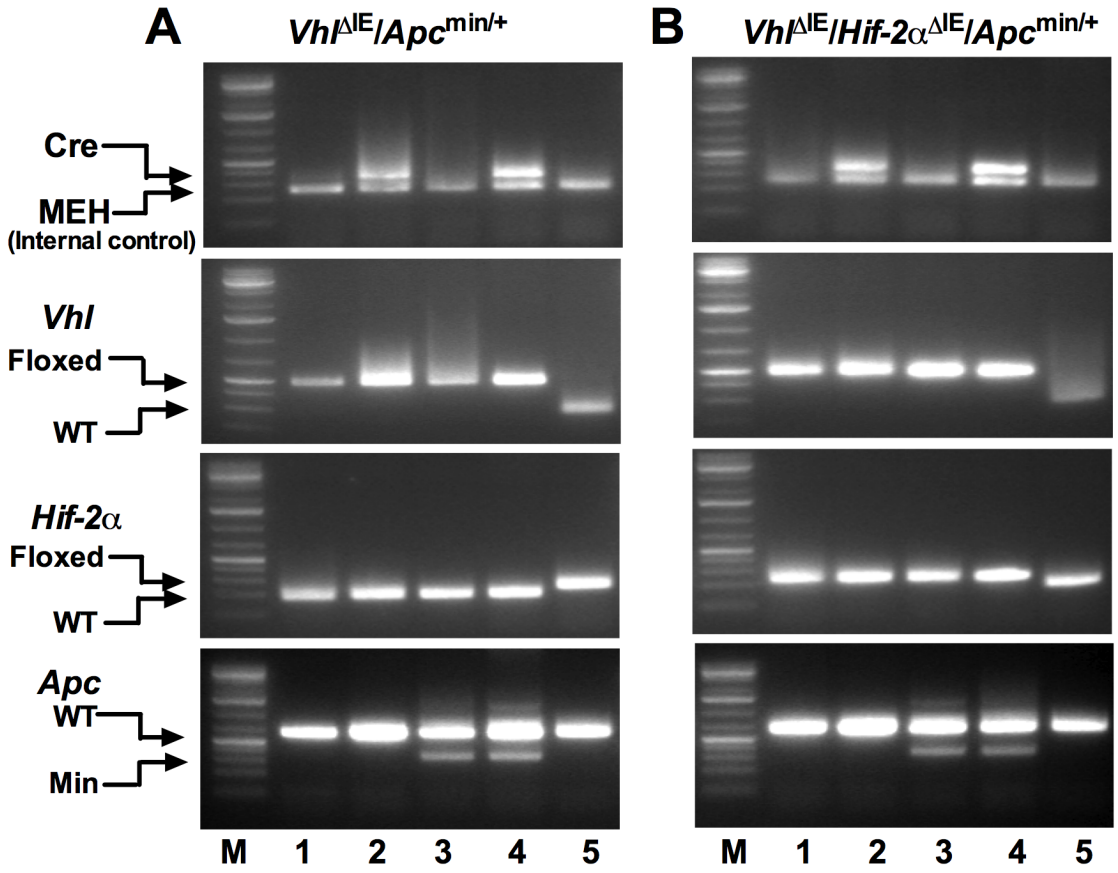
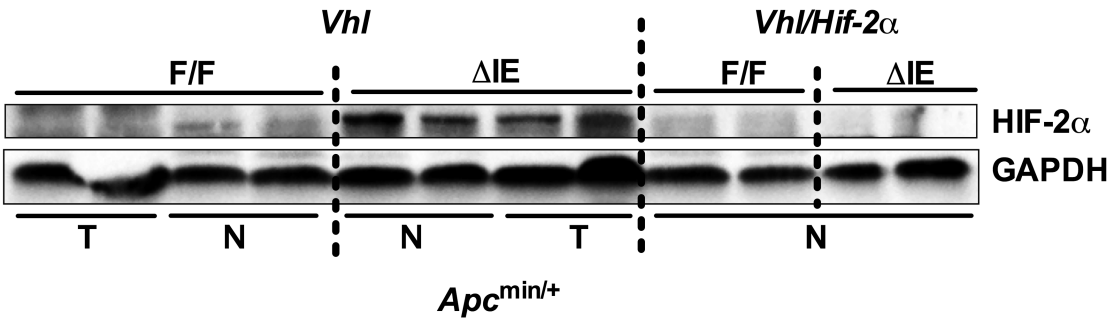
Supplemental Data: Figures 1-5 and Tables 1-3



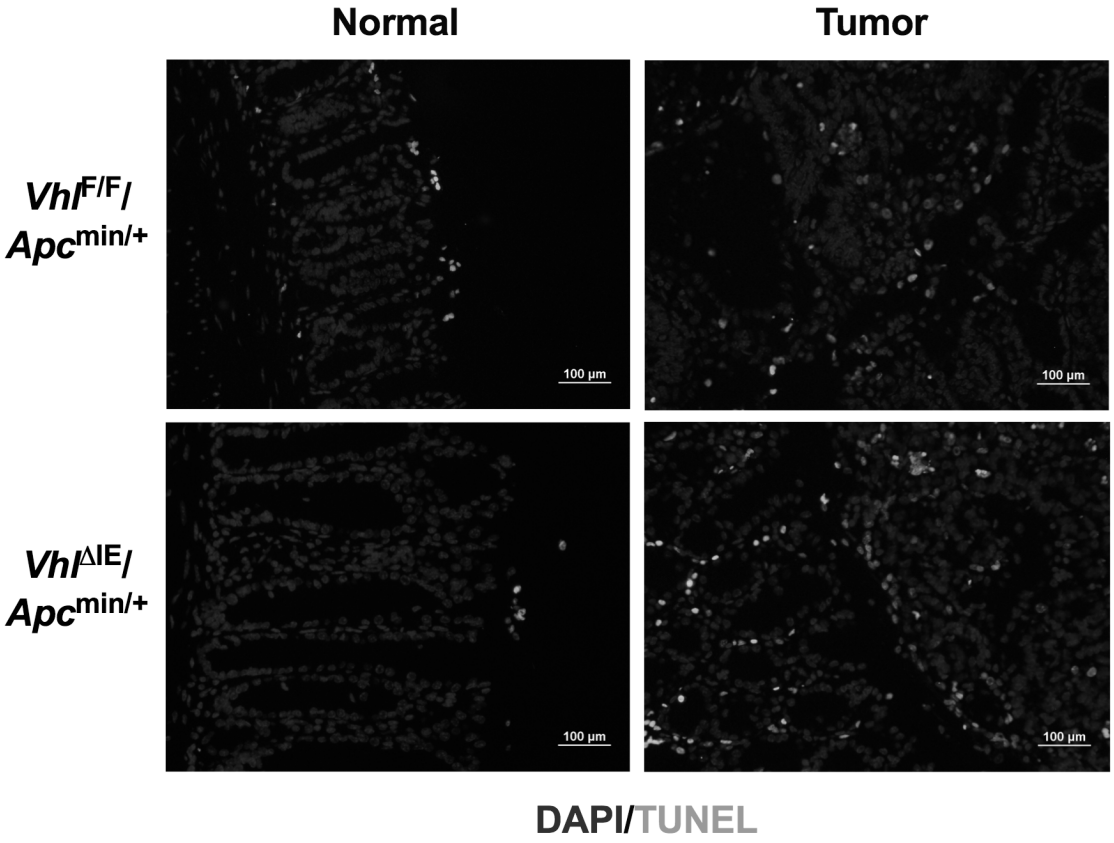
Supplemental Figure 1 Representative genotyping for *Vhl*$^{\Delta IE}$/Apc$^{min/+}$ and *Vhl*$^{\Delta IE}$/*Hif-2α*$^{\Delta IE}$/*Apc*$^{min/+}$ mouse lines.

(**A**) Tail DNA was extracted and genotyping for *Cre*, *Vhl*, *Hif-2α* and *Apc* were performed in *Vhl*$^{\Delta IE}$/Apc$^{min/+}$ mouse line. M, marker; 1, *Vhl*$^{F/F}$; 2, *Vhl*$^{\Delta IE}$; 3, *Vhl*$^{F/F}$/Apc$^{min/+}$; 4, *Vhl*$^{\Delta IE}$/Apc$^{min/+}$; 5, *Hif-2α*$^{\Delta IE}$. (**B**) Tail DNA was extracted and genotyping for *Cre*, *Vhl*, *Hif-2α* and *Apc* were performed in *Vhl*$^{\Delta IE}$/*Hif-2α*$^{\Delta IE}$/*Apc*$^{min/+}$ mouse line. M, marker; 1, *Vhl*$^{F/F}$/*Hif-2α*$^{F/F}$; 2, *Vhl*$^{\Delta IE}$/*Hif-2α*$^{\Delta IE}$; 3, *Vhl*$^{F/F}$/ *Hif-2α*$^{F/F}$/Apc$^{min/+}$; 4, *Vhl*$^{\Delta IE}$/*Hif-2α*$^{\Delta IE}$/Apc$^{min/+}$; 5, *Vhl*$^{F/F}$.



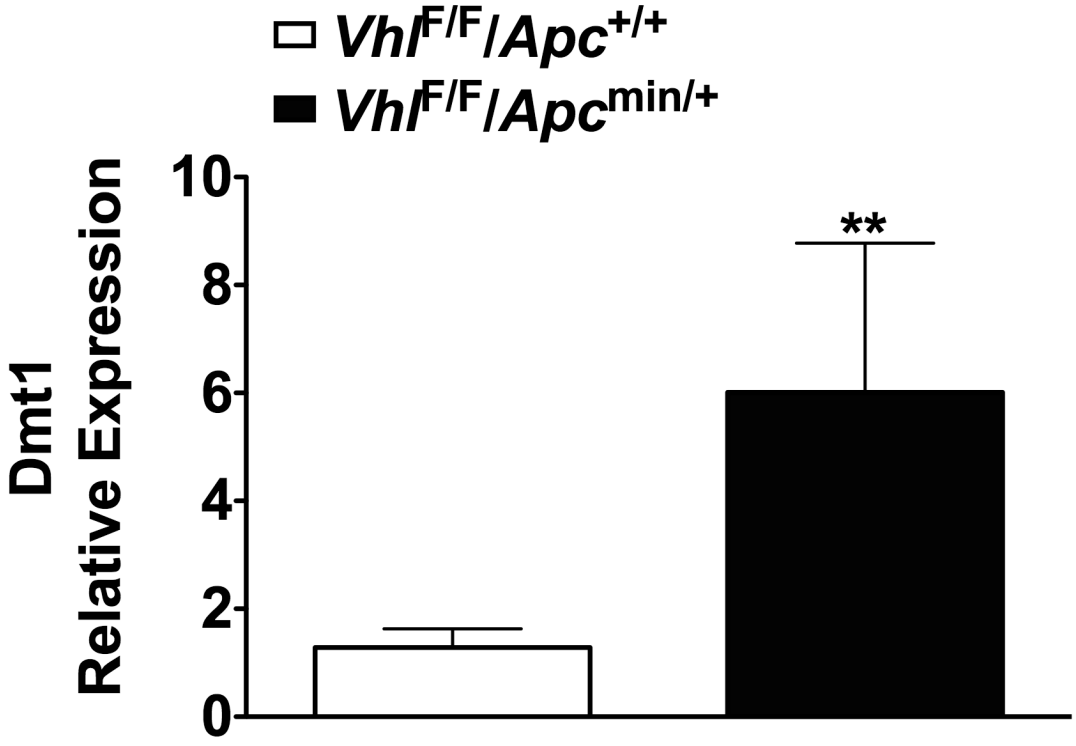
Supplemental Figure 2 HIF-2α Expression in the colons of *Vhl*$^{\Delta IE}$/Apc$^{min/+}$, *Vhl*$^{\Delta IE}$/*Hif-2α*$^{\Delta IE}$/*Apc*$^{min/+}$ and their wild-type littermate control mice.

Western Blot analysis for HIF-2α and GAPDH from normal and tumor colon tissues of 6-month-old *Vhl*$^{F/F}$/Apc$^{min/+}$, *Vhl*$^{\Delta IE}$/Apc$^{min/+}$, *Vhl*$^{F/F}$/*Hif-2α*$^{F/F}$/*Apc*$^{min/+}$ and *Vhl*$^{\Delta IE}$/*Hif-2α*$^{\Delta IE}$/*Apc*$^{min/+}$ mice. N, normal tissue; T, tumor tissue.



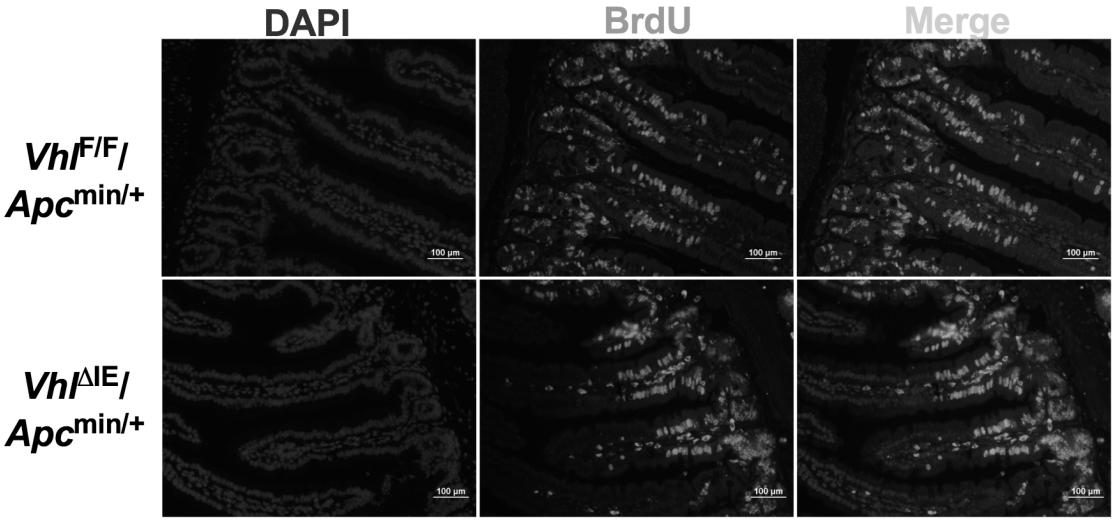
Supplemental Figure 3 TUNEL assay in the normal and tumor colons of *Vhl*$^{F/F}$/Apc$^{min/+}$ and *Vhl*$^{\Delta IE}$/Apc$^{min/+}$ mice.

TUNEL assay for the normal and tumor colons of 6-month-old *Vhl*$^{F/F}$/Apc$^{min/+}$ and *Vhl*$^{\Delta IE}$/Apc$^{min/+}$ mice.



Supplemental Figure 4 DMT-1 Expression in the small intestine of *Vhl*$^{F/F}$/*Apc*$^{min/+}$ mice.

qPCR analysis in the small intestine of *Vhl*$^{F/F}$/*Apc*$^{min/+}$ and *Vhl*$^{F/F}$/*Apc*$^{+/+}$ mice. Each bar represents the mean value ± S.D. **p<0.01 compared to *Vhl*$^{F/F}$/*Apc*$^{+/+}$mice.



Supplemental Figure 5 Disruption of *Vhl* in the small intestine does not increase proliferation.

BrdU staining of small intestine epithelial cells from 3-month-old $Vhl^{F/F}/Apc^{min/+}$ and $Vhl^{\Delta IE}/Apc^{min/+}$ mice.

Supplemental Table 1 Primers List

QPCR Primer	Sequence (5'-3')
β-actin F	TATTGGCAACGAGCGGTTCC
β-actin R	GGCATAGAGGTCTTTACGGATGT
Ccnd1 F	GGGTGGGTTGGAAATGAAC
Ccnd1 R	TCCTCTCCAAAATGCCAGAG
Dmt1 F	TGTTTGATTGCATTGGGTCTG
Dmt1 R	CGCTCAGCAGGACTTTCGAG

Supplemental Table 2 List of top 10 changed genes from the colons of $Vhl^{F/F}$ vs $Vhl^{\Delta IE}$ and $Vhl^{F/F}/Apc^{min/+}$ vs $Vhl^{\Delta IE}/Apc^{min/+}$.

Symbol	Description	Microarray*	Oncomine#
Xist	inactive X specific transcripts	Decrease	Decrease (5)
Myl7	myosin, light polypeptide 7, regulatory	Increase	No Change
Mpp4	membrane protein, palmitoylated 4 (MAGUK p55 subfamily member 4)	Increase	No Change
Nrn1	neuritin 1	Increase	Decrease (1)
Ndufa4l2	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4-like 2	Increase	Increase (3)
Slc11a2	**solute carrier family 11 (proton-coupled divalent metal ion transporters), member 2**	**Increase**	**Increase (19)**
Als2cr4	amyotrophic lateral sclerosis 2 (juvenile) chromosome region, candidate 4	Increase	Increase (14), Decrease (1)
Dnase1l2	deoxyribonuclease 1-like 2	Increase	Increase (4)
Ankrd37	ankyrin repeat domain 37	Increase	Increase (1) Decrease (2)
Steap4	STEAP family member 4	Increase	Decrease (4)

* Gene changes in $Vhl^{\Delta IE}$ compared to $Vhl^{F/F}$ mice.

Numbers in parenthesis indicate independent microarray reports for gene changes in colon cancer compared to normal tissue.