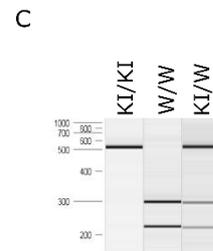
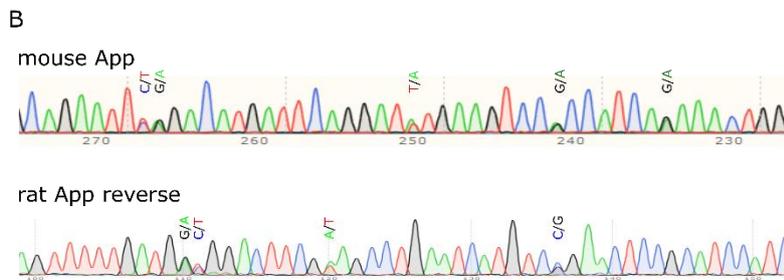
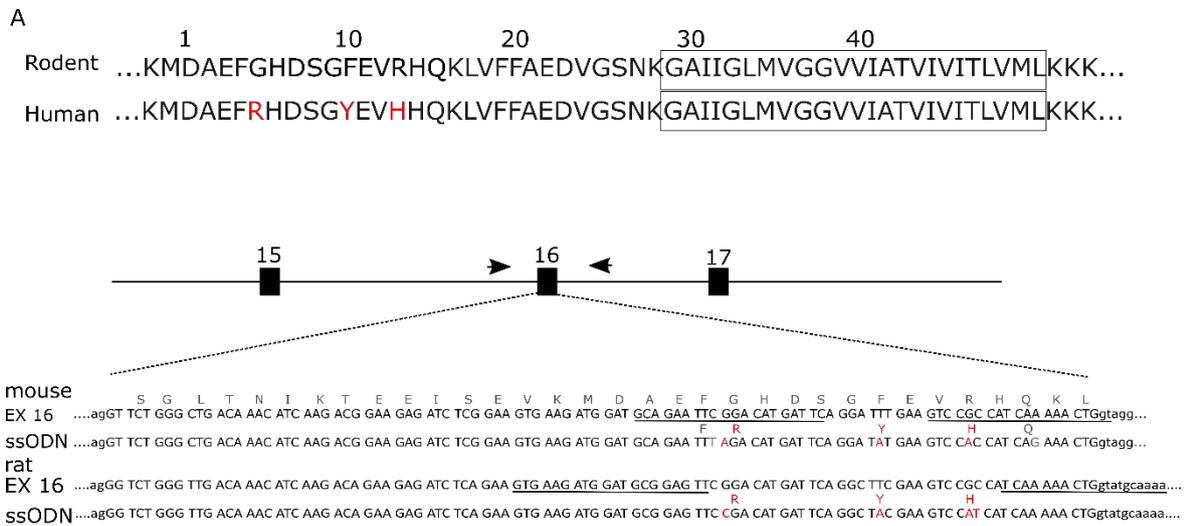


486 **Additional files**

487 **Additional file1**



488

489 **Additional file1. Generation of APP KI mice and rats by CRISPR Cas (A)** The top panel displays an

490 alignment between human A β and rodent A β peptide. Differences are indicated in red, boxes

491 represent transmembrane domains. The lower panel depicts the genomic organization and exon 16

492 sequence of the mouse and *App* gene. Exons are indicated as black boxes, arrows denote primers

493 used for genotyping and sequencing. Underlined sequences are CRISPR guides, ssODN represent the

494 template used for homologous recombination. Nucleotides and amino acids indicated in red are the

495 target sequences, nucleotides in green are silent mutations introduced to prevent Cas9 to recut after

496 homologous recombination. **(B)** Sanger sequencing results indicating the introduction of the point

497 mutations in one strand as indicated above the chromatograms. **(C)** PCR analysis of APP KI mice.

498 Digestion with EcoRI is indicative for KI allele as the restriction site is destroyed after gene editing.

499

500 **Additional file2**

A

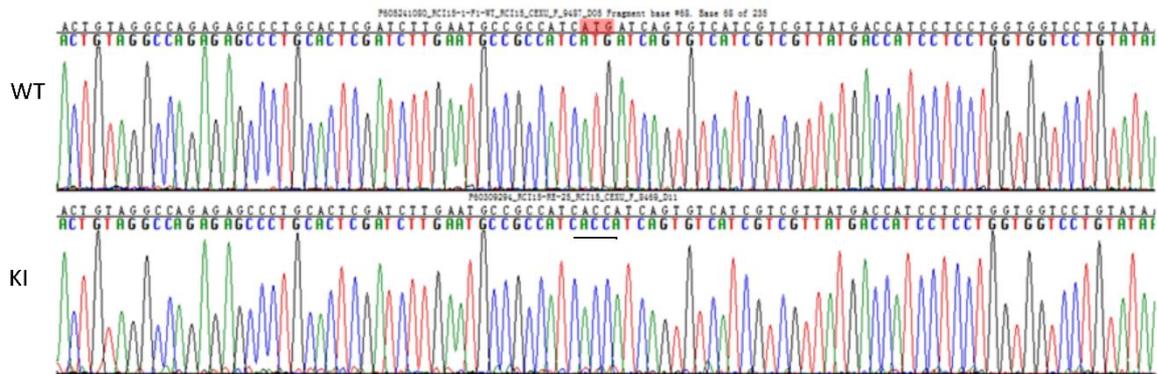
M139

PSEN1 Exon5 5'...CTG CAC TCG ATC TTG AAT GCC GCC ATC ATG ATC AGT GTC ATC GTC GTT ATG ACC ATC CTC...-3'

ssODN 5'...CTG CAC TCG ATC TTG AAT GCC GCC ATC ACC ATC AGT GTC ATC GTC GTT ATG ACC ATC CTC...-3'

T139

B



501

502 **Additional file2. Generation of M139T *Psen1* KI rats by CRISPR Cas. (A)** Partial sequence of exon 5 of

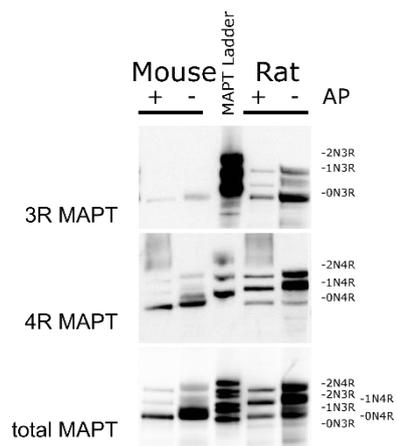
503 the mouse and *Psen1* gene. Underlined sequences indicate the CRISPR guide, ssODN represent the

504 template used for homologous recombination. Nucleotides and amino acids indicated in red are the

505 target sequences. **(B)** Sanger sequencing results indicating the introduction of the point mutations

506 (underlined).

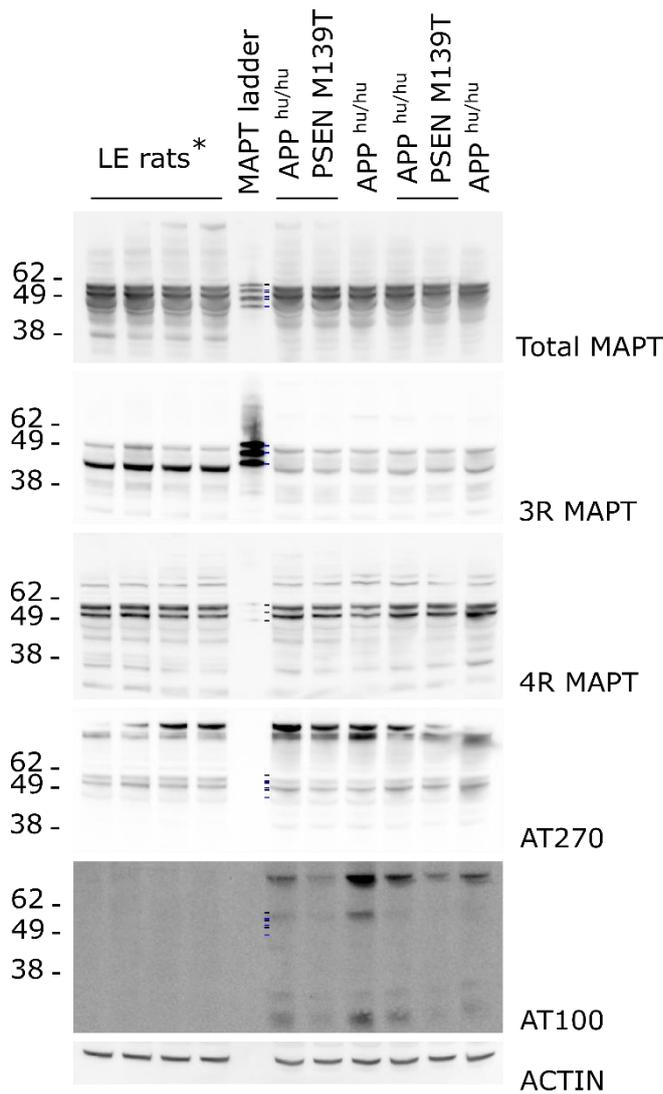
507 **Additional file3**



508

509 **Additional file3. Comparing MAPT splice isoforms between Mouse and Rat.** Analysis of MAPT
510 isoforms after dephosphorylation with alkaline phosphatase (AP). The extracts of cerebrum were
511 treated with (+) or without (-) alkaline phosphatase (AP) at 37 °C for 1h and immunoblotted with
512 RD3, RD4, Total MAPT. The middle lane is recombinant human MAPT (ladder). Mouse express mainly
513 0N4R splice variant compared to the more complex expression pattern in the rat brain lysates
514 showing all 6 splice forms. The estimated ratio 3R/4R MAPT = 1/13.

515 **Additional file4**



516

517 **Additional file4. MAPT protein analysis in two year old rats.** Immunoblot of MAPT in rat cerebrum
 518 with total Tau antibody, 3Rtau-specific antibody RD3, 4Rtau-specific antibody RD4, AT270 and AT100
 519 of two year old rats (n=2). LE rats* are cerebrum samples from wildtype Long Evans rats aged 14
 520 weeks. MAPT ladder is recombinant human MAPT (0N3R, 0N4R, 1N3R, 1N4R, 2N3R, 2N4R). Notice
 521 that mouse MAPT proteins are migrating faster compared to the corresponding human splice variant.