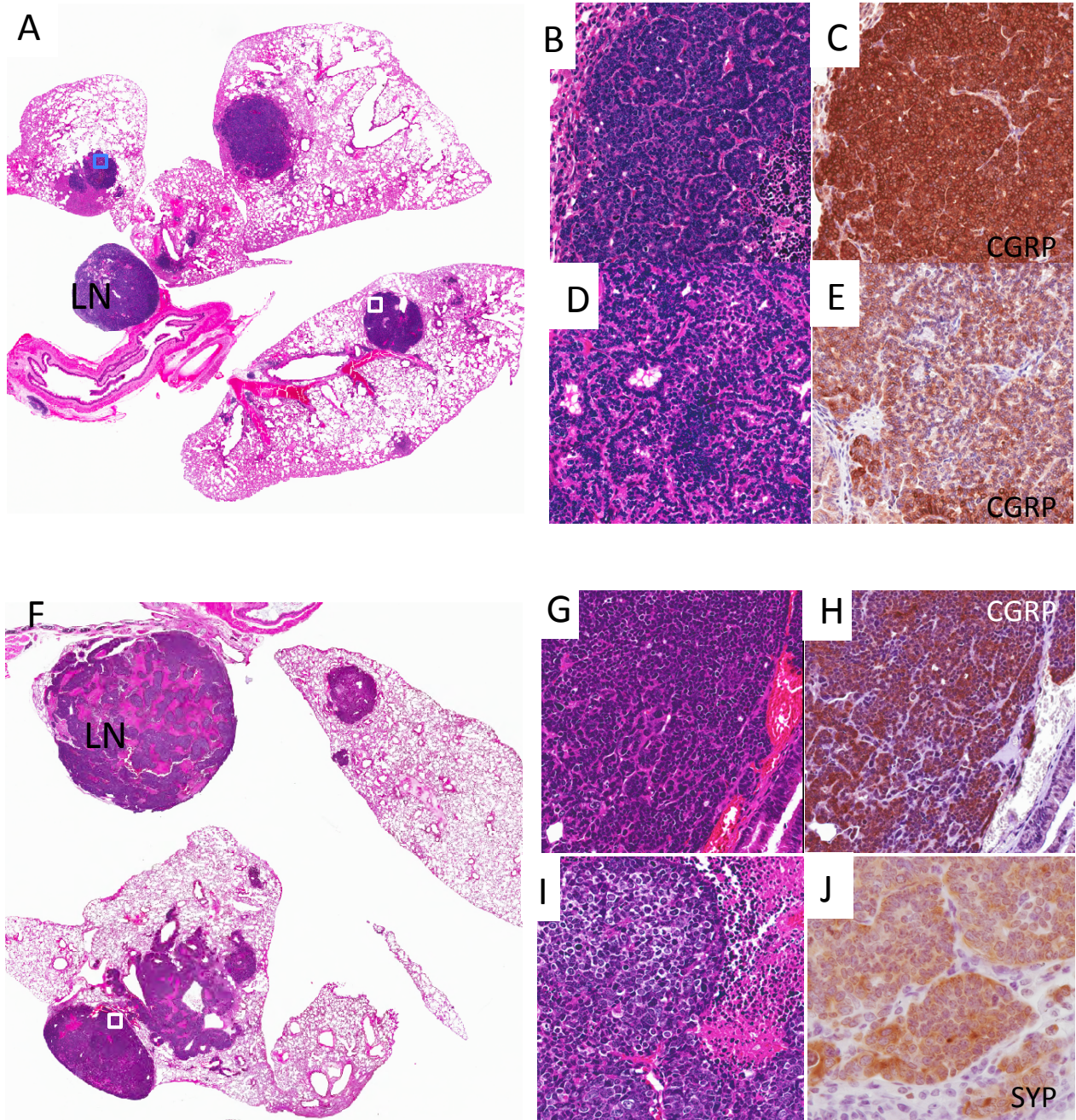
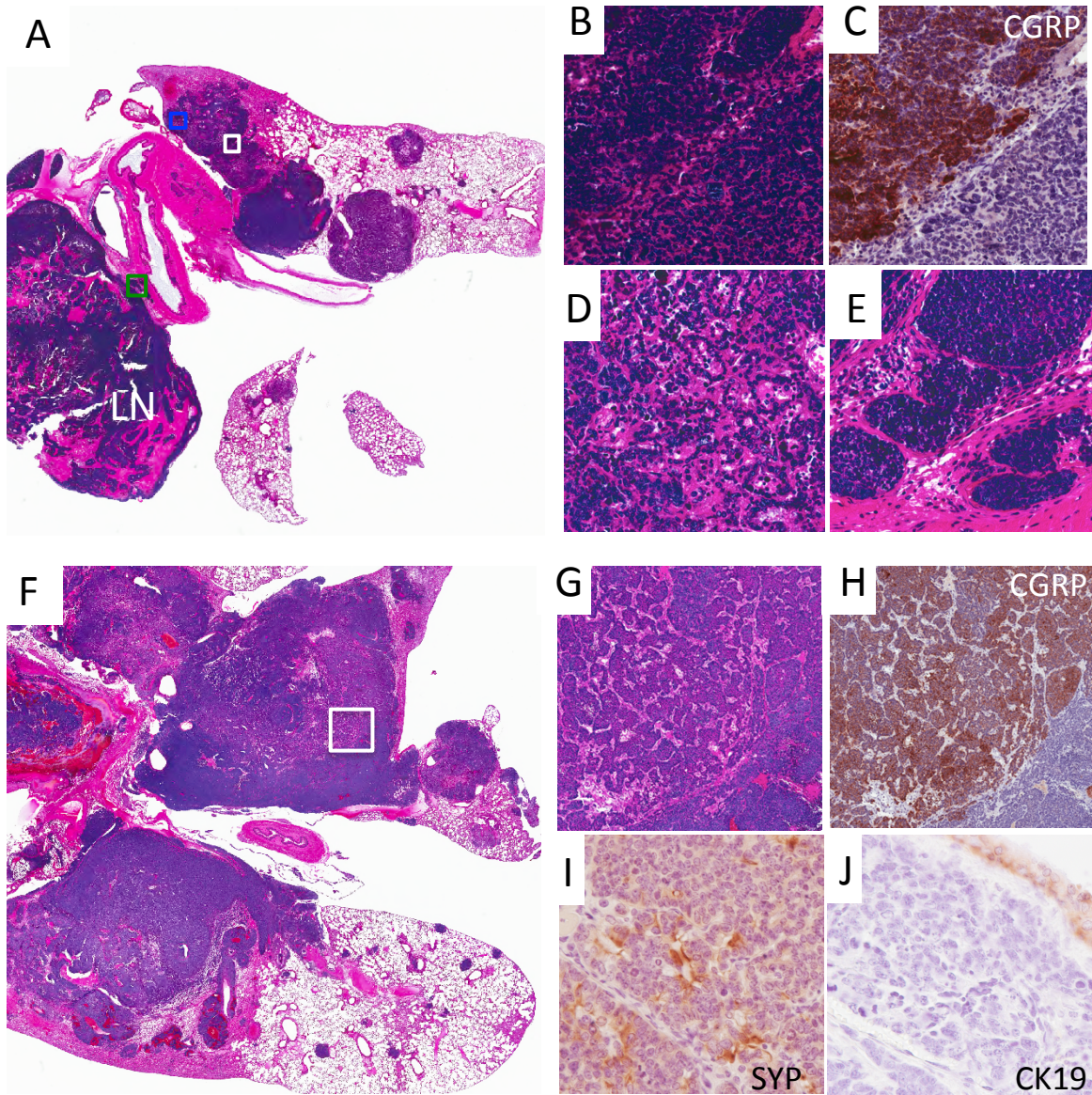


Rb^{lox/lox};p53^{lox/lox} AdCre

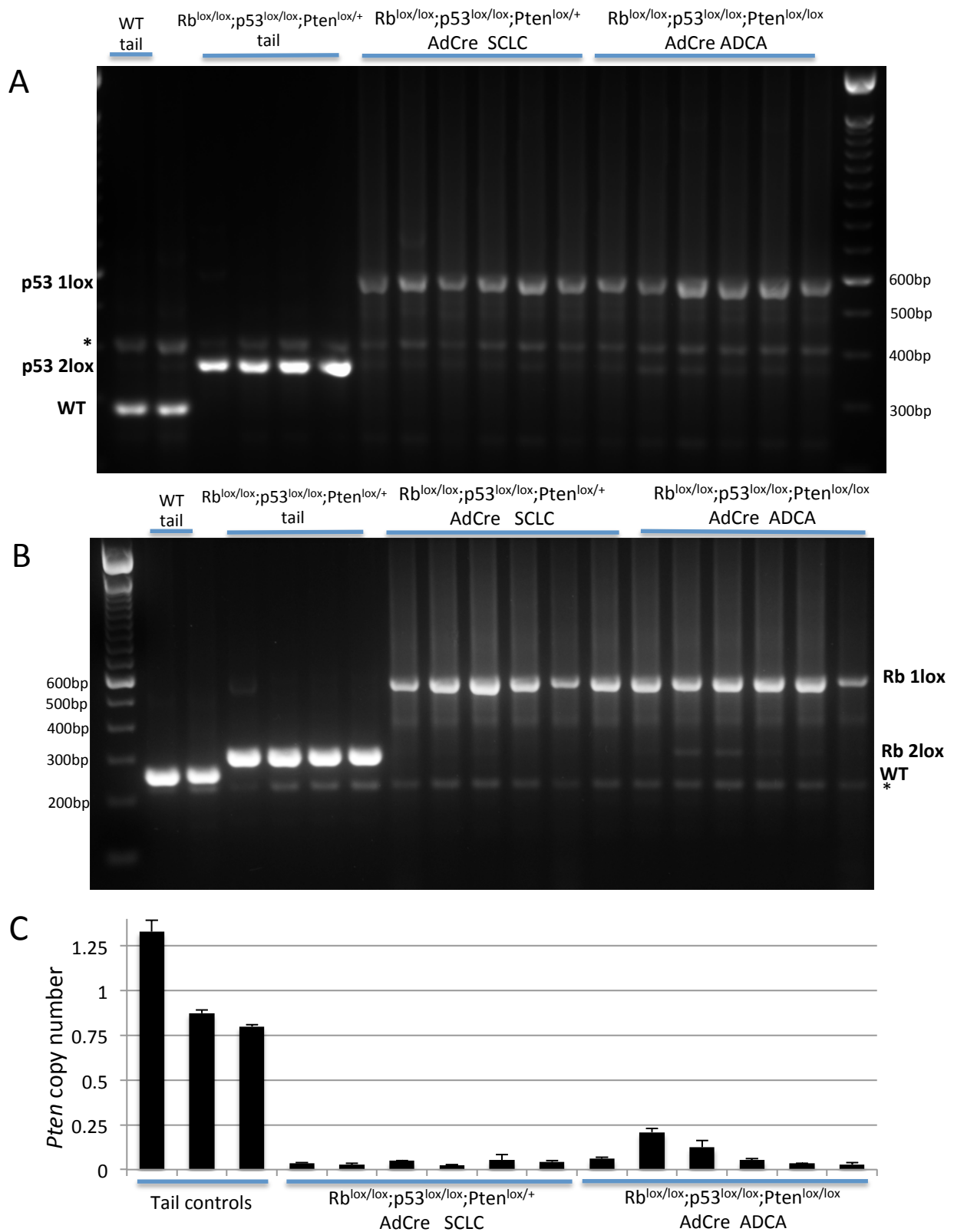


Supplemental Figure 1. Neuroendocrine lung tumors in *Rb/p53* AdCre model. **A)** H+E stain of tumor from Figure 1B with detail of SCLC histology from the region boxed in white magnified in **(B)**. This region shows the presence of SCLC with nesting growth pattern. CGRP immunostaining of this lesion is shown **(C)**. **D)** H+E showing region from (A) boxed in blue with features of acinar adenocarcinoma with neuroendocrine differentiation. This lesion stains positively for CGRP **(E)**. Histology **(F)** with boxed region magnified in **(G)** and CGRP staining **(H)** of a second *Rb/p53* SCLC case is also shown. **I)** Magnified region of SCLC metastasis to lymph node (LN). **J)** Synaptophysin positive *Rb/p53* SCLC.

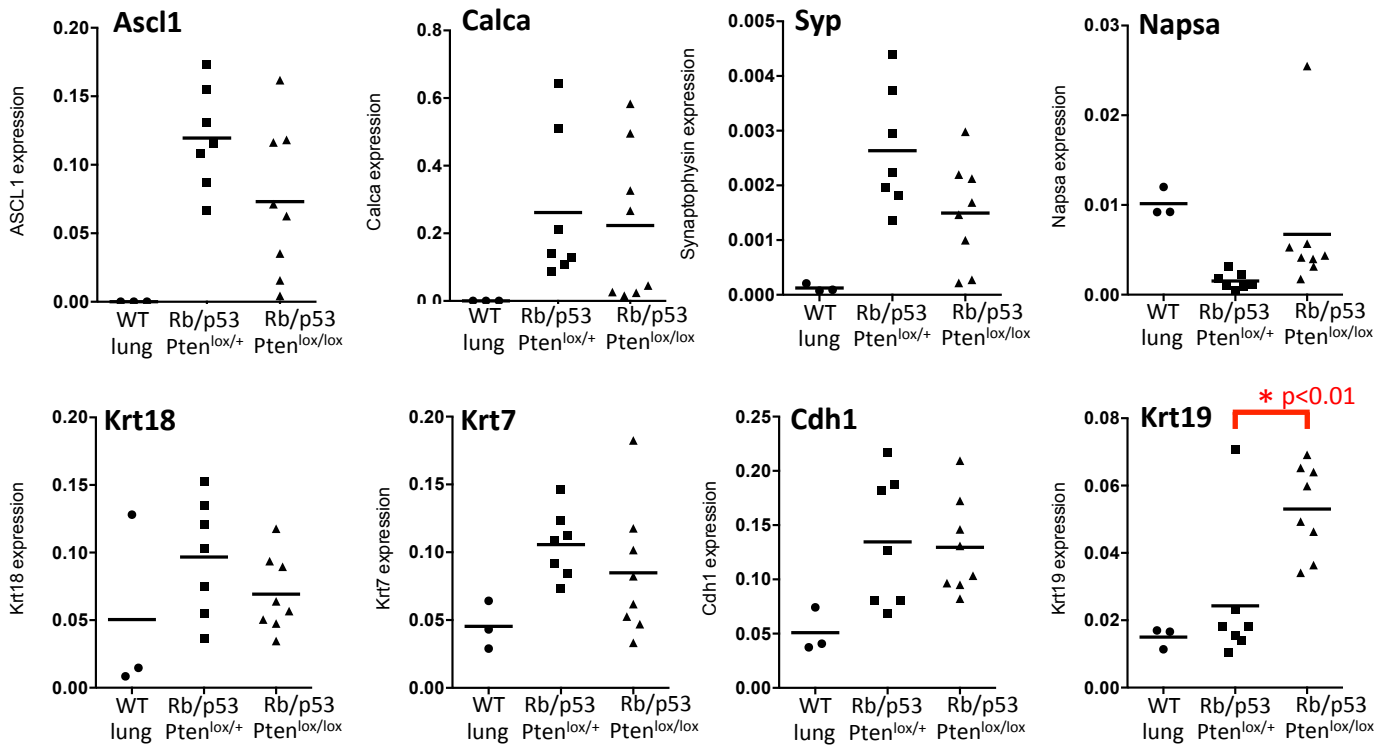
Rb^{lox/lox};p53^{lox/lox};Pten^{lox/+} AdCre



Supplemental Figure 2. Neuroendocrine lung tumors in *Rb/p53/Pten^{lox/+} AdCre* model. A) H+E stain of tumor from Figure 1C with white boxed region magnified in **(B)**. Magnified region shows the presence of SCLC region with solid growth pattern. **(C)** Heterogeneous CGRP immunostaining in area of lesion shown in **(B)**. **(D)** Blue boxed region from **(A)** with rosettes. **(E)** Magnified green boxed region from **(A)** showing metastatic SCLC **(F)** H+E staining of a second *Rb/p53/Pten^{lox/+} AdCre* case with magnified boxed region **(G)** showing tumor cell nests. Lesion stains positively for CGRP **(H)**. **(I)** Synaptophysin (SYP) and **(J)** CK19 immunohistochemistry shows tumor cells exhibit heterogeneous staining for synaptophysin and are negative for CK19.



Supplemental Figure 3. Analyses of *Rb*, *p53* and *Pten* recombination in lung tumors. A) PCR for *p53* status distinguishes between wild-type (288bp), *p53-2lox* (unrecombined, 370bp) and *p53 1-lox* (recombined, 612bp) alleles. Tumors show the *p53 1-lox* with absent *2-lox* band. **B)** PCR for *Rb* status distinguishes between wild-type (250bp), *Rb-2lox* (unrecombined, 310bp) and *Rb 1-lox* (recombined, 550bp) alleles. Tumors show the *Rb 1-lox* with absent or very minor *2-lox* band. * refers to non-specific band. **C)** Real-time PCR showing *Pten* exon 5 copy number in lung tumors from Rb^{lox/lox};p53^{lox/lox};Pten^{lox/+} and Rb^{lox/lox};p53^{lox/lox};Pten^{lox/lox} Ad-Cre infected animals and tail controls. Data are normalized to the *Actb* gene. Results show loss of heterozygosity for *Pten* in the *Pten* heterozygous lung tumors.



Supplemental Figure 4. Comparison of *Rb/p53/Pten^{lox/+}* vs. *Rb/p53/Pten^{lox/lox}* lung tumors for expression of neuroendocrine and other lung cancer markers. Real time PCR analysis of *Ascl1*, *Calca*, *Synaptophysin*, *Napsa*, *Krt18*, *Krt7*, *Cdh1* and *Krt19* markers, relative to *Actb*. Normal lung, and lung tumors from the *Rb/p53/Pten^{lox/+}* and *Rb/p53/Pten^{lox/lox}* models are shown. Both tumor models show heterogeneity for the neuroendocrine markers *Ascl1*, *Calca*, and *Syp*. The only marker tested with significant differences in expression between *Rb/p53/Pten^{lox/+}* and *Rb/p53/Pten^{lox/lox}* tumors was *Krt19*. Each sample was run in triplicate, plotted are the average expression values for each tumor, relative to *Actb*.