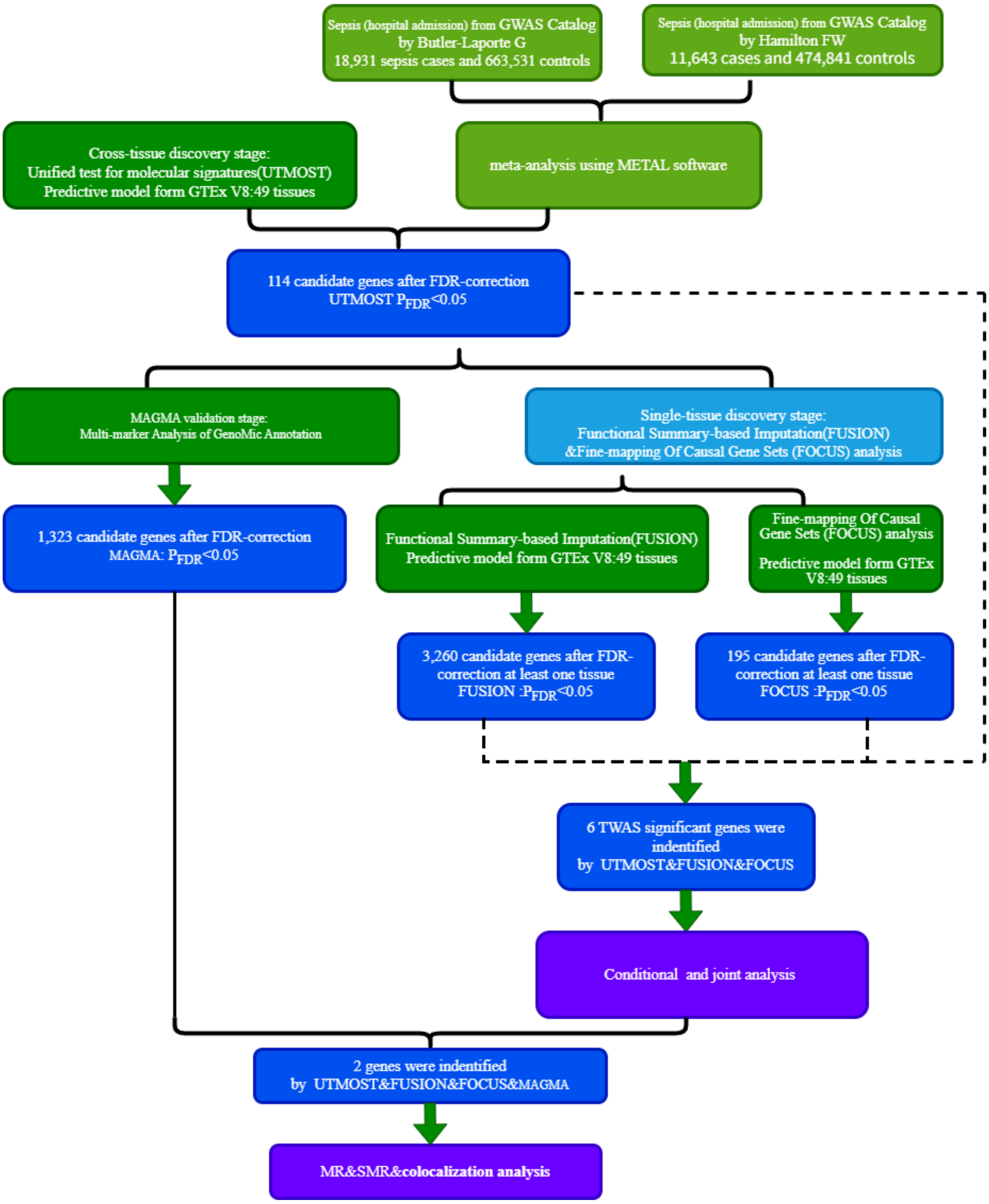
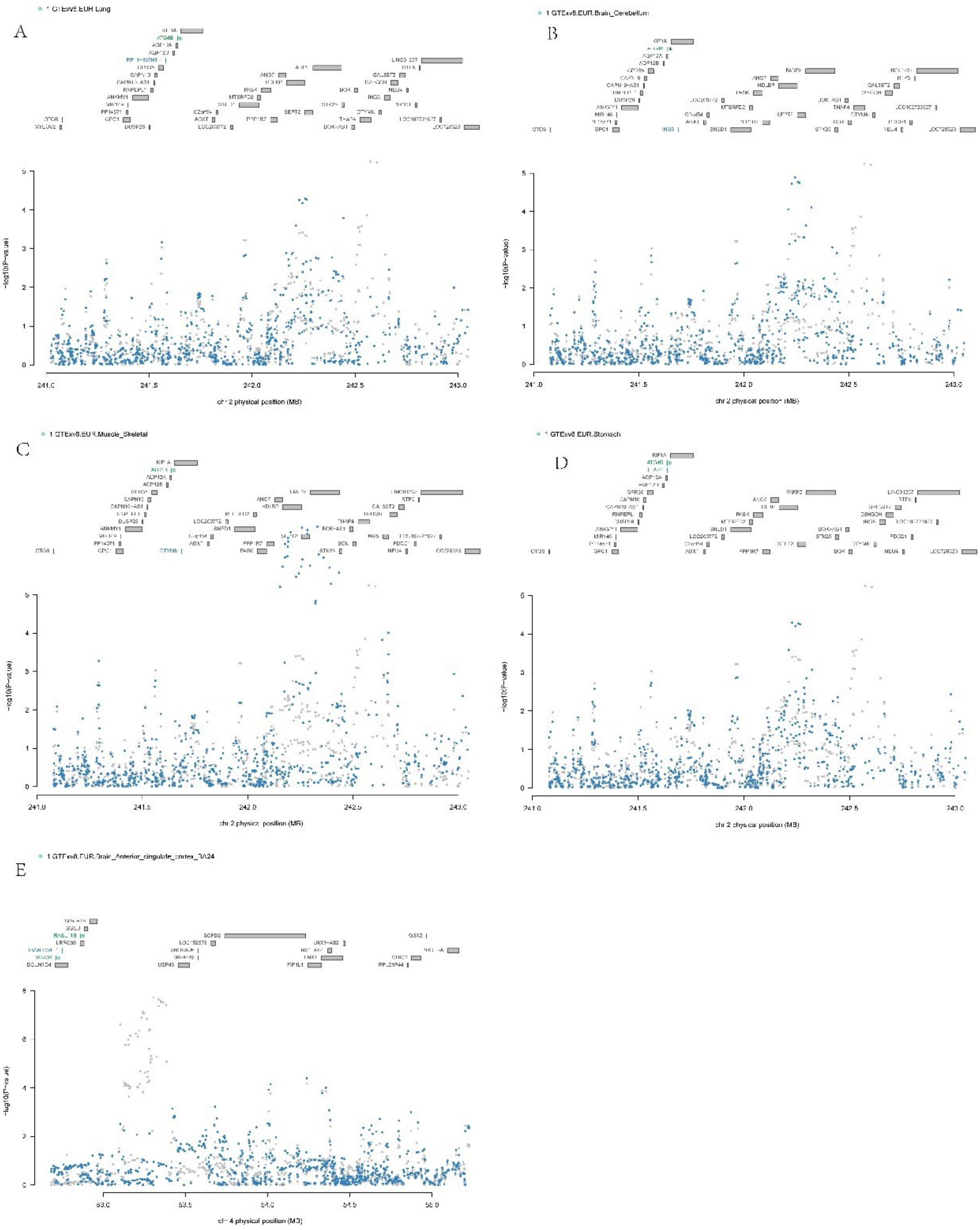
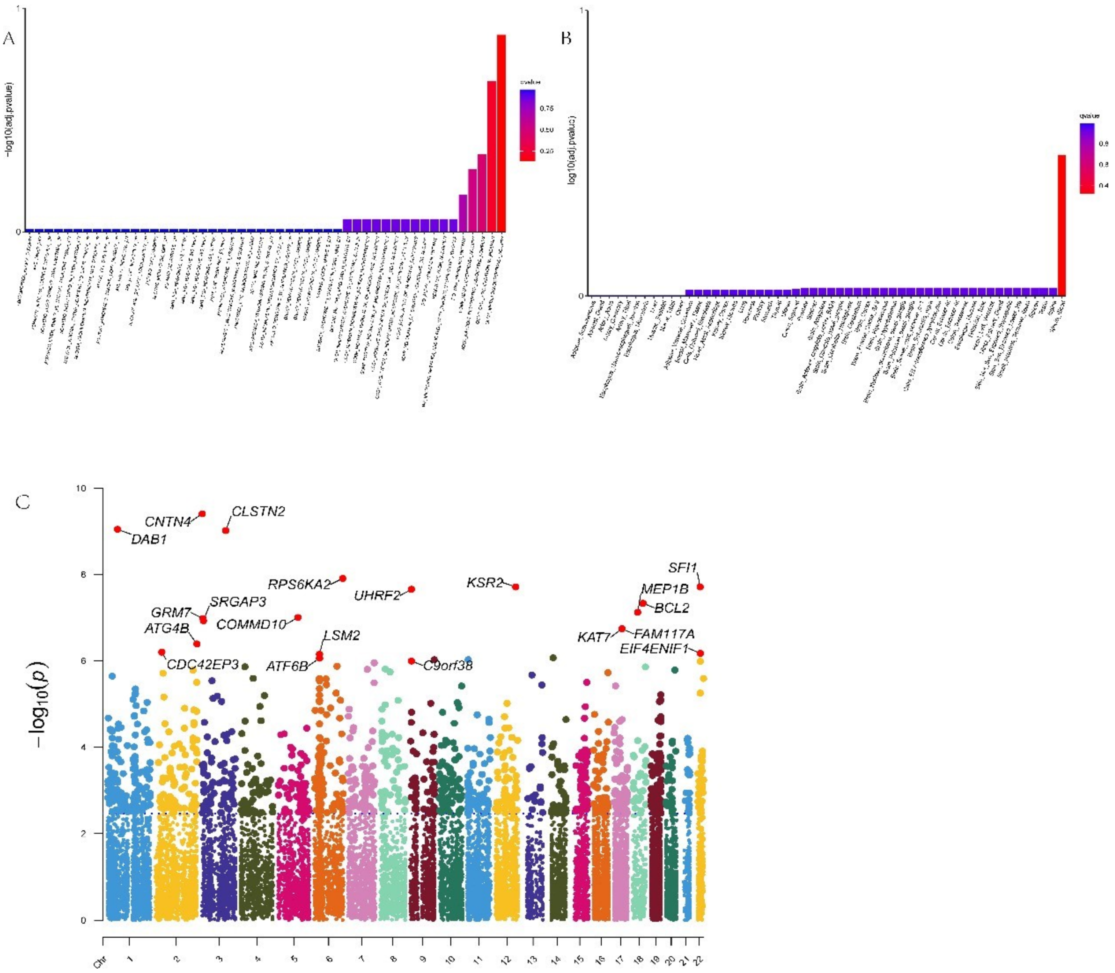


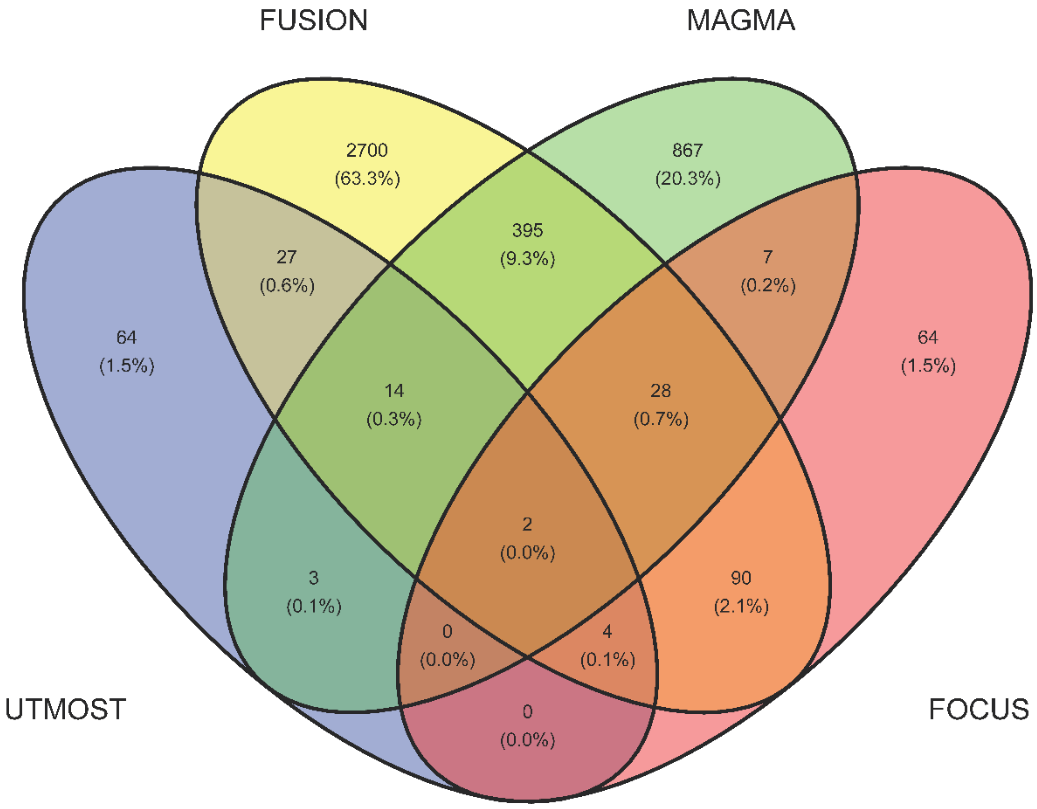
Supplementary Figure S1 The flowchart of this study. GWAS, genome-wide association; GTEx, Genotype-Tissues Expression Project; TWAS, transcriptome-wide association studies; UTMOST, unified test for molecular signatures; FUSION, functional summary-based imputation; FOCUS,Fine-mapping Of Causal Gene Sets analysis,MAGMA, multi-marker Analysis of GenoMic Annotation



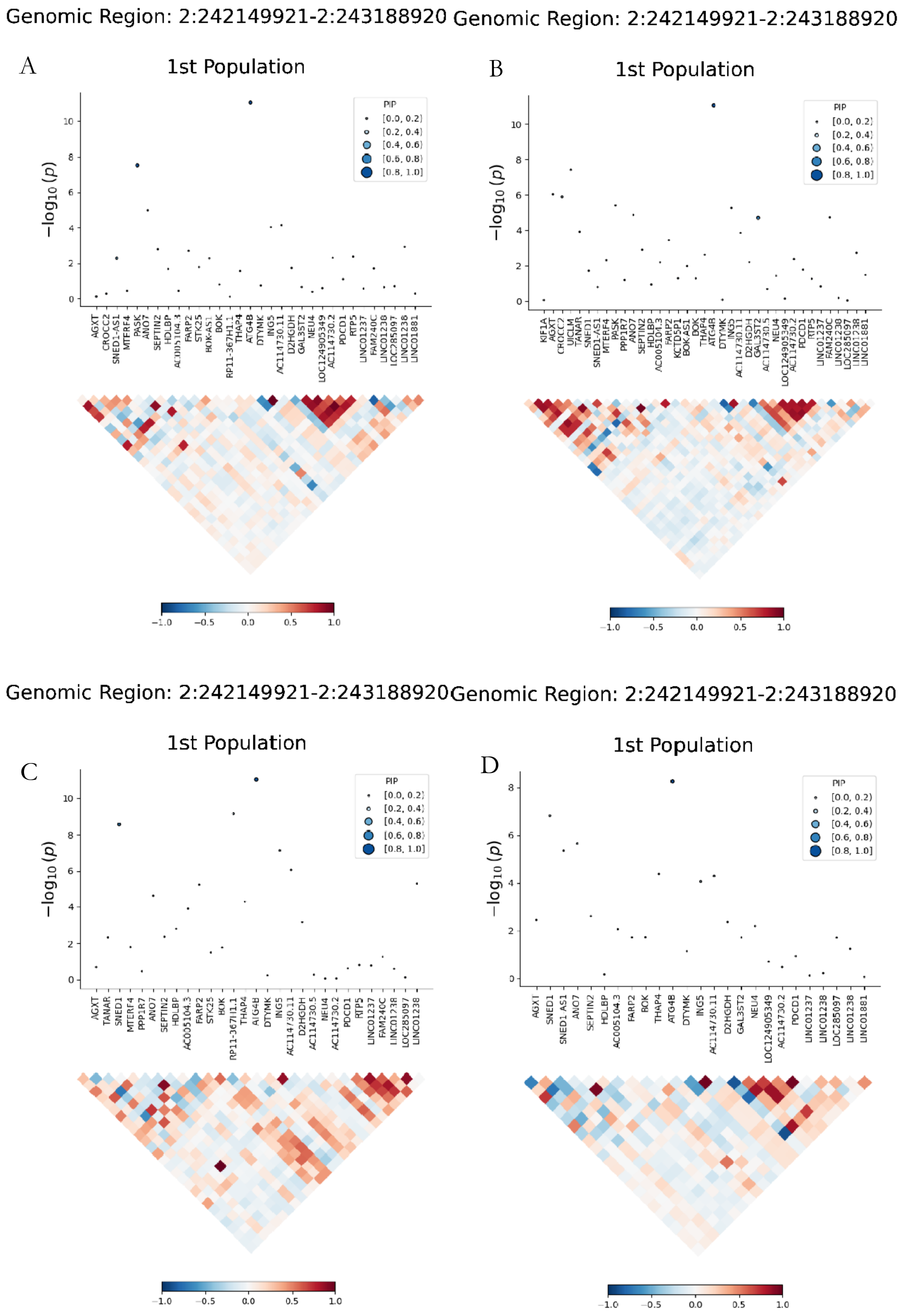
Supplementary Figure S2. Regional association of TWAS hits. (A), (B), (C)and (D) Chromosome 2 regional association plot. (E) Chromosome 4 regional association plot. The top panel highlights all genes in the region. The marginally associated TWAS genes are shown in blue, and the jointly significant genes are shown in green. The bottom panel shows a regional Manhattan plot of GWAS data before (grey) and after (blue) conditioning on the predicted expression of the green genes.



Supplementary Figure S3. MAGMA results for sepsis. **(A)** Bar plot of top enriched gene sets from MAGMA gene-set analysis.Each bar represents a specific gene set tested for enrichment, ordered along the X-axis by increasing $-\log_{10}$(q-value) shown on the Y-axis. Bar color denotes the magnitude of the q-value (red = most significant, blue = least). MAGMA tested over 10,000 GO, Reactome, PID, and WikiPathways sets and highlighted the following five as most significantly enriched (FDR < 0.05): GOMF_METALLOENDOPEPTIDASE_ACTIVITY;GOBP_CELL_PROLIFERATION_IN_MIDBRAIN;GOCC_NASCENT_POLYPEPTIDE_ASSOCIATED_COMPLEX;REACTOME_FCGR_ACTIVATION; PID_ALPHA_SYNUCLEIN_PATHWAY;**(B)** Bar plot of tissue-specific gene-set enrichment from MAGMA results. Each bar corresponds to a selected Gene Ontology or pathway term's $-\log_{10}$(q-value) in a given GTEx tissue (X-axis), with tissues ordered by decreasing enrichment. Bars colored red denote the most significant enrichments (q < 0.25), while blue indicates weaker enrichment (q > 0.75). Notably, whole blood shows the strongest enrichment, followed by spleen, brain regions (e.g., cerebellum), and lung, highlighting tissue-specific involvement of immune and inflammatory processes in sepsis. **(C)** Manhattan plot of the MAGMA gene-based analysis for sepsis. Each point represents a gene's association with sepsis, plotted by its genomic location on the X-axis (chromosomes 1–22) and the strength of association ($-\log_{10}$(p) from the gene-level test) on the Y-axis. Genes exceeding the FDR < 0.05 threshold are highlighted in red. A total of 1,323 genes reached significance, with top hits including *CNTN4, DAB1, CLSTN2, RPS6KA2, UHRF2, KSR2, SFI1, MEP1B, BCL2, KAT7, FAM117A,* and *EIF4ENIF1*.



Supplementary Figure S4 Venn diagram. MAGMA identified 1,323 significant genes associated with sepsis, FUSION identified 3,260, UTMOST cross-tissue analysis identified 114 and FOCUS identified 195, of which 2 were common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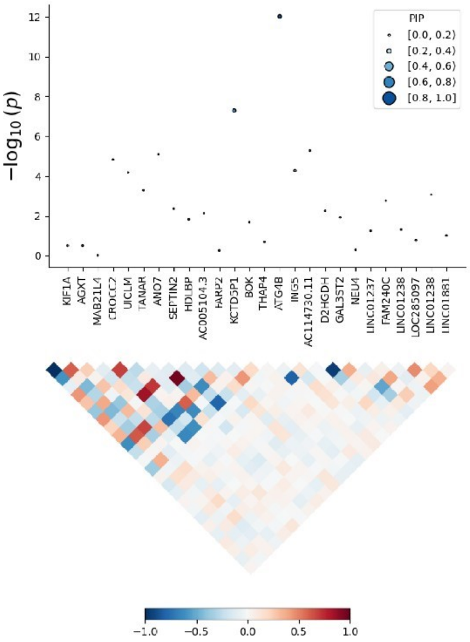
Genomic Region: 2:242149921-2:243188920
A
B
1st Population
1st Population
−log10 (p)
PIP
[0.0, 0.2)
[0.2, 0.4)
[0.4, 0.6)
[0.6, 0.8)
[0.8, 1.0]
AGXT
CROCC2
SNED1-AS1
MTERF4
PASK
ANO7
SEPTIN2
HDLBP
AC005104.3
FARP2
STK25
BOK-AS1
BOK
RP11-367H1.1
THAP4
ATG4B
DTYMK
ING5
AC114730.11
D2HGDH
GAL3ST2
NEU4
LOC124905349
AC114730.2
PDCD1
RTP5
LINC01237
FAM240C
LINC01230
LOC285097
LINC01238
LINC01881
KIF1A
UICLM
TANAR
SNED1
PPP1R7
KCTD5P1
AC114730.5
−1.0
−0.5
0.0
0.5
1.0
Genomic Region: 2:242149921-2:243188920
Genomic Region: 2:242149921-2:243188920
C
D
1st Population
1st Population

E



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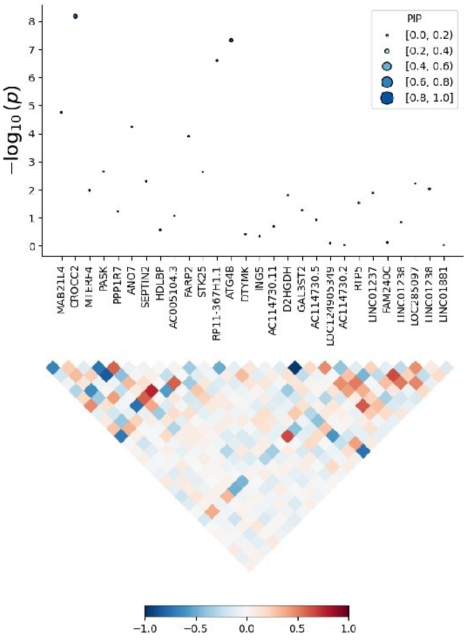
1st Population

F



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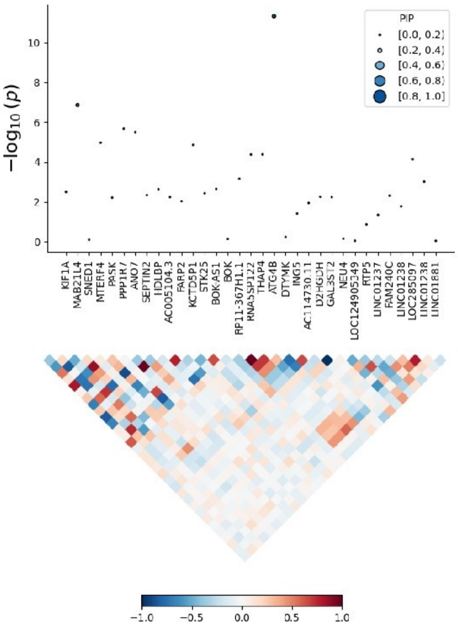
1st Population

G



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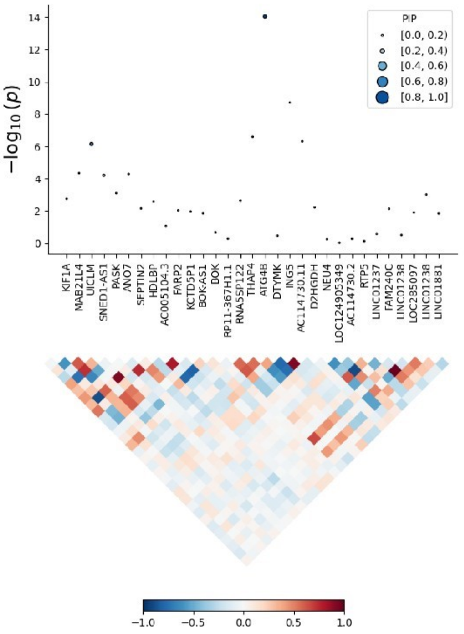
1st Population

H



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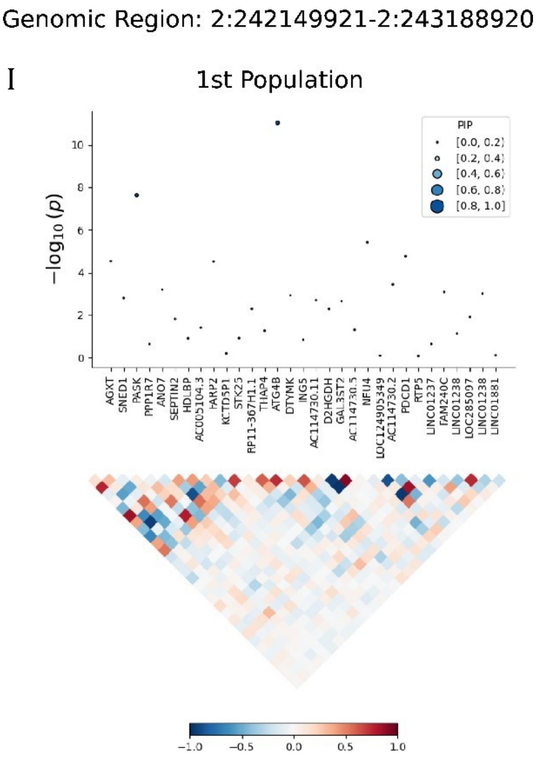
1st Population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4
6
8
10
PIP
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[0.2, 0.4)
[0.4, 0.6)
[0.6, 0.8)
[0.8, 1.0]
AGXT
SNED1
PASK
PPP1R7
ANO7
SEPTIN2
HDLBP
AC005104.3
FARP2
KCTD5P1
STK25
RP11-367H1.1
THAP4
ATG4B
DTYMK
ING5
AC114730.11
D2HGDH
GAL3ST2
AC114730.5
NEU4
LOC124905349
AC114730.2
PDCD1
RTP5
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LOC285097
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LINC01881
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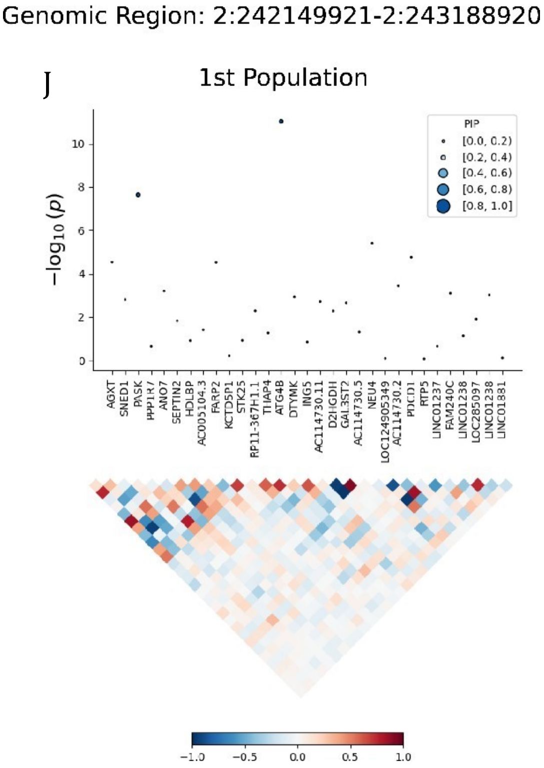
1.0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6
8
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PIP
[0.0, 0.2)
[0.2, 0.4)
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[0.8, 1.0]
AGXT
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PASK
PPP1R7
ANO7
SEPTIN2
HDLBP
AC005104.3
FARP2
KCTD5P1
STK25
RP11-367H1.1
THAP4
ATG4B
DTYMK
ING5
AC114730.11
D2HGDH
GAL3ST2
AC114730.5
NEU4
LOC124905349
AC114730.2
PDCD1
RTP5
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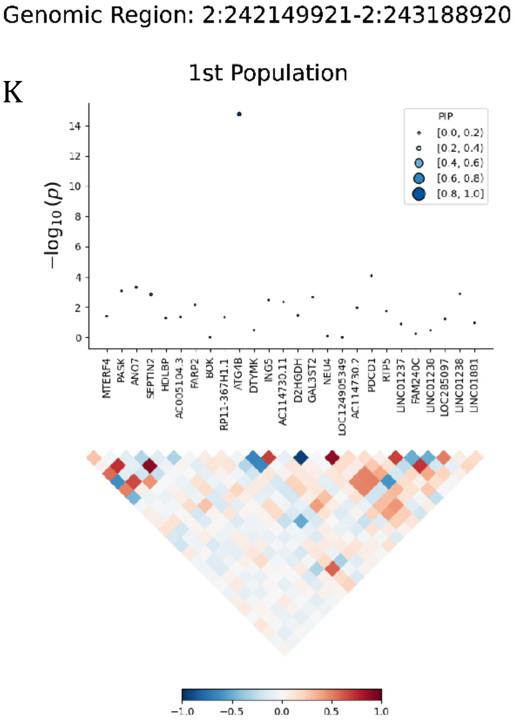
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4
6
8
10
12
14
PIP
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[0.2, 0.4)
[0.4, 0.6)
[0.6, 0.8)
[0.8, 1.0]
MTERF4
PASK
ANO7
SEPTIN2
HDLBP
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FARP2
BOK
RP11-367H1.1
ATG4B
DTYMK
ING5
AC114730.11
D2HGDH
GAL3ST2
NEU4
LOC124905349
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PDCD1
RTP5
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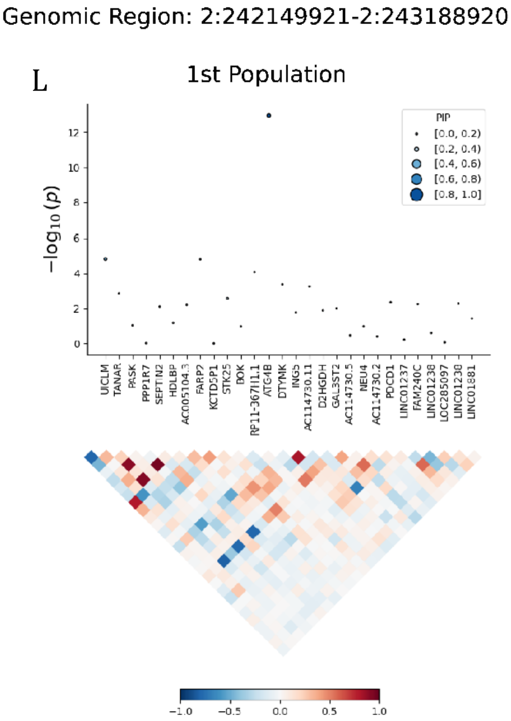
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4
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8
10
12
PIP
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UICLM
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SEPTIN2
HDLBP
AC005104.3
FARP2
KCTD5P1
STK25
BOK
RP11-367H1.1
ATG4B
DTYMK
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D2HGDH
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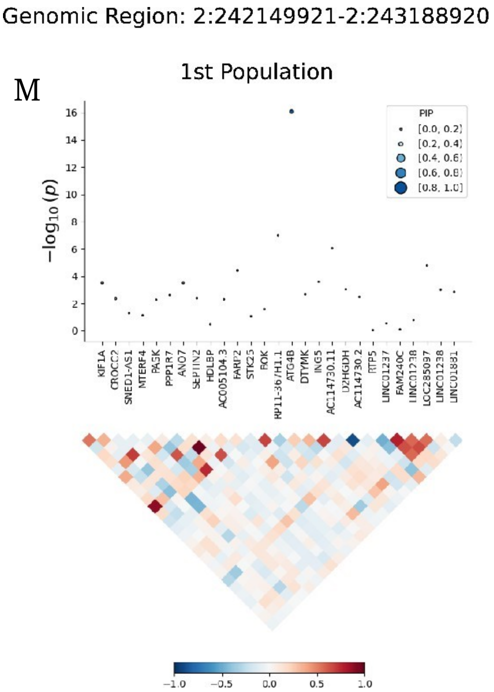
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8
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16
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SEPTIN2
HDLBP
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FARP2
STK25
BOK
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ATG4B
DTYMK
ING5
AC114730.11
D2HGDH
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RTP5
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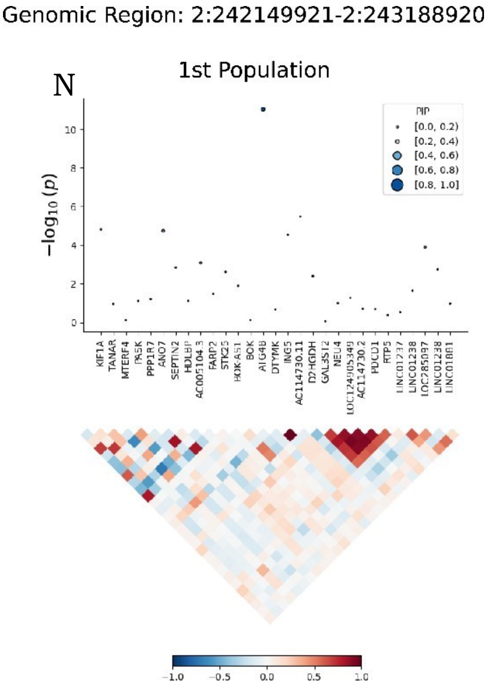
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HDLBP
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FARP2
STK25
BOK-AS1
BOK
ATG4B
DTYMK
ING5
AC114730.11
D2HGDH
GAL3ST2
NEU4
LOC124905349
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PDCD1
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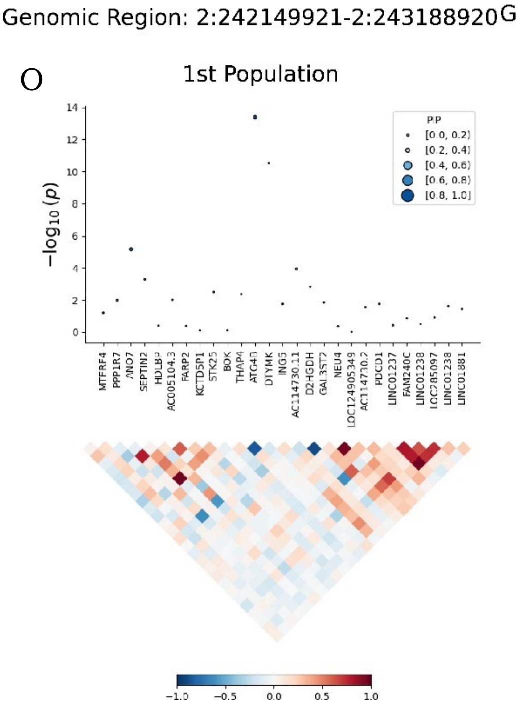
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FARP2
KCTD5P1
STK25
BOK
THAP4
ATG4B
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NEU4
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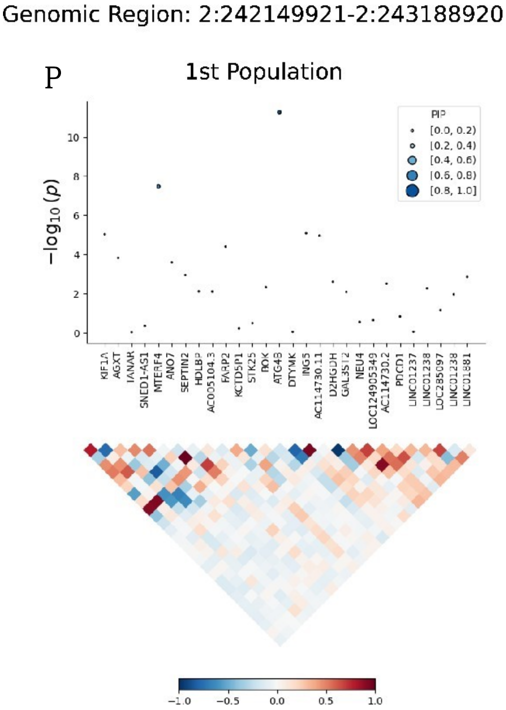
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MTERF4
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SEPTIN2
HDLBP
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FARP2
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STK25
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ATG4B
DTYMK
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D2HGDH
GAL3ST2
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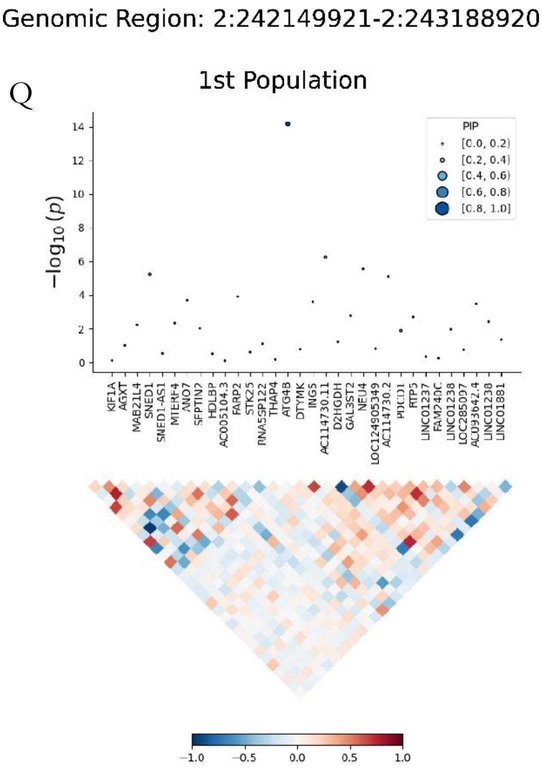
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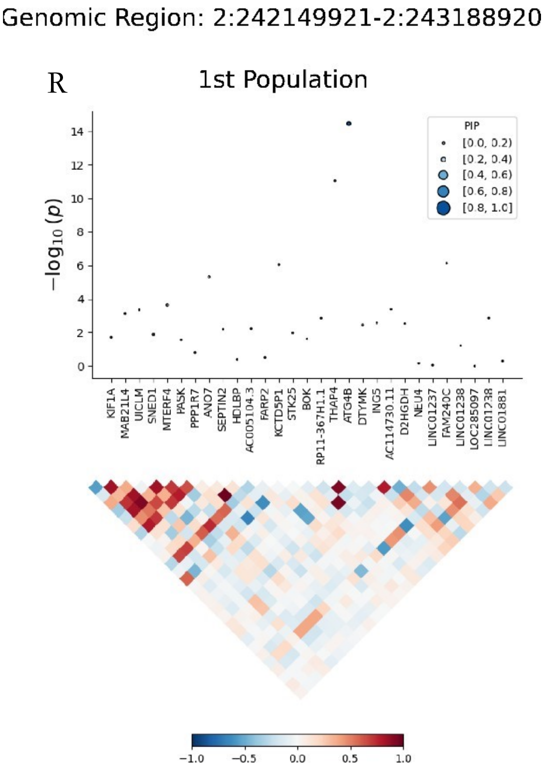
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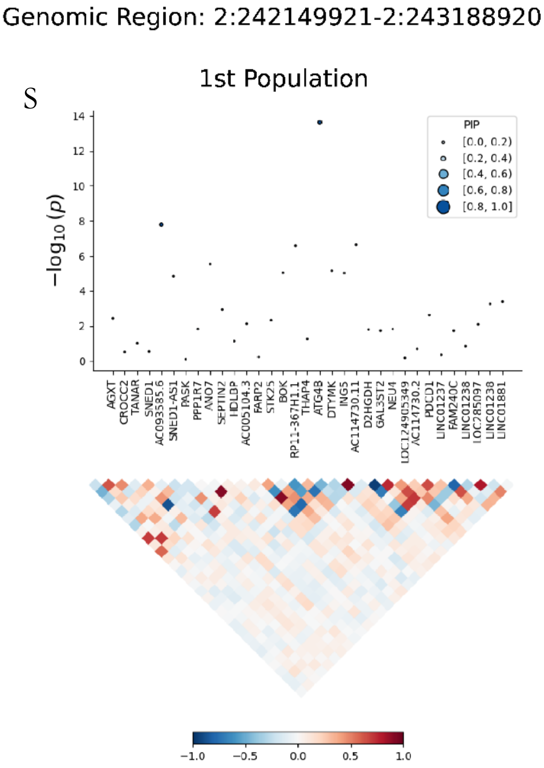
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1st Population
$-\log_{10}(p)$
PIP
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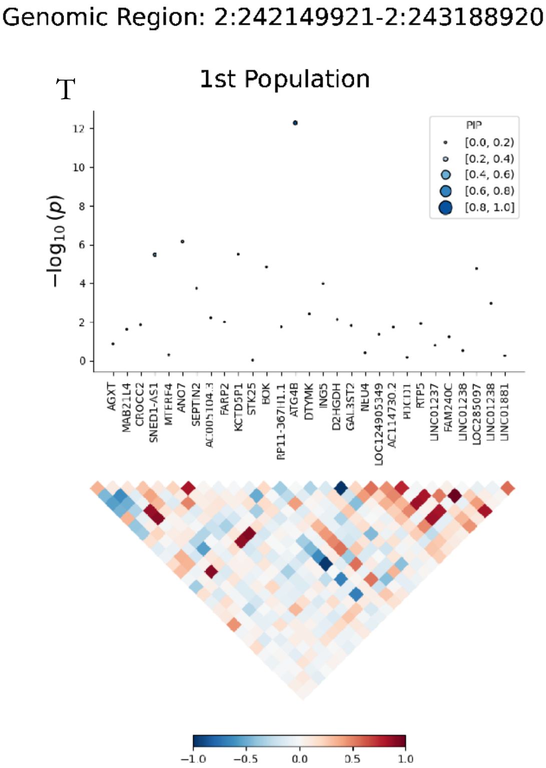
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[0.6, 0.8)
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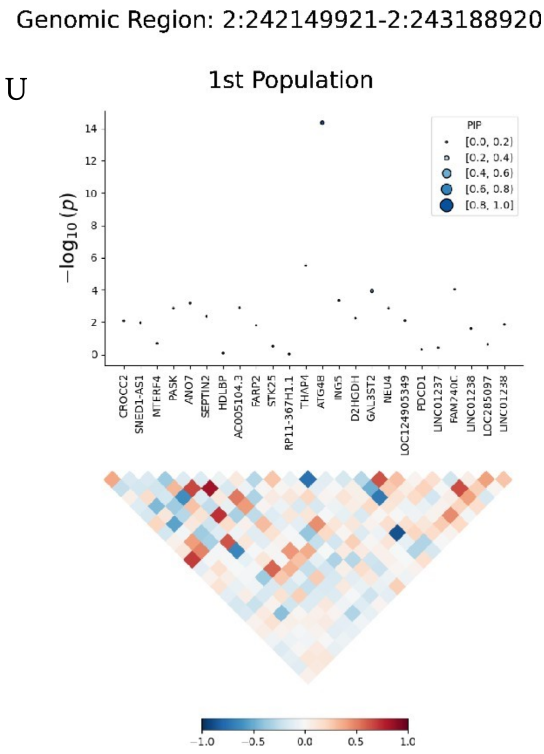

Genomic Region: 2:242149921-2:243188920
U
1st Population
$-\log_{10}(p)$
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2
4
6
8
10
12
14
PIP
[0.0, 0.2)
[0.2, 0.4)
[0.4, 0.6)
[0.6, 0.8)
[0.8, 1.0]
CROCC2
SNED1-AS1
MTERF4
PASK
ANO7
SEPTIN2
HDLBP
AC005104.3
FARP2
STK25
RP11-367H1.1
THAP4
ATG4B
ING5
D2HGDH
GAL3ST2
NEU4
LOC124905349
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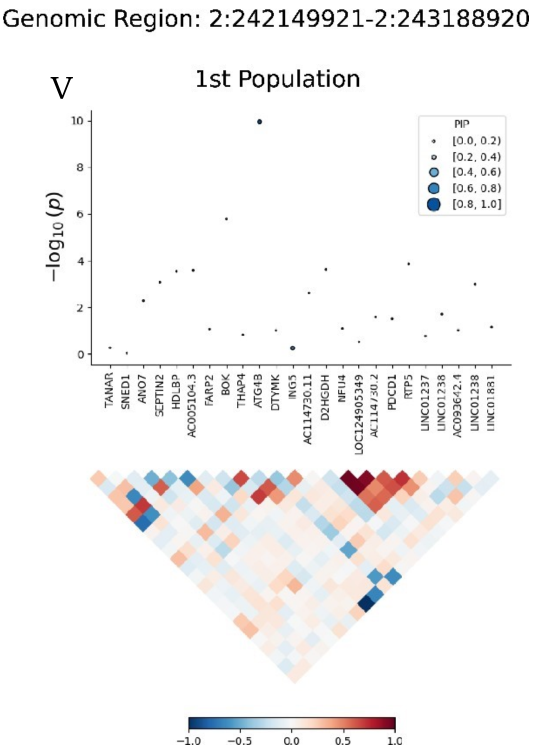

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1st Population
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4
6
8
10
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[0.2, 0.4)
[0.4, 0.6)
[0.6, 0.8)
[0.8, 1.0]
TANAR
SNED1
ANO7
SEPTIN2
HDLBP
AC005104.3
FARP2
BOK
THAP4
ATG4B
DTYMK
ING5
AC114730.11
D2HGDH
NEU4
LOC124905349
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PDCD1
RTP5
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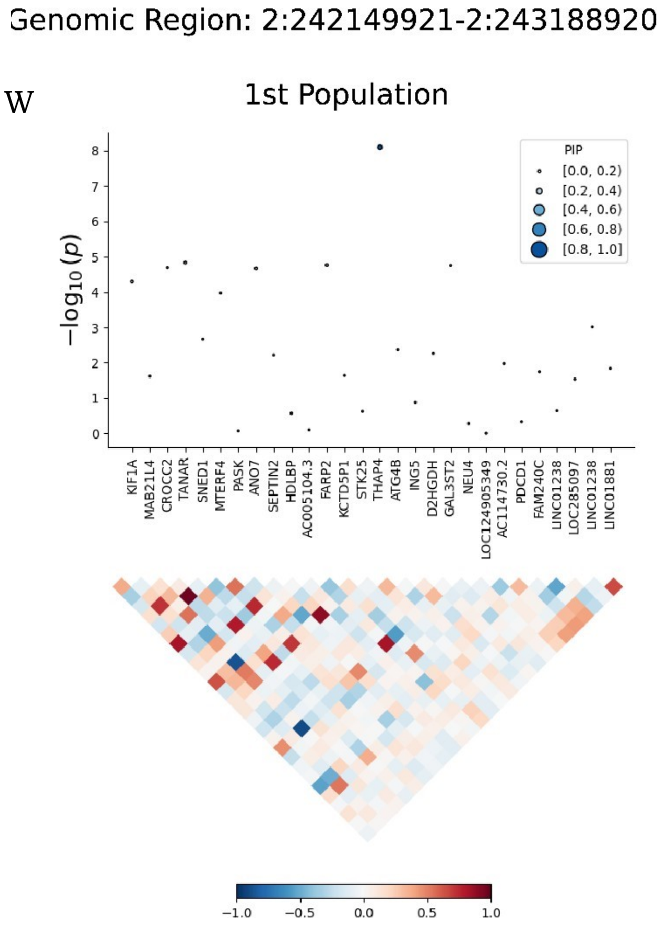

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1st Population
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3
4
5
6
7
8
PIP
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[0.4, 0.6)
[0.6, 0.8)
[0.8, 1.0]
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CROCC2
TANAR
SNED1
MTERF4
PASK
ANO7
SEPTIN2
HDLBP
AC005104.3
FARP2
KCTD5P1
STK25
THAP4
ATG4B
ING5
D2HGDH
GAL3ST2
NEU4
LOC124905349
AC114730.2
PDCD1
FAM240C
LINC01238
LOC285097
LINC01238
LINC01881
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−0.5
0.0
0.5
1.0

Supplementary Figure S5. FOCUS plot for *ATG4B* and *THAP4* in one region. **(A)** The plot contains the predicted expression correlation, TWAS summary statistics and PIP for *ATG4B* in the genomic locus 2:242149921-2:243188920 in the Adipose_Subcutaneous. **(B)** The plot contains the predicted expression correlation, TWAS summary statistics and PIP for *ATG4B* in the genomic locus 2:242149921- 2:243188920 in the Adipose_Visceral_Omentum. **(C)** The plot contains the predicted expression correlation, TWAS summary statistics and PIP for *ATG4B* in the genomic locus2:242149921- 2:243188920 in the Adrenal_Gland. **(D)** The plot contains the predicted expression correlation, TWAS summary statistics and PIP for *ATG4B* in the genomic locus 2:242149921-2:243188920 in the Artery_Aorta. **(E)** The plot contains the predicted expression correlation, TWAS summary statistics and PIP for *ATG4B* in the genomic locus 2:242149921-2:243188920 in the Artery_Coronary. **(F)** The plot contains the predicted expression correlation, TWAS summary statistics and PIP for *ATG4B* in the genomic locus 2:242149921-2:243188920 in the Brain_Caudate_basal_ganglia. **(G)** The plot contains the predicted expression correlation, TWAS summary statistics and PIP for *ATG4B* in the genomic locus2:242149921-2:243188920 in the Brain_Cerebellar_Hemisphere. **(H)** The plot contains the predicted expression correlation, TWAS summary statistics and PIP for *ATG4B* in the genomic locus 2:242149921-2:243188920 in the Brain_Cerebellum. **(I)** The plot contains the predicted expression correlation, TWAS summary statistics and PIP for *ATG4B* in the genomic locus 2:242149921- 2:243188920 in the Brain_Cortex. **(J)** The plot contains the predicted expression correlation, TWAS summary statistics and PIP for *ATG4B* in the genomic locus 2:242149921-2:243188920 in the Brain_Nucleus_accumbens_basal_ganglia. **(K)** The plot contains the predicted expression correlation, TWAS summary statistics and PIP for *ATG4B* in the genomic locus2:242149921-2:243188920 in the Colon_Sigmoid. **(L)** The plot contains the predicted expression correlation, TWAS summary statistics and PIP for *ATG4B* in the genomic locus 2:242149921-2:243188920 in the Colon_Transverse.

(M) The plot contains the predicted expression correlation, TWAS summary statistics and PIP for *ATG4B* in the genomic locus 2:242149921-2:243188920 in the Esophagus_Mucosa. **(N)** The plot contains the predicted expression correlation, TWAS summary statistics and PIP for *ATG4B* in the genomic locus 2:242149921-2:243188920 in the Lung. **(O)** The plot contains the predicted expression correlation, TWAS summary statistics and PIP for *ATG4B* in the genomic locus2:242149921-2:243188920 in the Muscle_Skeletal. **(P)** The plot contains the predicted expression correlation, TWAS summary statistics and PIP for *ATG4B* in the genomic locus 2:242149921-2:243188920 in the Nerve_Tibial.

(Q) The plot contains the predicted expression correlation, TWAS summary statistics and PIP for *ATG4B* in the genomic locus 2:242149921-2:243188920 in the Spleen. **(R)** The plot contains the predicted expression correlation, TWAS summary statistics and PIP for *ATG4B* in the genomic locus 2:242149921-2:243188920 in the Stomach. **(S)** The plot contains the predicted expression correlation, TWAS summary statistics and PIP for *ATG4B* in the genomic locus2:242149921-2:243188920 in the Thyroid. **(T)** The plot contains the predicted expression correlation, TWAS summary statistics and PIP for *ATG4B* in the genomic locus 2:242149921-2:243188920 in the Uterus. **(U)** The plot contains the predicted expression correlation, TWAS summary statistics and PIP for *ATG4B* in the genomic locus 2:242149921-2:243188920 in the Vagina. **(V)** The plot contains the predicted expression correlation, TWAS summary statistics and PIP for *ATG4B* in the genomic locus 2:242149921- 2:243188920 in the Whole_Blood. **(W)** The plot contains the predicted expression correlation, TWAS summary statistics and PIP for *THAP4* in the genomic locus2:242149921-2:243188920 in the Brain_Hippocampus.