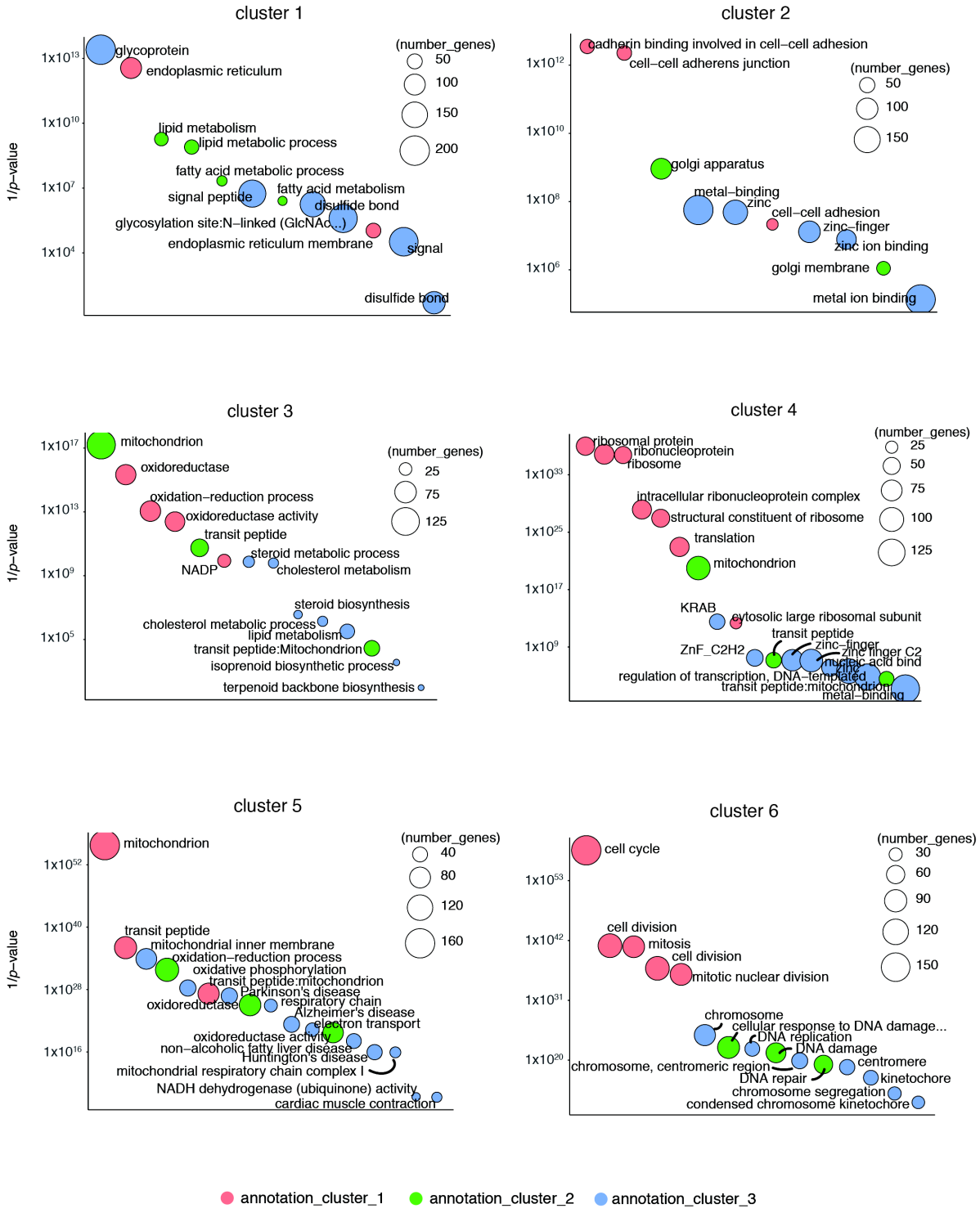


Figure S1. Related to Figure 1. GO DAVID analysis of WT liver regeneration gene clusters identified by unsupervised clustering from Figure 1C. Circles represent gene ontology categories that are most significantly enriched with y-axis being 1/*P*-value and size of circle proportional to number of genes in each category. Red, green, and blue depict the first, second, and third ranked GO DAVID annotation cluster by enrichment score, respectively.

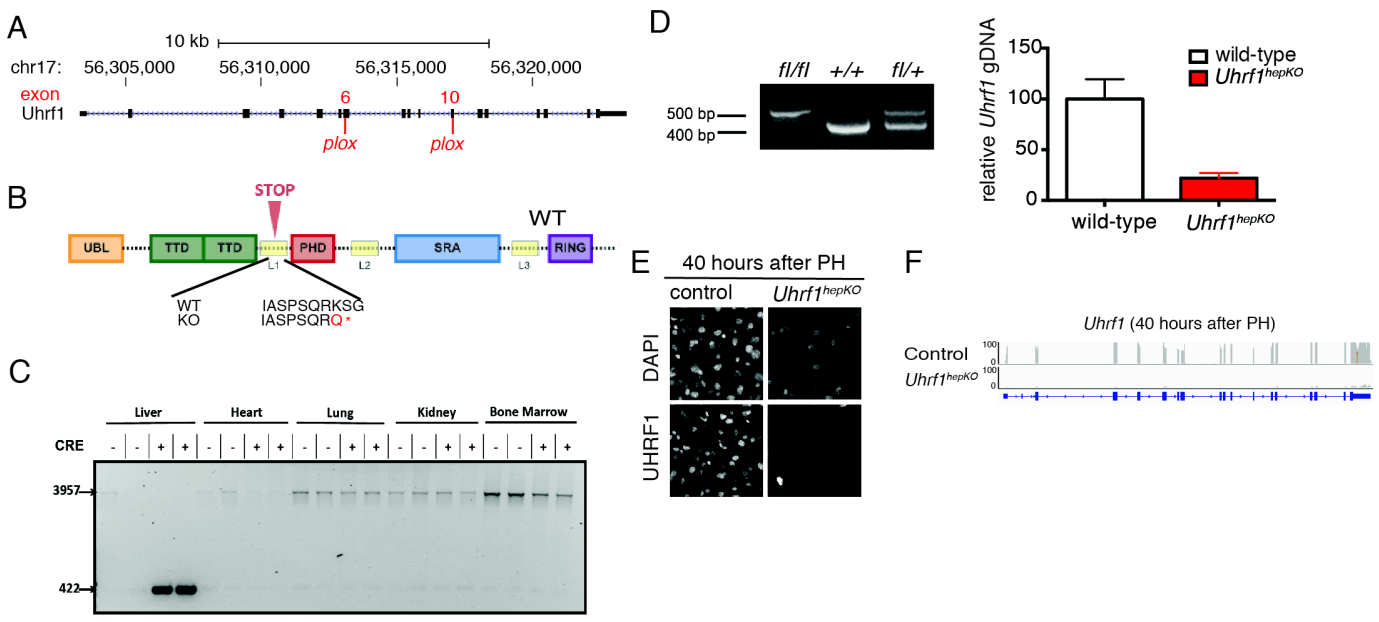
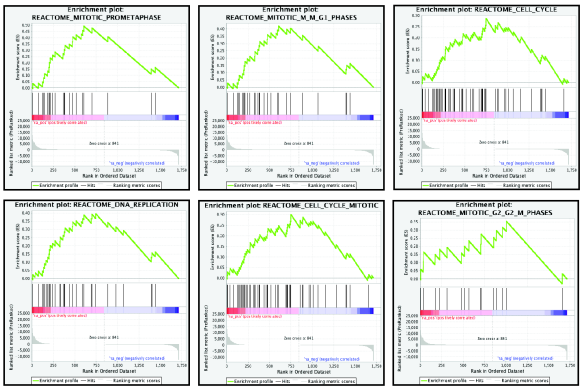


Figure S2. Related to Figure 2. (A) Cartoon illustration depicting where the flox sites are engineered within the *Uhrf1* gene locus. (B) Cartoon illustration depicting where the stop codon is engineered with respect to known domains in the UHRF1 protein in *Uhrf1*^{hepKO} mice. (C) PCR amplification of the *Cre* transgene gDNA isolated from various tissues of *Uhrf1*^{hepKO} mice (primer sequences found in supplementary table) with the 422 bp amplicon indicates presence of the *Cre* transgene and the 3957 bp amplicon corresponding to the wild-type allele. (D) PCR amplification of *Uhrf1* floxed or the corresponding WT alleles from gDNA isolated from whole liver tissue of homozygous floxed (*Uhrf1*$^{fl/fl}$), heterozygous floxed (*Uhrf1*$^{fl/+}$), or WT (*Uhrf1*$^{+/+}$) mice. (E) UHRF1 protein detected by immunofluorescence in WT or *Uhrf1*^{hepKO} mouse liver cryosections at 36 hours post-PH (N=1). (F) Expression of *Uhrf1* in the liver of WT or *Uhrf1*^{hepKO} mouse at 40 hours post-PH (time-point of maximum *Uhrf1* detection in regenerating liver of WT mice) detected by RNAseq as displayed on UCSC genome browser (N=1). Error bars represent s.d.

A

96 hours post-PH GSEA



REACTOME name	FDR
REACTOME_MITOTIC_PROMETAPHASE	0
REACTOME_MITOTIC_M_M_G1_PHASES	0
REACTOME_CELL_CYCLE	0
REACTOME_DNA_REPLICATION	0
REACTOME_CELL_CYCLE_MITOTIC	0
REACTOME_PHASE1_FUNCTIONALIZATION_OF_COMPOUNDS	0.002904
REACTOME_RESPONSE_TO_ELEVATED_PLATELET_CYTOSOLIC_CA2_	0.004591
REACTOME_BIOLOGICAL_OXIDATIONS	0.004182
REACTOME_HEMOSTASIS	0.01019
REACTOME_CYTOKINE_SIGNALING_IN_IMMUNE_SYSTEM	0.014683
REACTOME_IMMUNE_SYSTEM	0.01486
REACTOME_AXON_GUIDANCE	0.016362
REACTOME_SLC_MEDIATED_TRANSMEMBRANE_TRANSPORT	0.016176
REACTOME_PLATELET_ACTIVATION_SIGNALING_AND_AGGREGATION	0.022823
REACTOME_TRANSMEMBRANE_TRANSPORT_OF_SMALL_MOLECULES	0.028402
REACTOME_INTERFERON_SIGNALING	0.03601
REACTOME_MITOTIC_G2_G2_M_PHASES	0.045417
REACTOME_MRNA_PROCESSING	0
REACTOME_PROCESSING_OF_CAPPED_INTRON_CONTAINING_PRE_MRNA	0
REACTOME_MRNA_SPLICING	5.04E-04
REACTOME_ASPARAGINE_N_LINKED_GLYCOSYLATION	0.013192
REACTOME_METABOLISM_OF_RNA	0.014718
REACTOME_UNFOLDED_PROTEIN_RESPONSE	0.015005
REACTOME_POST_TRANSLATIONAL_PROTEIN_MODIFICATION	0.027909
REACTOME_METABOLISM_OF_PROTEINS	0.025762
REACTOME_HIV_INFECTION	0.024517

B

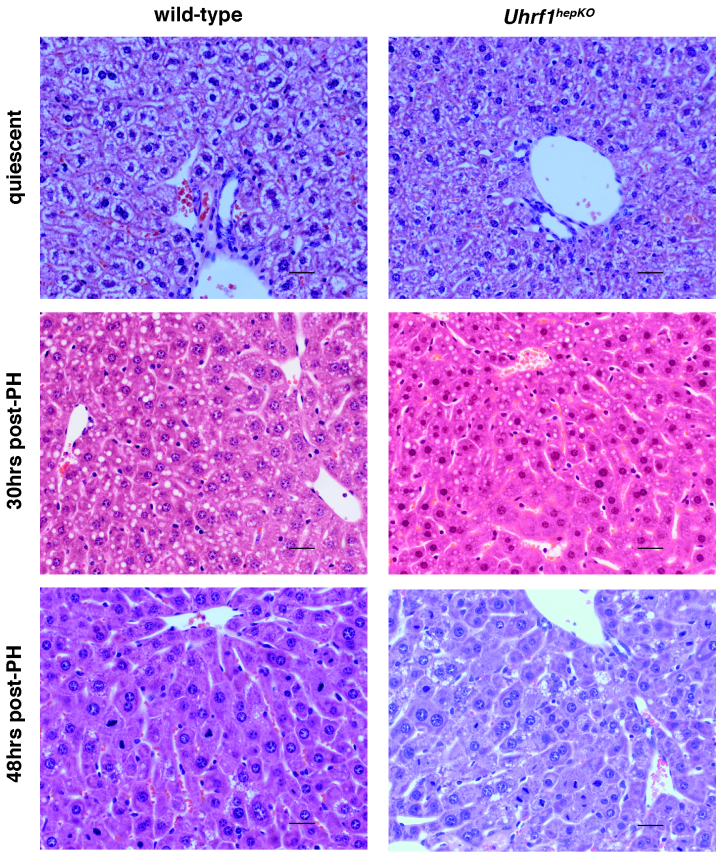


Figure S3. Related to Figure 5. (A) GSEA of differentially expressed genes at 96 hours post-PH showing most enriched pathways. (B) Representative hematoxylin and eosin staining of control and *Uhrf1*^{hepKO} livers during regeneration taken at 400X magnification.

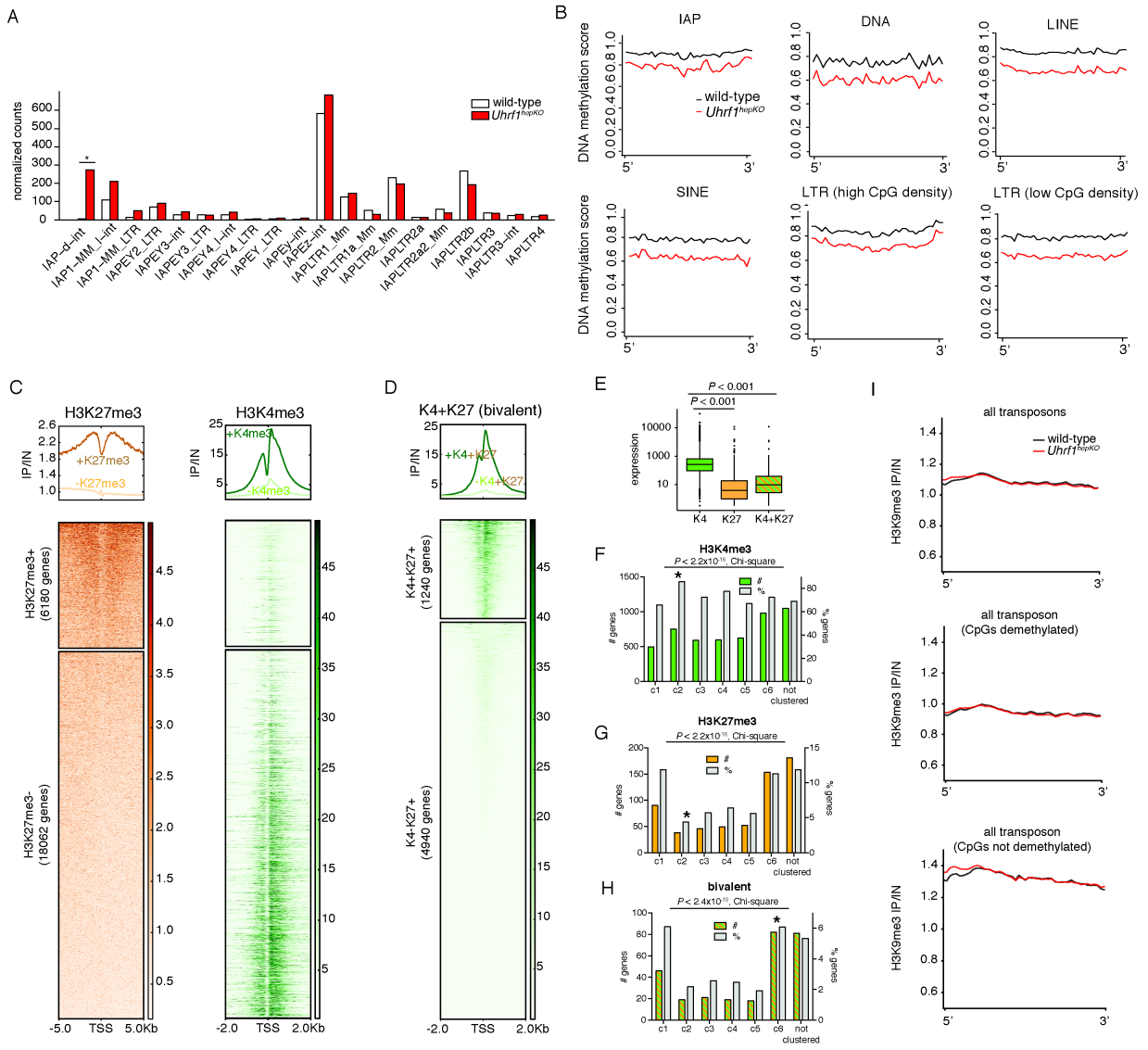


Figure S4. Related to Figure 6. (A) Comparing expression of 20 subfamilies of IAPs between wild-type and *Uhrf1*^{hepKO} quiescent livers, "*" denote significantly different between WT and KO. (B) K-means clustering of H3K27me3 ChIP-seq enrichment scores for all gene promoters into 2 groups ("H3K27me3+" and "H3K27me3-") and the corresponding H3K3me3 ChIP-seq enrichment scores plotted as heatmaps and averages. (C) K-means clustering of "H3K27me3+" promoters from A into 2 groups ("K4+ K27+" and "K4- K27+") according to H3K4me3 ChIP-seq enrichment scores. (D) Expression of genes marked by H3K4me3, H3K27me3, or both in the baseline liver. *** P<0.001 compared to the "H3K4me3" group by one-way ANOVA followed by Turkey's multiple comparison test. Number of genes from each gene cluster (identified in Fig. 1D) that have promoters marked with H3K4me3 (E, $P < 2.2x10^{-16}$, Chi-squared), H3K27me3 (F, $P < 2.2x10^{-16}$, Chi-squared), or both (G, $P < 2.2x10^{-16}$, Chi-square with * depicting the group that contributed the most to significance by residual calculations). (H) Average DNA methylation enrichment profiles for control and *Uhrf1*^{hepKO} mouse livers at eRRBS mapped IAP, DNA, LINE, SINE, high and low CpG density LTR family of TEs. (I) Average H3K9me3 ChIP-seq enrichment profiles for control and *Uhrf1*^{hepKO} mouse livers at all eRRBS mapped TEs, those with demethylated CpGs, and those with no change in CpGs.

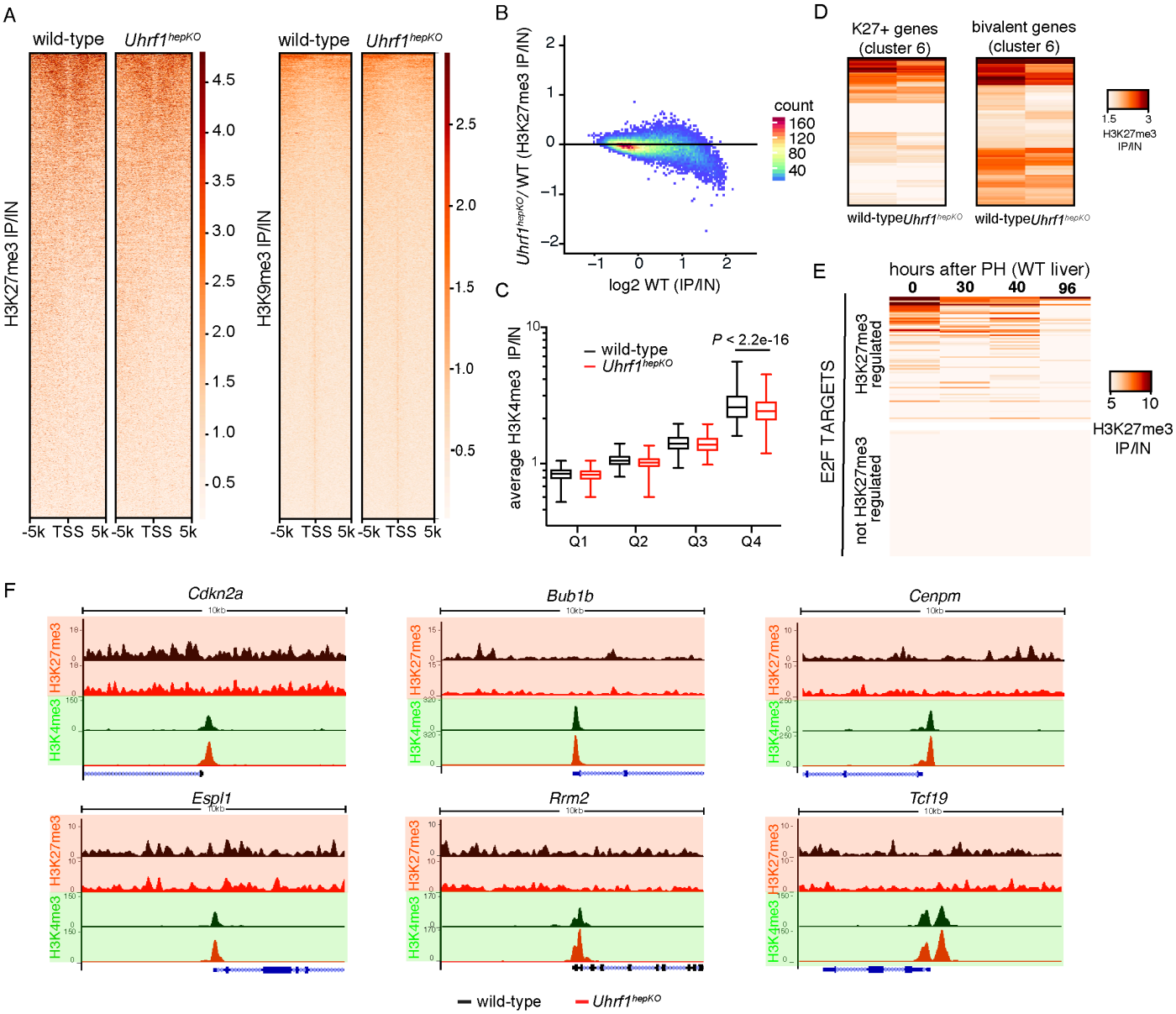


Figure S5. Related to Figure 7. (A) Heatmap showing a global decrease in H3K27me3 IP/IN signal in promoter of all genes but no change in H3K9me3. (B) H3K27me3 IP/IN signal for all promoters shown as scatter plot. (C) H3K27me3 IP/IN signal for all promoters broke down into quartiles and displayed as box-and-whisker plots. Error bars represent s.d. (D) Heatmap showing overall loss H3K27me3 IP/IN signal from 153 K27+ cluster 6 genes. (E) Heatmap showing overall loss H3K27me3 IP/IN signal from 82 K4+K27+ (bivalent) cluster 6 genes. (F) UCSC genome browser screenshots of 6 H3K27me3-regulated E2F targets from (E) that lost H3K27me3 and gained H3K4me3 in the promoter region in *Uhrf1*^{hepKO} livers.