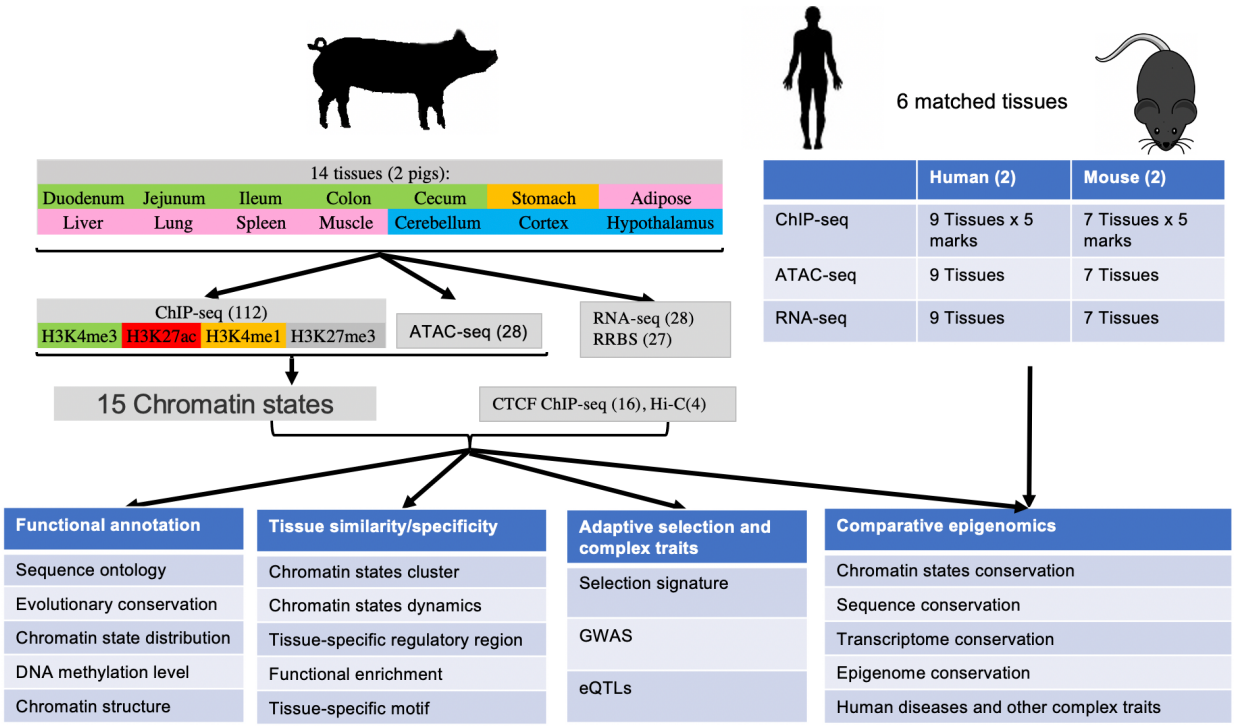
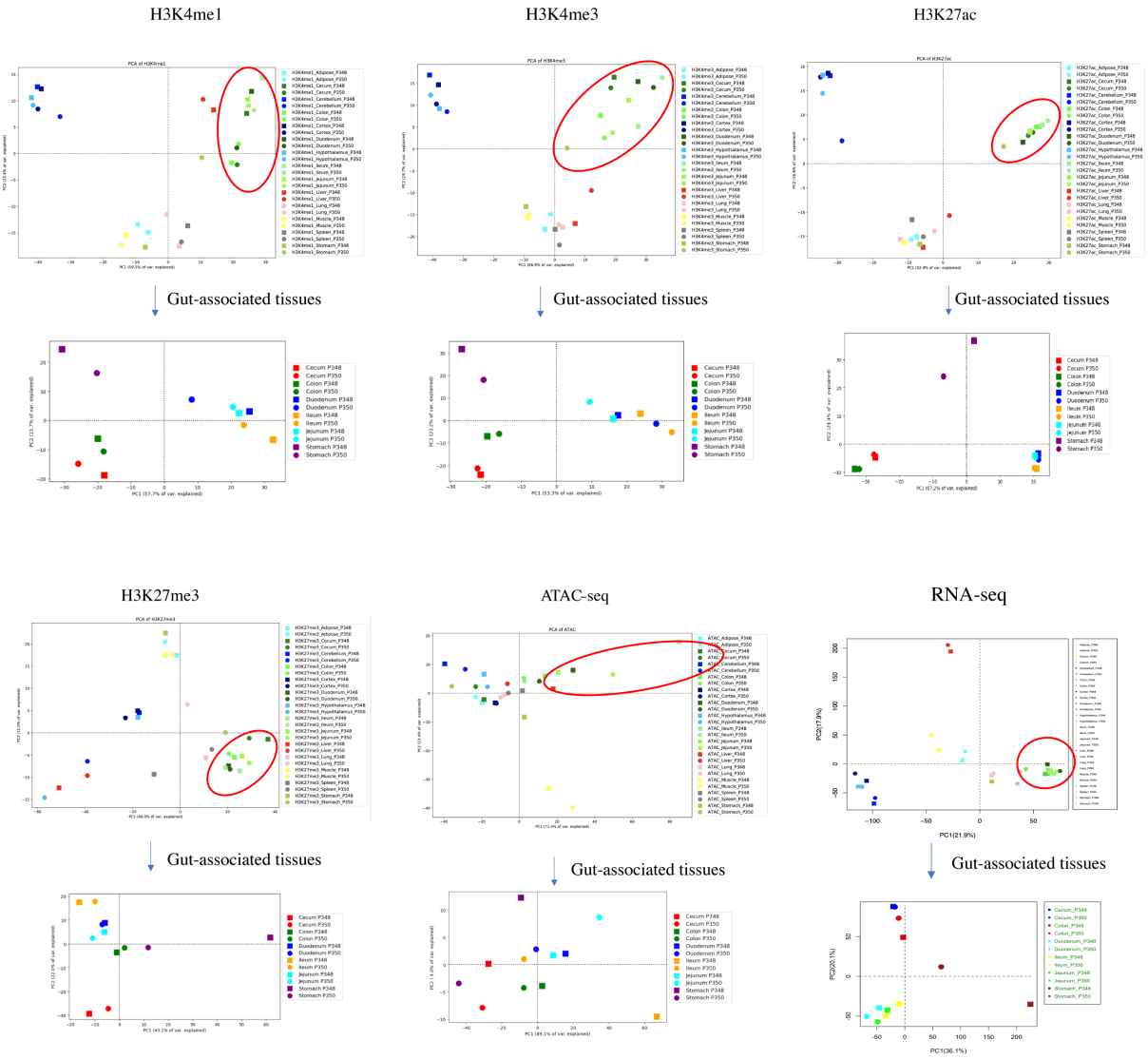
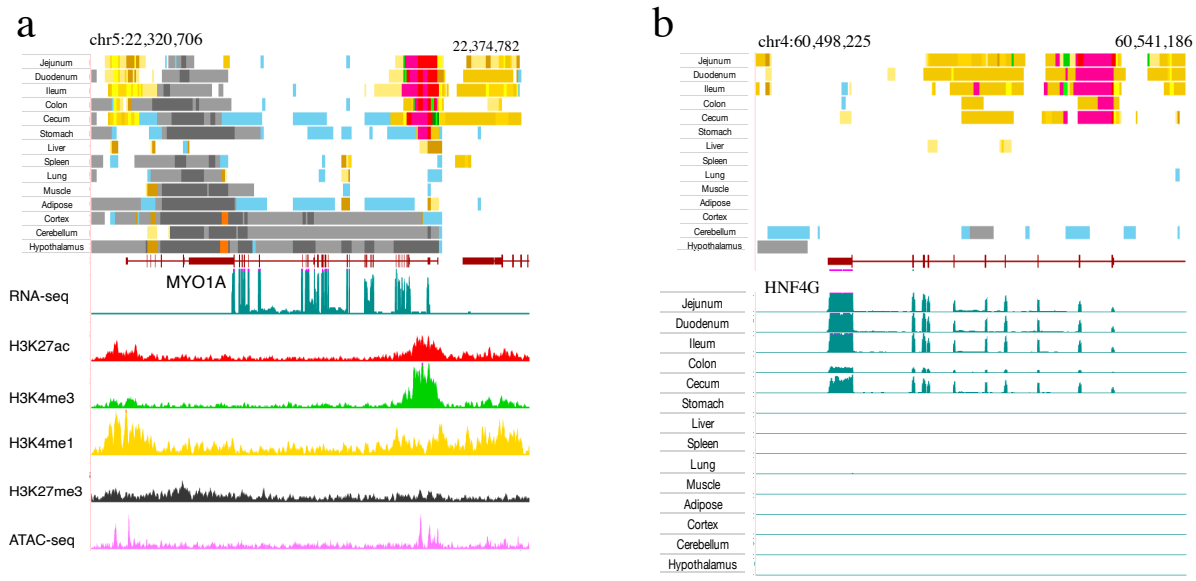


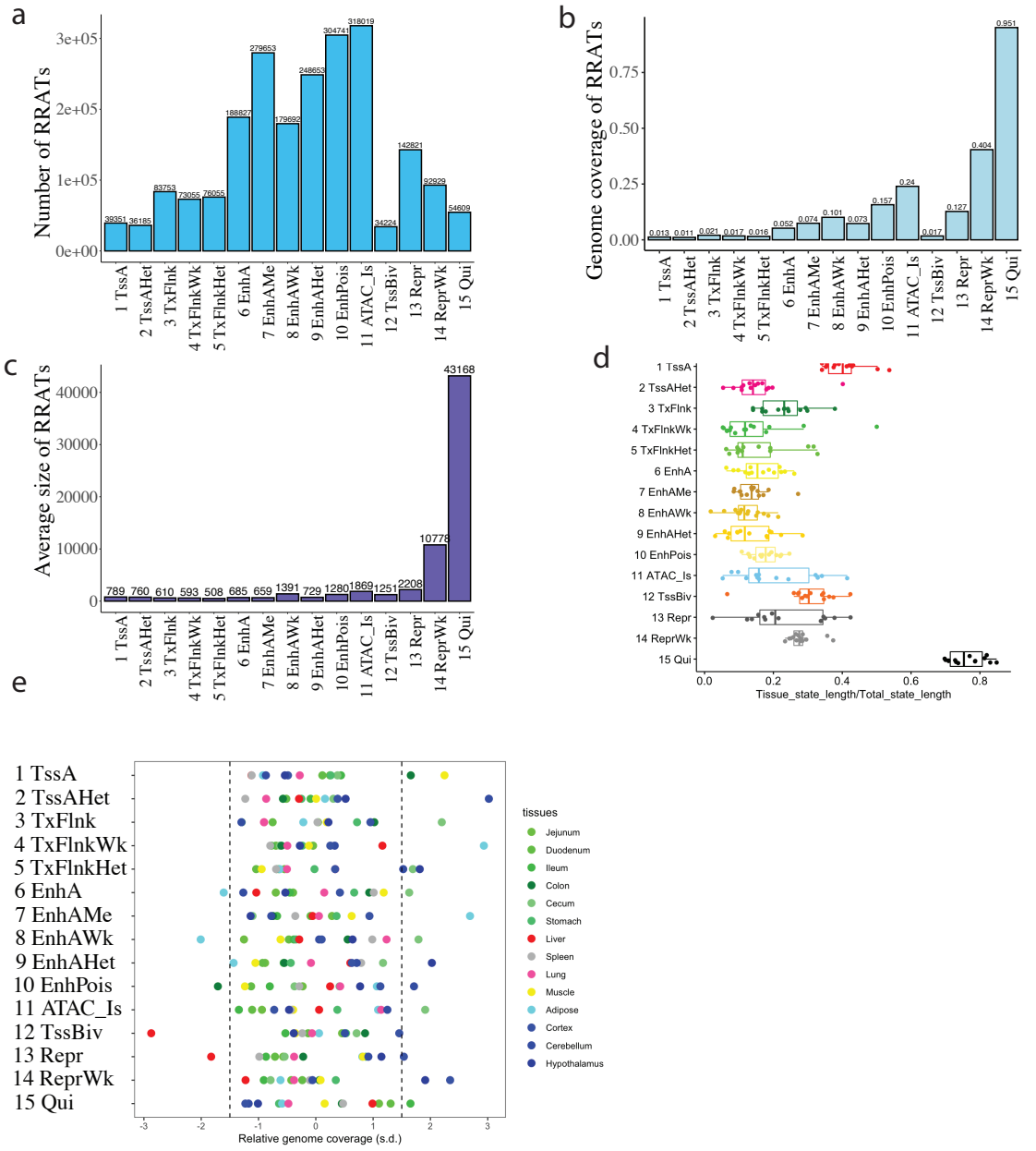
Supplementary Fig. 1 Study design of pig genome annotation and comparative epigenomic analysis. This study included 112 histone ChIP-seq, 28 ATAC-seq, 28 RNA-seq, 27 RRBS, 16 CTCF ChIP-seq, 4 Hi-C datasets cross 14 tissues from pig, and also integrated 126 human and 98 mouse datasets for comparative epigenomic analysis. The six matched tissues among pig, human, and mouse were small intestine, liver, spleen, lung, adipose, and brain cortex. The numbers in the brackets are the number of assays or samples included in the current study.



Supplementary Fig. 2 Principal component analysis (PCA) of five epi-marks and RNA-seq in 14 tissues in pig. The regions highlighted are gut-associated tissues.

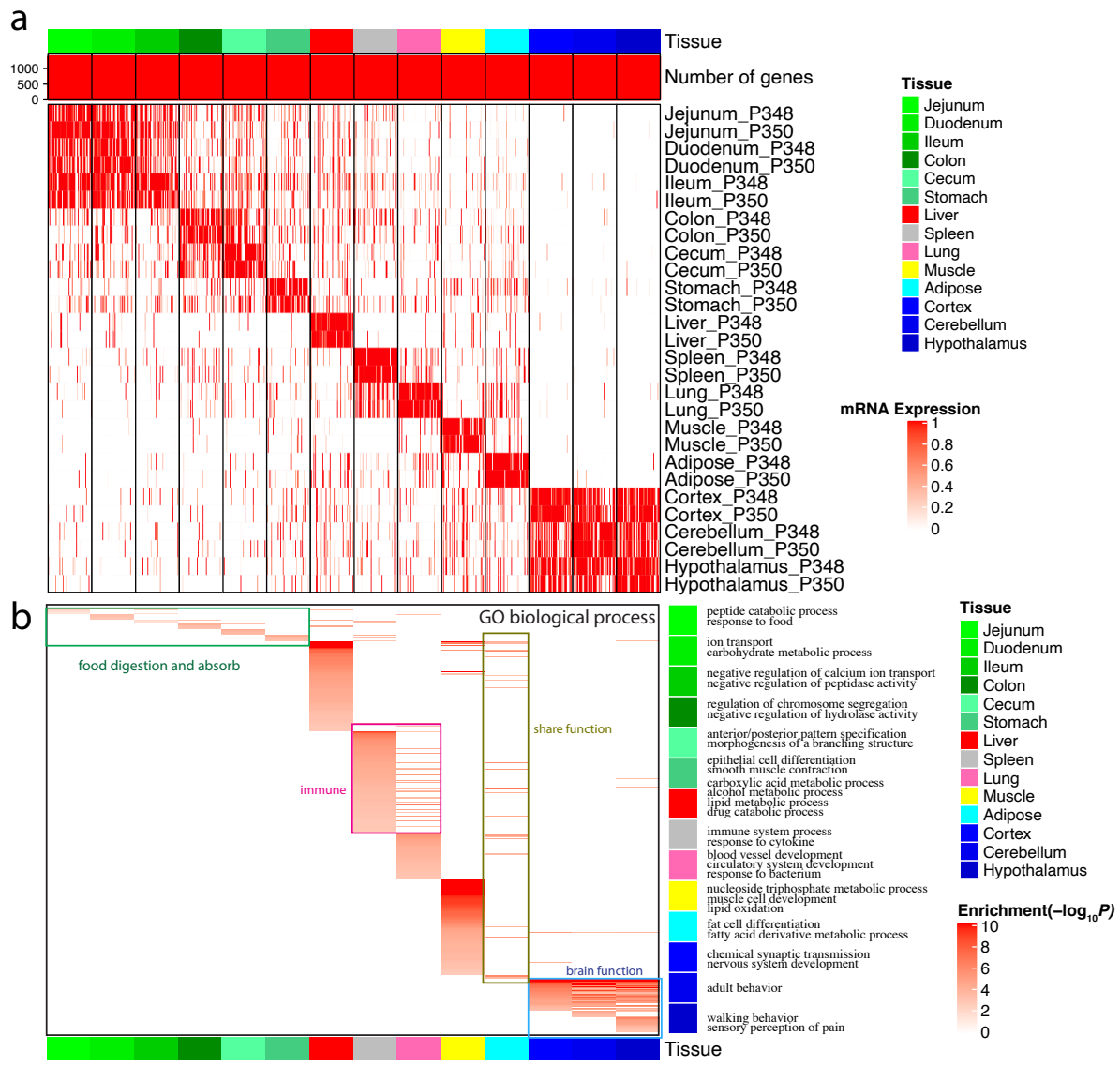


Supplementary Fig. 3 Example of regulation of gene expression by chromatin states. **a**, Chromatin state around *MYO1A* gene (chr5:22,320,706-22,374,782) in 14 tissues. **b**, Chromatin state around *HNF4G* (chr4:60,498,225-60,541,186) in 14 tissues. Vertical scale 0-200 for RNA-seq, 0-100 for H3K27ac and H3K4me3, and 0-50 for other marks and ATAC-seq.

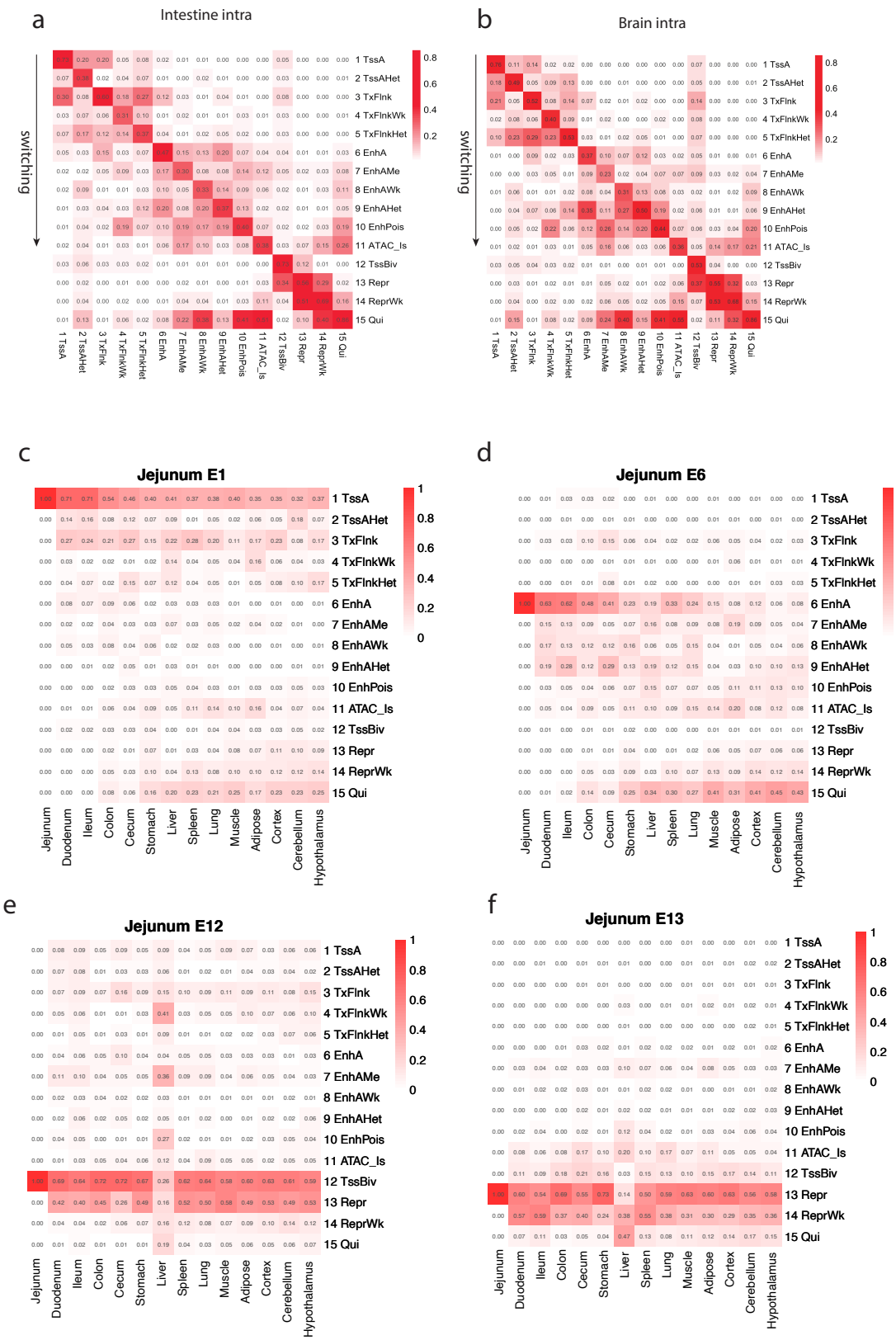


Supplementary Fig.4 **Total number, genome coverage and characterizations of regulatory elements at each chromatin state across 14 tissues. a**, Total number of regulatory regions across 14 tissues (RRATs) for each chromatin state. Totally we identified 2,097,958 regulatory elements (exclude Qui) spanning 14 tissues including 39.351 active promoters (TssA), 188,827 active strong enhancers (EnhA), and 142,821 repressors (Repr). **b**, Genome coverage of RRATs

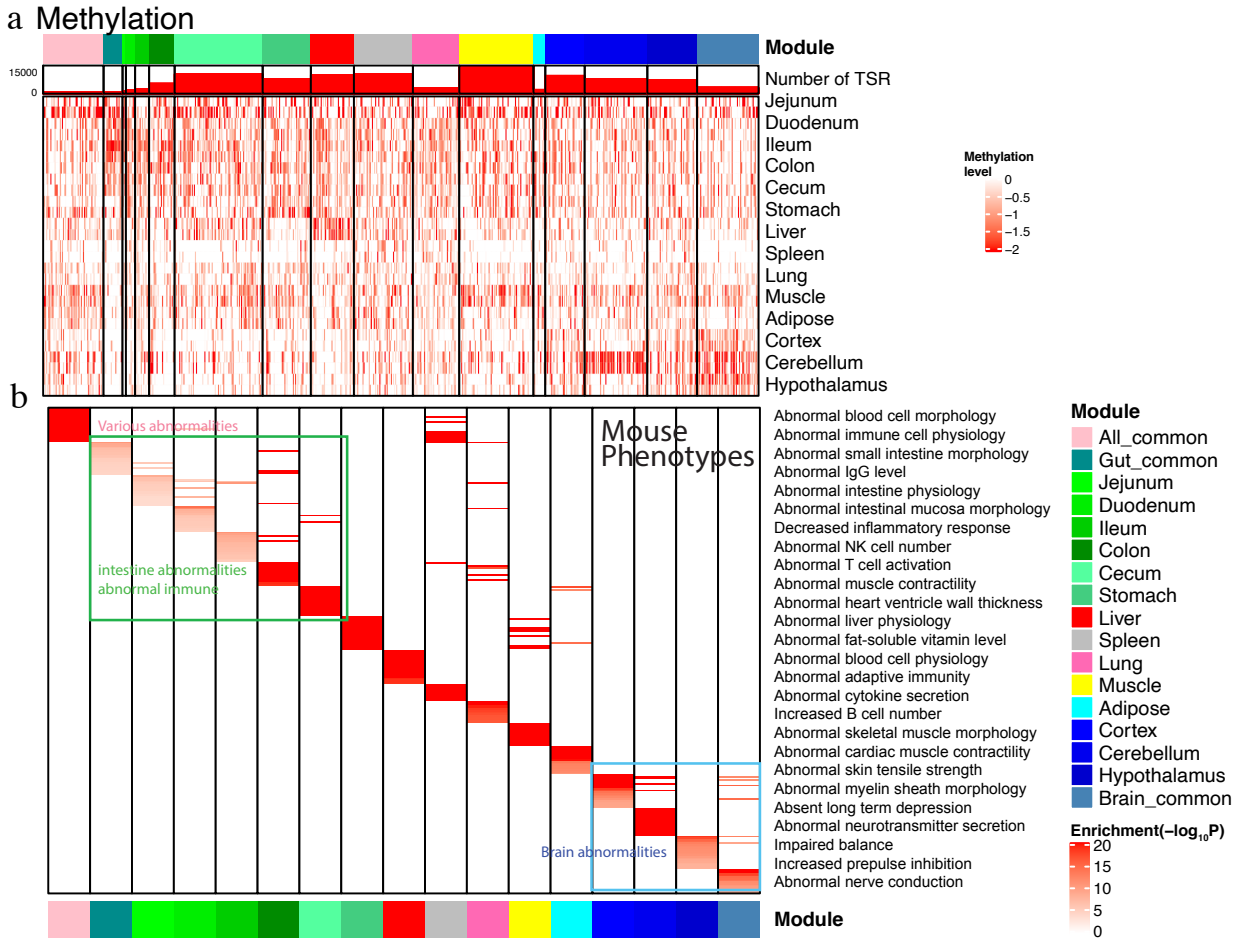
for each chromatin state. **c**, Average size of RRATs for each chromatin state. **d**, Average genome coverage for each chromatin state. **e**, Chromatin state relative genome coverage in different tissues.



Supplementary Fig. 5 The expression of tissue-specifically expressed genes (TSE) across 14 tissues (**a**) and their gene ontology (GO) functional enrichment (**b**).

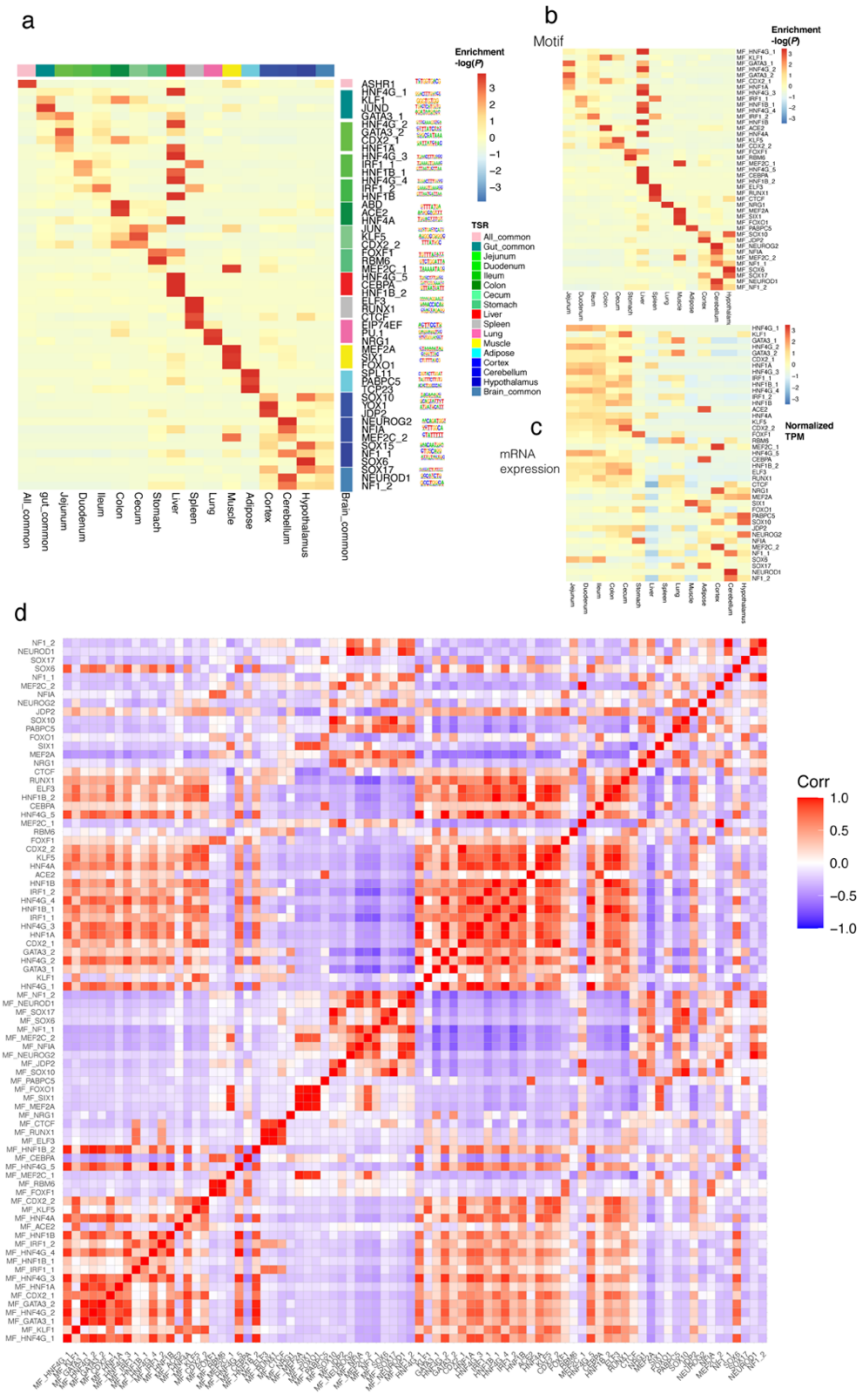

a
Intestine intra
switching
1 TssA
2 TssAHet
3 TxFlnk
4 TxFlnkWk
5 TxFlnkHet
6 EnhA
7 EnhAMe
8 EnhAWk
9 EnhAHet
10 EnhPois
11 ATAC_Is
12 TssBiv
13 Repr
14 ReprWk
15 Qui
0.8
0.6
0.4
0.2
b
Brain intra
switching
c
Jejunum E1
d
Jejunum E6
e
Jejunum E12
f
Jejunum E13
1
0.8
0.6
0.4
0.2
0
Jejunum
Duodenum
Ileum
Colon
Cecum
Stomach
Liver
Spleen
Lung
Muscle
Adipose
Cortex
Cerebellum
Hypothalamus

Supplementary Fig. 6 Chromatin states switching in tissues and TSE. **a,b** Chromatin states switching probabilities in between intestinal tissues, between brain tissues **c,d,e,f.** Chromatin state switching for proximal-promoters (E1), enhancers(E6), TssBivs (E12), repressors (E13) of tissue-specifically expressed genes (TSE) in jejunum. E1: 5,000bp around TSE gene's TSS, E6, E12, and E13: 25,000bp according to chromatin state density peak in Fig. 2g.

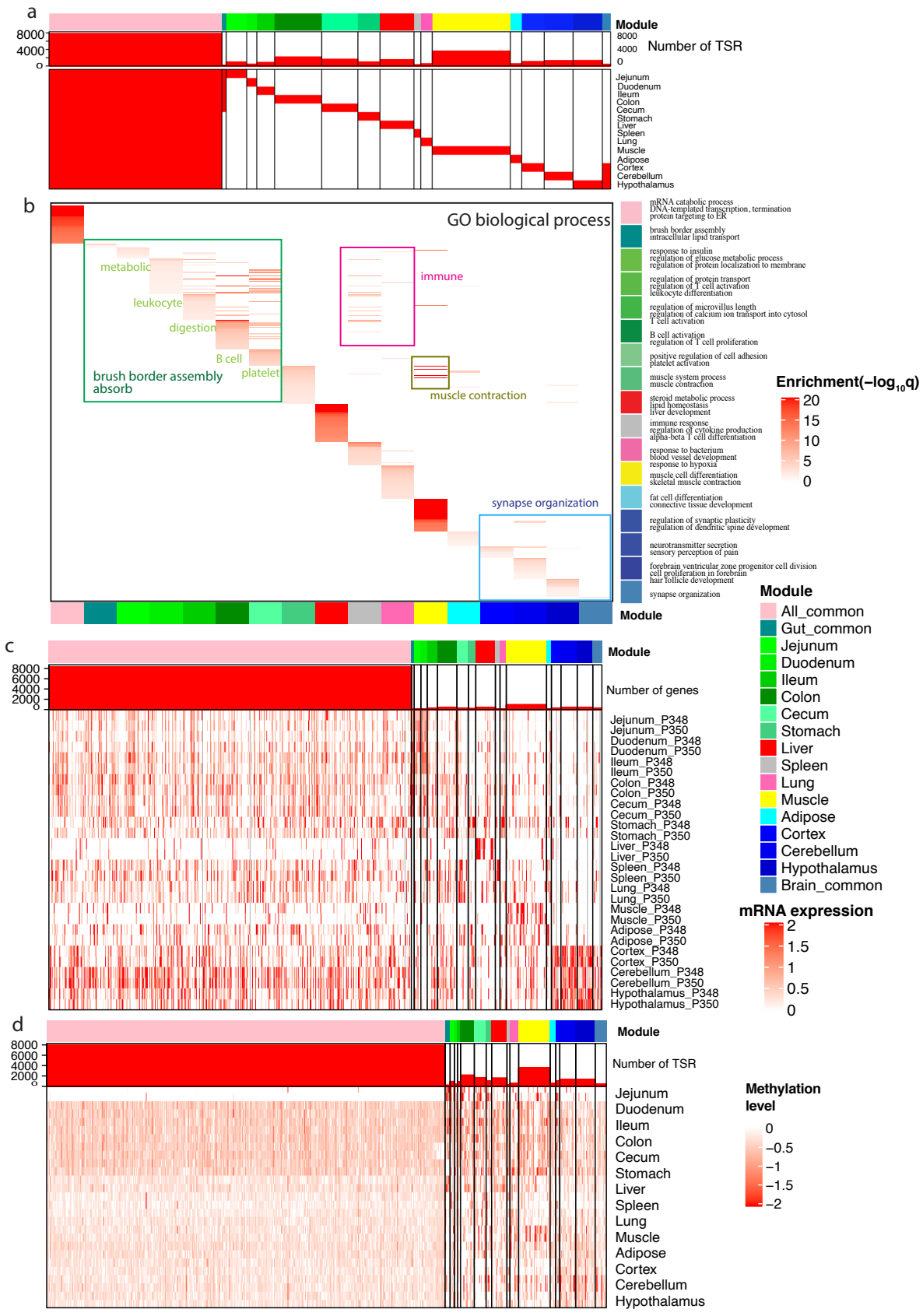


Supplementary Fig. 7 Methylation level and mouse phenotype enrichment of tissue-specific EnhAs. **a,** Methylation level of tissue-specific strong enhancers (EnhAs). The columns represent the genes in each module, the rows represent tissues. **b** Mouse phenotype enrichment of tissue-

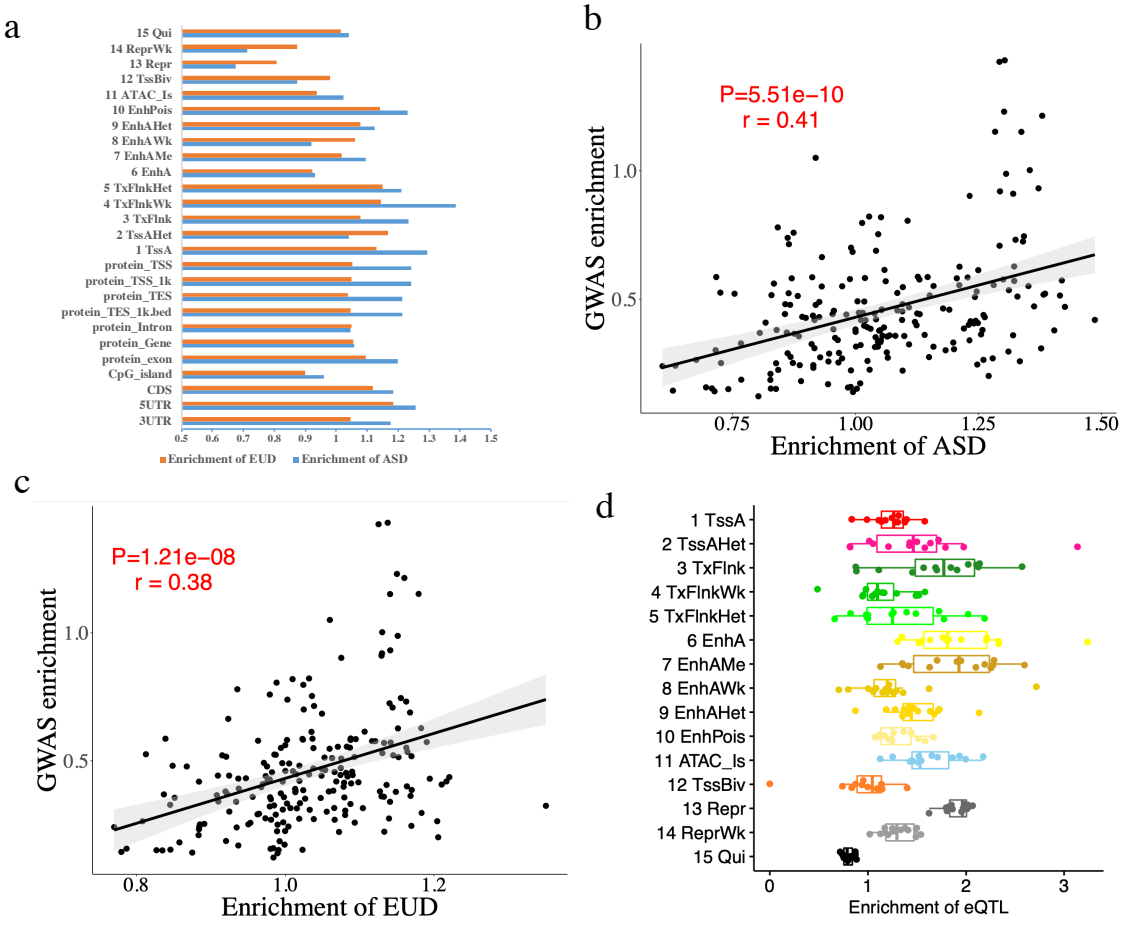
specific EnhAs. The columns represent 17 modules of strong enhancers. The rows represent phenotypes in each module.



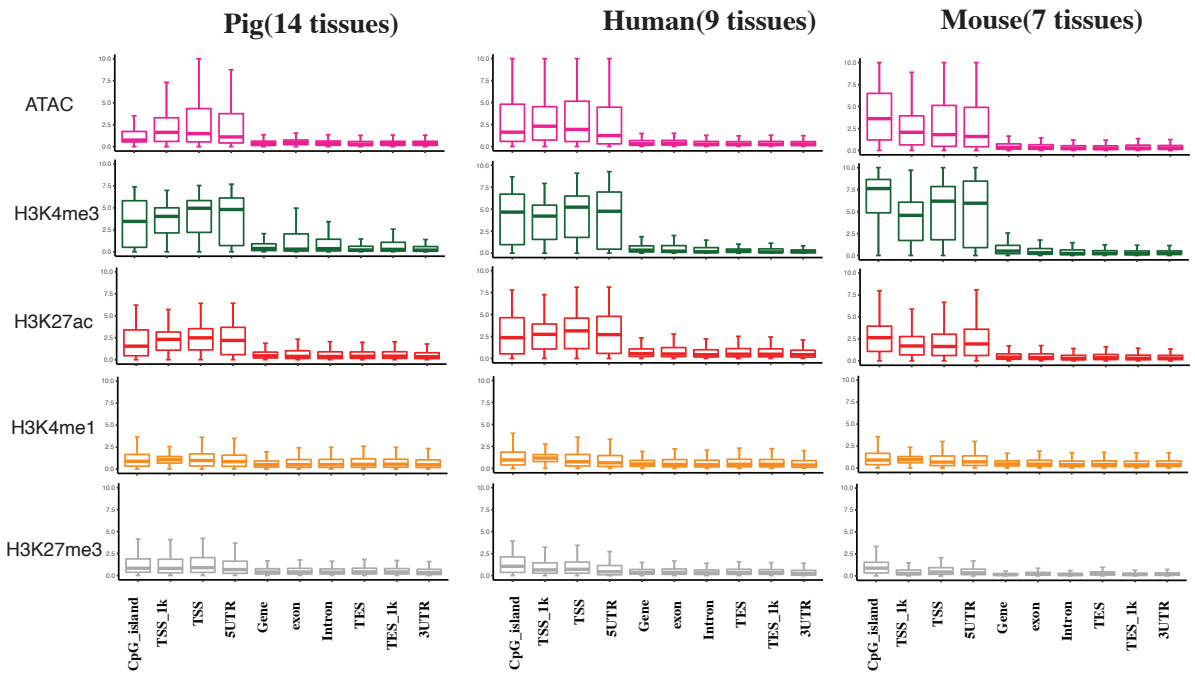
Supplementary Fig. 8 Motif enrichment of tissue-specific strong enhancers (EnhAs). **a,** Major motif enrichment in 14 tissues. **b,c,** The corresponded motif enrichment and mRNA expression in each tissues. (normalized and centered TPM). **d,** The correlation between motif enrichment and the mRNA expression of corresponding transcription factors' motif.


a
8000
4000
0
Module
Number of TSR
Jejunum
Duodenum
Ileum
Colon
Cecum
Stomach
Liver
Spleen
Lung
Muscle
Adipose
Cortex
Cerebellum
Hypothalamus
b
GO biological process
metabolic
leukocyte
digestion
B cell
brush border assembly
absorb
platelet
immune
muscle contraction
synapse organization
mRNA catabolic process
DNA-templated transcription, termination
protein targeting to ER
brush border assembly
intracellular lipid transport
response to insulin
regulation of glucose metabolic process
regulation of protein localization to membrane
regulation of protein transport
regulation of T cell activation
leukocyte differentiation
regulation of microvillus length
regulation of calcium ion transport into cytosol
T cell activation
B cell activation
regulation of T cell proliferation
positive regulation of cell adhesion
platelet activation
muscle system process
muscle contraction
steroid metabolic process
lipid homeostasis
liver development
immune response
regulation of cytokine production
alpha-beta T cell differentiation
response to bacterium
blood vessel development
response to hypoxia
muscle cell differentiation
skeletal muscle contraction
fat cell differentiation
connective tissue development
regulation of synaptic plasticity
regulation of dendritic spine development
neurotransmitter secretion
sensory perception of pain
forebrain ventricular zone progenitor cell division
cell proliferation in forebrain
hair follicle development
synapse organization
Module
Enrichment(−log10q)
20
15
10
5
0
Module
All_common
Gut_common
Jejunum
Duodenum
Ileum
Colon
Cecum
Stomach
Liver
Spleen
Lung
Muscle
Adipose
Cortex
Cerebellum
Hypothalamus
Brain_common
c
8000
6000
4000
2000
0
Module
Number of genes
Jejunum_P348
Jejunum_P350
Duodenum_P348
Duodenum_P350
Ileum_P348
Ileum_P350
Colon_P348
Colon_P350
Cecum_P348
Cecum_P350
Stomach_P348
Stomach_P350
Liver_P348
Liver_P350
Spleen_P348
Spleen_P350
Lung_P348
Lung_P350
Muscle_P348
Muscle_P350
Adipose_P348
Adipose_P350
Cortex_P348
Cortex_P350
Cerebellum_P348
Cerebellum_P350
Hypothalamus_P348
Hypothalamus_P350
mRNA expression
2
1.5
1
0.5
0
d
8000
6000
4000
2000
0
Module
Number of TSR
Jejunum
Duodenum
Ileum
Colon
Cecum
Stomach
Liver
Spleen
Lung
Muscle
Adipose
Cortex
Cerebellum
Hypothalamus
Methylation level
0
−0.5
−1
−1.5
−2

Supplementary Fig. 9 **Tissue-specific promoters (TssAs) and their potential functions in 14 tissues. a,** The number and enrichment distribution of 17 modules of promoters in tissues. TSR: tissue-specific regulatory elements. **b**, Functional enrichment of proximal (2000bp) genes for each module based on gene ontology (GO) biological processes. **c,** The mRNA expression (TPM) of promoters' target genes (2000bp around transcription start sites) in each module. **d,** Methylation level of tissue-specific promoters.

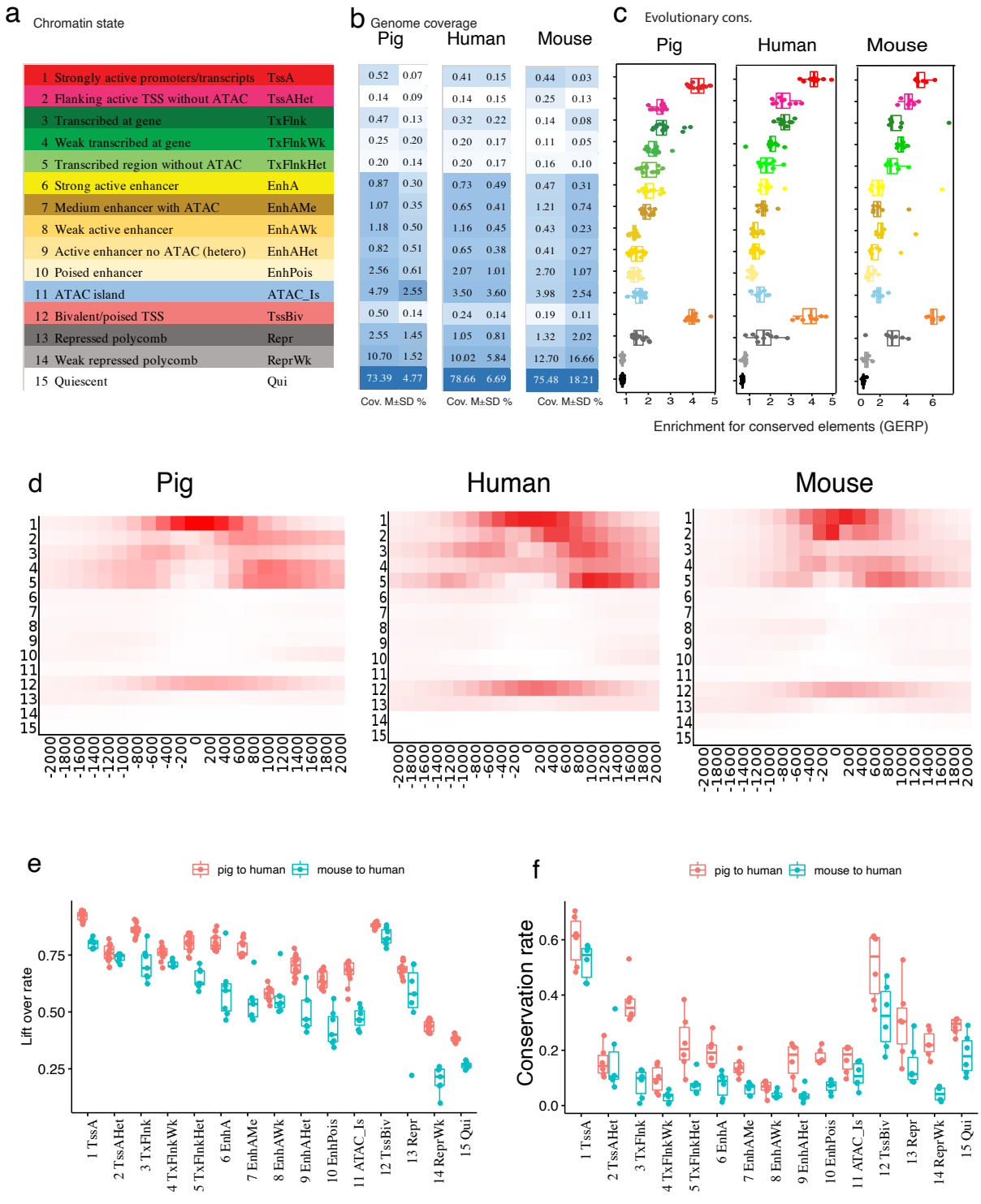


Supplementary Fig. 10 **Chromatin state enrichments of domestication selection signature and QTLs affecting complex traits in pigs. a,** Enrichment of selection signal of chromatin states compared with gene elements. ASD: Asian pig domestication; EUD: European pig domestication. **b,c,** Correlations among GWAS enrichment (44 traits) and domestication selection signature enrichment of chromatin states in tissues. **d**, Porcine muscle eQTL enrichment of chromatin states.



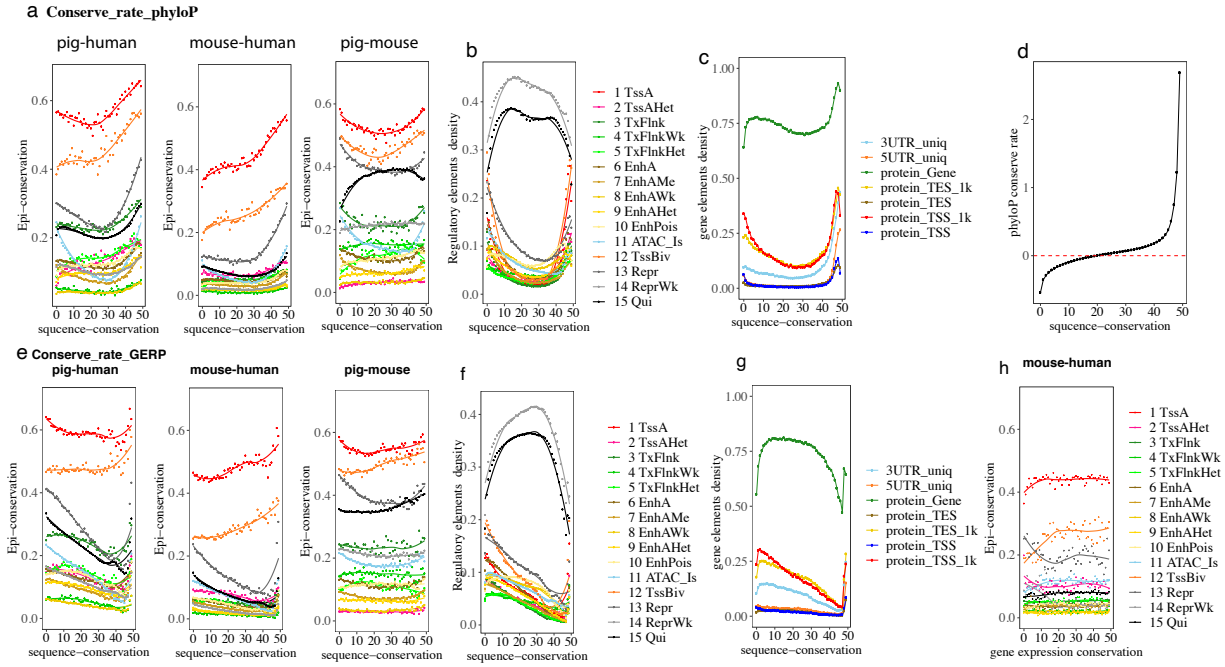
Supplementary Fig. 11 Traces of evolutionary conservation of epigenomes. Mark signal of gene elements among pig, human, and mouse.

87


a
Chromatin state
1 Strongly active promoters/transcripts TssA
2 Flanking active TSS without ATAC TssAHet
3 Transcribed at gene TxFlnk
4 Weak transcribed at gene TxFlnkWk
5 Transcribed region without ATAC TxFlnkHet
6 Strong active enhancer EnhA
7 Medium enhancer with ATAC EnhAMe
8 Weak active enhancer EnhAWk
9 Active enhancer no ATAC (hetero) EnhAHet
10 Poised enhancer EnhPois
11 ATAC island ATAC_Is
12 Bivalent/poised TSS TssBiv
13 Repressed polycomb Repr
14 Weak repressed polycomb ReprWk
15 Quiescent Qui
b
Genome coverage
Pig
Human
Mouse
Cov. M±SD %
c
Evolutionary cons.
Pig
Human
Mouse
Enrichment for conserved elements (GERP)
d
Pig
Human
Mouse
e
pig to human
mouse to human
Lift over rate
1 TssA
2 TssAHet
3 TxFlnk
4 TxFlnkWk
5 TxFlnkHet
6 EnhA
7 EnhAMe
8 EnhAWk
9 EnhAHet
10 EnhPois
11 ATAC_Is
12 TssBiv
13 Repr
14 ReprWk
15 Qui
f
pig to human
mouse to human
Conservation rate

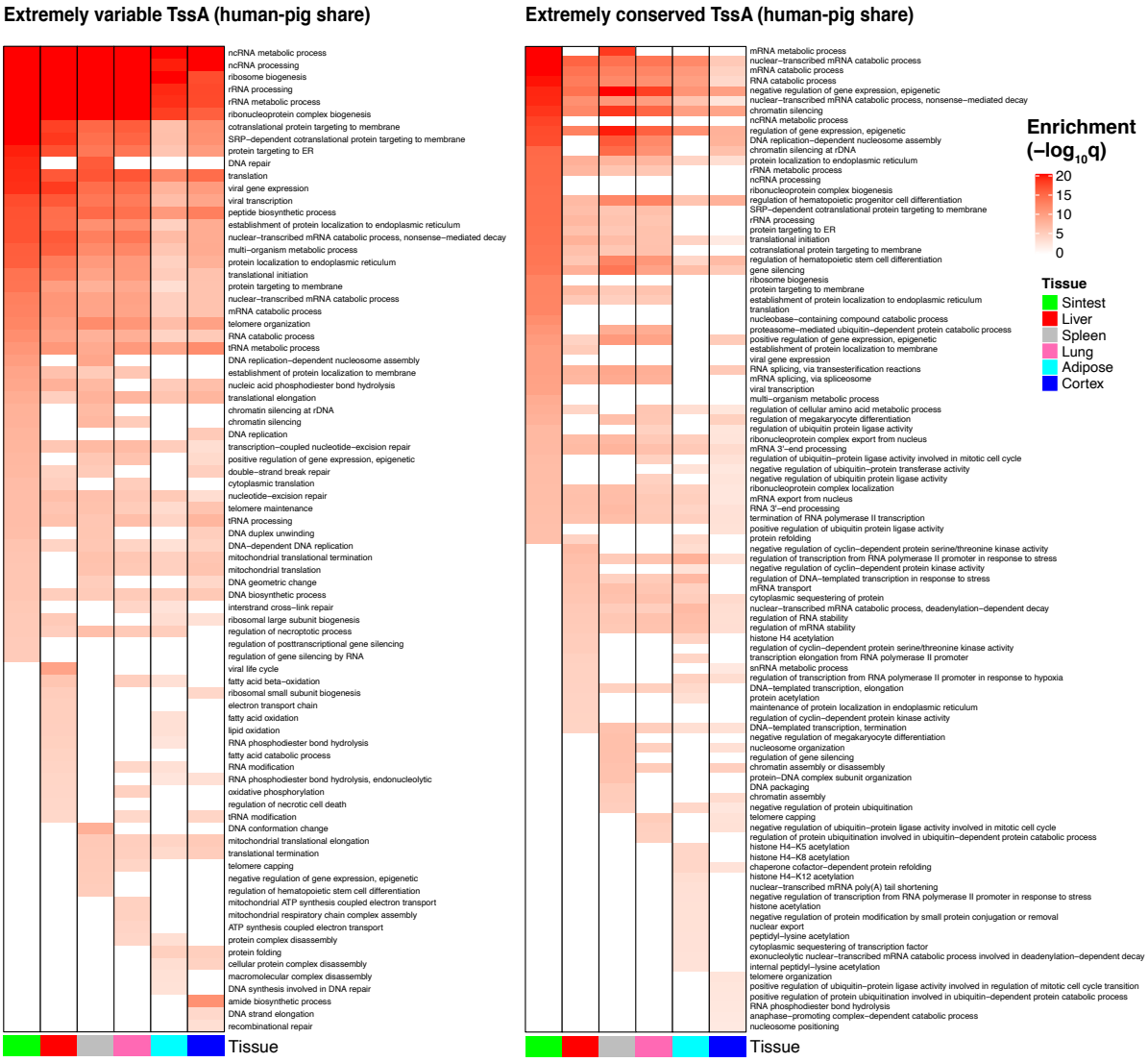
88

Supplementary Fig. 12 Chromatin state conservation in pig, human, and mouse. **a,** 15 chromatin states in three species genomes defined by the ChromHMM. **b,** Genome coverage for each chromatin state in three species. **c,** Fold enrichments of chromatin states for mammalian conserved elements (GERP) in three species. **d,** Enrichment of chromatin state around genes in three species. **e,** The difference of lift over rate for each chromatin state between pig to human and mouse to human. **f,** The difference of conservation rate of each chromatin state between pig to human and mouse to human.

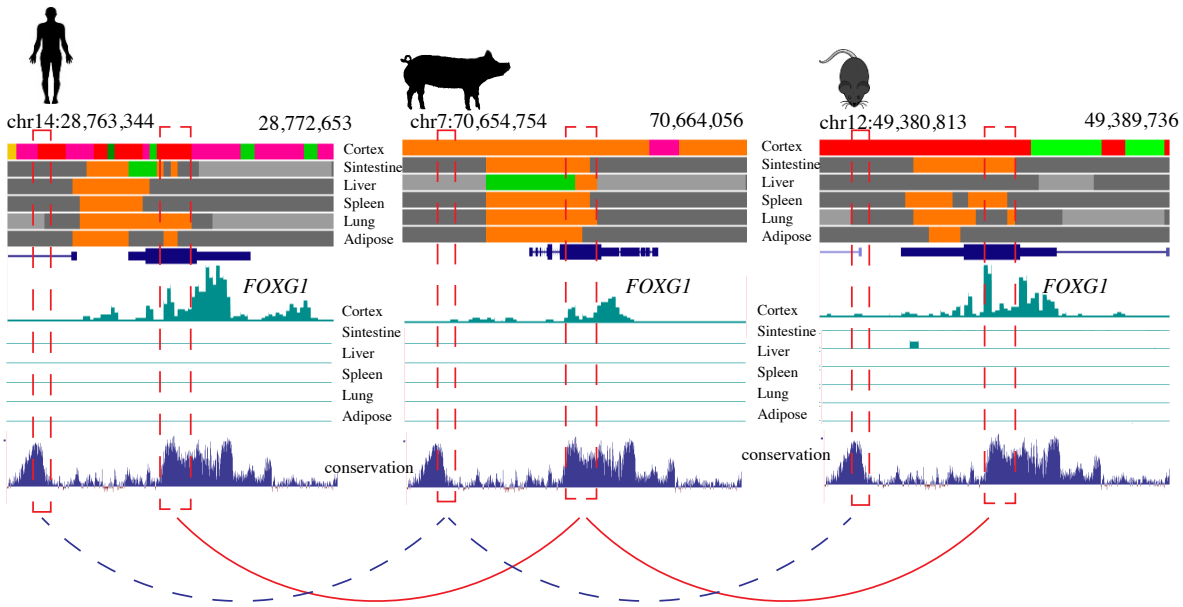


Supplementary Fig.13 Global comparison of genomic and epigenomic conservations. **a,** The relations between sequence conservation (phyloP conservation rate) and epigenomic conservation across 6 tissues. These segments were ordered from the fastest changing (0^{th}), to slowest changing (49^{th}). **b,** Regulatory elements density in different sequence conservation

segments. **c,** Gene elements densities in different sequence conservation segments. **d**, Average phyloP conservation rate in each segment. **e,** The relations between sequence conservation (GERP conservation rate) and epigenomic conservation. **f,g,** Regulatory and gene elements in different GERP conservation segments. **h**, Relationship between expression conservation and epigenomic conservation across 6 tissues in mouse-human pair. Expression conservation was based on expression of 14,302 orthologous genes among 3 species. Regions were ordered from the greatest difference (0^{th}), to smallest difference (49^{th}) in expression.



Supplementary Fig. 14 GO functional enrichments of TssA regulatory elements for sequences extremely variable (0^{th}) and extremely conserved regions (49^{th}).



115

116 Supplementary Fig. 15 Chromatin state, mRNA expression, sequence conservation around

117 *FOXG1* locus in pig, human and mouse. In sequence extremely conserved region, human

118 *FOXG1* has two brain cortex-specific TssAs (red dashed rectangle boxes) in which they are

119 TssABiv in pigs. Aim Forkhead Box G1(*FOXG1),* is very important gene in cortical cell fate

120 related with autism spectrum disorders and other brain disease[1,2], showed higher

121 *FOXG1*expression in human than that in pig brain cortex. Vertical scale 0-110 for RNA-seq.

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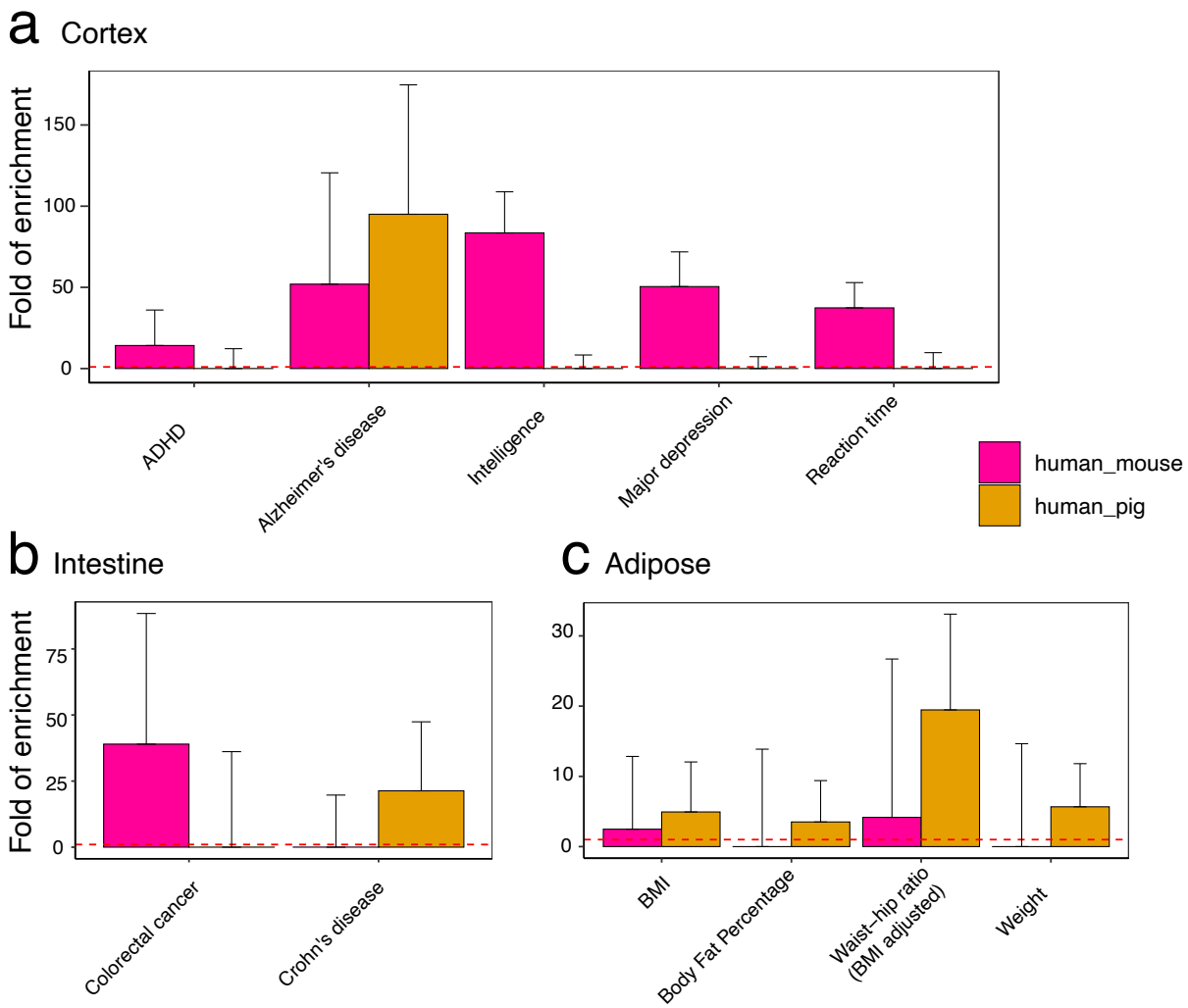

123

124 Supplementary Fig. 16 Different QTLs from human genome-wide association studies (GWAS)

125 (47 human diseases and complex traits) enrichment between human-pig and human-mouse

126 shared promoters (TssA) in brain cortex (**a**), small intestine (**b**), and adipose (**c**) tissues.

127

128

129

130

1. Mariani, J. *et al.* FOXG1-dependent dysregulation of GABA/glutamate neuron differentiation in autism spectrum disorders. *Cell* **162**, 375-390 (2015).
2. Hanashima, C., Li, S.C., Shen, L., Lai, E. & Fishell, G. Foxg1 suppresses early cortical cell fate. *Science* **303**, 56-59 (2004).