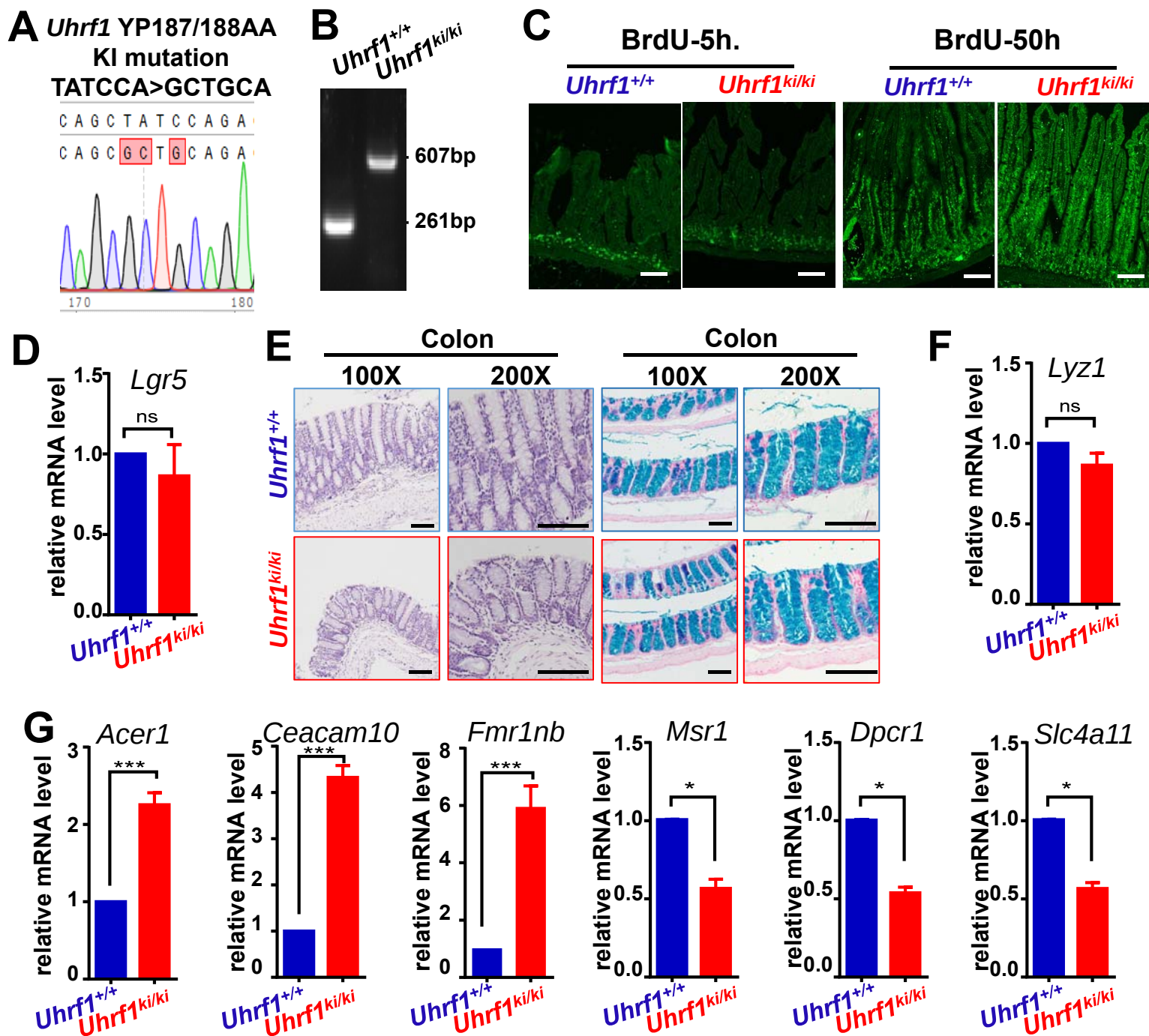
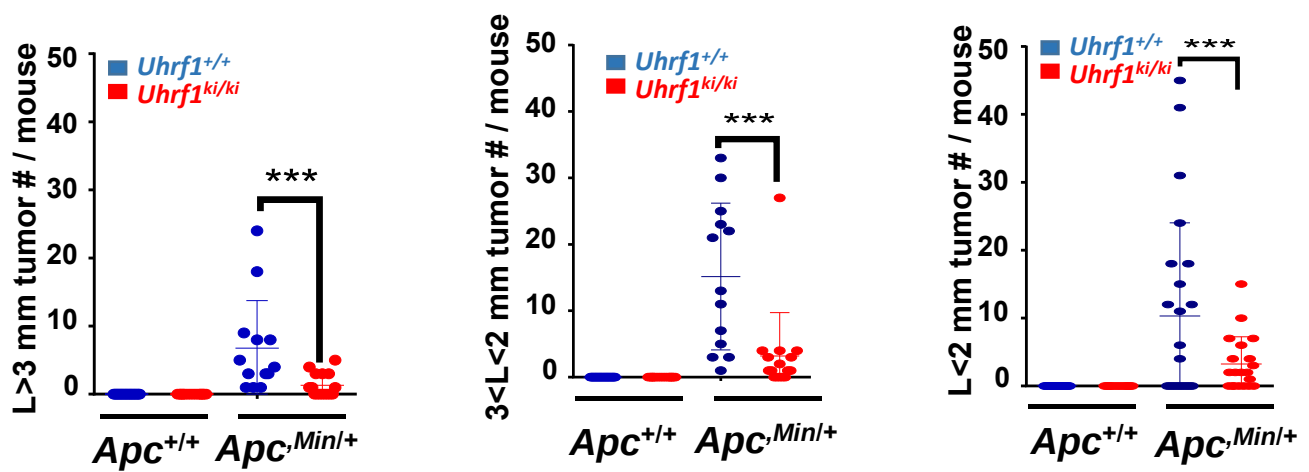
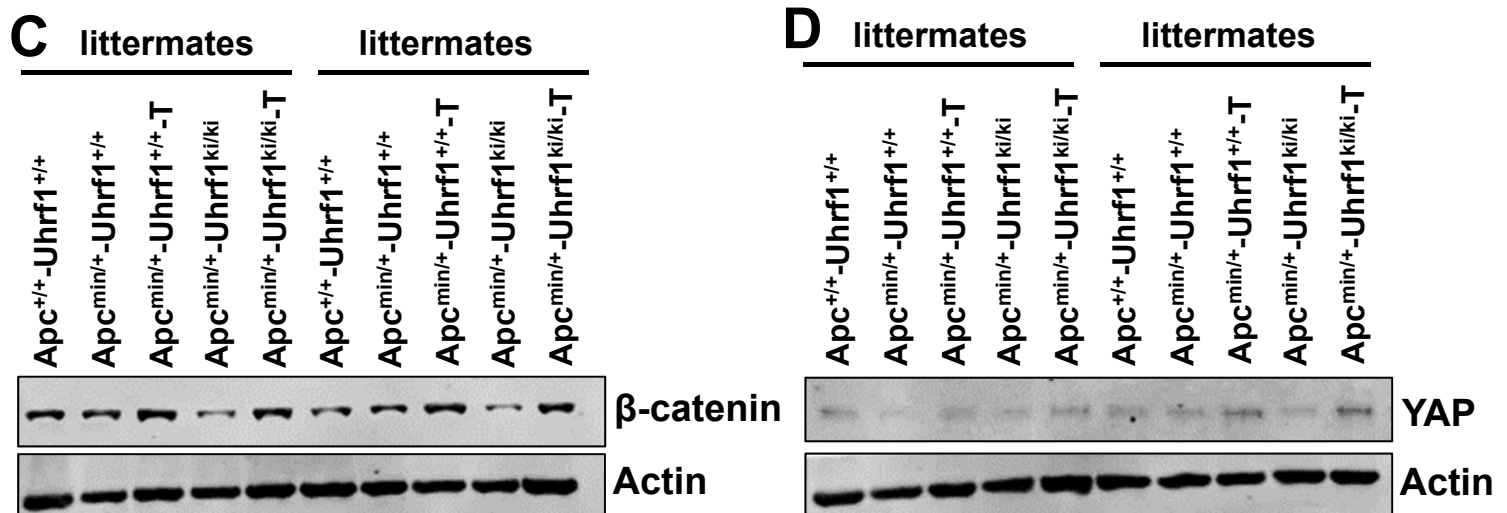
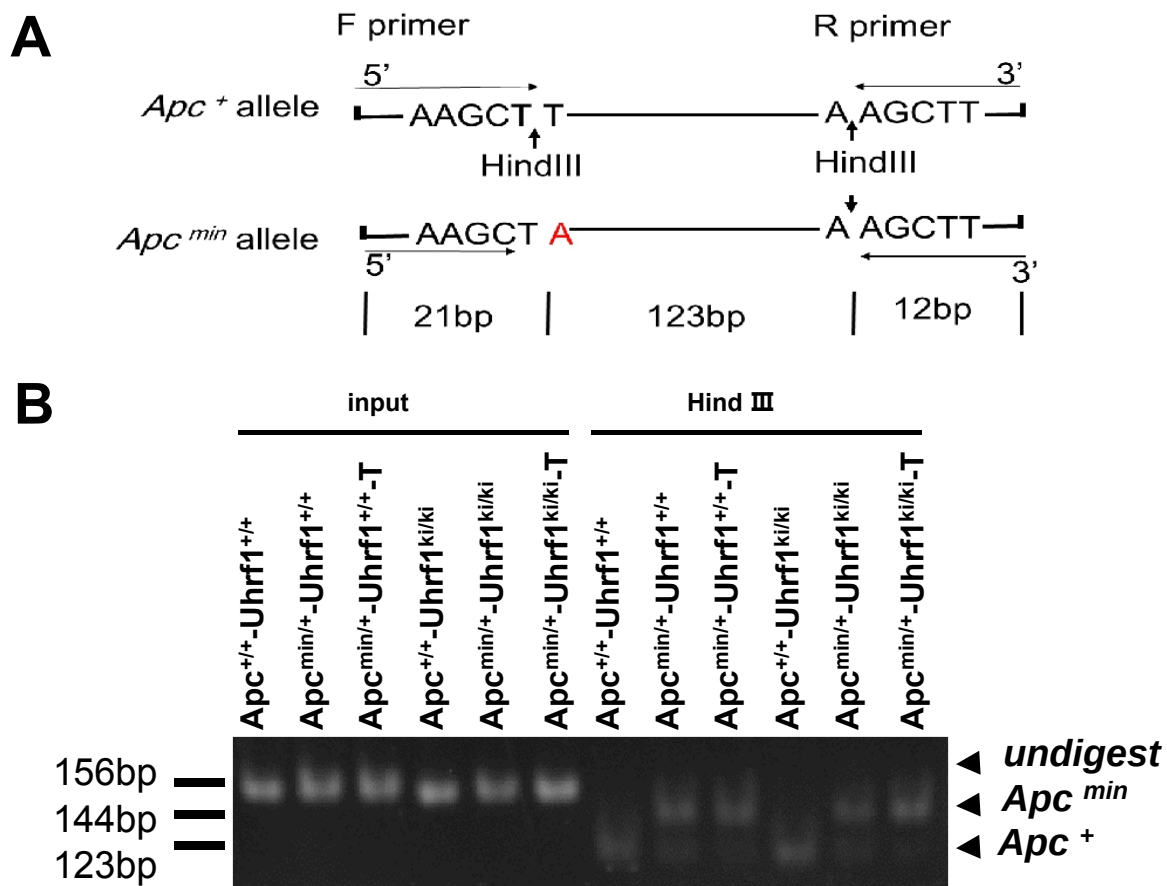




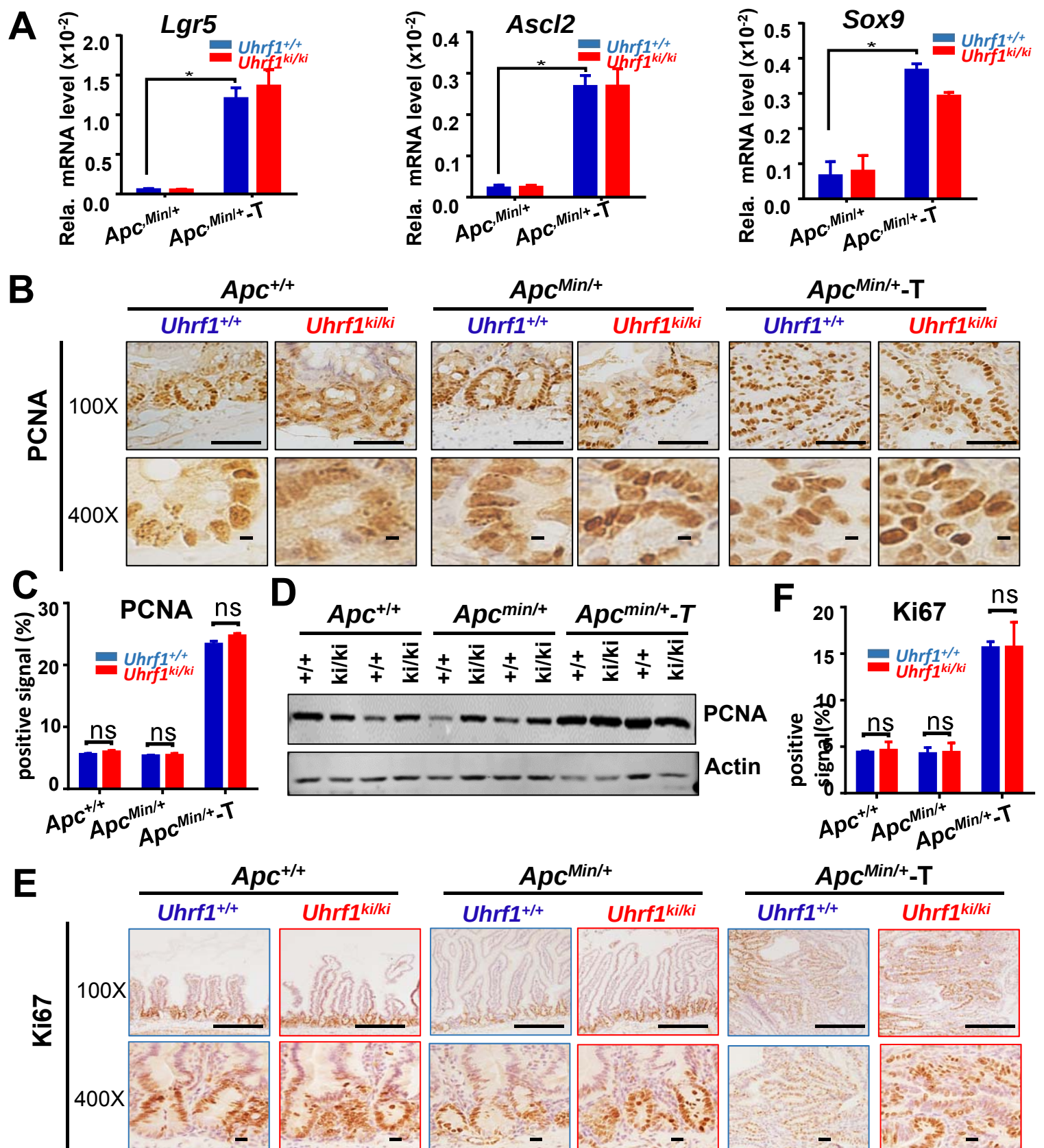
Supplementary Figure S1. Characterization of *Uhrf1*-TTD-KI (*Uhrf1*^{ki/ki}) mutant mice. (A) Genotyping by DNA sequencing. The representative sequencing data show GCTGCA sequence that encodes Alanine 187 and Alanine 188 in homozygous *Uhrf1*^{ki/ki} mutant mice. The corresponding sequence in *Uhrf1*^{+/+} mouse is TATCCA, which encodes Tyrosine 187 and Proline 188. (B) Genotyping by PCR-based DNA amplification. *Uhrf1*^{+/+} and *Uhrf1*^{ki/ki} mutant mice gave rise to a 261bp and a 607bp PCR product, respectively. (C) Representative immunofluorescence staining for incorporated BrdU in small intestinal sections from *Uhrf1*^{+/+} and *Uhrf1*^{ki/ki} mutant mice. Scale bars, 100 μ m. (D) qRT-PCR analysis showing similar levels of stem cell marker *Lgr5* in *Uhrf1*^{+/+} and *Uhrf1*^{ki/ki} mutant mice. ns, no significant with $p > 0.05$. (E) HE staining (left) and alcian blue staining (right) showing similar colon structure and numbers of Goblet cells in colon tissues from *Uhrf1*^{+/+} and *Uhrf1*^{ki/ki} mutant mice. Shown were representative results from 8-week mice. Scale bar, 100 μ m. (F) qRT-PCR analysis showing similar levels of Paneth cell marker *Lyz1* in *Uhrf1*^{+/+} and *Uhrf1*^{ki/ki} mutant mice. (G) Verification of differential gene expression by qRT-PCR analysis. The differentially expressed genes were identified by RNA-seq analysis. For (D), (F) and (G), the level of mRNA in the *Uhrf1*^{+/+} mice was set as 1 for each gene. *Uhrf1*^{+/+}, n=3; *Uhrf1*^{ki/ki}, n=3. Error bars, S.E. *** $p < 0.001$; * $p < 0.05$.



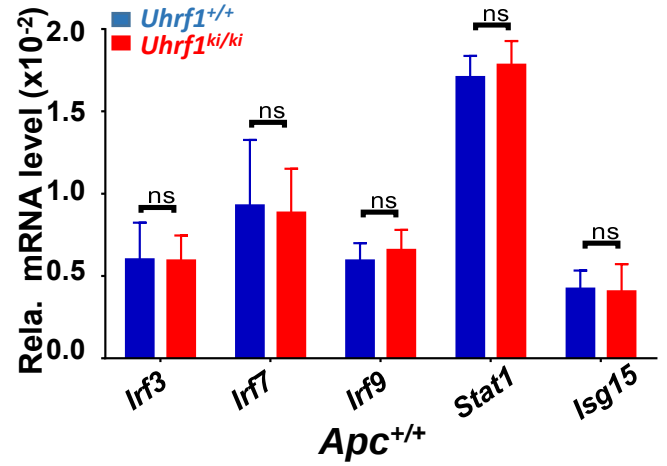
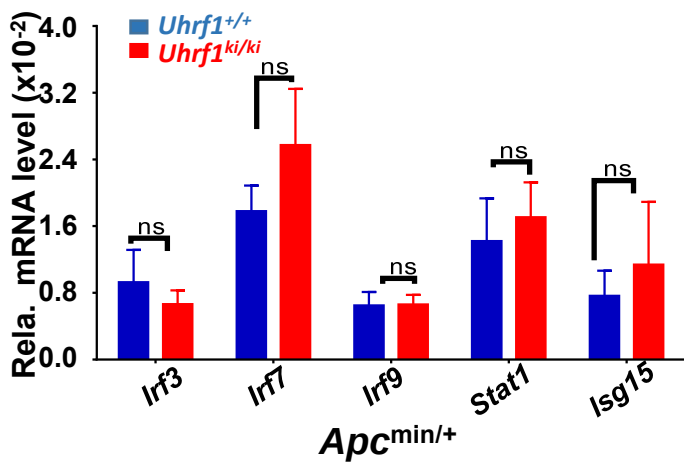
Supplementary Figure S2. Intestinal tumorigenesis is substantially suppressed in *Uhrf1*^{ki/ki}/*Apc*^{min/+} mice. Tumors were classified according to sizes into groups with diameter > 3 mm, 3 mm < L < 2 mm, and L < 2 mm. The tumors were then plotted according to the numbers of tumors per mouse. The numbers of mice analyzed: *Uhrf1*^{+/+}/*Apc*^{+/+}, n=21; *Uhrf1*^{ki/ki}/*Apc*^{+/+}, n=16; *Uhrf1*^{+/+}/*Apc*^{min/+}, n=23; and *Uhrf1*^{ki/ki}/*Apc*^{min/+}, n=20. Error bars, S.E. ***p < 0.001.



Supplementary Figure S3. DNA hypomethylation caused by *Uhrf1*-TTD-KI mutation has no effect on *Apc* LOH and activation of Wnt and Hippo pathways in *Apc*^{min/+} mice. (A) The schematic diagram of PCR-based detection of *Apc* LOH. The *Apc*⁺ and *Apc*^{min} alleles differ in HindIII digestion, with a 123 bp product for *Apc*⁺ allele and 144 bp product for *Apc*^{min} allele. (B) *Apc*⁺ LOH was detected in small intestinal tissues and tumors from both *Uhrf1*^{+/+}/*Apc*^{min/+}; *Uhrf1*^{ki/ki}/*Apc*^{min/+} mice. PCR-based assay of *Apc* locus was performed with genomic DNA from small intestinal epithelium cells or microdissected tumors from *Uhrf1*^{+/+}/*Apc*^{+/+}, *Uhrf1*^{ki/ki}/*Apc*^{+/+}, *Uhrf1*^{+/+}/*Apc*^{min/+}, and *Uhrf1*^{ki/ki}/*Apc*^{min/+} mice. (C-D) Western blot analysis showing the levels of β -catenin (C) and YAP (D) in small intestinal epithelium cells from *Apc*^{+/+}-*Uhrf1*^{+/+}, *Apc*^{min/+}-*Uhrf1*^{+/+} and *Apc*^{min/+}-*Uhrf1*^{ki/ki} mice, or microdissected tumors from *Apc*^{min/+}-*Uhrf1*^{+/+} and *Apc*^{+/+}-*Uhrf1*^{ki/ki} mice. Note that tumors from both *Apc*^{min/+}-*Uhrf1*^{+/+} and *Apc*^{min/+}-*Uhrf1*^{ki/ki} mice have elevated levels of β -catenin and YAP proteins. In B-D, *Apc*^{min/+}-*Uhrf1*^{+/+}-T and *Apc*^{min/+}-*Uhrf1*^{ki/ki}-T represent the tumor samples from *Apc*^{min/+}-*Uhrf1*^{+/+} and *Apc*^{min/+}-*Uhrf1*^{ki/ki} mice, respectively.



Supplementary Figure S5. DNA hypomethylation caused by *Uhfr1*-TTD-KI mutation does no affect tumor cell proliferation. (A) qRT-PCR analysis showing the relative expression levels of intestinal stem cell markers *Lgr5*, *Ascl2* and *Sox9* in intestinal epithelium cells or microdissected tumors from mice as indicated. *Uhfr1*^{+/+}/*Apc*^{Min/+}, n=8; *Uhfr1*^{ki/ki}/*Apc*^{Min/+}, n=8; *Uhfr1*^{+/+}/*Apc*^{Min/+ -T}, n=3; and *Uhfr1*^{ki/ki}/*Apc*^{Min/+ -T}, n=3. Error bars, S.E. *p < 0.05. (B) IHC analysis showing the levels of PCNA in small intestinal tissues or tumors from different mice. Scale bar, 50µm. (C) Quantitative results of PCNA positive cells based on IHC results in (B). N=3 for each samples. (D) Western blot results showing the levels of PCNA proteins in small intestinal epithelium cells or microdissected tumors from various mice as indicated. (E) IHC analysis showing the levels of Ki67 in small intestinal tissues or tumors from various mice. Scale bar, 50µm. (F) Quantitative results of Ki67 positive cells based on IHC results in (E). N=3 for each samples.



Supplementary Figure S6. DNA hypomethylation caused by *Uhrf1*-TTD-KI mutation does no lead to activation of interferon pathway in *Apc*^{min/+} mice. Relative levels of key interferon pathway genes were examined by qRT-PCR analysis. The total RNAs were prepared from small intestinal epithelium cells derived from various mice as indicated. Note there is no activation of the interferon genes tested in *Uhrf1*^{+/+}/*Apc*^{min/+} and *Uhrf1*^{ki/ki}/*Apc*^{min/+} mice. The relative mRNA levels were normalized to *Actin*. *Uhrf1*^{+/+}/*Apc*^{+/+}, n=3; *Uhrf1*^{ki/ki}/*Apc*^{+/+}, n=3; *Uhrf1*^{+/+}/*Apc*^{min/+}, n=3 and *Uhrf1*^{ki/ki}/*Apc*^{min/+}, n=3). Error bars, S.E. ns (non significant).