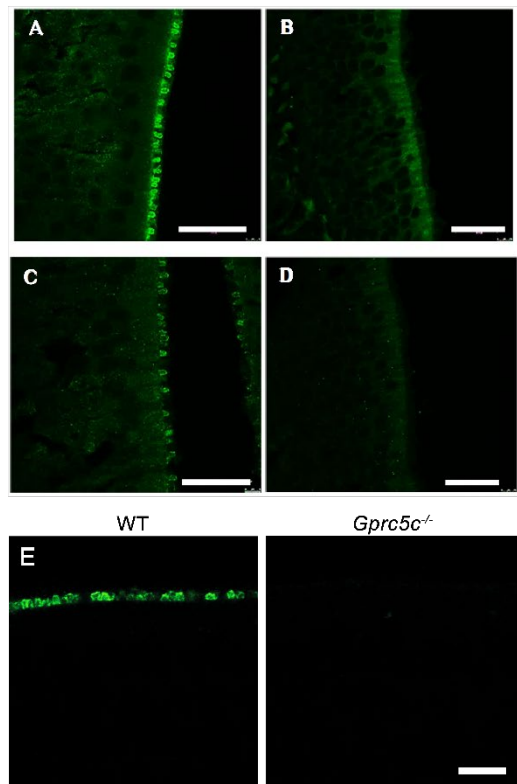
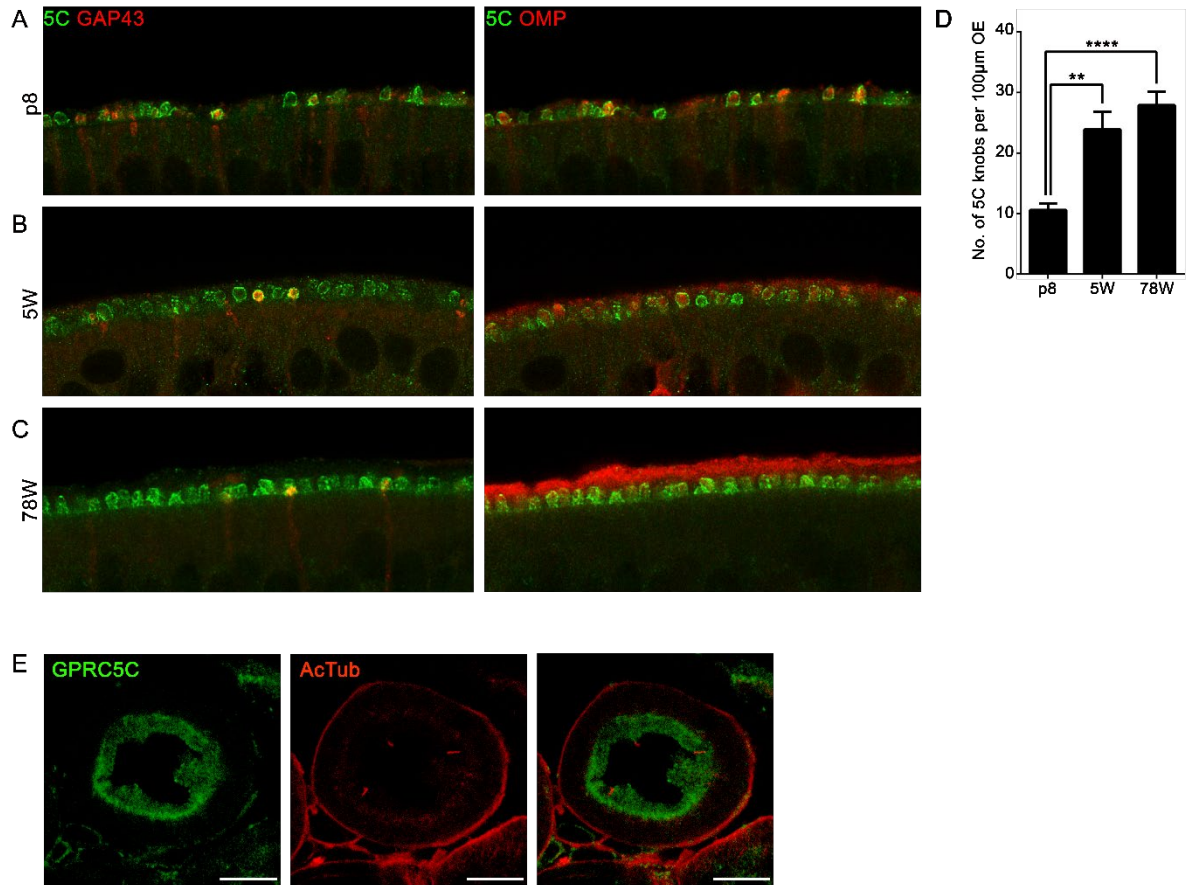


1 Supplemental Figures



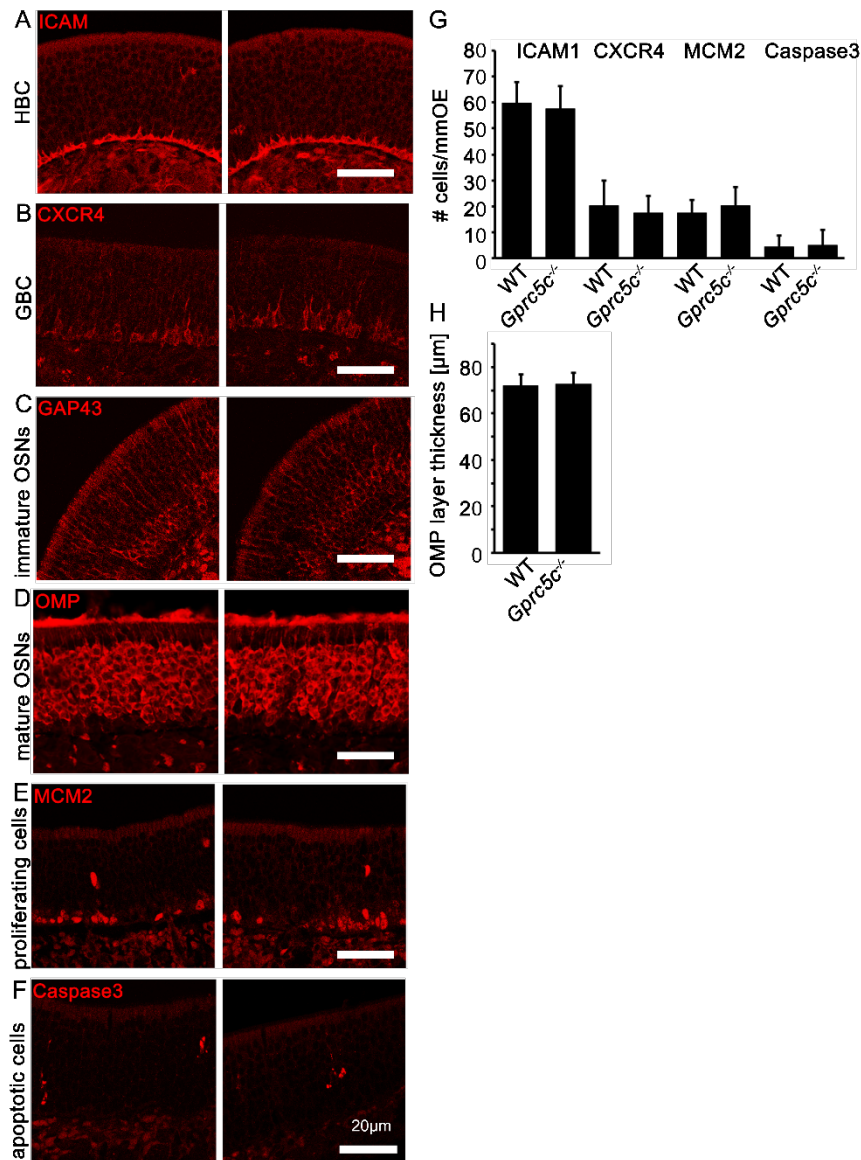
3 Supplemental Figure S1 Antibody validation

4 (A) Affinity chromatography purified anti-GPRC5C antibody showed staining specific to the
5 dendritic knob layer of OSNs. (B) Secondary antibody control showed no staining (C) Faint
6 staining of the knobs was also seen in sections treated with the immune serum. (D) No specific
7 staining was seen in section treated with pre-immune serum. (E) Affinity chromatography
8 purified anti-GPRC5C antibody showed staining in WT, but not in *Gprc5c*^{-/-} OSNs. Scale bars
9 20μm



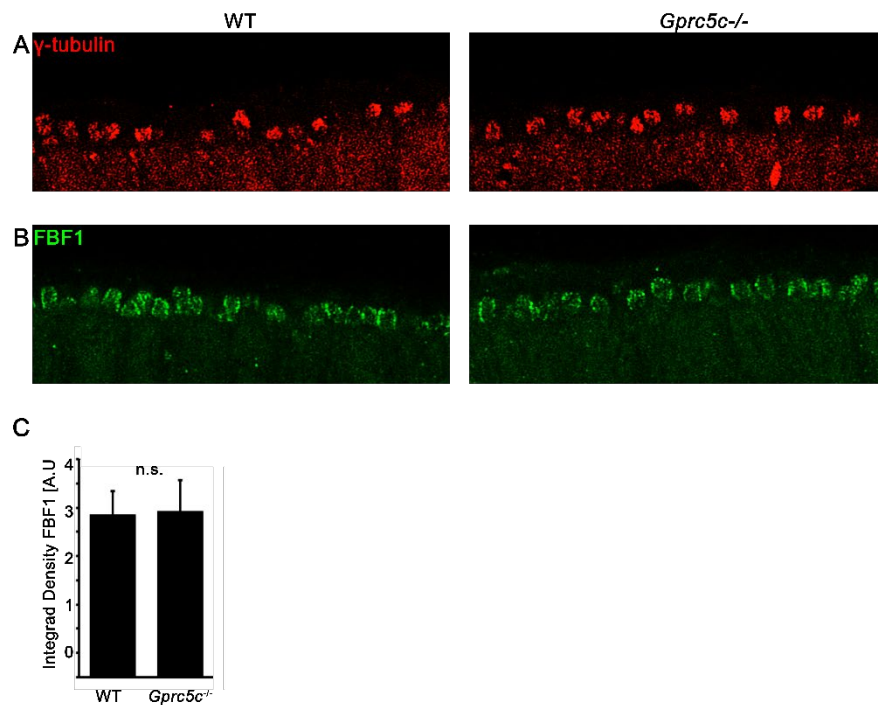
Supplemental Figure S2. Supplemental data for Figure 1

(A-D) GPRC5C expression during post-natal development: Confocal images of OE coronal cryosections of mice aged (A) 8 days postnatal (P8), (B) 5weeks (5W), and (C) 78 weeks (78W) immunolabeled for GPRC5C (green) and GAP43 (red) (left panel) and GPRC5C (green) and OMP (red) (right panel). GPRC5C staining is detected in the dendritic knobs of mature and immature neurons in young mice (P8) and continues to be expressed throughout adulthood (5W, 78W). **(D)** Quantification of GPRC5C positive knobs across different ages. One-way ANOVA and Tukey's multiple comparison test showed a significant increase in number of GPRC5C positive knobs in 5 weeks and 78 weeks old animals in comparison to p8 animals. (n=3, error bars represent SEM, ** $p < 0.05$, **** $p < 0.0001$). **(E) GPRC5C is not associated with primary cilia in the kidney:** Confocal images of single renal proximal tubule of mice aged 3 months immunostained with anti-GPRC5C antibody (green) and acetylated tubulin (red). Staining was not specifically associated with primary cilia. Scale bar 10μm.



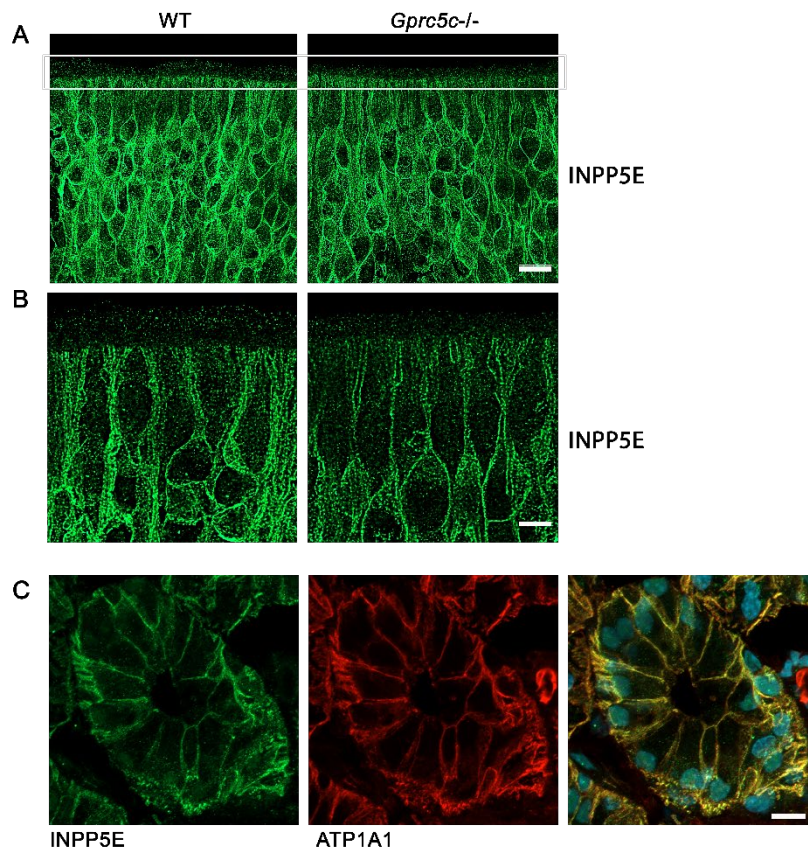
Supplemental Figure S3. Neurogenesis is not affected in *Gprc5c*^{-/-} OSNs

Confocal images of WT and 5C^{-/-} adult OE cryosections immunolabeled for: (A) ICAM1 as a marker for HBCs; (B) CXCR4 as a marker for GBCs; (C) GAP43 as a marker for immature OSNs; (D) OMP as a marker for mature OSNs; (E) MCM2 as a marker for proliferating cells and (F) Caspase3 as a marker for apoptotic cells. The labelling of these marker proteins is comparable between WT and *Gprc5c*^{-/-} OE. (G) Cells counted in projections of confocal stacks of 16 μm thickness (n=3 animals per group, Student's t-test p>0.05, error bars represent SEM). (H) Thickness of the layer of OMP-positive mature neurons (n=3 animals per group, Student's t-test p>0.05, error bars represent SEM). Scale bars (A-F): 20 μm.



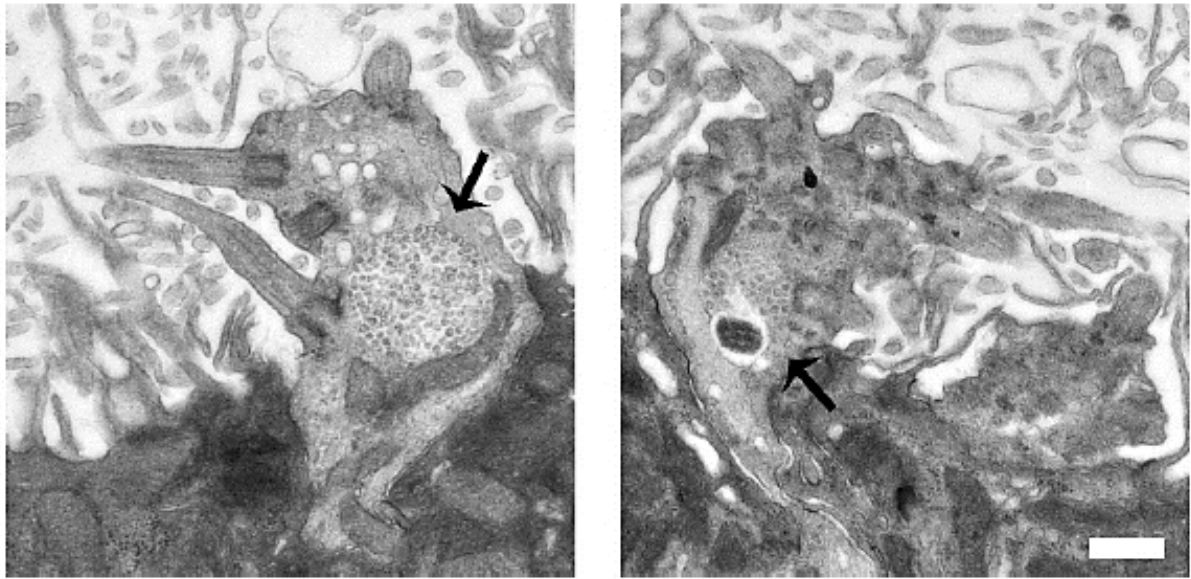
Supplemental Figure S4. Localization of dendritic knob markers in *Gprc5c*^{-/-} mice

Confocal images of WT and *Gprc5c*^{-/-} adult mouse OE cryosections immunolabeled for (A) γ -tubulin, a marker for basal bodies within dendritic knobs that is comparable between WT and *Gprc5c*^{-/-} OE (B) Ciliary gate protein FBF1 showing no difference in staining pattern between WT and *Gprc5c*^{-/-} OE. (C) Quantification of staining intensity of FBF1. Student's t-test showed no significant difference (n=3). Scale bar: 5 μ m.



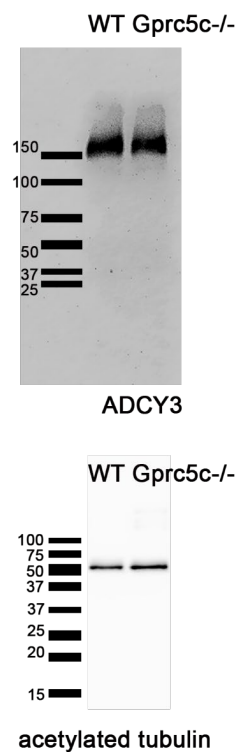
Supplemental Figure S5. Cross-reactivity of INPP5E antibody with ATP1A1

(A) Immunofluorescence labeling of cryosection of WT and *Gprc5c*^{-/-} OE labeled with an antibody against INPP5E. Labeling occurs on the basolateral plasma membrane, only a very faint ciliary labeling (boxed) is present. Basolateral labeling may occur from labeling of ATP1A1, since both antibodies were reported to bind a shared epitope (<https://zfin.org/ZDB-PUB-160713-11#fish>). Scale bar 10μm. (B) Higher magnification. Scale bar 5μm. (C) Co-labeling of ATP1A1 (red) and INPP5E (green) in follicular cells of the thyroid gland, marked basolateral staining is present in both stainings indicating binding of the INPP5E antibody to ATP1A1. Scale bar 20μm.



71 **Supplemental Figure S6 Multivesicular bodies in dendritic knobs of *Gprc5c*^{-/-} OE**

72 TEM analysis of ultrathin sections showing the presence of multivesicular bodies in the
 73 dendritic knobs of *Gprc5c*^{-/-} OE. Multivesicular bodies are synonymous with late endosomes
 74 and belong to the endosomal pathway. Scale bar 200nm.



76 **Supplemental Figure S7 Uncropped pictures of blots, imaged with a Western Blot**

77 **Imager.** Upper blot: anti-ADCY3 (Figure 5F); lower blot anti acetylated tubulin (Figure 3Q)

**Table S1: Antibodies used
in this study.**

antibody	host species	Dilution	company (order number)
GPRC5C	rabbit	1:200	Home made (see Figure S1)
Acetylated tubulin	mouse	1:1000	Sigma (T-6793)
Phalloidin-A568		1:500	Invitrogen (A-12380)
IP3R	mouse	1:200	BD Biosciences (610312)
Arl13b	mouse	1:200	NeuroMab (N295B/66)
DCX	guinea pig	1:100	Synaptic Systems (326 004 LOT 1-4)
FBF1	rabbit	1:50	Proteintech (11531-1-AP)
MKS3	rabbit	1:200	BiCell Scientific (90103)
ADCY3	rabbit	1:200	Santa Cruz (sc-588)
CNGA2	goat	1:200	Santa Cruz (sc-13700)
CNGA4	guinea pig	1:100	Michalakakis S, Reisert J, Geiger H, Wetzel C, Zong X, Bradley J, Spehr M, Huttel S, Gerstner A, Pfeifer A, Hatt H, Yau KW and Biel M (2006). J Biol Chem 281:35156-66. doi: 10.1074/jbc.M606409200
PACS1	goat	1:100	Santa Cruz (sc-8465)
GNAL	rabbit	1:200	Santa Cruz (sc-383)
Or5d18	rabbit	1:200	Home made (Rasche S, Toetter B, Adler J, Tschapek A, Doerner JF, Kurtenbach S, Hatt H, Meyer H, Warscheid B and Neuhaus EM (2010). Chem Senses 35:239-45. doi: 10.1093/chemse/bjq007
PI4,5P2	mouse	1:200	Invitrogen (A-21327, clone 2C11)
PI4P	mouse	1:200	Echelon Biosciences (Z-P004)
INPP5E	rabbit	1:100	Proteintech (17797-1-AP)
ATP1A1	rabbit	1:500	Abcam (ab76020)
MT-CO1	mouse	1:100	Abcam (ab14705)
Caspase3	rabbit	1:500	Cell Signaling (9664S)
CXCR4 (2B11, N-term)	rat	1:500	Affymetrix (14-9991-82)
Gamma-tubulin	rabbit	1:500	Sigma (T3559)
GAP43	mouse	1:500	Merck Millipore (MAB347)

MCM2 (BM-28)	mouse	1:200	BD Biosciences (610700)
ICAM1	goat	1:200	R&D Systems (AF796)
OMP	goat	1:500	Wako (544-10001)
RAB11		1:50	Proteintech (CL488-15903)
pS6	rabbit	1:100	Cell Signaling (2215S)
Alexa Fluor® 488 anti-goat	donkey	1:500	Thermo Fisher Scientific (A-11055)
Alexa Fluor® 488 anti-mouse	donkey	1:500	Thermo Fisher Scientific (A-21202)
Alexa Fluor® 488 anti-rabbit	donkey	1:500	Thermo Fisher Scientific (A-21206)
Alexa Fluor® 488 anti-rat	donkey	1:500	Thermo Fisher Scientific (A-21208)
Alexa Fluor® 568 anti-goat	donkey	1:500	Thermo Fisher Scientific (A-11057)
Alexa Fluor® 568 anti-mouse	donkey	1:500	Thermo Fisher Scientific (A-10037)
Alexa Fluor® 568 anti-rabbit	donkey	1:500	Thermo Fisher Scientific (A-10042)
Rhodamine Red TM -X anti-rat	donkey	1:500	Jackson Immuno Research (706-295-148)
Alexa Fluor® 633 anti-goat	donkey	1:500	Thermo Fisher Scientific (A-21094)
Alexa Fluor® 647 anti-rabbit	donkey	1:500	Thermo Fisher Scientific (A-31573)
Alexa Fluor® 647 anti-rat	donkey	1:500	Jackson Immuno Research (712-605-153)