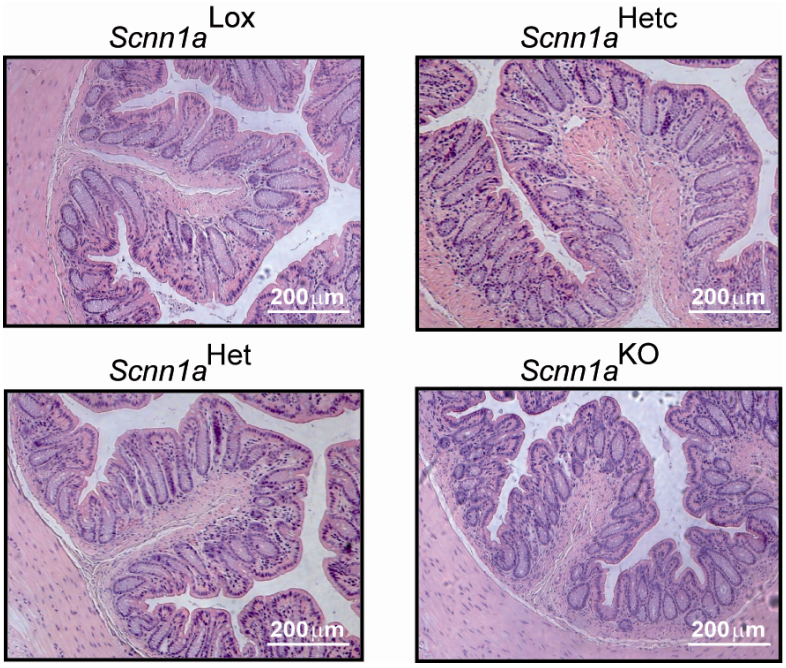
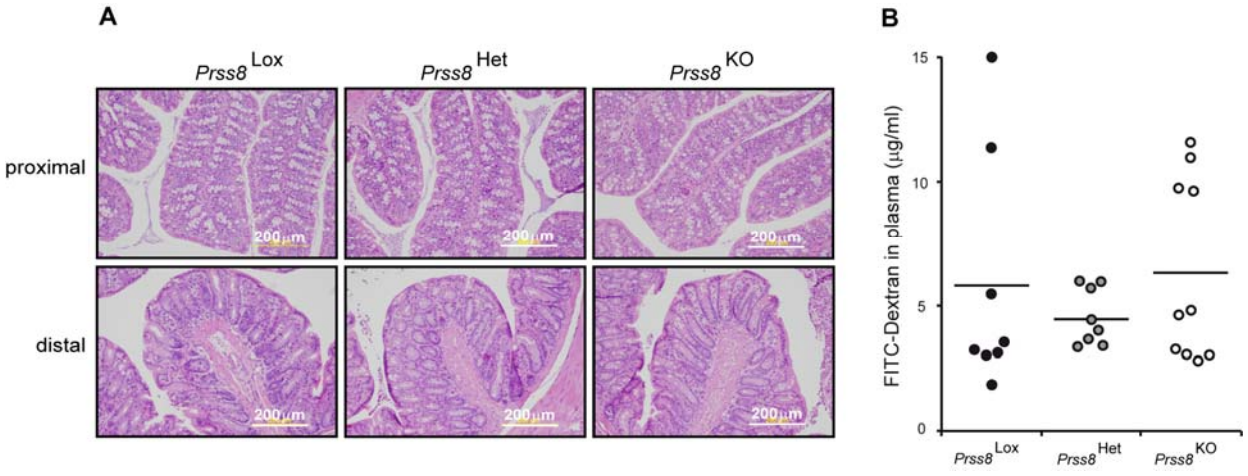


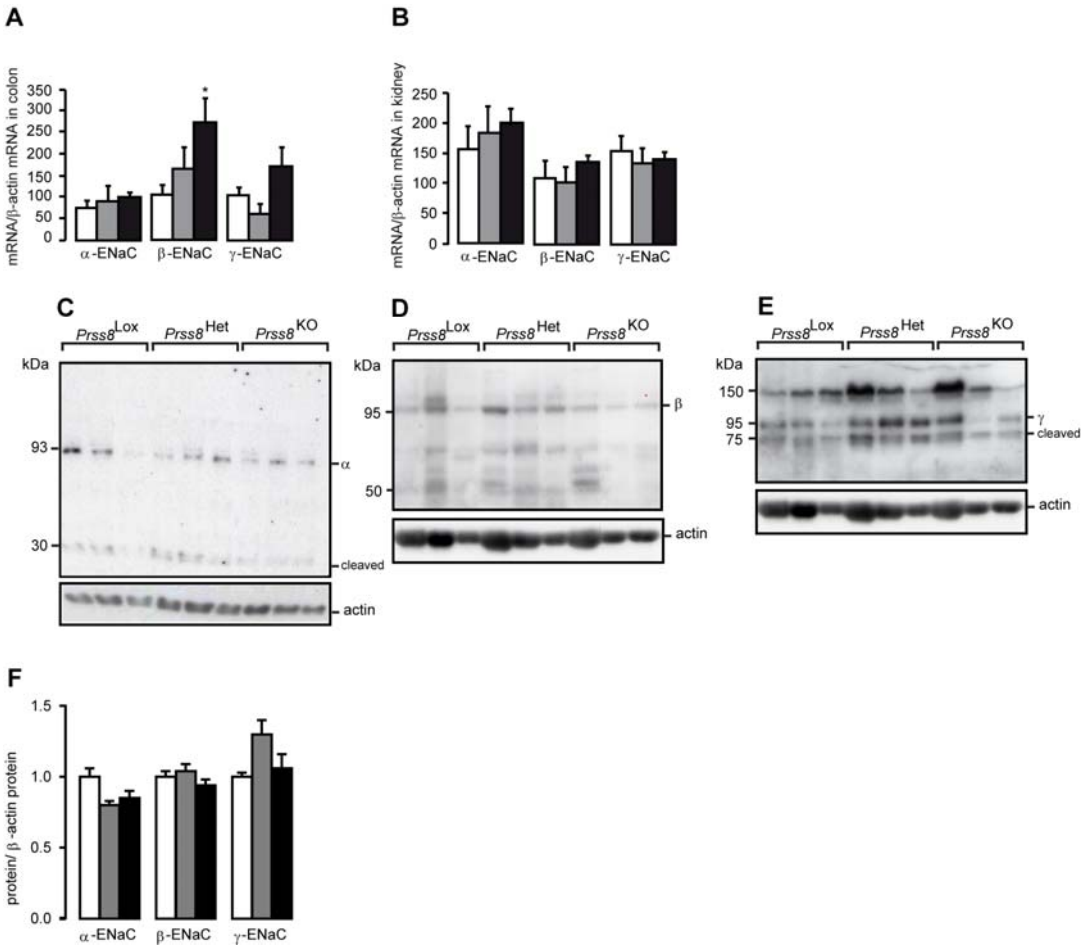
Supplementary Figure 1. Colon histology in *Scnn1a*^{KO} mice

Light photomicrographs of representative distal colon sections from age-matched (2 months old) *Scnn1a*^{Lox}, *Scnn1a*^{Het} and *Scnn1a*^{KO} littermates (H&E-staining); n=3 animals/genotpye. Scale bar, 200 µm.



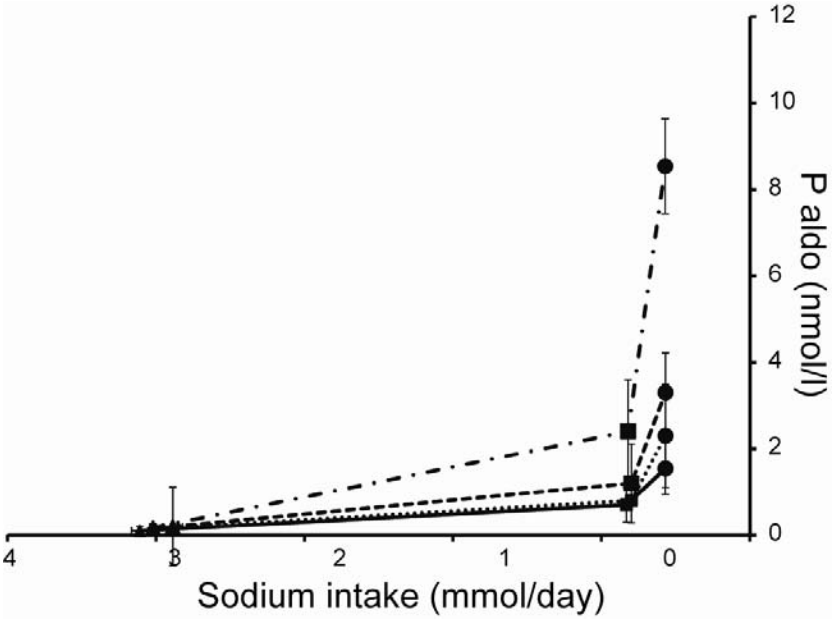
Supplementary Figure 2. Normal colon histology and intestinal permeability in *Prss8*^{KO} mice

(A) Light photomicrographs of representative proximal and distal colon sections from *Prss8*^{Lox}, *Prss8*^{Het} and *Prss8*^{KO} littermates stained with haematoxylin and eosin; for each genotype, 3 independent animals were analyzed. Scale bar, 200 µm **(B)** Measurement of intestinal permeability in *Prss8*^{Lox} (n=8, closed circles), *Prss8*^{Het} (n=8, half-open circles) and *Prss8*^{KO} (n=10, open circles) mice. Horizontal bar indicates the average.



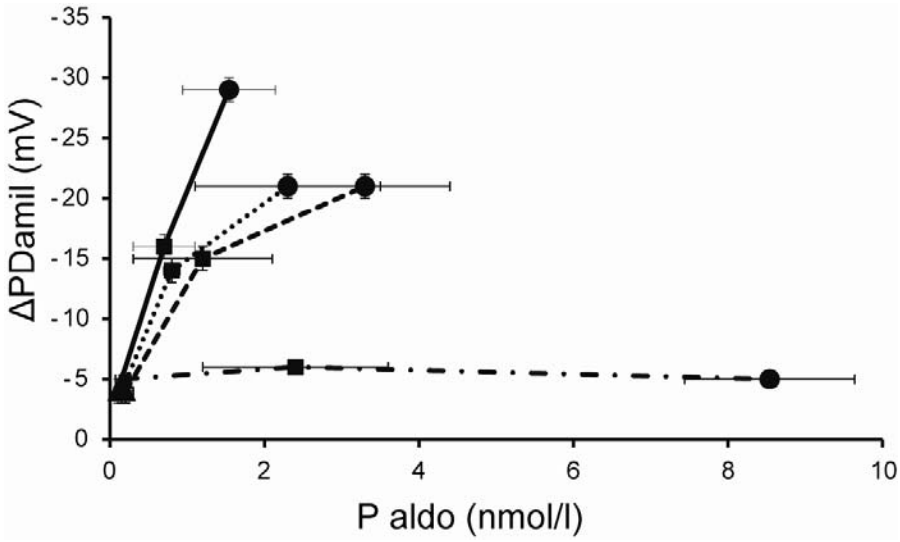
Supplementary Figure 3. Expression of ENaC subunits in kidney and distal colon of *Prss8*^{KO} mice

(**A and B**), Quantification of α (left), β (middle) and γENaC mRNA transcript expression in **(A)** distal colon and **(B)** kidney by quantitative RT-PCR from *Prss8*^{Lox} (white), *Prss8*^{Het} (grey) and *Prss8*^{KO} (black bar) mice. Results are expressed as the ratio of ENaC mRNA subunits to β-actin mRNA (n ≤ 6 mice per group); *, $P< 0.05$. Representative immunoblot showing the expression of alpha (93kDa) (**C**), beta (95kDa) (**D**) and gamma ENaC (95kDa) (**E**) subunit and β-actin protein in scraped colon cells from *Prss8*^{Lox}, *Prss8*^{Het} and knockouts *Prss8*^{KO}; (n=3 mice per group). (**F**) Quantification of α, β and γENaC protein in *Prss8*^{Lox}, *Prss8*^{Het} and *Prss8*^{KO} colon samples. β-actin expression is shown as loading control; in each experiment, 3 mice were used per group. Values are mean ± S.E.M.



Supplementary Figure 4. Plasma aldosterone levels in response to salt intake in *Scnn1a*^{KO} mice

Plasma aldosterone values were done from animals maintained on a high (▲), regular (■) or low (●) salt diet. For each genotype, *Scnn1a*^{Lox} mice (n= 6; —), *Scnn1a*^{Het} (n= 7; ---), *Scnn1a*^{Hetc} (n=6; ⋯) and *Scnn1a*^{KO}, (n=7; ·-·-·) animals, the average P_{Aldo} values are plotted against the corresponding average sodium intake values (vertical and horizontal bars indicate S.E.M values).



Supplementary Figure 5. Mineralocorticoid resistance in *Scnn1a*^{KO} mice

ΔPD_{-Amil} and P_{Aldo} values were taken from the experiments summarized in Fig. 2 and 3. For each genotype (*Scnn1a*^{Lox}(n= 6; —), *Scnn1a*^{Het}(n= 7; ---), *Scnn1a*^{Hetc} (n=6; ···) and *Scnn1a*^{KO}(n=7; -·-·-·-), the average ΔPD_{amil} values are plotted against the corresponding average P_{aldo} values from animals maintained on a high (▲), regular (■) or low (●) salt diet (vertical and horizontal bars indicate S.E.M. values). Linear regression of the mean values revealed a significantly ($P < 0.05$) flatter slope in *Scnn1a*^{KO} animals compared with the *Scnn1a*^{Lox}, *Scnn1a*^{Het}, *Scnn1a*^{Hetc} mice.