

Figure S1: Impact of R47H variant of TREM2 on tau pathology in 3-month-old PS19 mice. Representative images of pTau staining (AT8, AT180 and PG5) in the piriform cortex (A, E, I) and hippocampus (B, F, J) from PS19-T2^{CV} and PS19-T2^{R47H} mice. (Scale bars: 1 mm). Quantification of the percent area covered by pTau staining (AT8, AT180 and PG5) in the piriform cortex (C, G, K) and hippocampus (D, H, L). Data are presented as mean \pm SEM. Significance was determined using an unpaired, two-tailed Mann Whitney's test due to the nonparametric data set. Significance was defined as $*p < 0.05$ (PS19-T2^{CV}, $n=16$ and PS19-T2^{R47H} $n=14/15$). ELISA results showing concentrations of pTau (p.Ser202-Thr205 and p.Thr181) and total tau and pTau/total tau ratio in the hippocampus were quantified using a human-tau (htau) specific sandwich ELISA to measure pTau (L), total tau (M) and pTau/total tau ratio (L). pTau and total tau (L and M) were normalized on total protein concentration. Data are presented as mean \pm SEM. Significance was determined by an unpaired, two-tailed Student's t test (PS19-T2^{CV}, $n=15$ and PS19-T2^{R47H} $n=12$).

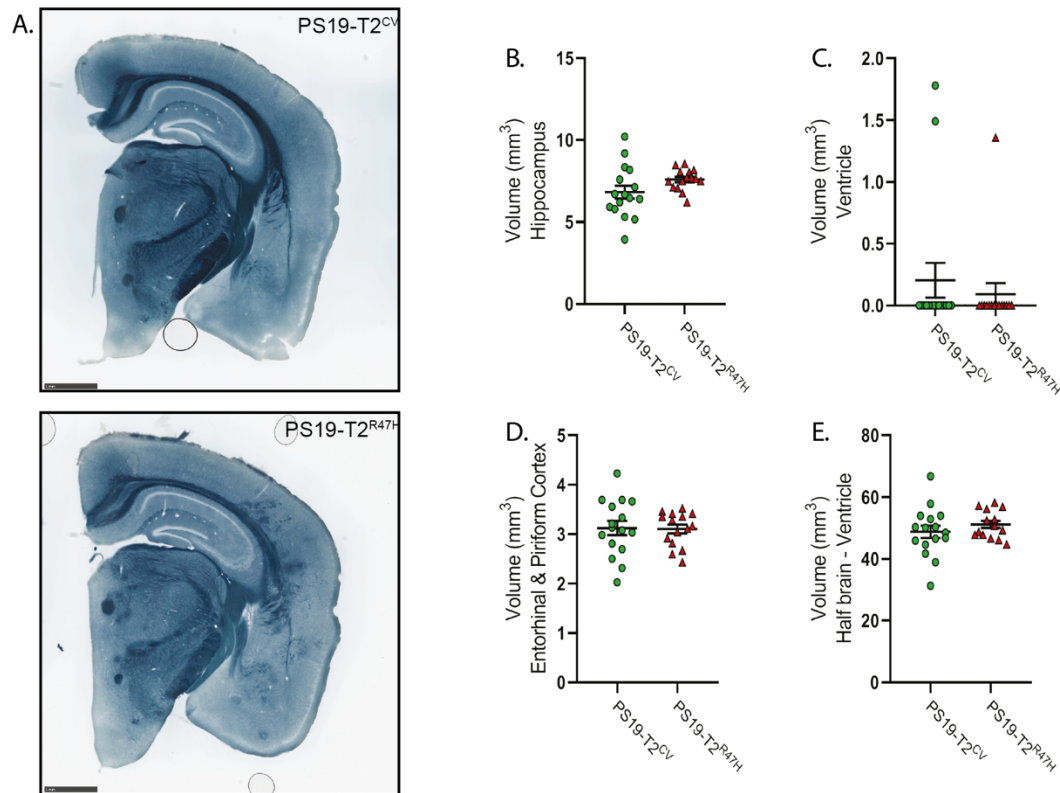


Figure S2: Impact of R47H variant of TREM2 on brain volume in 3-month-old PS19 mice. Representative images of PS19-T2^{CV} and PS19-T2^{R47H} brain sections stained with Sudan black at 3 months of age (A) (Scale bars, 1 mm). Quantification of the average volume of the hippocampus (B), ventricles (C), entorhinal and piriform cortex (D) and half brain minus ventricle (E). Data are presented as mean \pm SEM. Significance was determined by an unpaired, two-tailed Student's t test (PS19-T2^{CV}, n=16 and PS19-T2^{R47H} n=15).

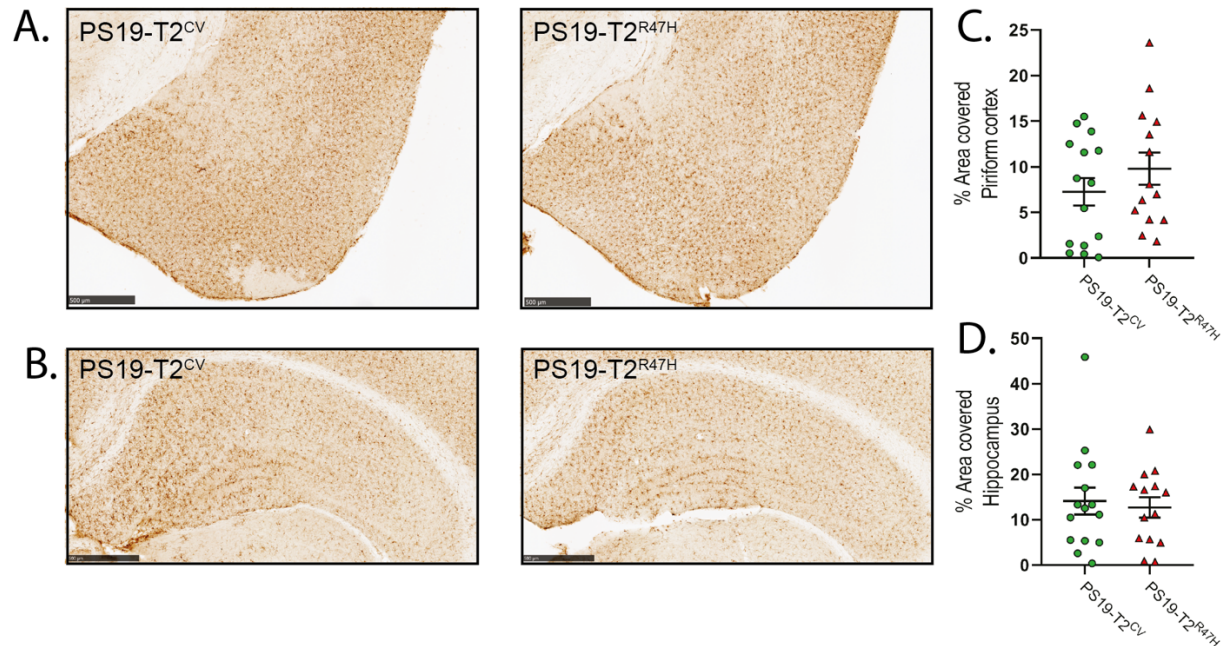


Figure S3: Impact of R47H variant of TREM2 on microgliosis in 3-month-old PS19 mice. Representative images of Iba1 staining in the piriform cortex (A) and hippocampus (B) from PS19-T2^{CV} and PS19-T2^{R47H} mice. (Scale bars: 0.5 mm). Quantification of the percent area covered by Iba1 staining in the piriform cortex (C) and hippocampus (D). Data is presented as mean \pm SEM. Significance was determined using an unpaired, two-tailed Mann Whitney's test due to the nonparametric data set (PS19-T2^{CV}, n=15 and PS19-T2^{R47H} n=14).

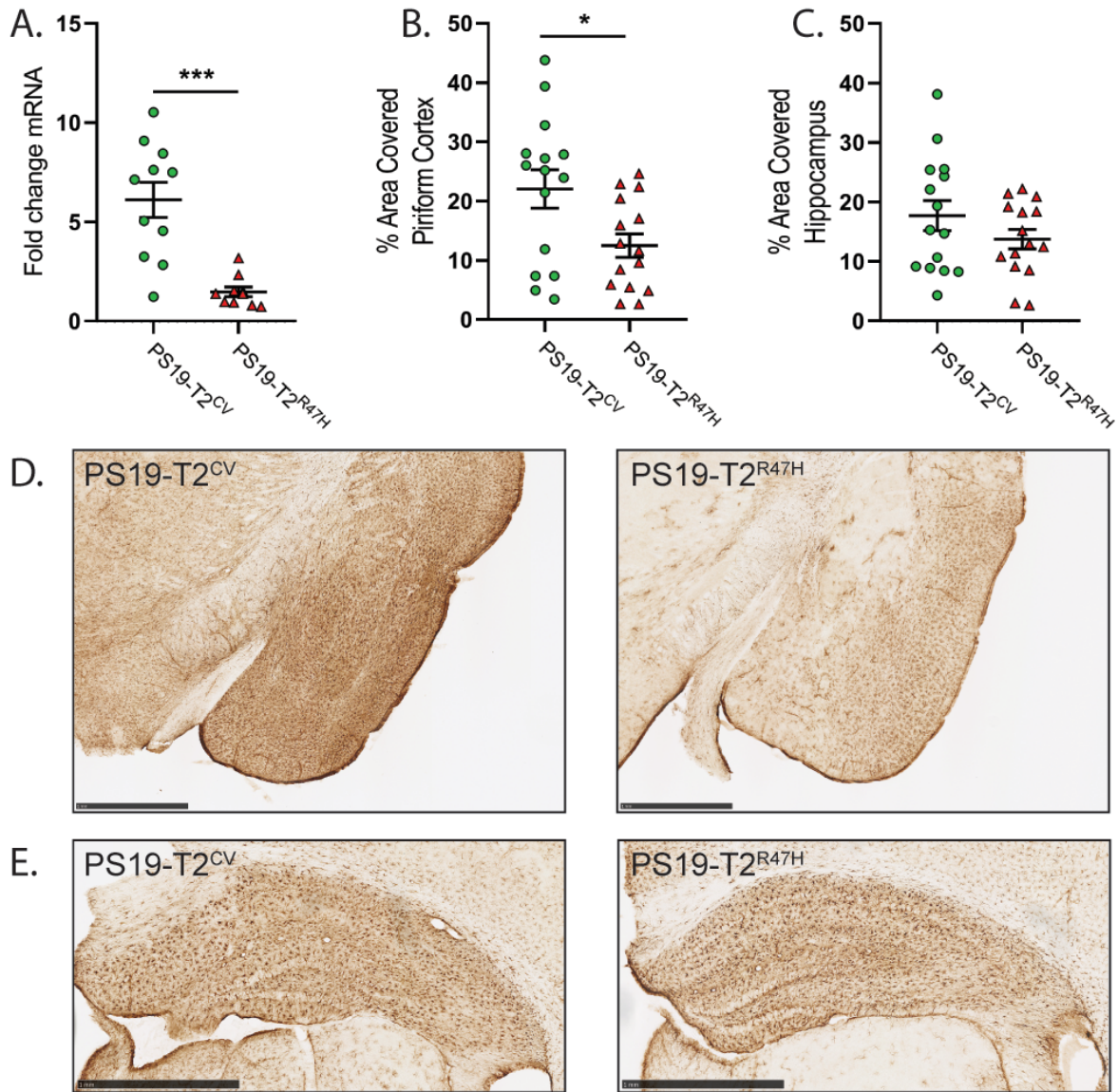


Figure S4: R47H variant of TREM2 decreases astroglialosis in 9-month-old PS19 mice. Expression of cortical GFAP mRNA of 9-month-old PS19-T2^{CV} and PS19-T2^{R47H} mice (A) (PS19-T2^{CV}, n=11 and PS19-T2^{R47H} n=10). Quantification of the percent area covered by GFAP staining in the piriform cortex (B) and hippocampus (C) (PS19-T2^{CV}, n=15 and PS19-T2^{R47H} n=15). Representative images of GFAP staining in the piriform cortex (D) and hippocampus (E) from PS19-T2^{CV} and PS19-T2^{R47H} mice (Scale bars: 1 mm). Data are presented as mean \pm SEM. Significance was determined by an unpaired, two-tailed Student's t test. Significance was defined as * p < 0.05 and *** p < 0.001

TREM2 genotype	APOE genotype	Age	Sex	CDR	Braak
CV	23	91.081	M	3	V
CV	34	81.259	F	3	VI
CV	44	72.203	M	3	VI
CV	24	88.764	F	3	VI
CV	33	90.2642	F	2	VI
CV	33	80.975	M	3	VI
CV	33	95.734	F	3	VI
CV	34	84.471	F	1	III
CV	33	91.165	M	1	III
R47H	33	90.642	M	3	V
R47H	34	88.225	F	3	IV
R47H	33	85.637	M	3	V
R47H	33	93.985	F	3	NA
R47H	34	78.231	M	3	V
R62H	34	77.714	M	3	V
R62H	34	78.981	F	3	NA
R62H	33	84.375	F	3	VI
R62H	34	89.306	F	3	VI
R62H	44	89.369	F	3	NA

Supplementary Table 1. Demographic information for TREM2^{R47H}, TREM2^{R62H}, and TREM2^{CV} AD cases used in figure 7. NA: Not Available.