Supplementary information

Supplementary Figure legends:

Figure S1. APP expression and processing in APPPS1^{+} mice is not affected by *Prnp* genotypes. APP expression and processing by secretases were similar in 2-month-old APPPS1^{+}*Prnp*$^{+/+}$, APPPS1^{+}*Prnp*$^{+/o}$ and APPPS1^{+}*Prnp*$^{o/o}$ mice. (*A*) Full-length APP and C-terminal fragments (α-βCTF) are not affected by *Prnp* genotype. Left panel: representative SDS-PAGE followed by immunoblotting using an APP C-terminal antibody detecting full-length APP and α-βCTF; actin was used as loading control. Right panel: quantitation of chemiluminescence for APP, α-CTF and β-CTF. (*B*) Human soluble Aβ_{42} levels as assessed by ELISA. Each symbol indicates a mouse.

Figure S2. Genetic background associates with differences in insoluble Aβ_{42} levels in APPPS1^{+} mice. APPPS1^{+} mice (on a C57B/6 background) were crossed with *Prnp*$^{o/o}$ mice (on a mixed C57BL/6 and 129/Sv background) to generate F1 and F2 mice as depicted in the pedigree. Insoluble Aβ_{42} levels are plotted against the number of 129/Sv specific microsatellite markers. Each symbol denotes a mouse. Average ± standard deviation for each group is displayed as well.

Figure S3. Overexpression of PrP in APPPS1^{+} mice. Expression of PrP^{C} in brains from APPPS1^{+}*Prnp*$^{+/+}$, APPPS1^{+}*tga20*$^{tg/-}$*Prnp*$^{o/o}$ and APPPS1^{+}*tga20*$^{-/-}$*Prnp*$^{+/o}$ mice were analyzed by ELISA. Each symbol indicates a mouse. Significance was determined by one-way ANOVA *$p< 0.05$.

Figure S4. Recombinant PrP binds synthetic Aβ_{42} through its amino proximal domain. (*A*) SDS-PAGE followed by protein blotting with an anti-human Aβ (6E10) antibody was used to characterize Aβ_{42} preparations (20, 10 or 5 ng of synthetic protein in each lane) for the experiments (B-D). (*B*) Titration of human Aβ_{42} onto immobilized recombinant PrP (recPrP$_{23\text{-}231}$) obtained by ELISA showed binding of recPrP$_{23\text{-}231}$ to Aβ_{42}. (*C*) Binding of human Aβ_{42} to recPrP$_{121\text{-}231}$ was reduced in presence of the POM2 and POM3 antibodies

against the N-proximal region of PrP^C. The epitope of POM2 lies within the octapeptide repeat region of PrP^C, giving rise to four binding sites between residues 58 and 88. The epitope recognized by POM3 corresponds to amino acids 95-100 of mouse PrP. POM2, POM3, and IgG1 isotype control were utilized at different concentrations (100nM, 10nM, 1nM). Values are averages ± SD. Significance was determined by one-way ANOVA ***$p < 0.001$. (*D*) Comparison between the binding curves for human $A\beta_{42}$ to immobilized $recPrP_{23\text{-}231}$ or truncated $recPrP_{121\text{-}231}$. Removal of the N-terminal region, as in $recPrP_{121\text{-}231}$, prevented binding to $A\beta_{42}$.

Figure S5. Amyloid pathology and associated inflammatory response. Hippocampi of 4-month-old wild-type mice (1st row) and various APPPS1 mice (rows 2-5). The APPPS1 mice displayed similar degree of amyloid deposition, microglial activation, and astrocytosis. A 12-month-old $APPPS1^{+}tga20^{tg/-}Prnp^{+/o}$ mouse (bottom row) showed more pronounced amyloid deposition and associated inflammatory responses. HE: hematoxilin/eosin; Iba1: microglial marker; GFAP: glial fibrillary acidic protein, a marker of reactive astrocytes. Scale bar: 500 μm.

Figure S6. Crossing of genetically modified mice used in this study. A representative pedigree showing intercrossing of several mutant mice is depicted. Grey scale indicates different levels of PrP^C. Brown symbol: designate expression of anchorless, soluble PrP. The orange border denotes the presence of APP/PS1 transgenes. Parallel lines indicate brother-sister crossing. $APPPS1^-$ mice are not represented (with one exception) in the pedigree for clarity, but were included as controls in the actual experiments. $Prnp^o$ and $Prnp^-$ denote by convention the "Zurich-I" and "Edbg" knockout alleles of *Prnp,* respectively.

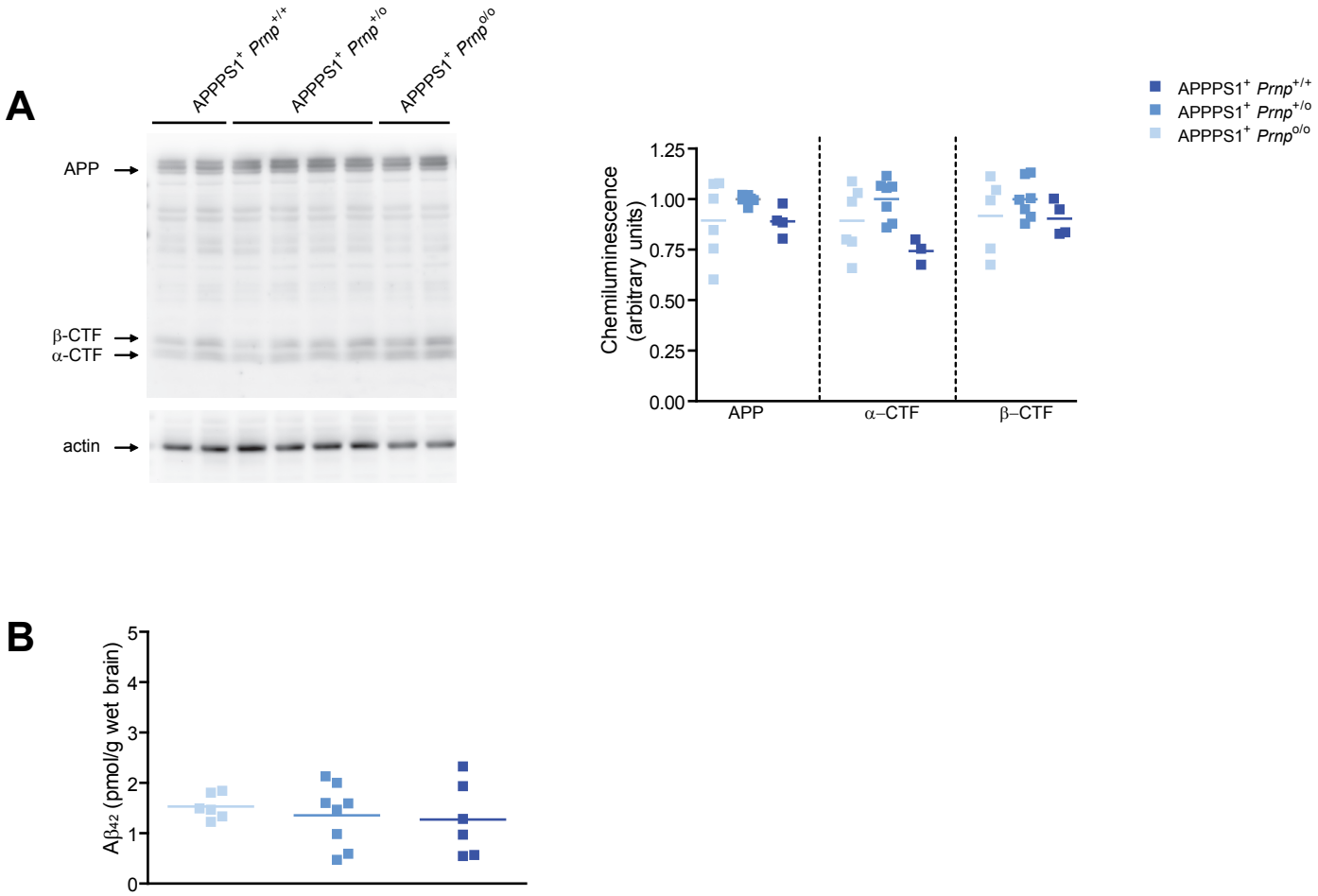
A
APPPS1+ Prnp+/+
APPPS1+ Prnp+/o
APPPS1+ Prnp o/o
APP
β-CTF
α-CTF
actin
Chemiluminescence (arbitrary units)
1.25
1.00
0.75
0.50
0.25
0.00
APP
α–CTF
β–CTF
B
Aβ42 (pmol/g wet brain)
5
4
3
2
1
0

Figure S1

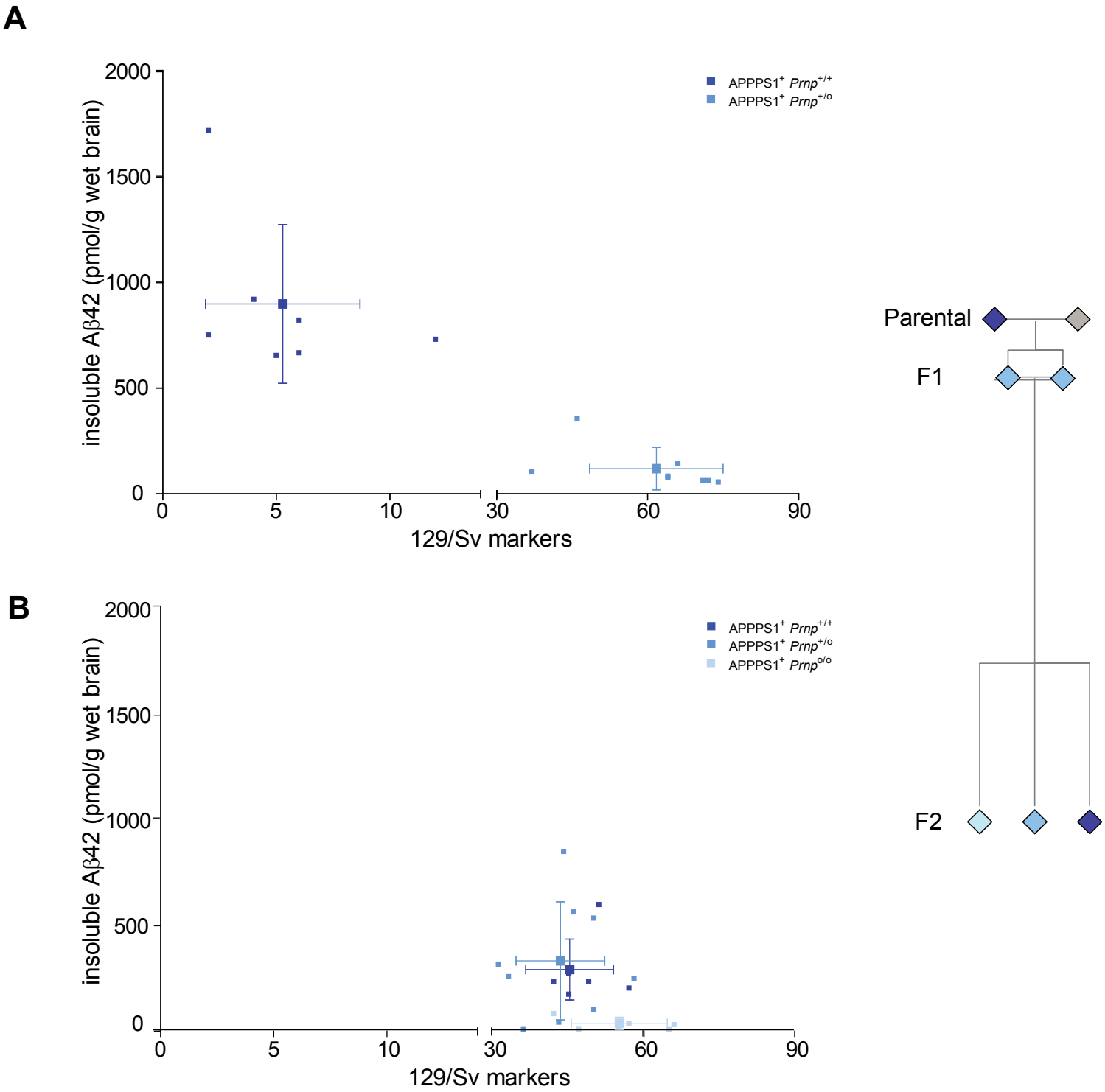
A
insoluble Aβ42 (pmol/g wet brain)
2000
1500
1000
500
0
0
5
10
30
60
90
129/Sv markers
APPPS1+ Prnp+/+
APPPS1+ Prnp+/o
B
insoluble Aβ42 (pmol/g wet brain)
2000
1500
1000
500
0
0
5
10
30
60
90
129/Sv markers
APPPS1+ Prnp+/+
APPPS1+ Prnp+/o
APPPS1+ Prnpo/o
Parental
F1
F2

Figure S2

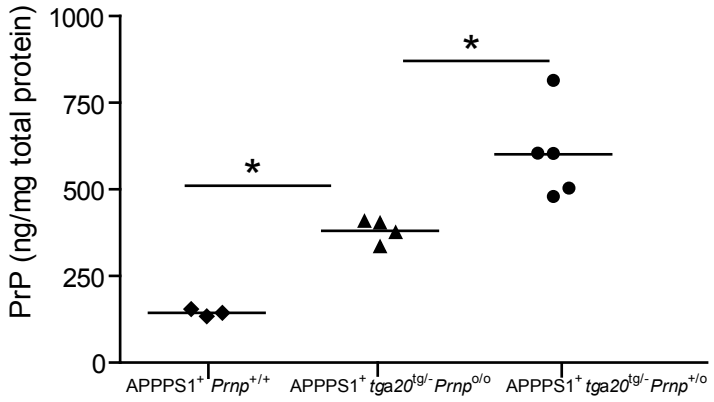
PrP (ng/mg total protein)
1000
750
500
250
0
*
*
APPPS1+ Prnp+/+
APPPS1+ tga20tg/- Prnpo/o
APPPS1+ tga20tg/- Prnp+/o

Figure S3

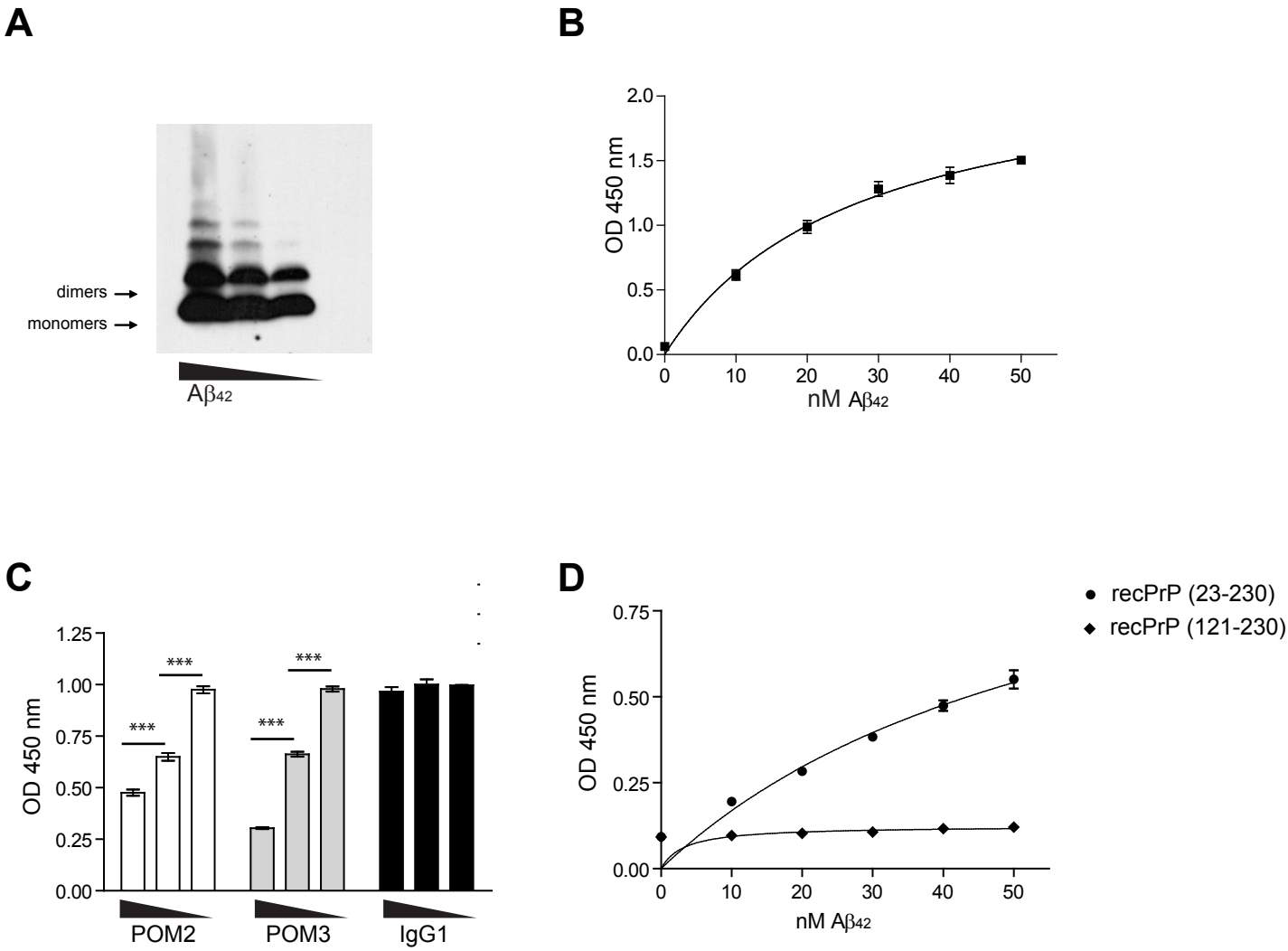
A
dimers
monomers
Aβ42
B
OD 450 nm
nM Aβ42
C
OD 450 nm
***
POM2
POM3
IgG1
D
recPrP (23-230)
recPrP (121-230)
OD 450 nm
nM Aβ42

Figure S4

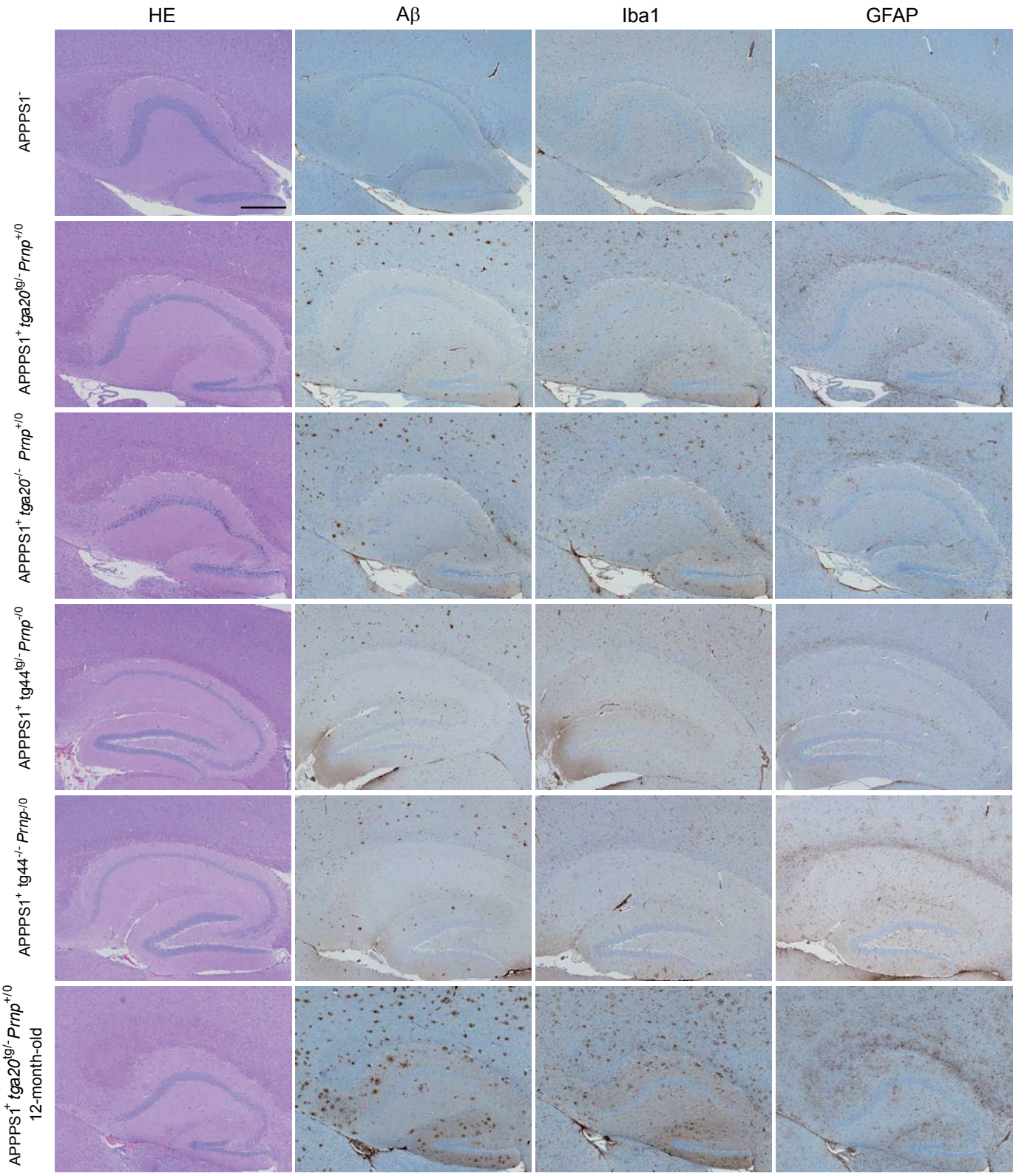
HE
Aβ
Iba1
GFAP
APPPS1-
APPPS1+ tga20tg/- Prnp+/0
APPPS1+ tga20-/- Prnp+/0
APPPS1+ tg44tg/- Prnp-/0
APPPS1+ tg44-/- Prnp-/0
APPPS1+ tga20tg/- Prnp+/0
12-month-old

Figure S5

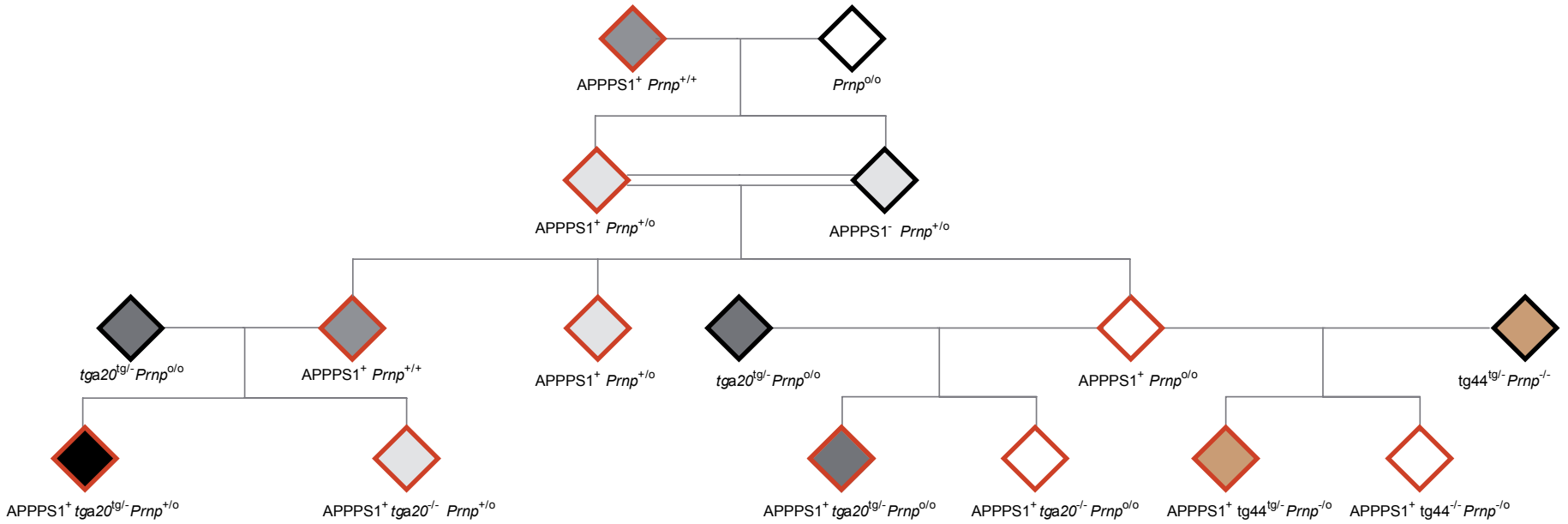
APPPS1+ Prnp+/+
Prnpo/o
APPPS1+ Prnp+/o
APPPS1- Prnp+/o
tga20tg/- Prnpo/o
APPPS1+ Prnp+/+
APPPS1+ Prnp+/o
tga20tg/- Prnpo/o
APPPS1+ Prnpo/o
tg44tg/- Prnp-/-
APPPS1+ tga20tg/- Prnp+/o
APPPS1+ tga20-/- Prnp+/o
APPPS1+ tga20tg/- Prnpo/o
APPPS1+ tga20-/- Prnpo/o
APPPS1+ tg44tg/- Prnp-/o
APPPS1+ tg44-/- Prnp-/o

Figure S6