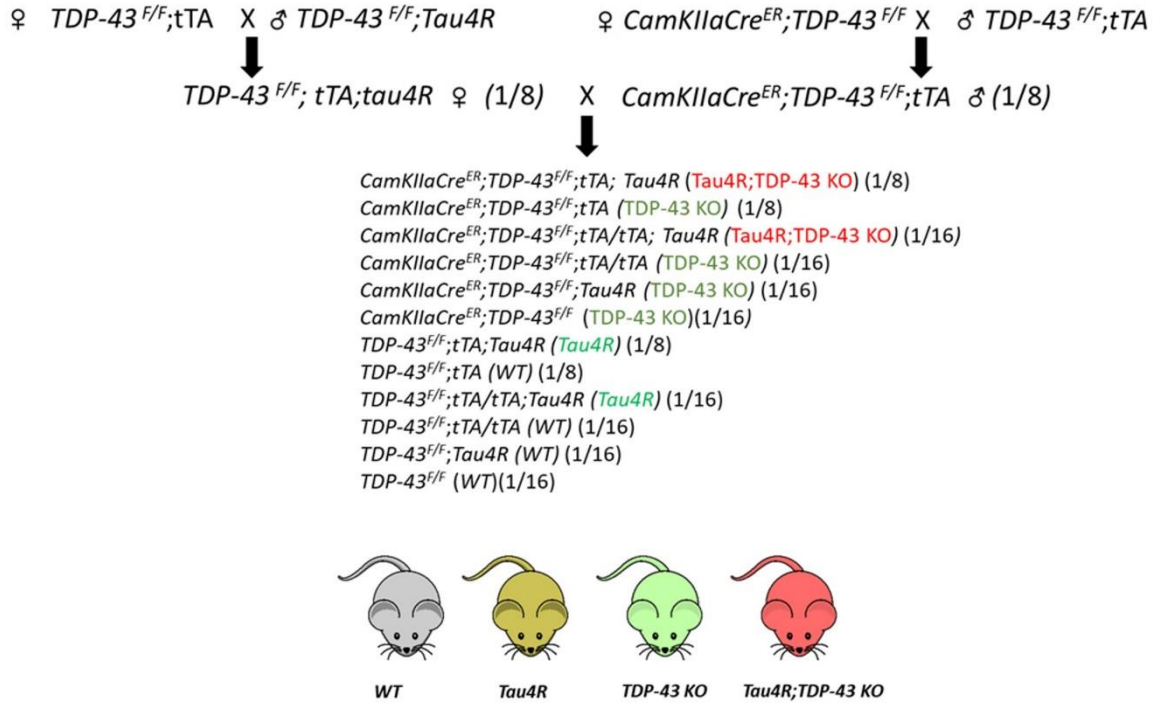
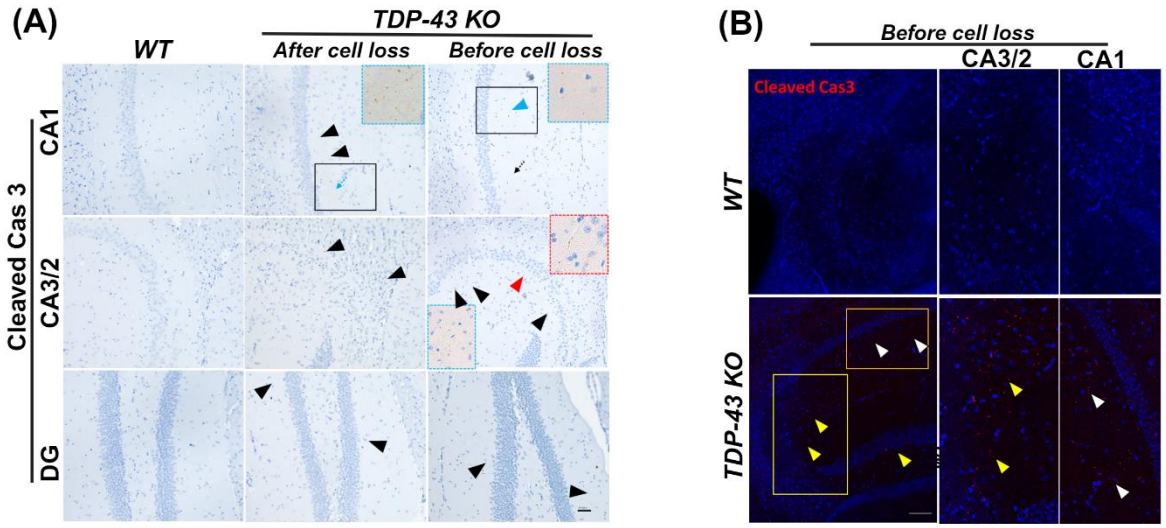
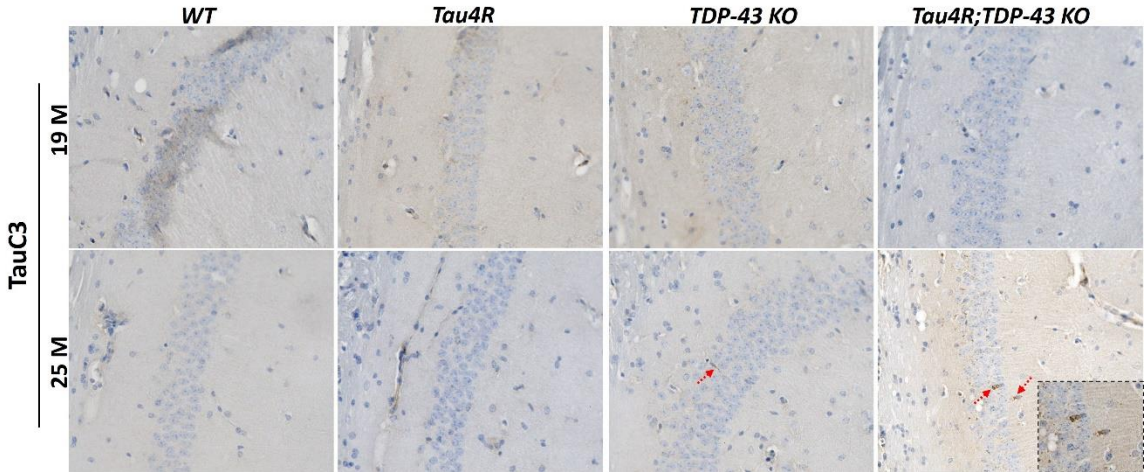
## Supplementary Figures



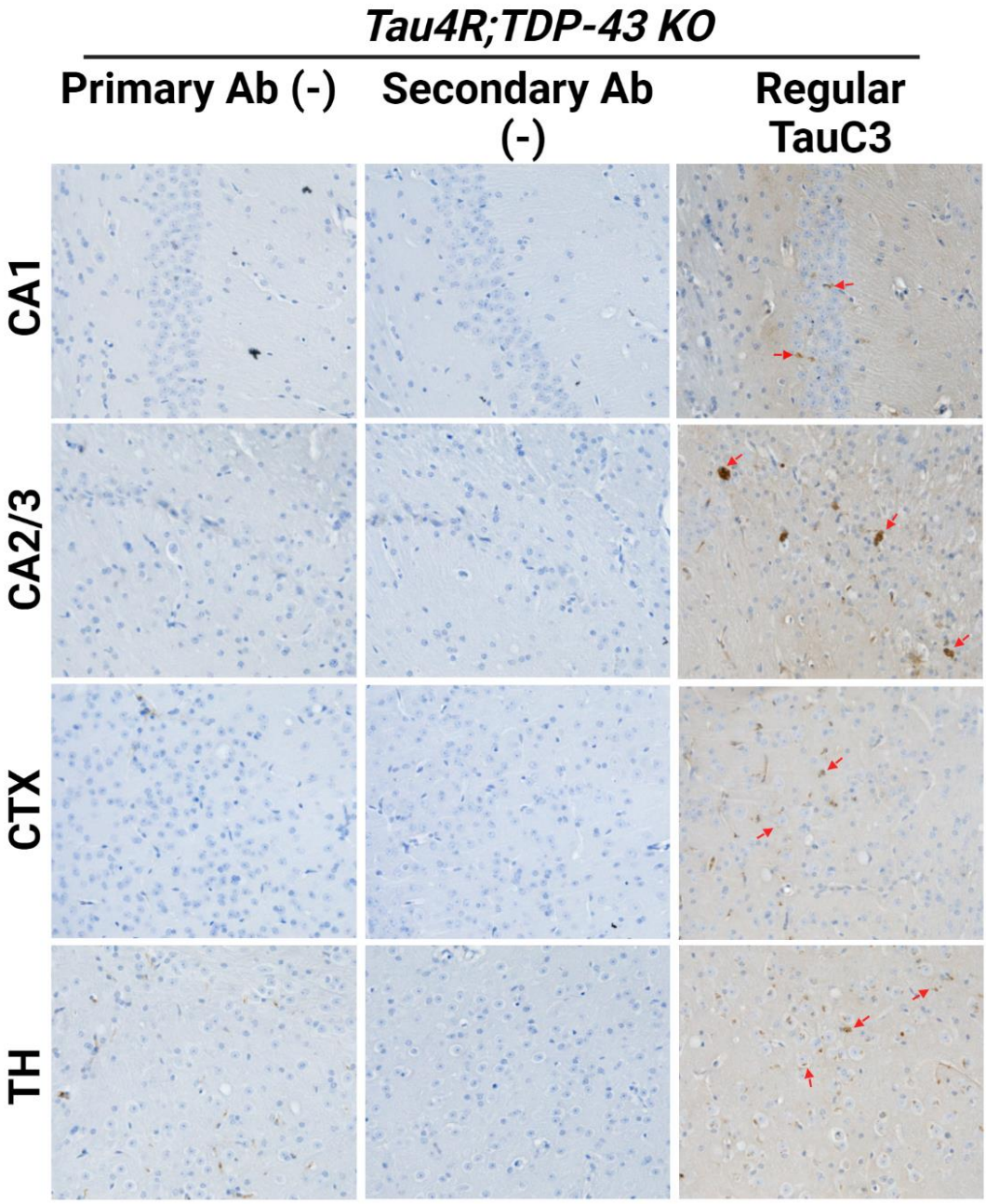

**Supplementary Figure 1:** Breeding strategy for generating *CaMKII-CreER;Tardbp$^{f/f}$;hTau4R* mice and littermate controls. (#) Indicates the Mendelian frequency of pups from each litter expected to carry the genotype of interest



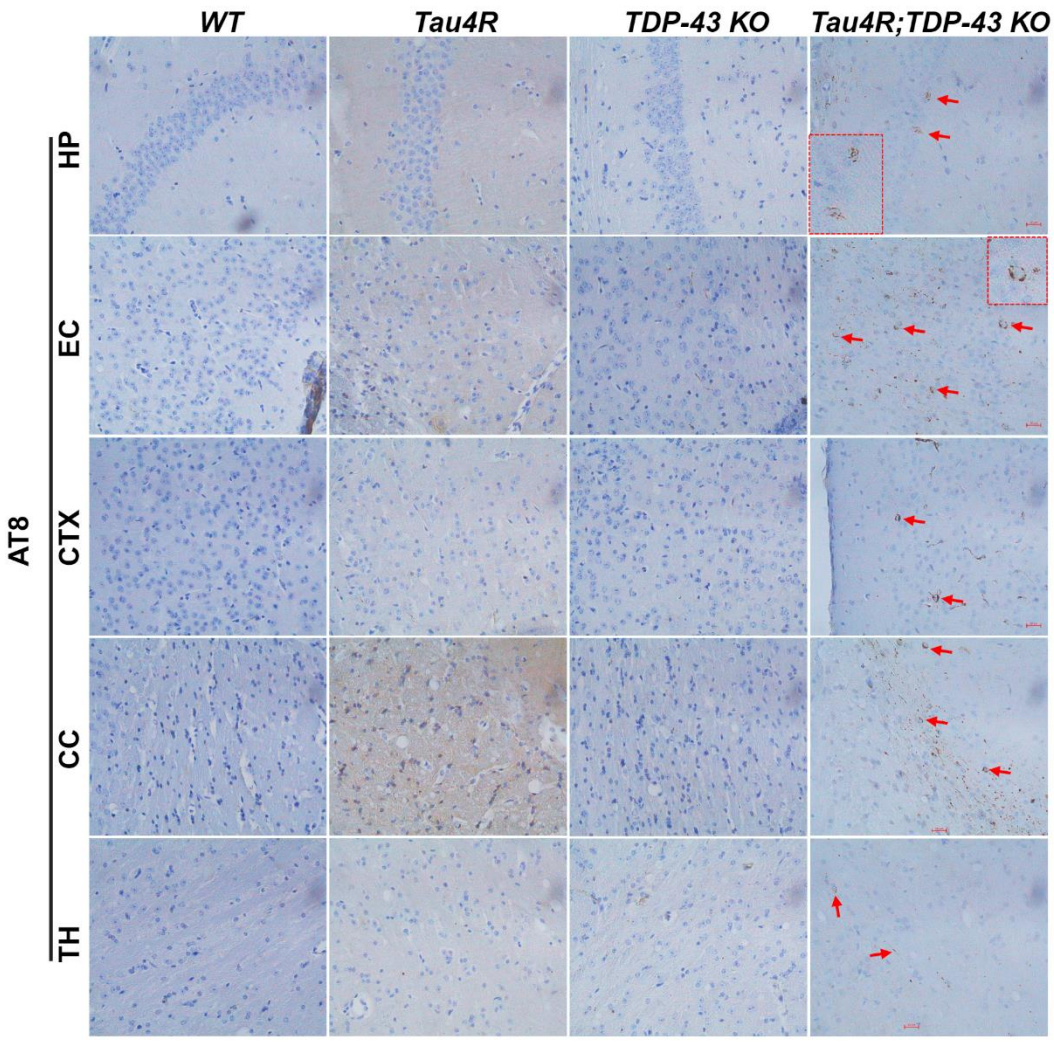

**Supplementary Figure 2: (A) Immunohistochemical analysis of** *WT* (left column) and *TDP-43 KO* mice (middle column; after cell loss) and before cell loss (*TDP-43 KO* 4 M, right column) using antiserum against cleaved caspase 3 in the CA1, CA3/2 and DG subregion of the hippocampus, arrow heads indicating the immunoreactivity enlarged view in inset (scale bar, 50μm). **(B)** Immunofluorescence of cleaved caspase 3 corroborating the immunohistochemistry before the neuron loss 2M after deletion (Figure 1 B), showing cleaved caspase 3 immunofluorescence in CA1, CA3/2 and DG subregions as arrow heads indicate (left column) enlarged view in middle (CA3/2) and right column (DG) (scale bar, 100μm).



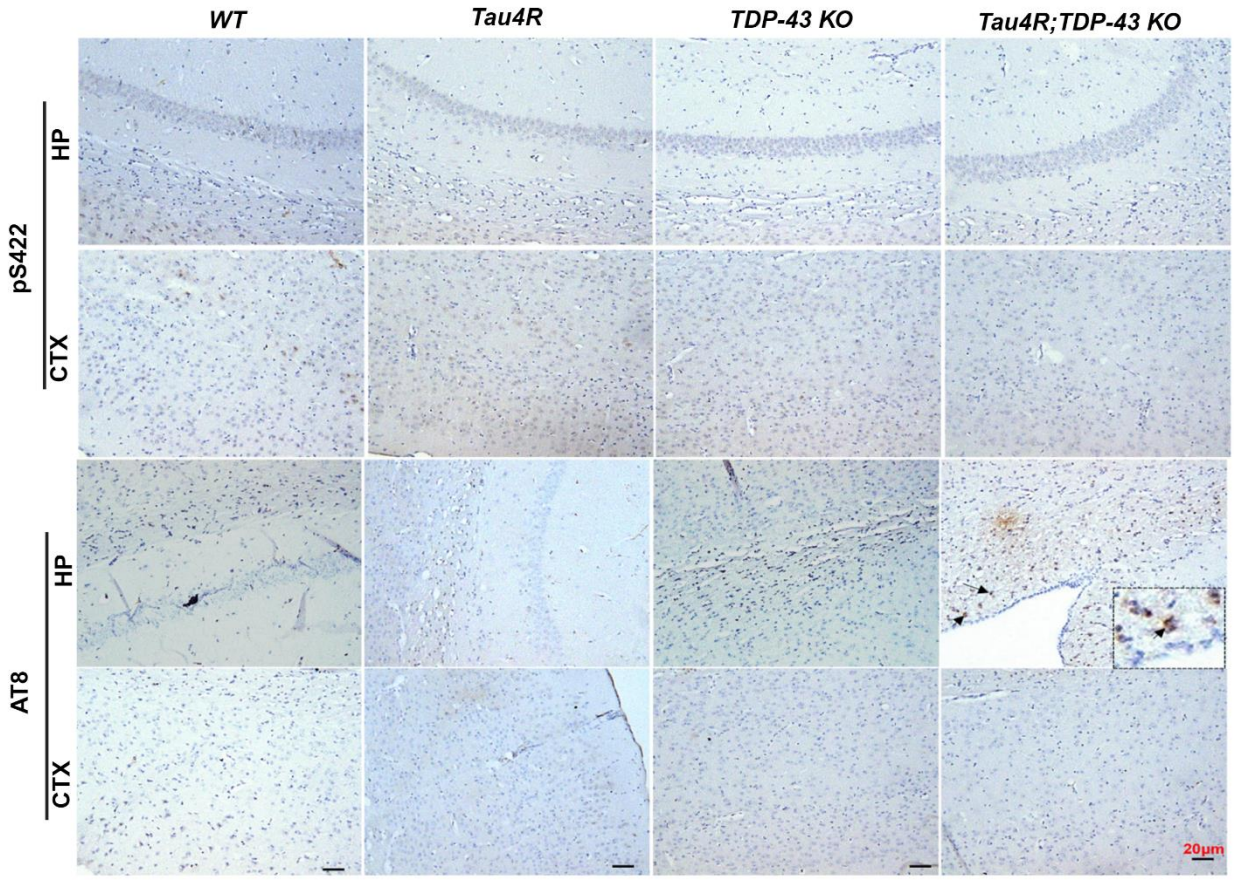

**Supplementary Figure 3:** Immunohistochemical analysis of cleaved tau (TauC3) in brain sections of 19 and 25 M old *WT* (n=3), *Tau4R* (n=4), *TDP-43 KO* (n=5) and *Tau4R;TDP-43 KO* mice (n=4) in the CA1 region of the hippocampus using antiserum against truncated tau. The arrowheads show the cleaved tau signal in *TDP-43 KO* and *Tau4R;TDP-43 KO* aged (25 M), but not in WT and Tau4R transgenic mice.



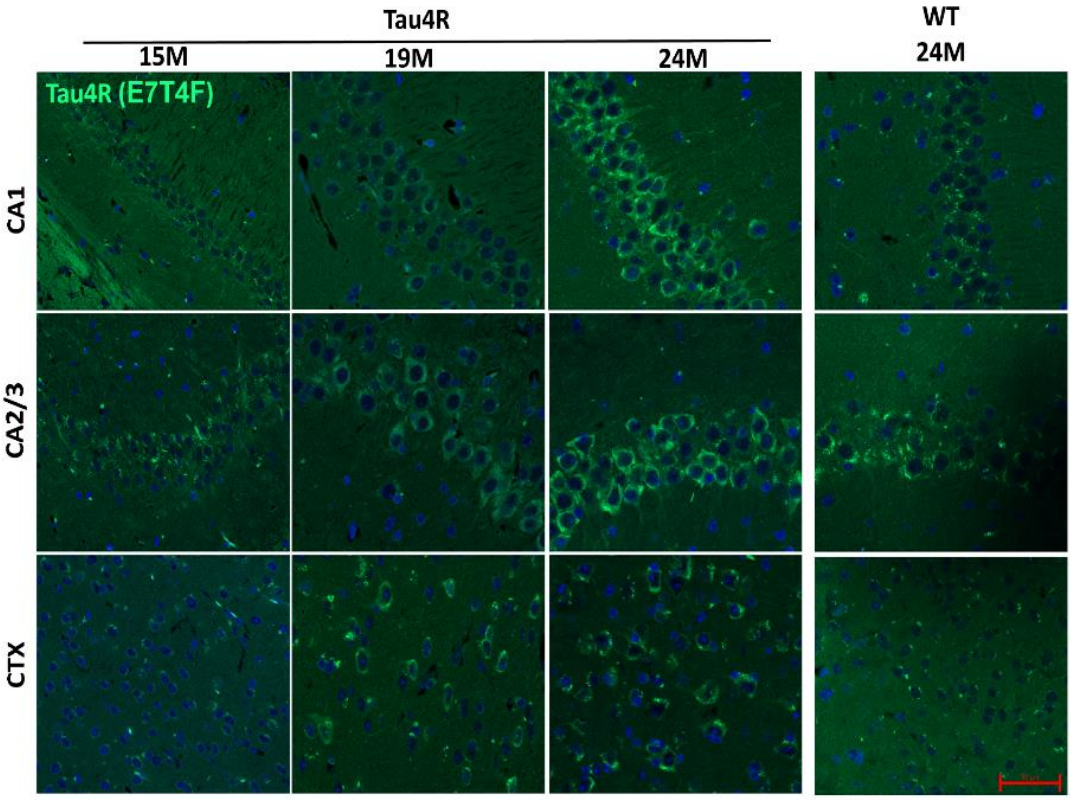

**Supplementary Figure 4: Testing the specificity of TauC3 immunoreactivity:** Immunohistochemical analysis of cleaved tau (TauC3) in brain sections of 25 M old *Tau4R;TDP-43 KO* mice; shows immunoreactivity in regular staining with TauC3 antibody in different brain regions (Right column). The arrowheads show the cleaved tau signal. The without primary antibody (Left column) and secondary antibody (Middle column) incubation show no immunoreactivity (brown staining).




**Supplementary Figure 5**: Immunohistochemistry of pathological tau (AT8) in brain regions of *Tau4R;TDP-43 KO* old mice (25 M) mice, pathological tau tangles could be detected. The brain regions are entorhinal cortex (EC), cerebral cortex (CTX), hippocampus (HP); carpus callosum (CC) and thalamus (TH). Scale bar, 20μm.




**Supplementary Figure 6:** Immunohistochemistry analysis in hippocampus and cortex using antibodies specific to endogenous phosphorylated tau, pS422 (upper panel) and AT8 (lower panel). Arrowhead shows probably some brown staining of AT8 but not pS422 around the ventricle side of hippocampus in *Tau4R;TDP-43 KO* mice (n=5) at the age of 19 M (scale bar, 20μm), but staining does not look like pathological tau. The sections were counterstained with hematoxylin (blue).




**Supplementary Figure 7:** Immunofluorescence analysis corroborated the immunohistochemistry of tau4R fragment and showed an age-dependent increase in the accumulation of hTau4R fragment using 4R repeat recognizing antibody (Tau4R;E7T4F) in subregions of HP and CTX of *Tau4R* mice (aging 15, 19 & 24 M), but not in *WT* mice right panel (24M) (Scale bar, 50 μm)