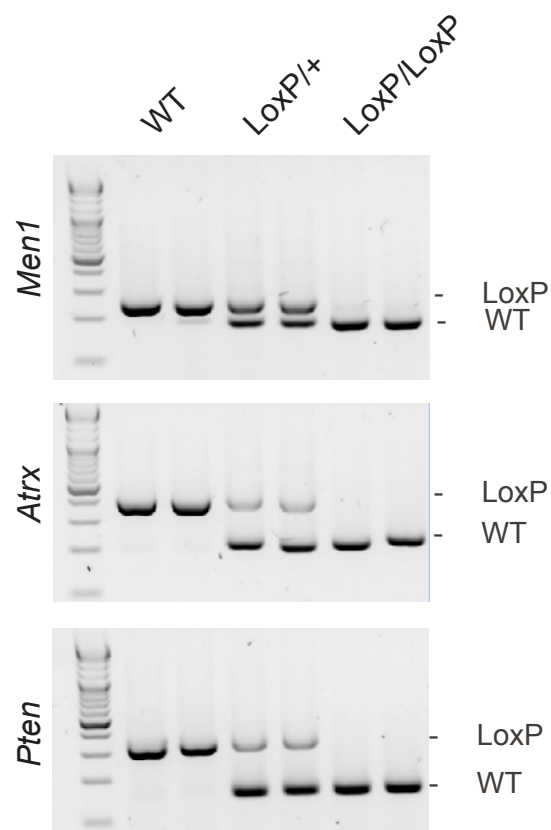
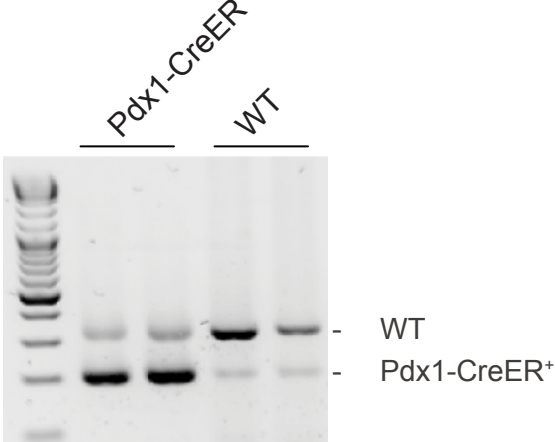


Supplementary Figure 1

A



B

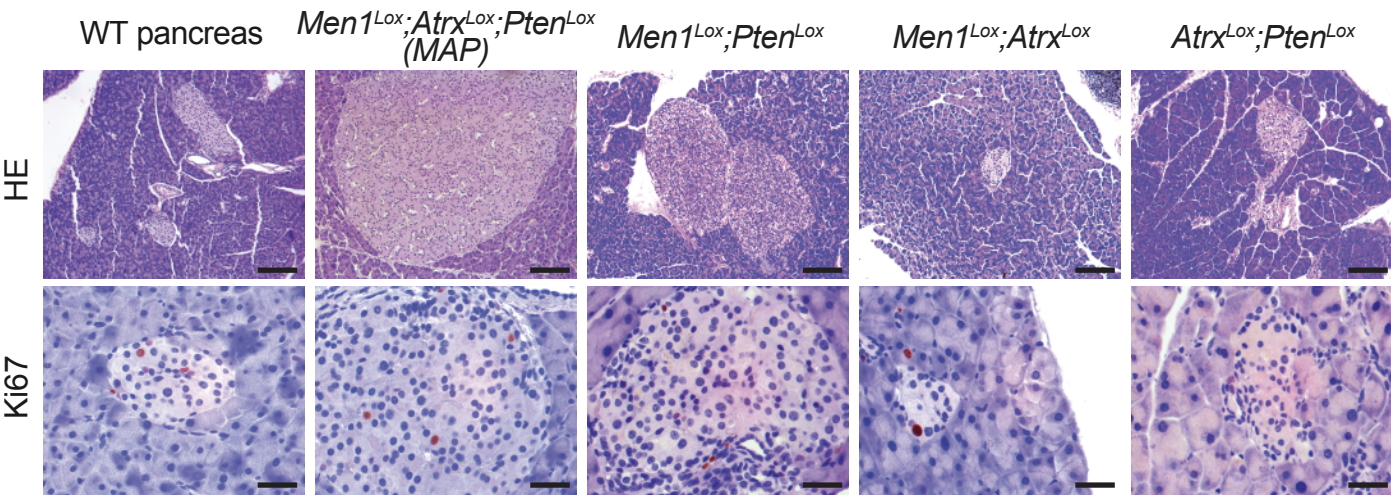


Supplementary Figure 1. Confirmation of *Pdx1-CreER*, *Men1*^{LoxP/LoxP}, *Atrx*^{LoxP/LoxP}, and *Pten*^{LoxP/LoxP} mutant mouse strains.

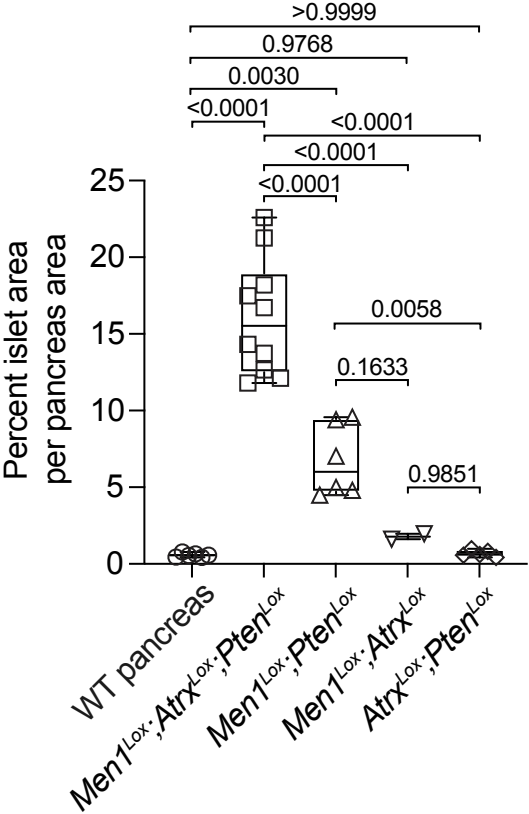
A-B. Confirmation of *Men1*^{LoxP/LoxP}, *Atrx*^{LoxP/LoxP}, and *Pten*^{LoxP/LoxP} conditional alleles (A) and *Pdx1-CreER* transgenic strain (B) by PCR on DNA isolated from mouse tail biopsies from indicated mouse genotypes, expected products sizes are marked (see Methods).

Supplementary Figure 2

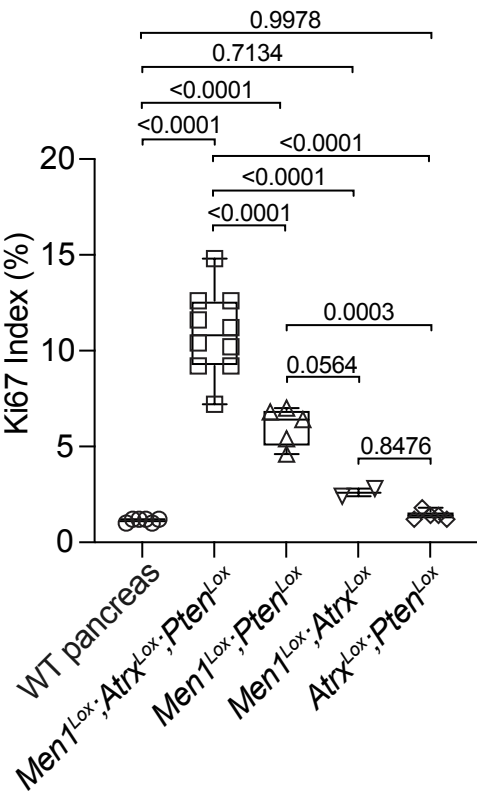
A



B



C



Supplementary Figure 2. Analyses of tumorigenic potential of pancreas neuroendocrine specific co-deletions of *Men1*^{LoxP/LoxP}, *Atrx*^{LoxP/LoxP}, and *Pten*^{LoxP/LoxP}.

A. Representative HE staining and Ki67 immunohistochemistry (marker of proliferating cells) of pancreas tissue from wildtype and indicated mutant strains. Tamoxifen-induced recombination of indicated conditional mutant alleles is mediated using pancreatic neuroendocrine cells-specific *Pdx1-CreER* strain. Analyses performed at 8 months after tumor induction (as in Fig 2B). Scale bars, 200 μ m (histology) and 50 μ m (Ki67 IHC).

B. Analyses of pancreatic neuroendocrine cells area per total pancreas area in wildtype, and indicated mutant strains at 8 months after tumor induction. *P*-values were calculated by one-way ANOVA with Tukey's multiple comparisons test.

C. Quantification of Ki67 index of pancreatic neuroendocrine cells from wildtype and indicated mutant strains at 8 months after tumor induction. *P*-values were calculated by one-way ANOVA with Tukey's multiple comparisons test.

Supplementary Figure 3

A

Mouse ID	Sex	Survival (days)	Observations	Insulin	NET marker Synaptophysin	Tumor burden	Ki67 Index (%)
1	F	338	WL	+	+	18.3	15.4
2	F	386	WL, LW	+	+	28.8	10.4
3	F	306	WL, LW	+	+	26.4	11.2
4*	F	314	WL, LW	n.a.	n.a.	n.a.	n.a.
5*	F	355	WL, J	n.a.	n.a.	n.a.	n.a.
6	M	384	WL, LW	+	+	21.8	12.4
7	M	397	WL, PPT	+	+	19.5	15.8
8	M	347	WL, LW	+	+	30.7	20.4
9	M	380	WL, PPT	+	+	45.1	25.2
10	M	336	WL, LW	+	+	32.5	19.6
11	M	299	WL, LW	+	+	53.2	25.4
12	M	395	WL, LW	+	+	54.7	28.4

WL, Weight loss

LW, Limb weakness

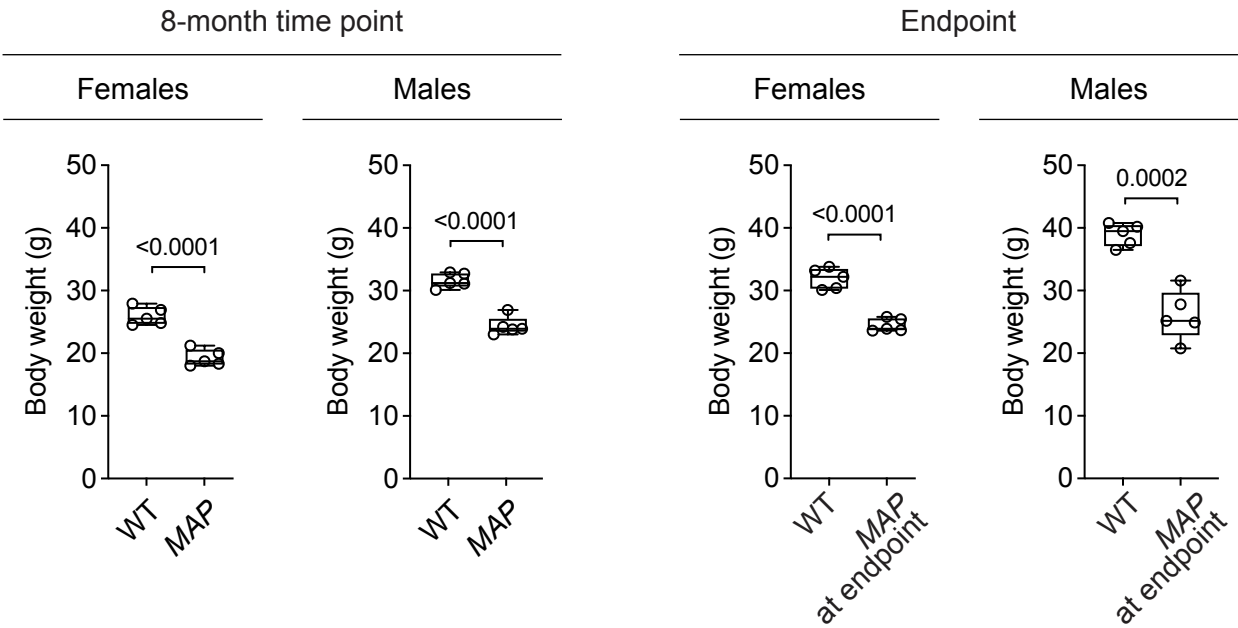
PPT, partial paralysis/tremors of the hindquarters

J, Jaundice

n.a., not analyzed

*, post mortem

B



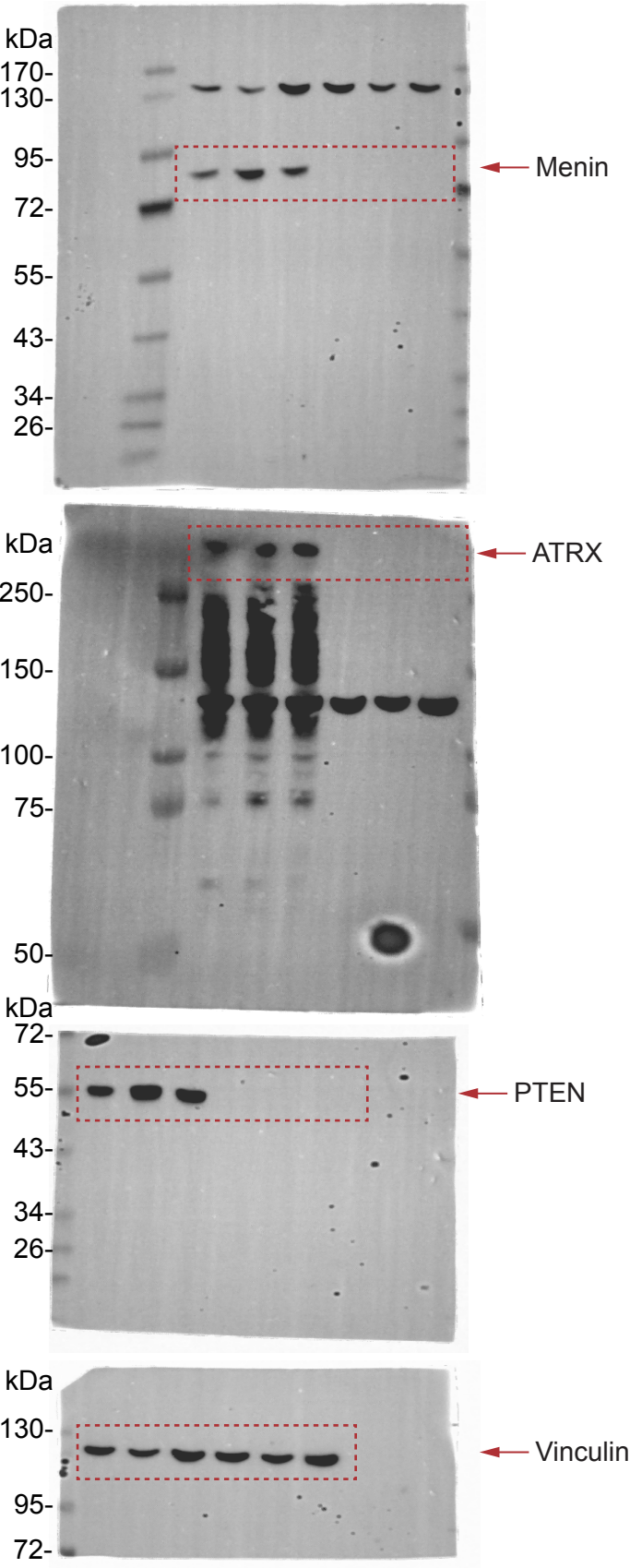
Supplementary Figure 3. Evaluation of clinical spectrum of disease and expression of neuroendocrine differentiation markers in *MAP* mouse model

A. Analysis of the clinical spectrum of disease observed in *MAP* mutant model at endpoint.

B. Body weight of *MAP* mutant mice at 8-month timepoint and endpoint. Age-matched wildtype mice are shown as control. *P*-values were calculated by the Student's t-test.

Supplementary Figure 4

Uncropped immunoblot images - Figure 2C



Supplementary Figure 4. Source data - uncropped immunoblotting images from Figure 2C.