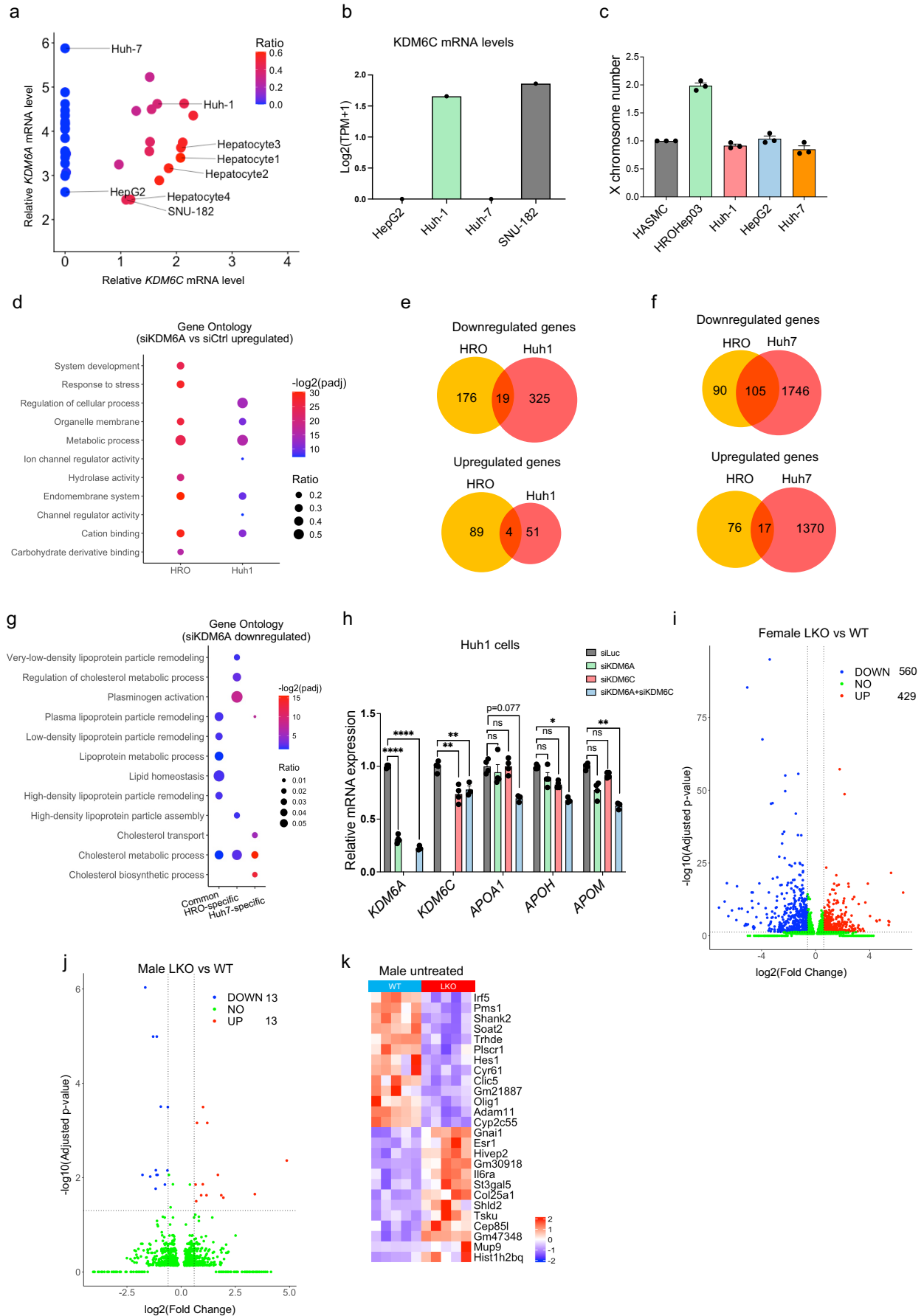
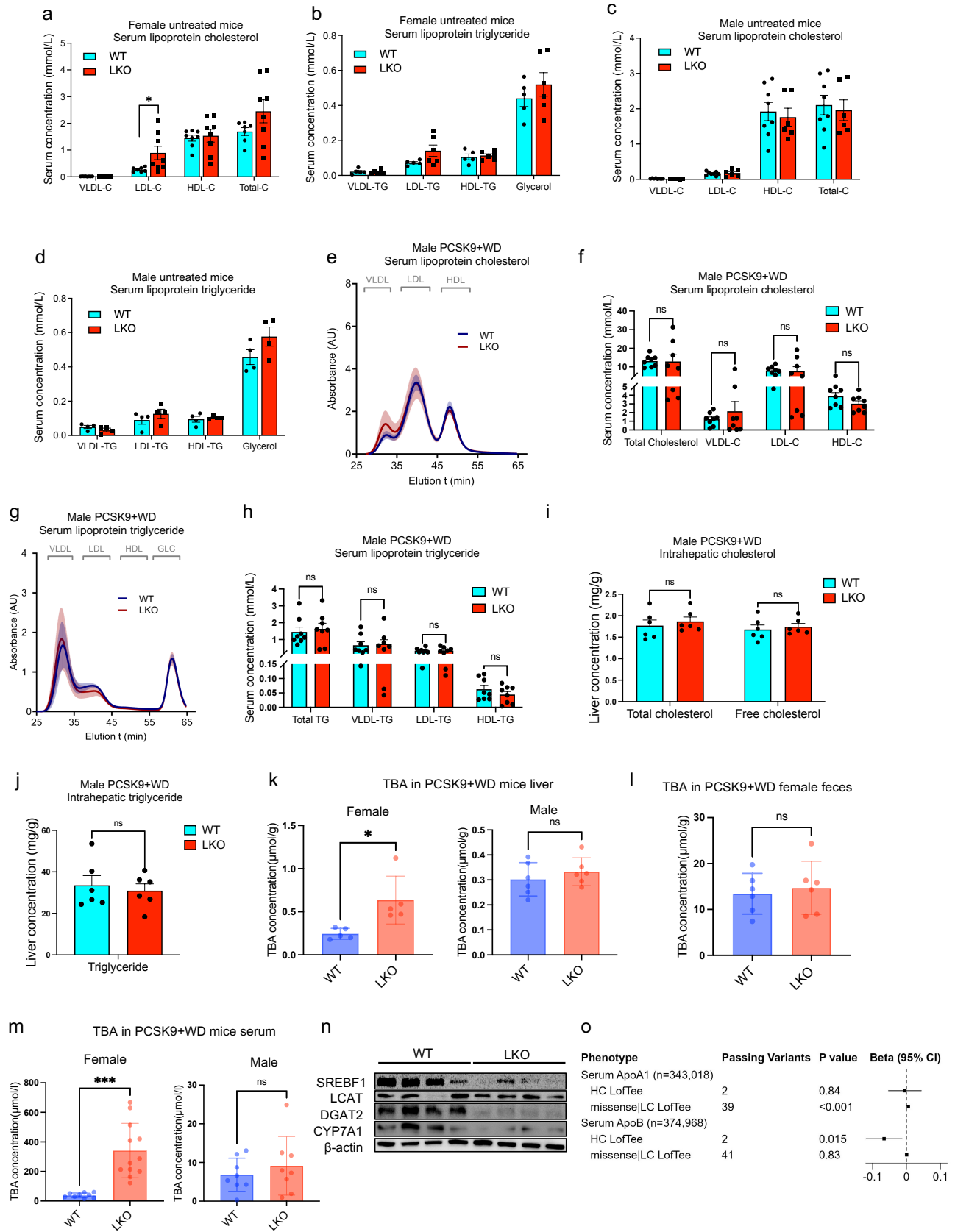
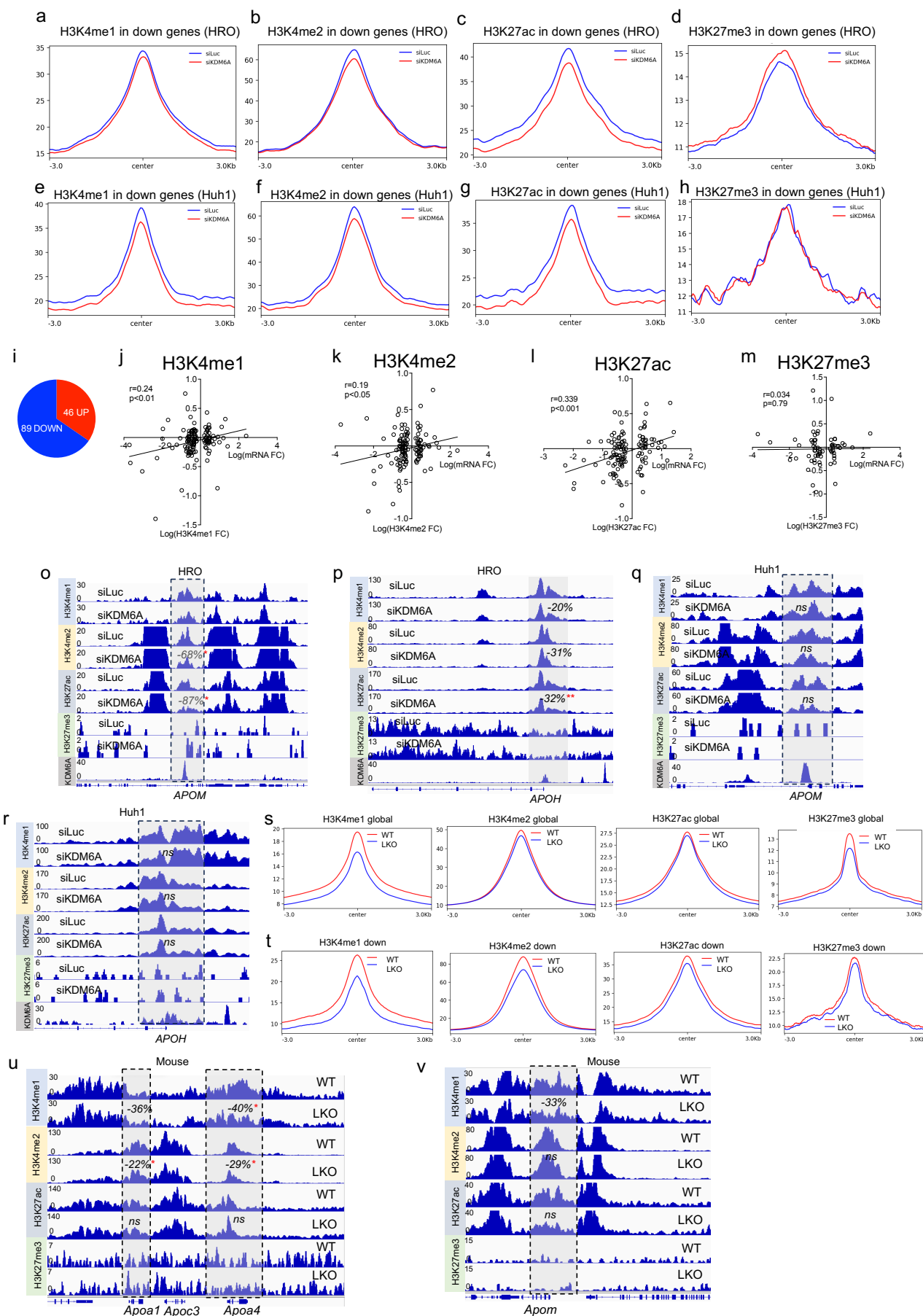




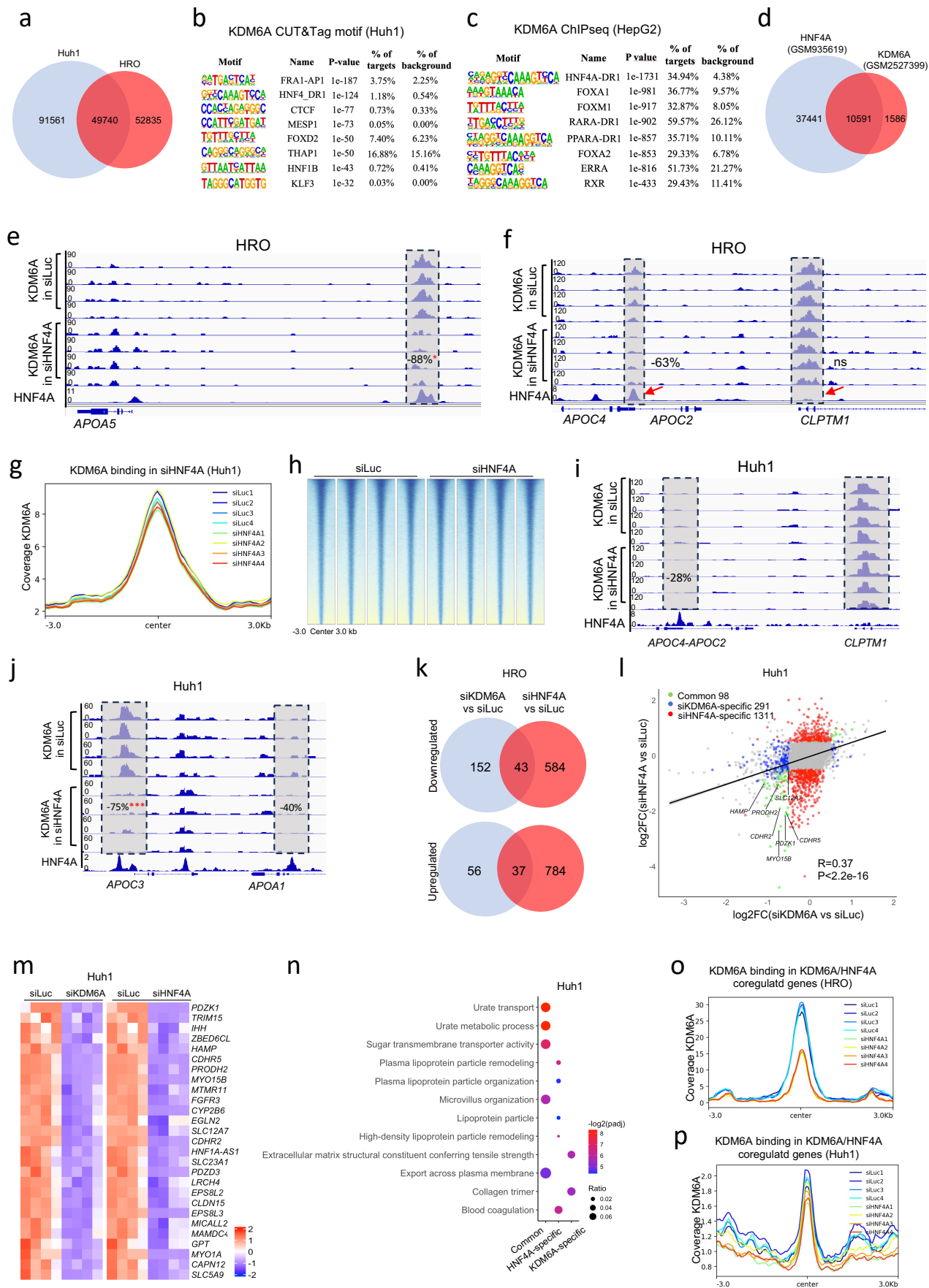
Supplementary Figure 1: (a) Correlation of *KDM6A* mRNA expression with *KDM6C* changes in 31 male liver cell lines and 4 male patients. The color represents the *KDM6A/KDM6C* ratio in each cell line. (b) *KDM6C* mRNA levels in different types of male liver cell lines. (c) X chromosome number in different types of male liver cell lines. (d) Gene ontology analysis in the increased genes upon *KDM6A* knockdown in HRO and Huh1 cells. The size of the dots shows the gene ratio; the color of each dot represents $-\log_2(\text{padj})$ of each pathway. (e) Venn diagram of the downregulated (upper panel) and upregulated (lower panel) genes between HRO and Huh1 cells upon *KDM6A* knockdown. (f) Venn diagram of the downregulated (upper panel) and upregulated (lower panel) genes between HRO and Huh7 cells upon *KDM6A* knockdown. (g) Gene ontology analysis of HRO- and Huh7-specific and commonly regulated genes. The size of the dots represents gene ratio, and the color of the dots shows $-\log_2(\text{padj})$. (h) qPCR analysis of key lipoprotein genes in si*KDM6A*, si*KDM6C* and double knockdown Huh1 cells. (n=3 or 4 in each group), one-way ANOVA followed by Tukey's test. Volcano plot showing the transcriptomic changes upon liver-specific *KDM6A* knockout in (i) female and (j) male mice. The blue, red and green dots represent downregulated, upregulated and unchanged genes. (k) Heatmap showing transcriptomic changes upon *KDM6A* liver knockout in male chow diet mice. All data are represented as mean $\pm$ s.e.m. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$.



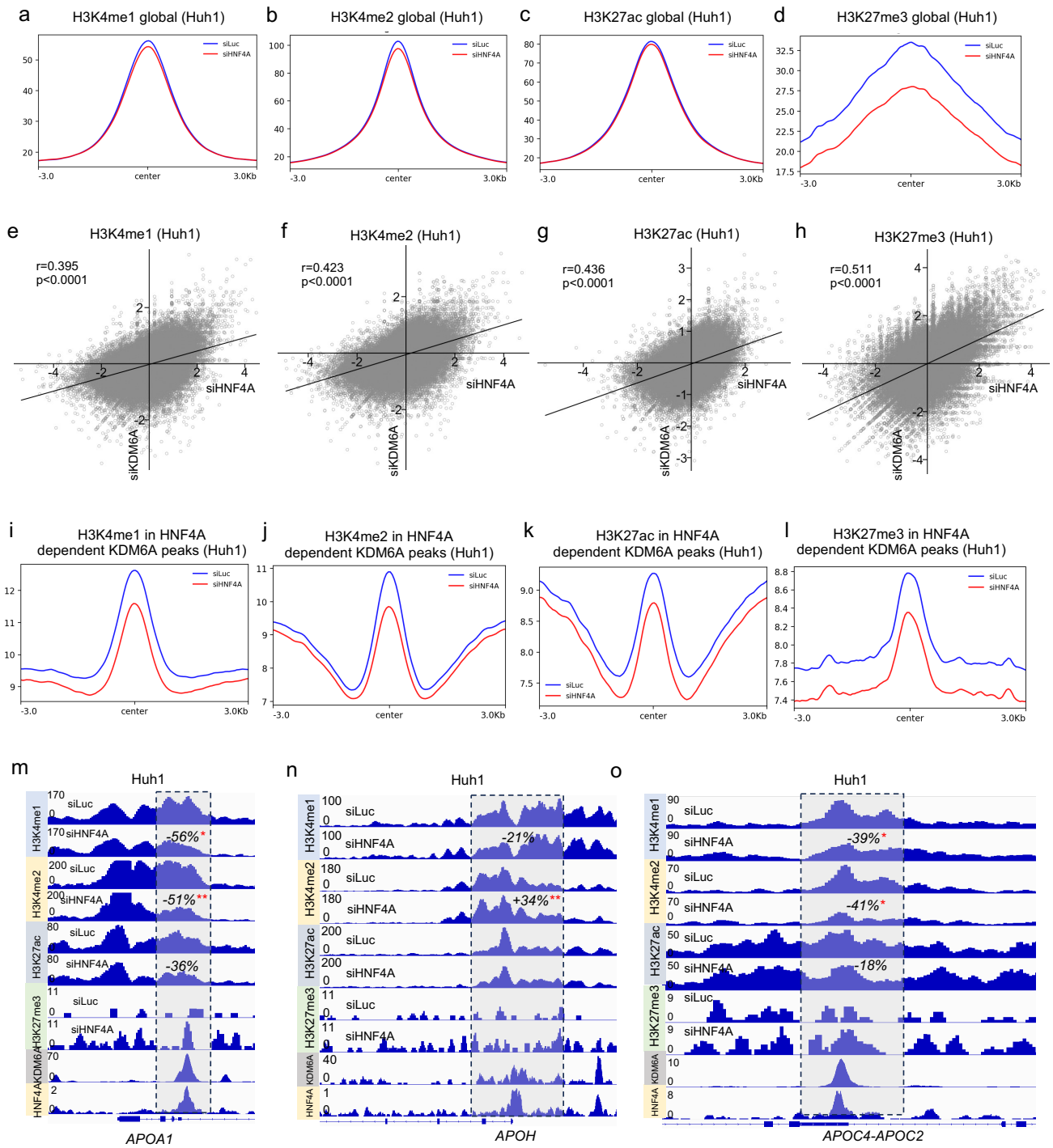
Supplementary Figure 2: *Kdm6a* LKO promoted atherosclerosis in vivo. FPLC quantification of **(a)** lipoprotein cholesterol (n=8) and **(b)** triglyceride (n=5 WT, n=6 LKO) in chow diet fed female mice, two-tailed unpaired Student's t test. FPLC quantification of **(c)** lipoprotein cholesterol (n=8 WT, n=6 LKO) and **(d)** triglyceride (n=4 WT and n=4 LKO) analysis in chow diet fed male mice, two-tailed unpaired Student's t test. **(e)** FPLC curve and **(f)** quantification of lipoprotein cholesterol, and **(g)** FPLC curve and **(h)** quantification of lipoprotein triglyceride in male AAV- PCSK9 mice upon (n=8 WT, n=8 LKO), two-tailed unpaired Student's t test. Intrahepatic **(i)** cholesterol and **(j)** triglyceride levels in triglyceride in WT and LKO male mice upon AAV- PCSK9 injection and western diet feeding (n=6 in each group), two-tailed unpaired Student's t test. **(k)** Intrahepatic total bile acid levels in AAV- PCSK9 female (n=5 WT, n=5 LKO) and male (n=6 WT, n=6 LKO) mice, two-tailed unpaired Student's t test. **(l)** Feces total bile acid levels in AAV-PCSK9 female WT and LKO (n=6 WT, n=6 LKO) mice, two-tailed unpaired Student's t test. **(m)** Serum total bile acid levels in AAV-PCSK9 female WT and LKO (n=9 WT, n=12 LKO) and male (n=8 WT, n=8 LKO) mice, two-tailed unpaired Student's t test. **(n)** WB analysis of WT (n=4) and LKO (n=4) female AAV-PCSK9 mouse liver biopsies. **(o)** Analysis of patient rare variants association with serum ApoA1 and ApoB in the T2D portal. All data are represented as mean $\pm$ s.e.m. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$.



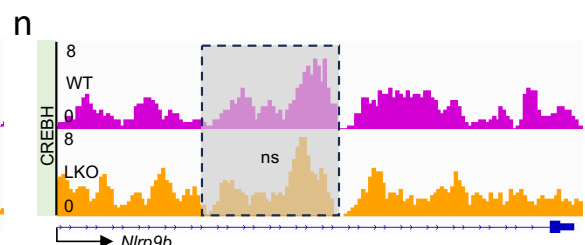
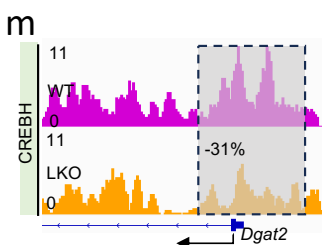
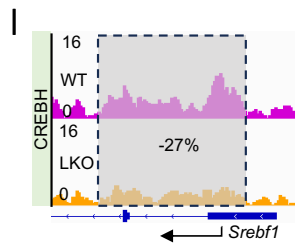
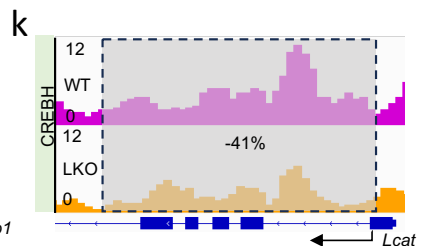
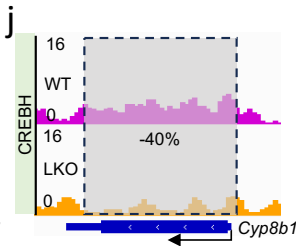
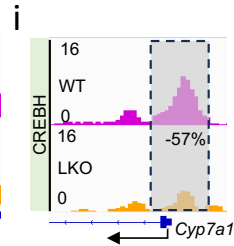
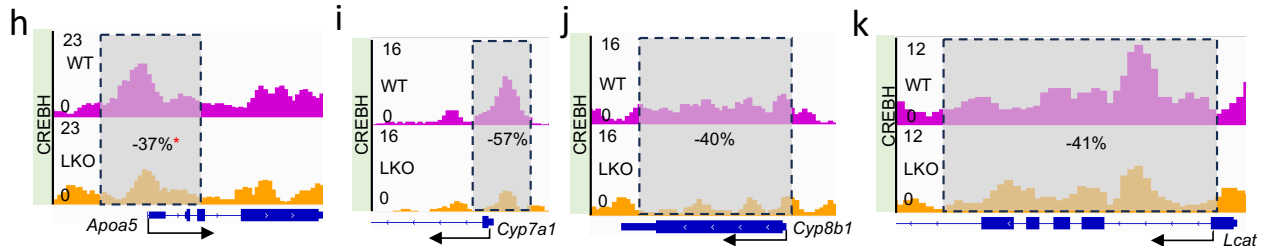
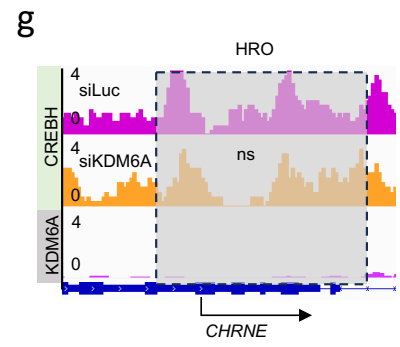
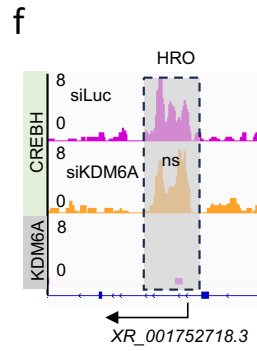
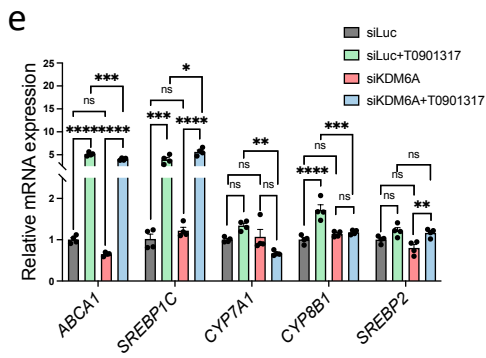
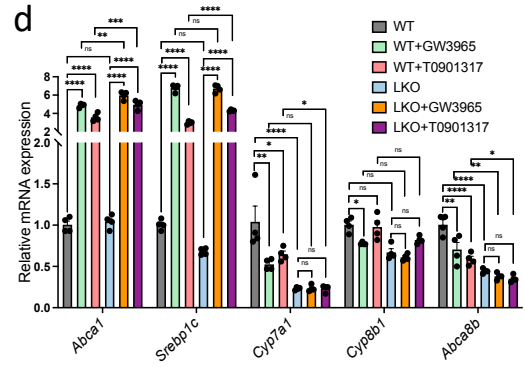
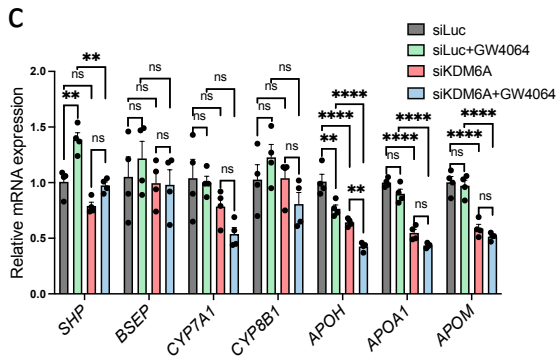
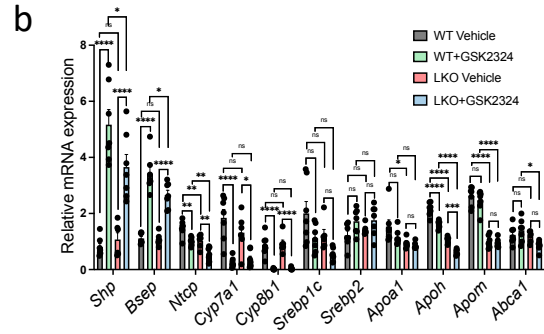
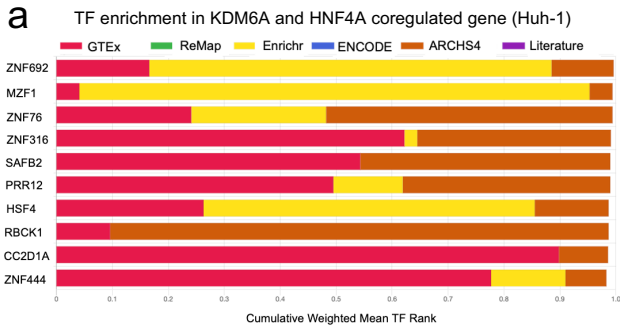
Supplementary Figure 3: KDM6A regulated lipoprotein and cholesterol metabolic genes are independent of its enzymatic activities. Coverage plot of **(a)** H3K4me, **(b)** H3K4me2, **(c)** H3K27ac and **(d)** H3K27me3 ChIPseq in downregulated gene loci upon KDM6A knockdown in HRO cells. Coverage plot of **(e)** H3K4me, **(f)** H3K4me2, **(g)** H3K27ac and **(h)** H3K27me3 ChIPseq in downregulated gene loci upon KDM6A knockdown in Huh1 cells. **(i)** Pie chart showing the number and percentage of up- and downregulated LnC genes upon KDM6A knockdown in HRO cells. Correlation of LnC gene expression with **(j)** H3K4me1, **(k)** H3K4me2, **(m)** H3K27ac and **(n)** H3K27me3 changes in HRO cells. Genome browser screenshots of H3K4me1, H3K4me2, H3K27ac and H3K37me3 ChIPseq results in siLuc and siKDM6A HRO cells at **(o)** *APOM* and **(p)** *APOH* loci in HRO cells. Genome browser screenshots of H3K4me1, H3K4me2, H3K27ac and H3K37me3 ChIPseq results in siLuc and siKDM6A at **(q)** *APOM* and **(r)** *APOH* loci in Huh1 cells. Coverage plot of H3K4me1, H3K4me2, H3K27ac and H3K27me3 ChIP-seq peaks in the female WT and LKO mouse liver **(s)** genome widely and at **(t)** downregulated gene loci. Genome browser screenshot of H3K4me1, H3K4me2, H3K27ac and H3K27me3 ChIP-seq at **(u)** *Apoa1/Apoc3/Apoa4* gene cluster and **(v)** *Apom* locus in female WT and LKO mouse liver samples (merged bigwig files from n=3 in each group).



Supplementary Figure 4: KDM6A interplays with HNF4A to control lipoprotein and cholesterol metabolic genes. **(a)** Venn diagram showing the overlapped KDM6A CUT&Tag peaks in Huh1 and HRO cells. Motif analysis of KDM6A **(b)** CUT&Tag peaks in Huh1 and **(c)** ChIPseq peaks in HepG2 cells. **(d)** Venn diagram showing the overlapped HNF4A and KDM6A ChIPseq peaks in HepG2 cells. Genome browser screenshot showing KDM6A CUT&Tag peaks at siLuc and siHNF4A in HRO cells, HNF4A ChIP-seq peaks at **(e)** *APOA5* and **(f)** *APOC2/APOC4* gene cluster. **(g)** Coverage plot and **(h)** heatmap of the genome wide KDM6A CUT&Tag peak changes upon HNF4A knockdown in Huh1 cells (n=4). Screenshots of genome browser showing KDM6A CUT&Tag peaks in siLuc and siHNF4A transfected Huh1 cells, HNF4A (GSM935619) and KDM6A (GSM257399) ChIP-seq peaks at **(i)** *APOC4-APOC2* gene cluster, *CLPTM1* (control gene) locus and **(j)** *APOA1/APOC3* gene cluster. **(k)** Venn diagram to compare the downregulated (upper panel) and upregulated (lower panel) genes in siKDM6A and siHNF4A RNAseq of HRO cells. **(l)** Correlation analysis of RNA-seq between KDM6A (x axis) and HNF4A (y axis) knockdown in HRO cells. The blue, red and green dots represent KDM6A- and HNF4A-specific and commonly regulated genes, non-parametric Spearman's test. **(m)** Heatmap showing the representative KDM6A and HNF4A commonly regulated genes in Huh1 cells. **(n)** Gene ontology analysis of KDM6A- and HNF4A-specific and commonly downregulated genes in Huh1 cells. The size of the dots means gene ratio and the color shows $-\log_2(\text{padj})$. Coverage plot of the KDM6A CUT&Tag peak changes of KDM6A/HNF4A coregulated genes upon HNF4A knockdown in **(o)** HRO and **(p)** Huh1 cells (n=4).



Supplementary Figure 5: HNF4A coregulated epigenetic changes with KDM6A in the liver cells. Coverage plots of (a) H3K4me1, (b) H3K4me2, (c) H3K27ac and (d) H3K27me3 in siLuc and siHNF4A transfected Huh1 cells. Correlation analysis (e) H3K4me1, (f) H3K4me2, (g) H3K27ac and (h) H3K27me3 ChIP-seq changes in siKDM6A and siHNF4A transfected Huh1 cells x and y axis represents log2(fold change) of each peak. Coverage plots of (i) H3K4me1, (j) H3K4me2, (k) H3K27ac and (l) H3K27me3 in HNF4A dependent KDM6A peaks. Genome browser screenshots of H3K4me1, H3K4me2, H3K27ac and H3K27me3 ChIP-seq at (m) *APOA1*, (n) *APOH* and (o) *APOC2/APOC4* gene cluster in siLuc and siHNF4A transfected Huh1 cells (merged bigwig files from n=4 in each group). Spearman's correlation test was performed to compare the siHNF4A and siKDM6A peaks.



Supplementary Figure 6: KDM6A removal affected CREBH but not FXR or LXR in the liver. **(a)** Transcription factor enrichment analysis of KDM6A and HNF4A coregulated genes in Huh1 cells by CHEA3. qPCR analysis of **(b)** floxed and LKO female mouse livers after injection with FXR agonist GSK2324 (n=6 or 7 in each group), one-way ANOVA followed by Tukey's test; **(c)** siLuc and siKDM6A transfected HRO cells treated with FXR agonist GW4064 (n=4 in each group), one-way ANOVA followed by Tukey's test; **(d)** floxed and LKO female primary mouse hepatocytes treated with LXR agonists GW3965 and T0901317 (n=4 in each group), one-way ANOVA followed by Tukey's test; **(e)** siLuc and siKDM6A transfected HRO cells treated with LXR agonist T0901317 (n=4 in each group), one-way ANOVA followed by Tukey's test. Genome browser screenshots of CREBH binding in HRO cells at **(f)** *XR_001752718.3* and **(g)** *CHRNE* gene loci. Crebh ChIP-seq peaks in AAV-PCSK9 female WT and LKO mice at **(h)** *Apoa5*, **(i)** *Cyp7a1*, **(j)** *Cyp8b1*, **(k)** *Lcat*, **(l)** *Srebf1*, **(m)** *Dgat2*, **(n)** *Nlrp9b* gene cluster. All data are represented as mean $\pm$ s.e.m. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$.