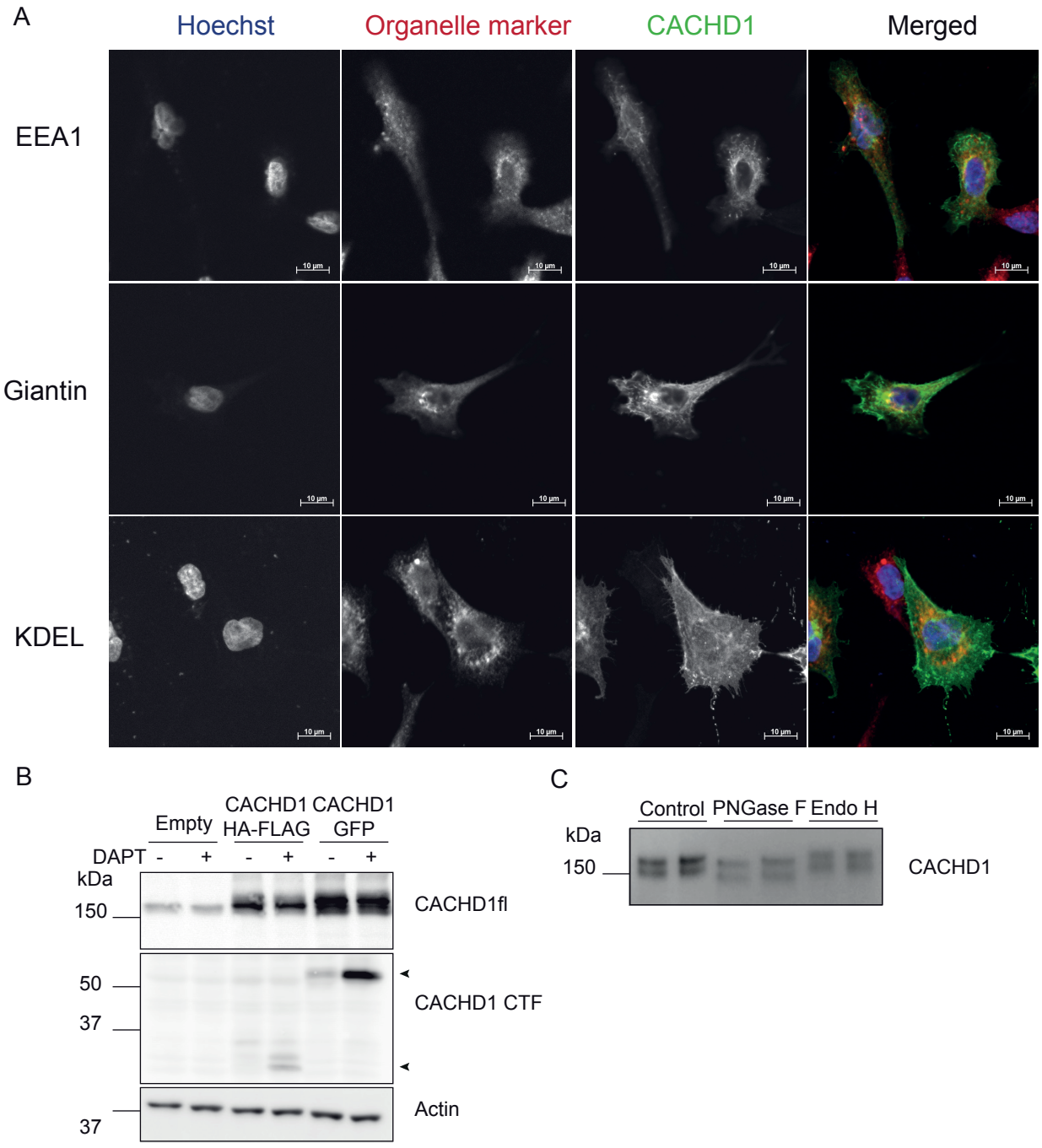
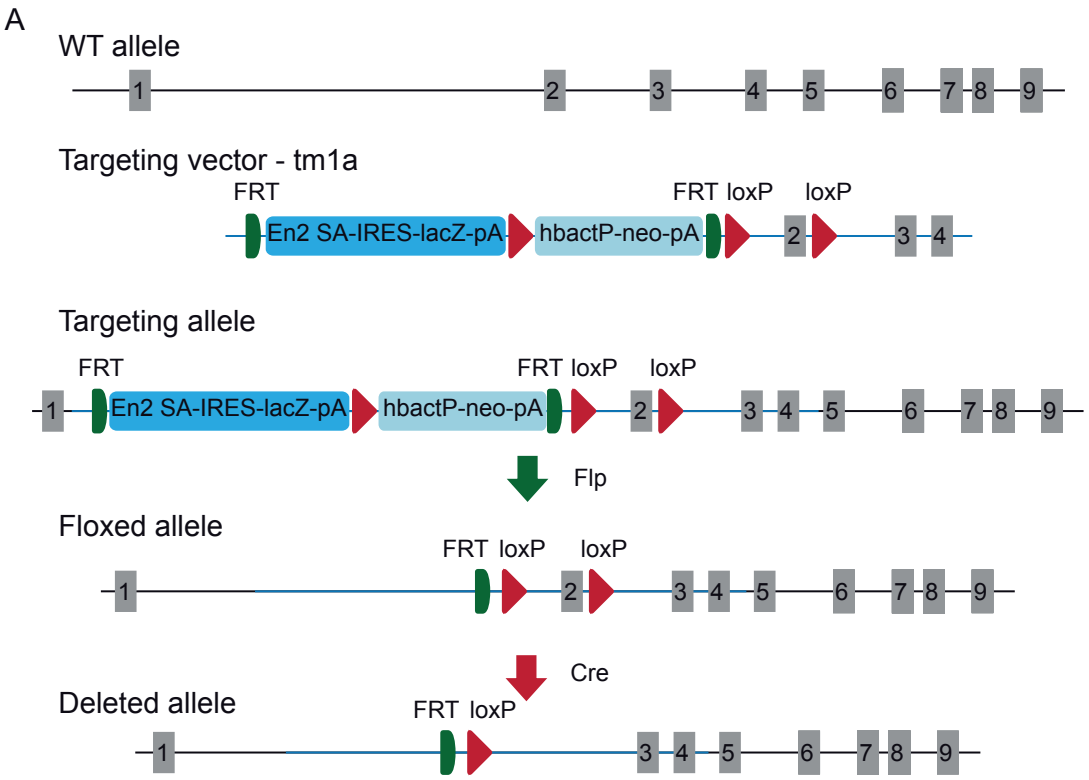
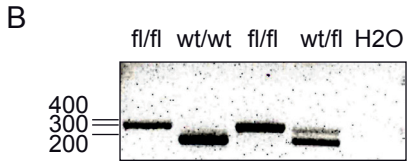
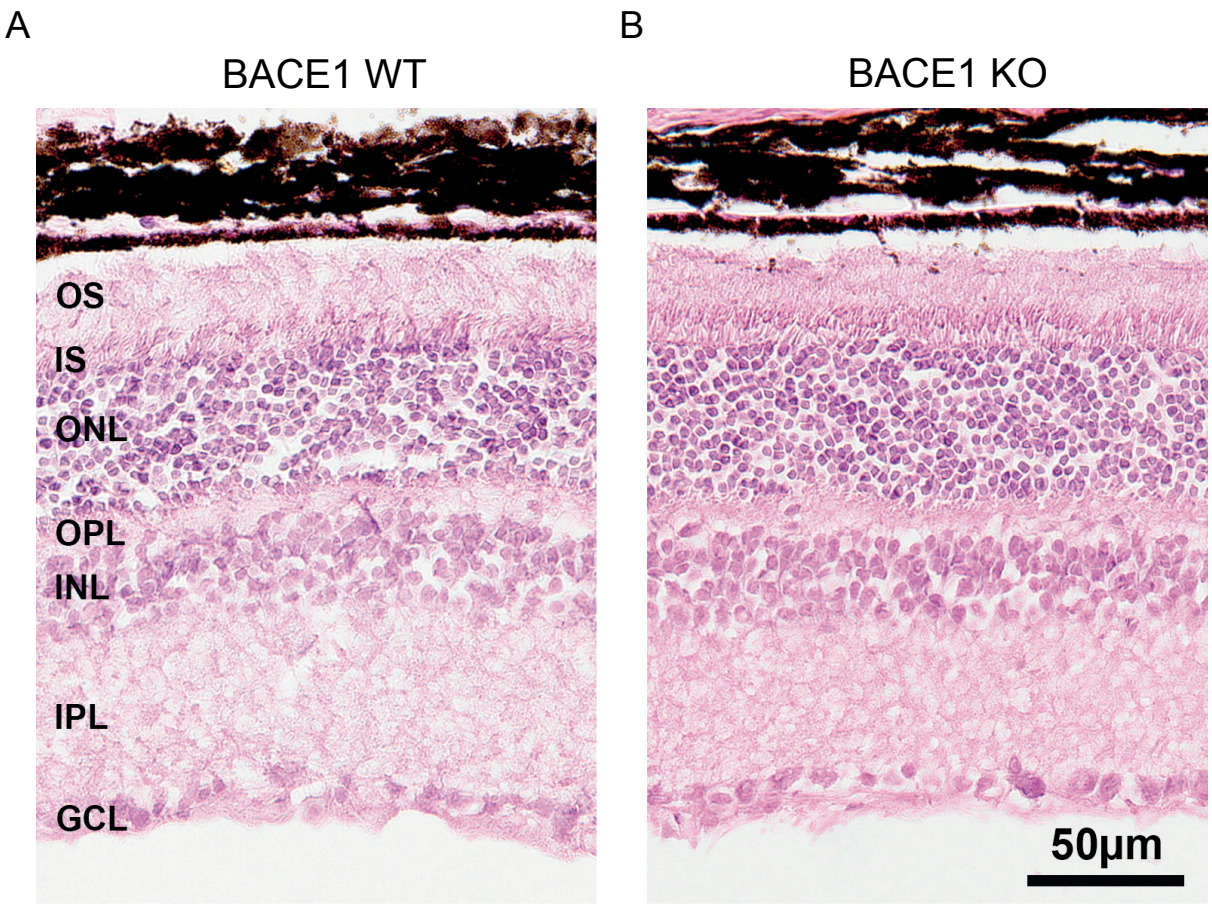


Supplementary figure 1. CACHD1 is mostly located on the cell membrane and in the Golgi apparatus. (A) COS7 cells were transiently transfected with a CACHD1-GFP construct and stained with organelle markers. CACHD1 expression was found throughout the cell with particularly strong staining at the plasma membrane. Additional stainings with EEA1, Giantin and KDEL, markers for early endosomes, Golgi apparatus and endoplasmic reticulum, respectively, demonstrated the highest colocalization with the Golgi apparatus marker. (B) Expression of CACHD1-GFP was monitored by immunoblot and compared to CACHD1 with an N-terminal HA and a C-terminal FLAG-tag (CACHD1 HA-FLAG). The apparent molecular weight of CACHD1-GFP was slightly higher than of CACHD1 HA-FLAG, given the larger molecular weight of GFP. Likewise, after inhibition of γ-secretase with DAPT the observed C-terminal fragment had a higher apparent molecular weight for CACHD1-GFP than for CACHD1 HA-FLAG. (C) Deglycosylation of endogenous CACHD1 in neuronal lysates reveals that its glycans can be removed with PNGaseF, but not with EndoH, demonstrating that the CACHD1 undergoes complex N-glycosylation.

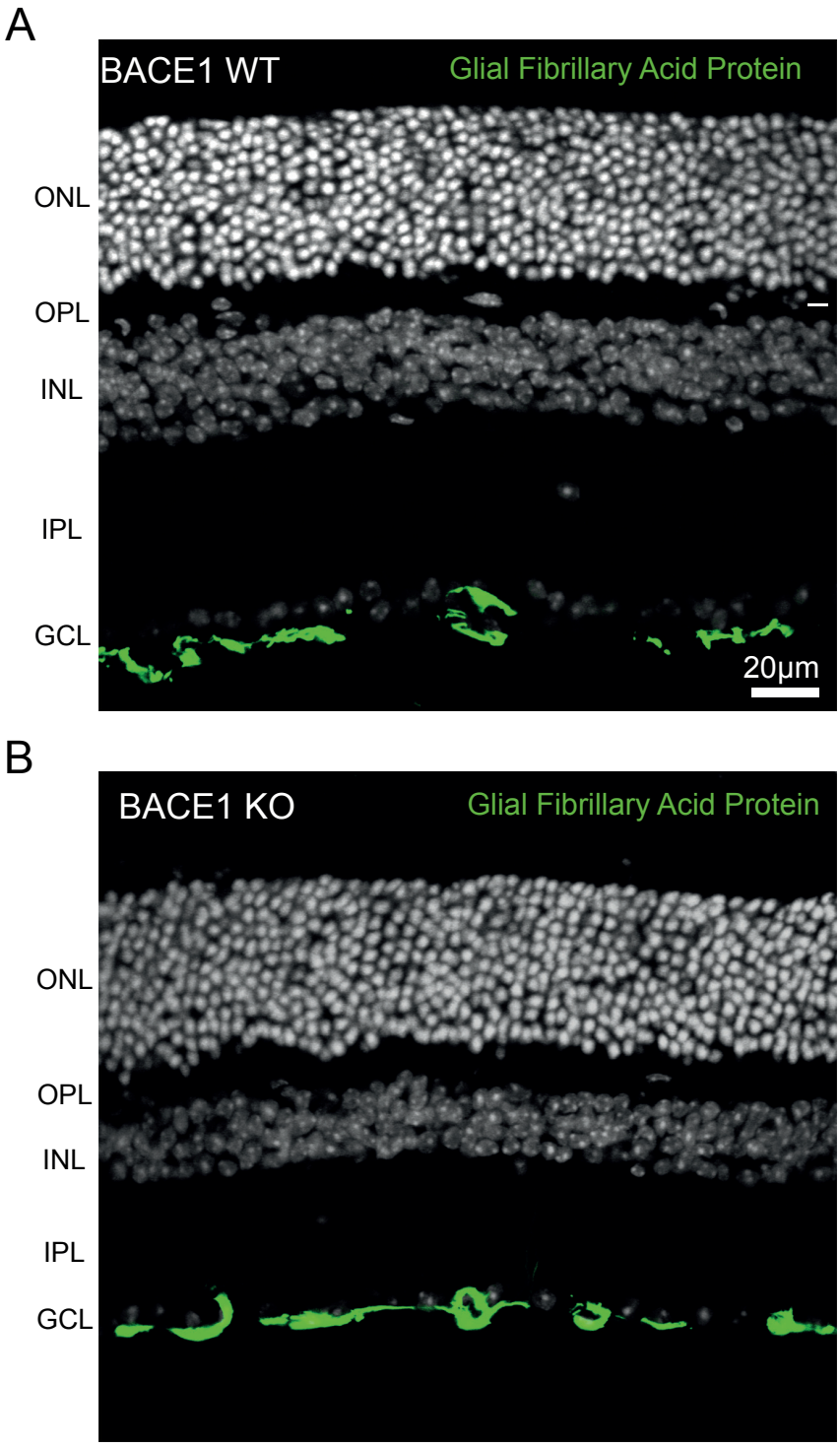




Supplementary figure 2. Generation of conditional BACE1 knockout mice (BACE1 coKO). (A) For homologous recombination, a EUCOMM based vector was used that contained loxP (red arrowheads)-flanked exon 2 of the Bace1 gene (marked as Targeting vector – tm1a). In order to remove the SA-IRESlacz (blue box) and β-actin promoter-neomycin (light blue box) selectable marker cassette that are surrounded by flip recombinase target (FRT) sites (green boxes), the mice were crossed with FLP recombinase-containing mice. FLP recombination between FRT sites excises the two cassettes to generate the floxed allele of the BACE1 gene exon 2 (marked as Floxed allele). Neurons were prepared from these floxed mice and lentivirally transduced in vitro with iCre recombinase (Cre), which results in deletion of exon 2, thus generating BACE1 KO cells (marked as Deleted allele). Exons are marked in gray numbered boxes. (B) Genotyping result of floxed and WT mice.



Supplementary figure 3. Retinal histology in BACE1 KO mice. Representative histological images taken from the central area of retinal cross-sections from 4-month-old BACE1 WT (A) and BACE1 KO (B) mice. Tissue sections were stained with hematoxylin and eosin to reveal the retinal morphology. Mean total retinal thickness was 232.9 ± 1.787 µm in BACE1 WT vs 230.1 ± 1.335 µm in BACE1 KO ($p = 0.278$, $n= 3$, unpaired Student's t-test).



Supplementary figure 4. Retinal degeneration marker analyzed in BACE1 KO. Representative confocal scans from retinal cross-sections from 4-month-old BACE1 WT (A) and BACE1 KO (B) mice immunolabeled for glial fibrillary acid protein (GFAP). GFAP induction in Müller glial cells is commonly observed in acute and chronic models of retinal degeneration. There was no sign of induction of GFAP in BACE1 KO retina.