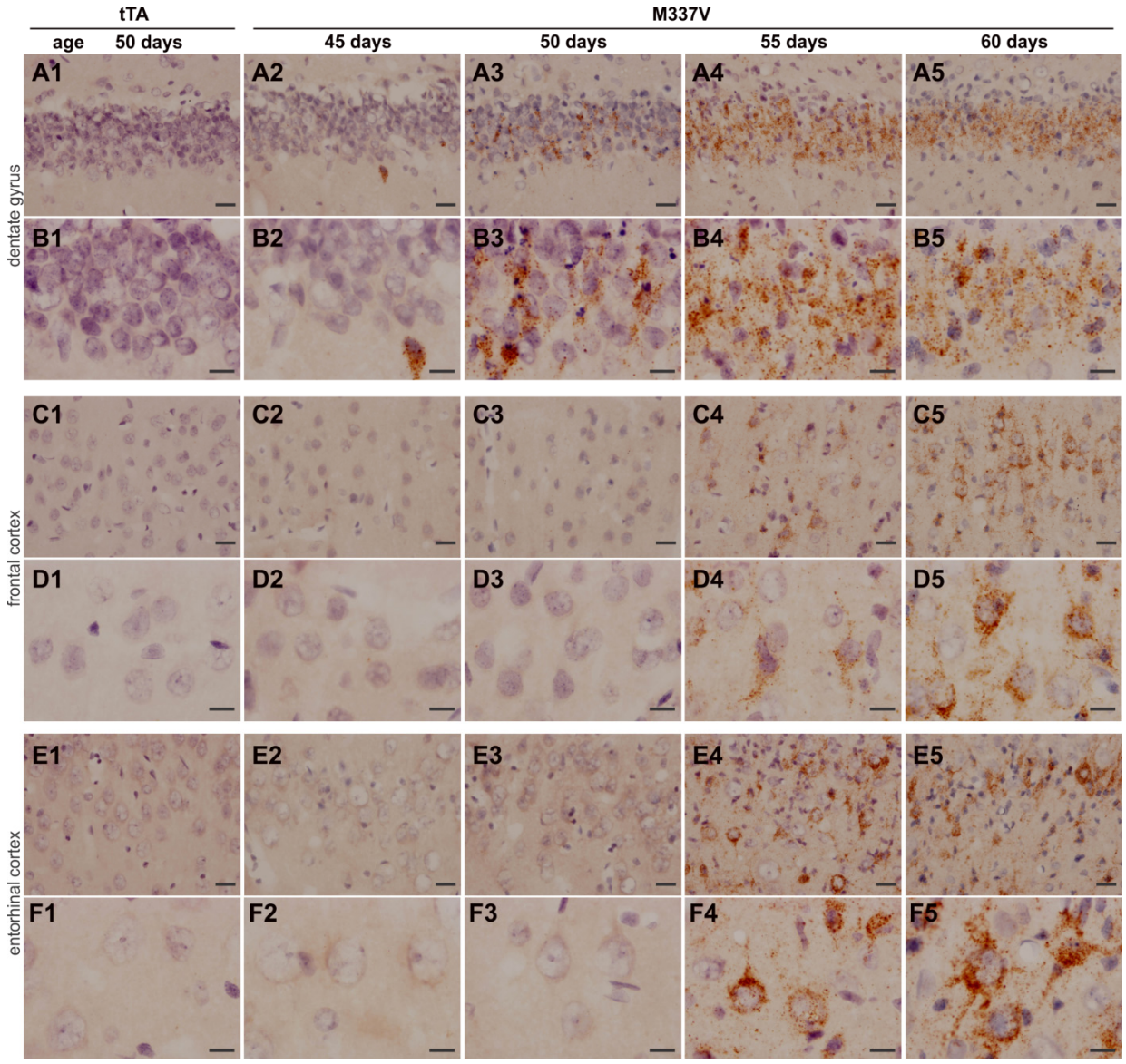

Figure S1: Ubiquitin progressively forms aggregates in mutant TDP-43 transgenic rats. (**A-F**) Immunohistochemistry shows that ubiquitin aggregates were progressively developed in the brain of Camk2a-tTA/TRE-TDP43^{M337V} double transgenic rats (M337V), but not in the tissues of Camk2a-tTA single transgenic rats (tTA). Tissue sections were first immunostained with an antibody against ubiquitin and were then counterstained with haematoxylin to display the nuclei. Scale bars: A1-5, C1-5, and E1-5, 20 μm; B1-5, D1-5, and F1-5, 10 μm.

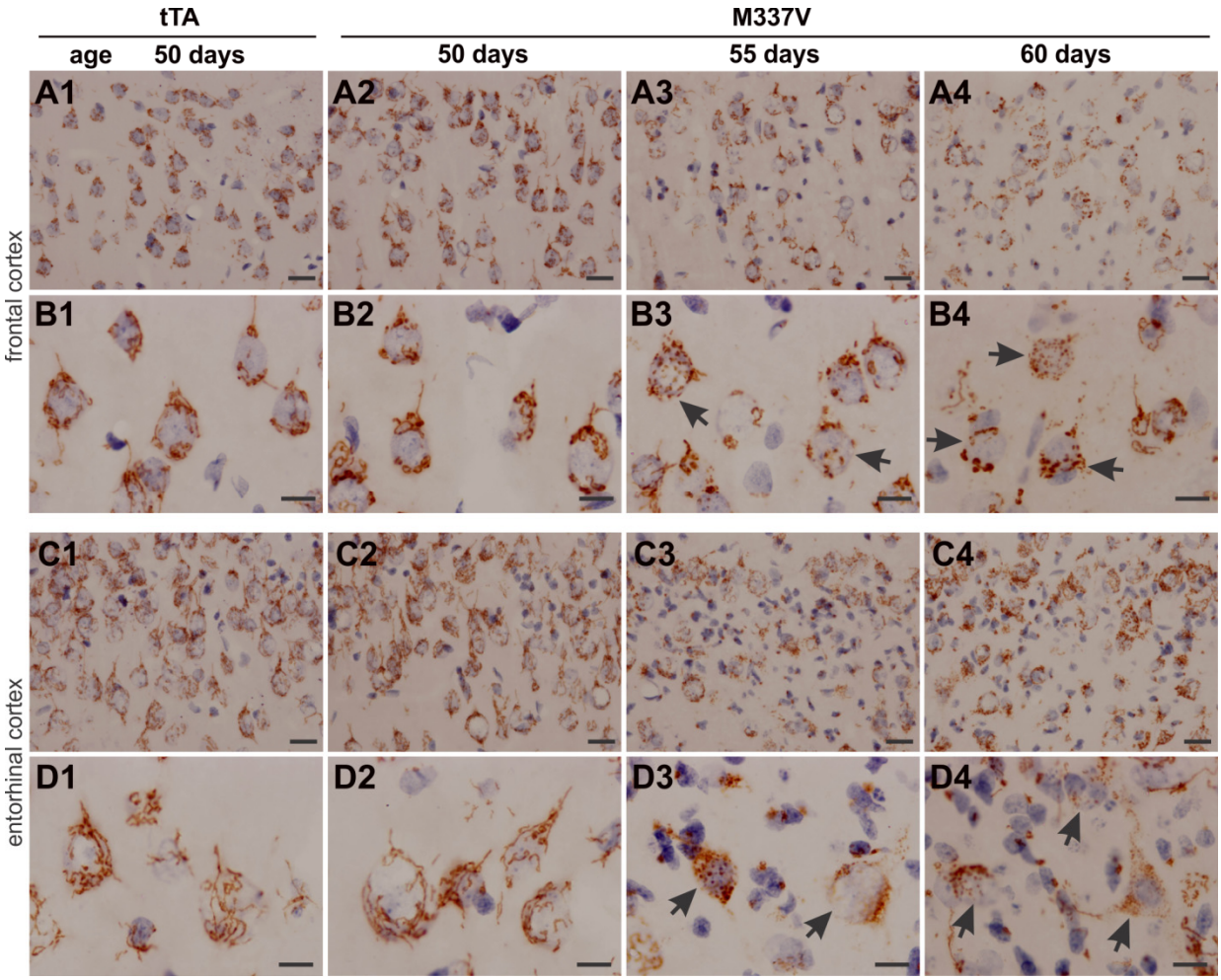

Figure S2: Golgi complexes are progressively fragmented in mutant TDP-43 transgenic rats. (**A-D**) Immunohistochemistry reveals that Golgi complexes were progressively fragmented in the brains of Camk2a-tTA/TRE-TDP43^{M337V} double transgenic rats (M337V), but not in the tissues of Camk2a-tTA single transgenic rats (tTA). Tissue sections were immunostained with an antibody against GM130—a marker of Cis-Golgi complex and were counterstained with haematoxylin to display the nuclei. Arrows point to the cells with fragmented Golgi complex. Scale bars: A1-4 and C1-4, 20 μm; B1-4 and D1-4, 10 μm.

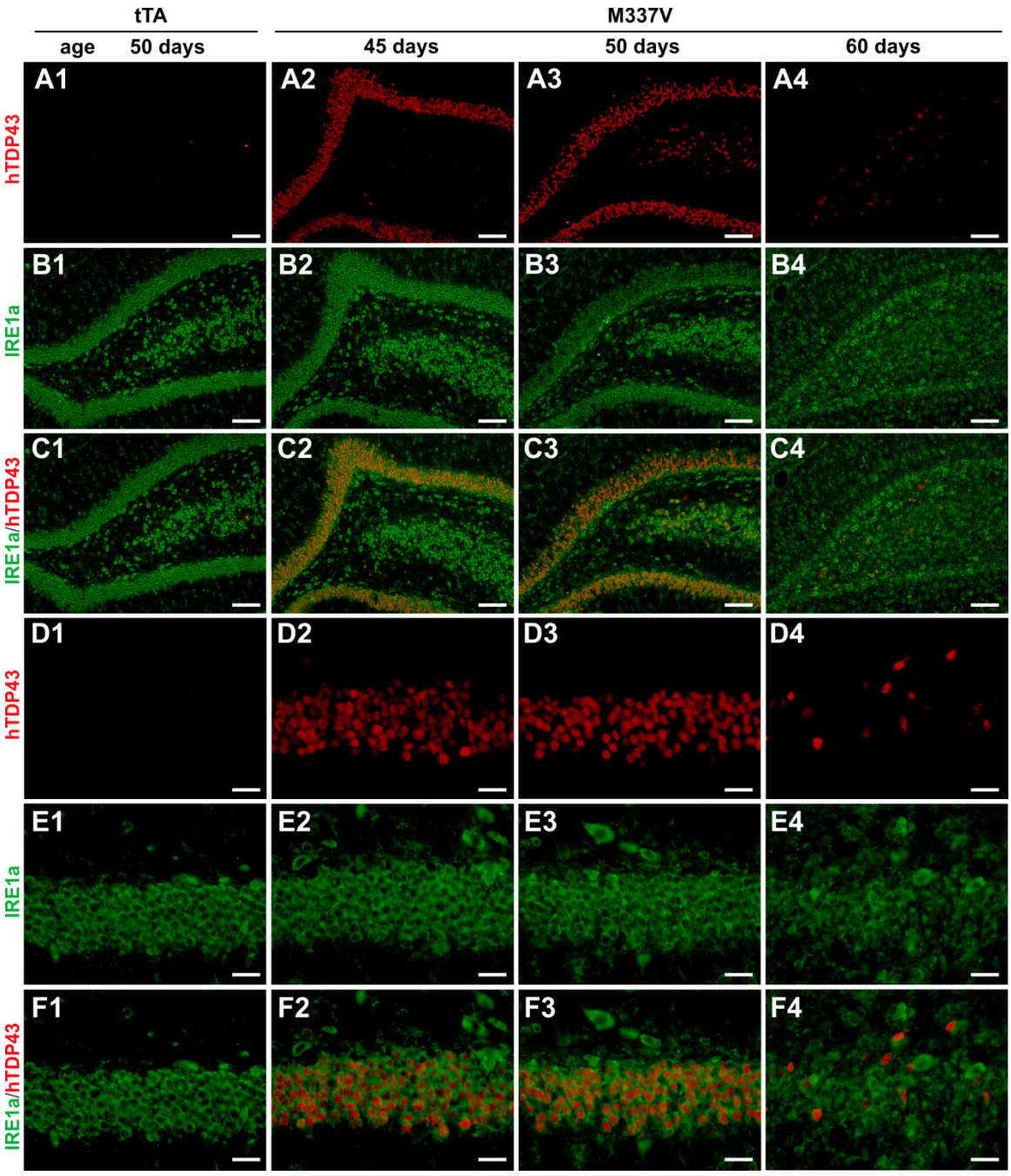

Figure S3: Expression of IRE1α in neurons is unaltered in mutant TDP-43 transgenic rats. (**A-F**) double-labeling immunofluorescence staining reveals that expression of IRE1α (a proximate sensor of ER stress) was unaltered in neurons expressing mutant human TDP-43 (hTDP43), but was upregulated in reactive glial cells. Hippocampus was taken from Camk2a-tTA/TRE-TDP43^{M337V} double (M337V) or Camk2a-tTA single (tTA) transgenic rats at defined ages. Scale bars: A-C, 100 μm; D-F, 25 μm.

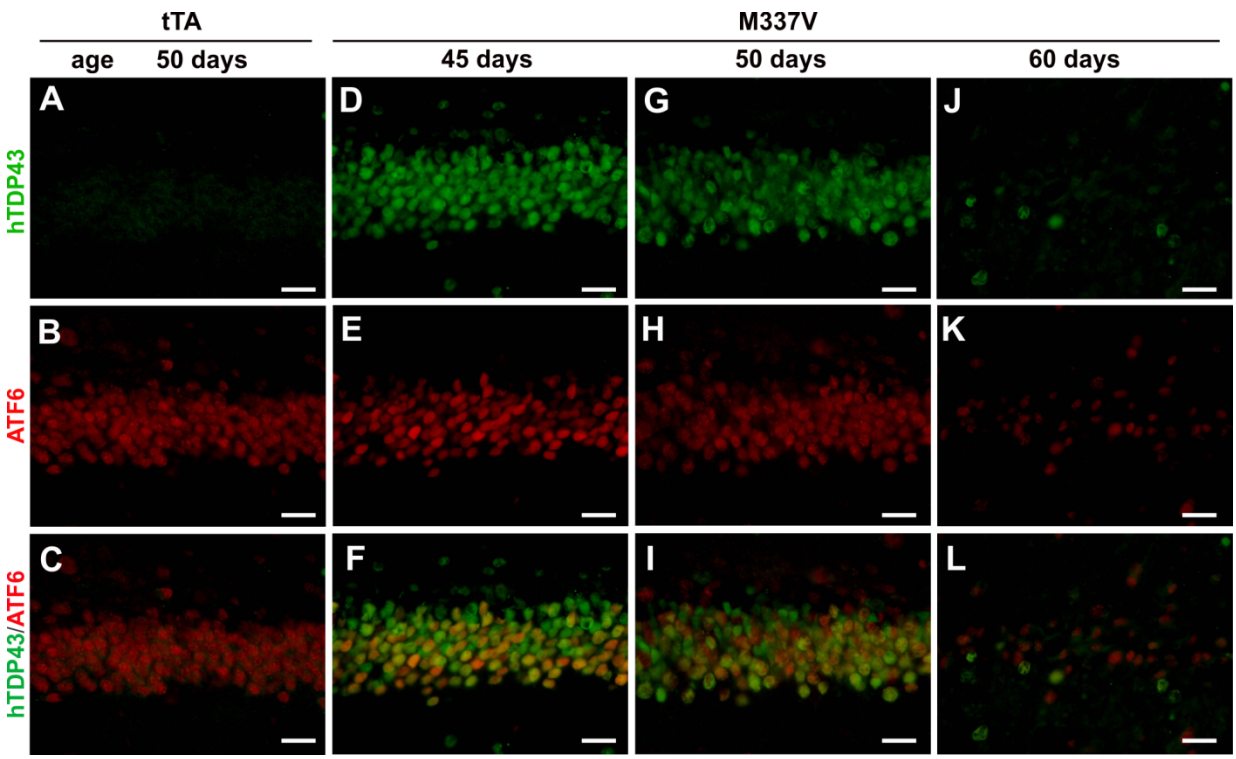

Figure S4: Expression of ATF6 is stable in neurons expressing mutant TDP-43. (**A-L**) Immunofluorescence staining reveals that expression of ATF6 protein (a proximate sensor of ER stress) remained stable in the transgenic cells through disease stages. Dentate gyrus was taken from Camk2a-tTA/TRE-TDP43^{M337V} double (M337V) or Camk2a-tTA single (tTA) transgenic rats at defined ages. Scale bars: 25 μm.

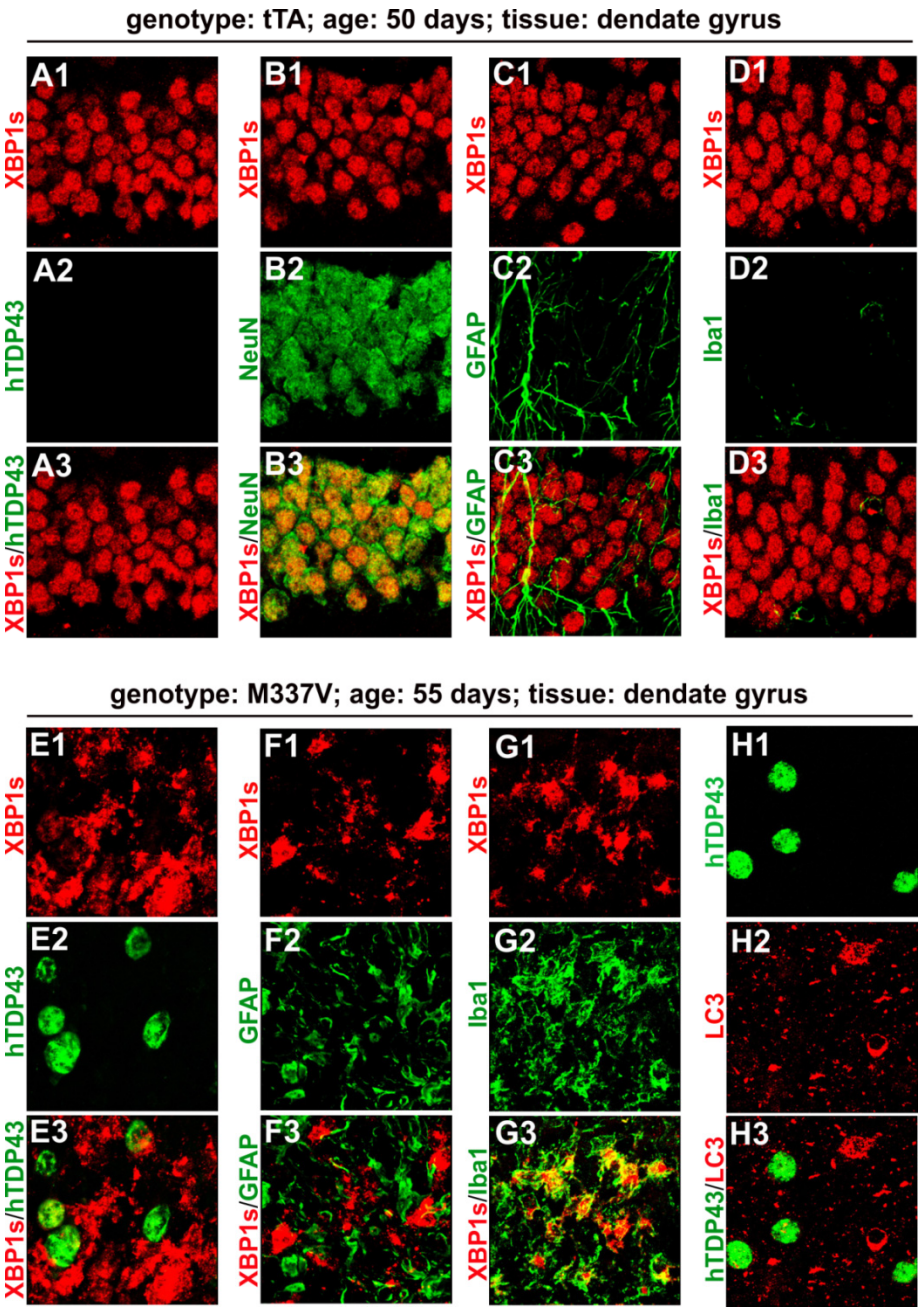

Figure S5: Neurons are depleted of spliced XBP1 in mutant TDP-43 transgenic rats. (**A-D**) Confocal microscopy reveals that expression of spliced XBP1 (XBP1s) was mainly restricted to neurons in the normal rats carrying tTA single transgene (tTA). (**E-G**) Immunofluorescence staining reveals that XBP1s was depleted in neurons expressing mutant human TDP-43 (E1-E3) and that XBP1s was upregulated in reactive microglia (G1-G3), but not in reactive astrocytes (F1-F3). (**H**) Immunofluorescence staining reveals that neurons expressing mutant TDP-43 expressed the marker of autophagy (LC3) at undetectable levels.