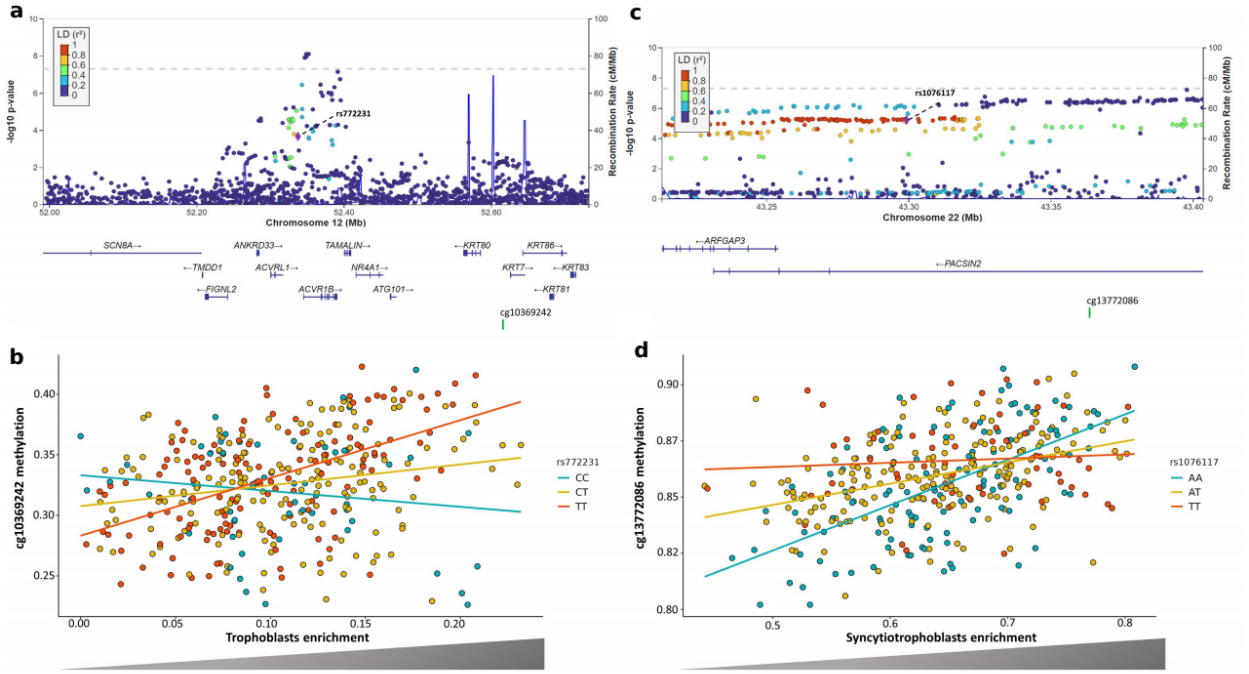
Supplementary Figure 5. SMR plots. The Y-axes show the logarithmic P-values of the placental *cis*-mQTLs (maroon crosses in the middle panels), SCZ-GWAS (grey dots in the upper panels) and SMR approaches (diamonds in the upper panels). Particularly, diamonds represent CpG sites that result from SMR. If blue, diamonds are CpGs in the region that did not reach statistical significance in SMR (Bonferroni $P_{SMR} < 0.05$), while if maroon, diamonds represent the statistically significant hits. Finally, filled maroon diamonds indicate that those CpGs passed the HEIDI test. Golden arrows in the lower panels represent genes while light green arrows mark the significant CpGs that passed HEIDI and correlated with the gene expression levels in placenta of **a** *SFMBT1* in chromosome 3 and **b** *VPS37B* in chromosome 12.


a
cg24566824 methylation
rs9783402 genotype
CC
CT
TT
R = 0.25
p = 0.00034
GLB1L3 expression
cg24566824 methylation
b
cg26232451 methylation
rs16887343 genotype
AA
AG
GG
R = −0.39
p = 1.8e-08
LETM2 expression
cg26232451 methylation
c
rs2082481 genotype
R = 0.28
p = 7.4e-05
SLC6A16 expression
cg09250473 methylation
d
cg16960402 methylation
rs57216949 genotype
GG
GT
TT
R = −0.18
p = 0.01
PSMG3 expression
cg16960402 methylation
e
cg07009376 methylation
rs7775835 genotype
CC
CT
TT
R = −0.031
p = 0.67
ZSCAN12 expression
cg07009376 methylation

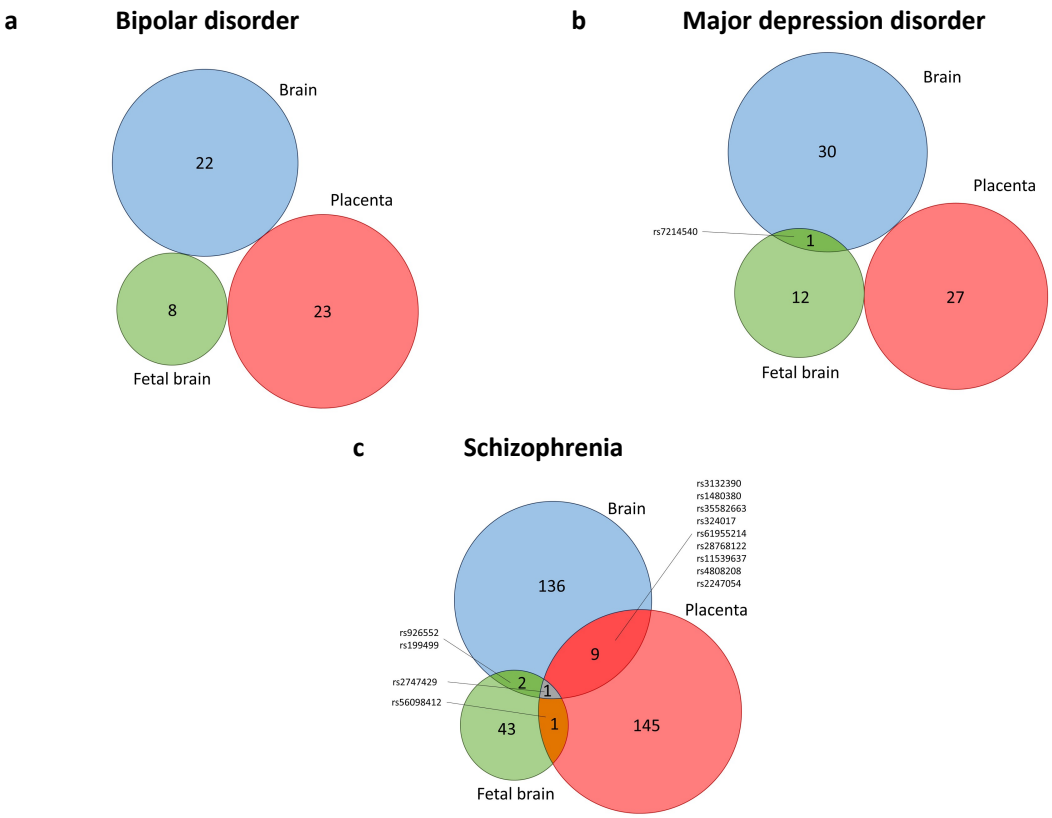
Supplementary Figure 6. Some of the most relevant placental mQTLs and eQTMs presenting a significant colocalization and pleiotropic association with SCZ. In all mQTL dotplots, the X-axes represent the beta methylation values of each mSite, ranging from 0 to 1. And the Y-axes display the genotype of each mVariant. In all eQTM dotplots, the X-axes represent the beta methylation values of each eQTM-CpG, ranging from 0 to 1. And the Y-axes display the placental gene expression. In **a** placental DNAm of cg24566824 is associated with rs9783402 genotype and *GLB1L3* placental expression. In **b** placental DNAm of cg26232451 is associated with rs16887343 genotype and *LETM2* placental expression. In **c** placental DNAm of cg09250473 is associated with rs2082481 genotype and *SLC6A16* placental expression. In **d** placental DNAm of cg16960402 is associated with rs57216949 genotype and *PSMG3* placental expression. In **e** placental DNAm of cg07009376 is associated with rs7775835 genotype and *ZSCAN12* placental expression.



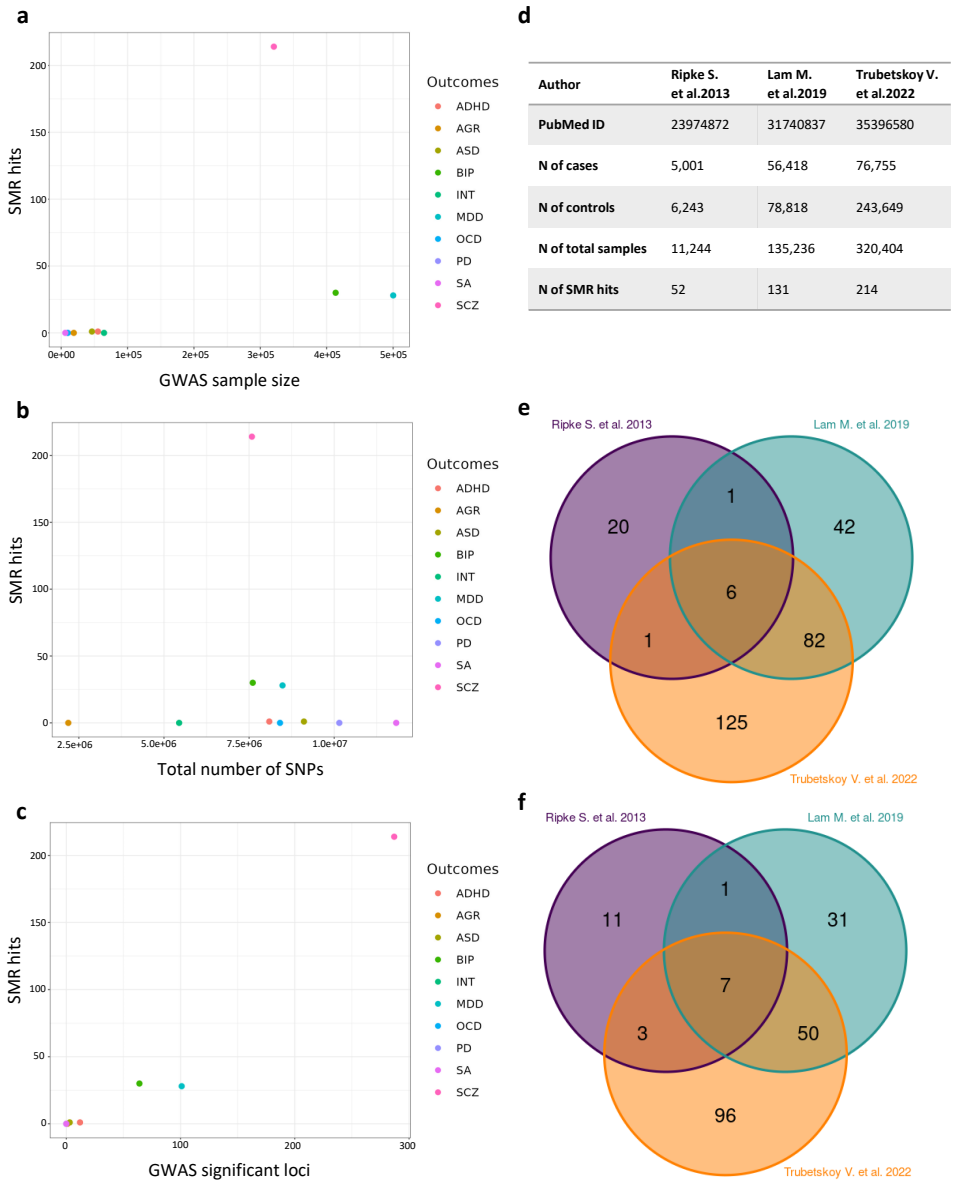
Supplementary Figure 7. One CpGs is pleiotropically associated with SCZ, and marked by two independent signals. The two mVariants rs880638 and rs1233572 highlighted as purple diamonds, are shown in the original (top) and the conditional (bottom) SCZ GWAS in the **a** locusZoom plot. The X-axis displays the involved genomic region in chromosome 6 in Mb, showing the distribution of the coding genes in the locus, as well as the location of the mSite cg27314558. The Y-axis shows the -log10 p-value from the original and conditional GWAS, and the SNPs are colour coded as a function of the LD with the highlighted SNP considering the 1000G reference panel. Additionally, the UCSC region with UCSC genes and Illumina EPIC Methylation Array probes tracks from region chr6:28,760,00-28,800,000 can be found in the same panel. cg27314558 has been highlighted in red. The two significant mQTLs, rs880638-cg27314558 and rs1233572-cg27314558, are plotted in the **b** dotplots, where Y-axes represent the cg27314558 DNAm beta values, ranging from 0 to 1. The X-axis displays the genotype of the corresponding SNPs. The hypothesis of the pleiotropical association between the SNPs, the DNAm values of the CpGs in placenta, and SCZ are schematically represented in **c**. The vertical pleiotropy (or causal association) hypothesis is represented with a blue background, and the horizontal pleiotropy hypothesis is highlighted with a yellow background.



Supplementary Figure 8. **Significant SMR hits with the TB- and STB-imQTLs in MDD and BIP.** The significant MDD-SMR hit with the TB-imQTL, rs772231-cg10369242, is plotted in **a** and **b** locusZoom and dotplot, respectively. Significant BIP-SMR hit with the STB-imQTL, rs1076117-cg13772086 is plotted in **c** and **d** locusZooms and dotplots, respectively. In both locusZooms, the X-axes display the genomic region involved in Mb, and the Y-axes represent the -log10 p-values from the original GWAS used. Each imVariant is highlighted as a purple diamond, and the surrounding SNPs are colour coded as a function of the LD with the highlighted SNP. In both dotplots, the X-axes represent the beta methylation values of each imSite, ranging from 0 to 1. And the Y-axes display the genotype of each imVariant.



Supplementary Figure 9. Overlap between the SMR results in brain, placenta and fetal brain, in BIP, MDD and SCZ. The overlap between the mVariants pleiotropically associated between the three tissues and BIP, MDD and SCZ are represented in the **a**, **b** and **c** Venn diagrams, respectively.



Author	Ripke S. et al.2013	Lam M. et al.2019	Trubetskoy V. et al.2022
PubMed ID	23974872	31740837	35396580
N of cases	5,001	56,418	76,755
N of controls	6,243	78,818	243,649
N of total samples	11,244	135,236	320,404
N of SMR hits	52	131	214

Supplementary Figure 10. Correlation between the statistical power of GWAS and SMR results. We calculated the correlation between the number of SMR hits and **a** the GWAS sample size, **b** the total number of SNPs per GWAS, and **c** the GWAS significant loci in all the neuropsychiatric disorders studied. We also run SMR with two previous SCZ GWAS (apart from Trubetskoy *et al.* 2022). The characteristics of these studies are summarized in table **d**, and the overlap among studies in terms of **e** mQTLs and **f** mVariants are represented as Venn Diagrams.