Supplemental Material

Figure S1. SUT-2 Expression in transgenic lines. Immunoblotting of SUT-2 protein reveals that SUT-2::GFP is highly over-expressed in our P_{sut-2}::SUT::GFP transgenic *C. elegans* line (CK195). SUT-2 levels are at least 7-fold over-expressed in CK195 as compared to controls. Likewise, line T337 expresses at least 2-fold more SUT2 relative to non-Tg controls. *sut-2 (bk741)* animals carry a putative null mutation in the *sut-2* gene and exhibit essentially no full length protein.

Figure S2. SUT-2 overexpression does not modify polyQ toxicity. The *C. elegans* model of polyQ neurotoxicity does not show obvious changes in response to overexpression of SUT-2. This is contrast to data shown in Fig 1B, where SUT2 overexpression exacerbates tau neurotoxicity.

Figure S3. Transgenic overexpression of SUT-2 enhances tau induced neurodegenerative changes. Triple transgenic worms expressing the T337, SUT-2::GFP, and a P_{unc-25}*::*GFP reporter transgene marking the cell bodies and processes of all *C. elegans* GABAergic neurons was compared with T337; P_{unc-25}*::*GFP double transgenic animals. Day 3 animals were scored for neurodegenerative neuronal loss. Arrows depict sites of neurodegenerative changes associated with the tau phenotype. Note increased neurodegeneration associated with transgenic SUT-2 expression.

Figure S4. MSUT2 antibody specifically recognizes MSUT2 protein in nuclear speckles. Immuno-absorption studies were carried out by staining normal control

patient brain sections with MSUT2 antibody immunodepleted with (right) or without (left) recombinant MSUT2 protein. Arrows indicate MSUT2 labeled nuclei in neurons *(C)* or Ependymal cells *(A)*. Immuno-depletion of the antibody preparation with MSUT2 recombinant protein causes an absence of specific staining *(B, D).* Note the prominent speckle like staining pattern shown in the nucleus (arrows).

Figure S5. MSUT2 levels do not change in AD cerebellum. Relative to the MTL sections shown in Fig 5, immunohistochemical staining reveals markedly reduced neuronal MSUT2 staining in cerebellum sections in both AD patients (A) and controls *(B)*. Both cases and controls have similar low level neuronal immunoreactivity with MSUT2 antibodies. Arrows depict weak but specific nuclear MSUT2 staining within the nuclei of Purkinje cells. In contrast cerebellar ependymal cells stain robustly for MSUT2 regardless of disease state (C, D). (E) Frozen cerebellar tissue samples were only available for a subset of the temporal cortex samples evaluated in Fig 4. MSUT2 levels in cerebellar protein extracts were examined by immunoblotting with MSUT2 and actin specific antibodies. Lysates from 2 age matched controls and AD diseased brains were compared. Note little MSUT2 is detected in cerebellum (exposure time in Fig S5E is 3 times longer than that shown in Fig 4). There is no clear trend in cerebellar MSUT2 levels, but MSUT2 appears to be at least as abundant in cerebellum of AD subject relative to controls.

Figure S6. Non-specific RNAi treatment does not alter MSUT2 localization or aggresome formation. HEK/tau cells were subjected to nonspecific siRNA treatment

(IDT Trifecta transfection control duplex) using identical transfection conditions as used for MSUT2 siRNA transfection shown in Fig 6B-E. Fixed cells were double immunofluorescence stained for tau (green) and MSUT2 (red) and examined with immunofluorescence microscopy. Note lack of effect of random duplex siRNA treatment on MSUT2 protein localization or aggresome formation.

Movie S1: CK195

Movie S2: N2

Movie S3: CK200

Movie S4: CK10

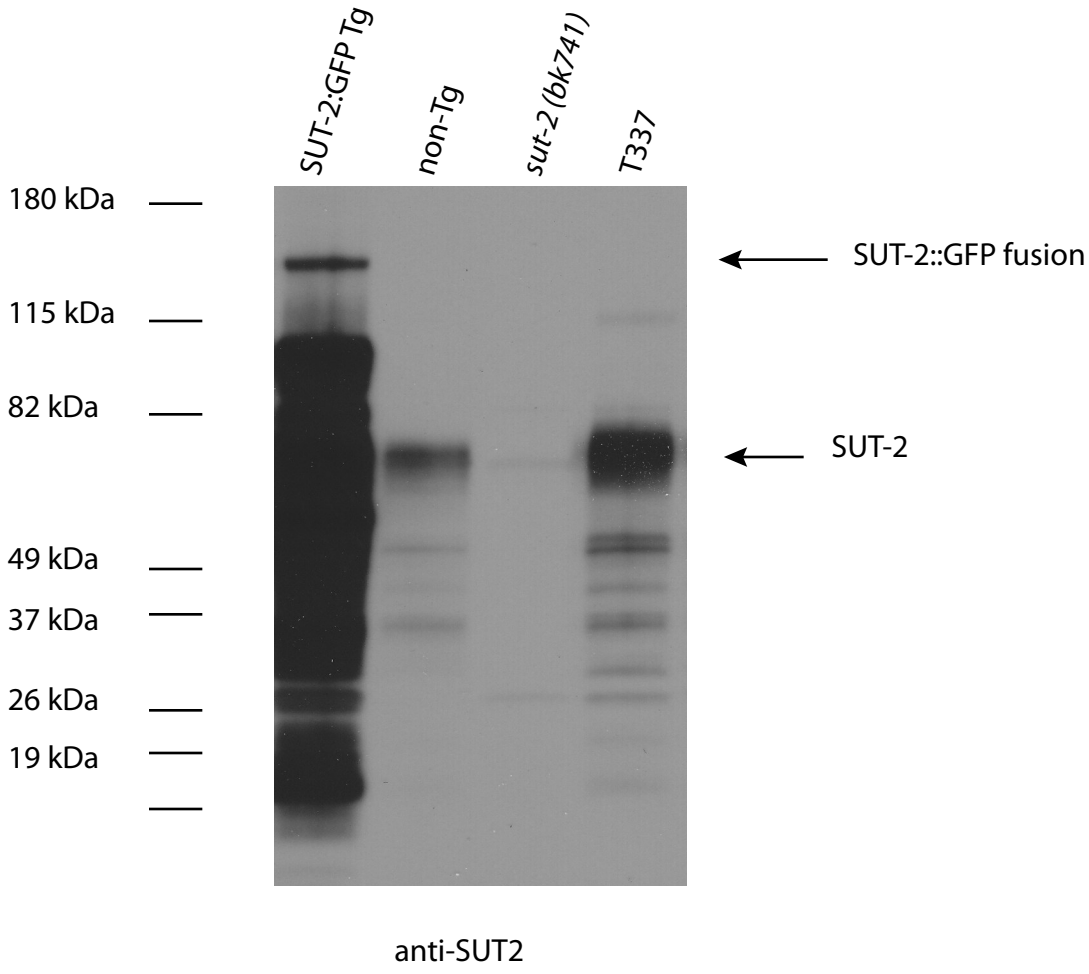
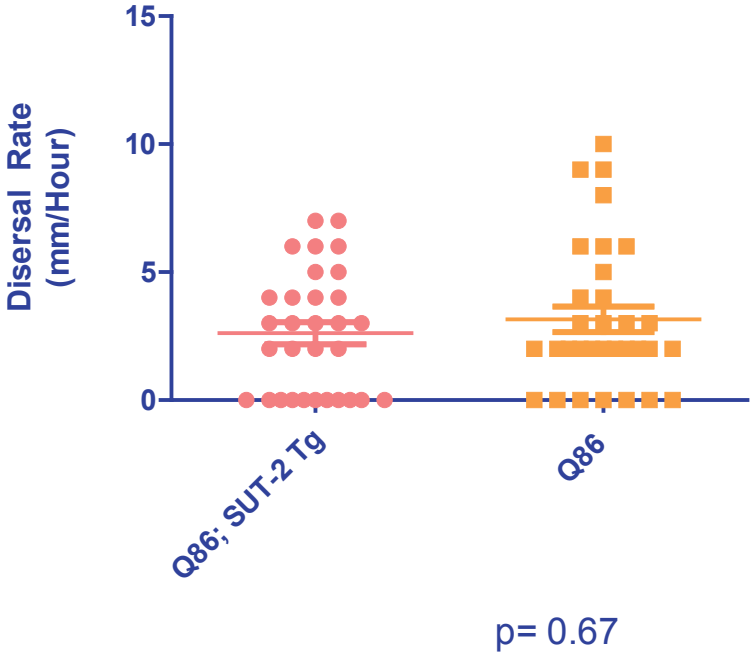

SUT-2:GFP Tg
non-Tg
sut-2 (bk741)
T337
180 kDa
115 kDa
82 kDa
49 kDa
37 kDa
26 kDa
19 kDa
SUT-2::GFP fusion
SUT-2
anti-SUT2

Fig S1

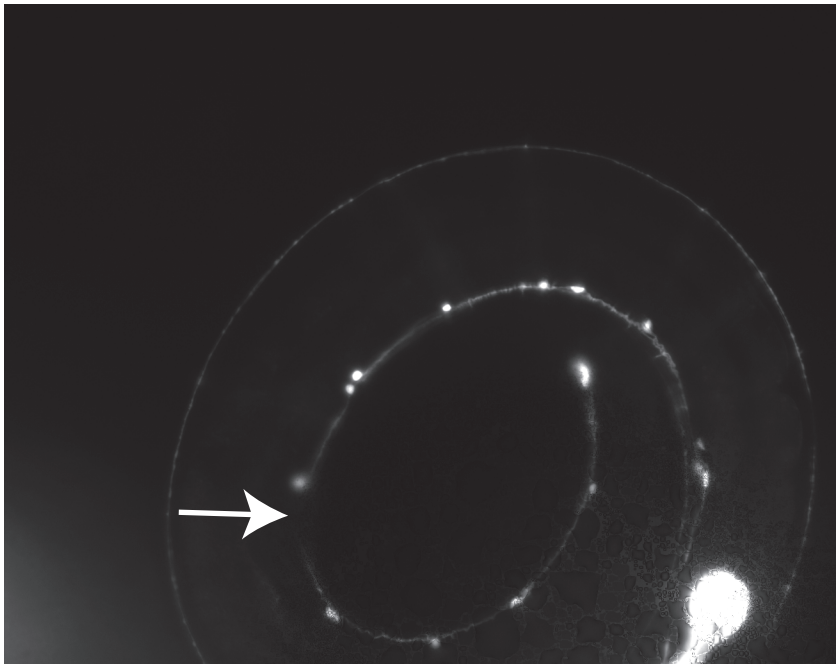
SUT-2 Overexpression and PolyQ neurotoxicity



p= 0.67

Fig S2

T337



T337; SUT-2 Tg

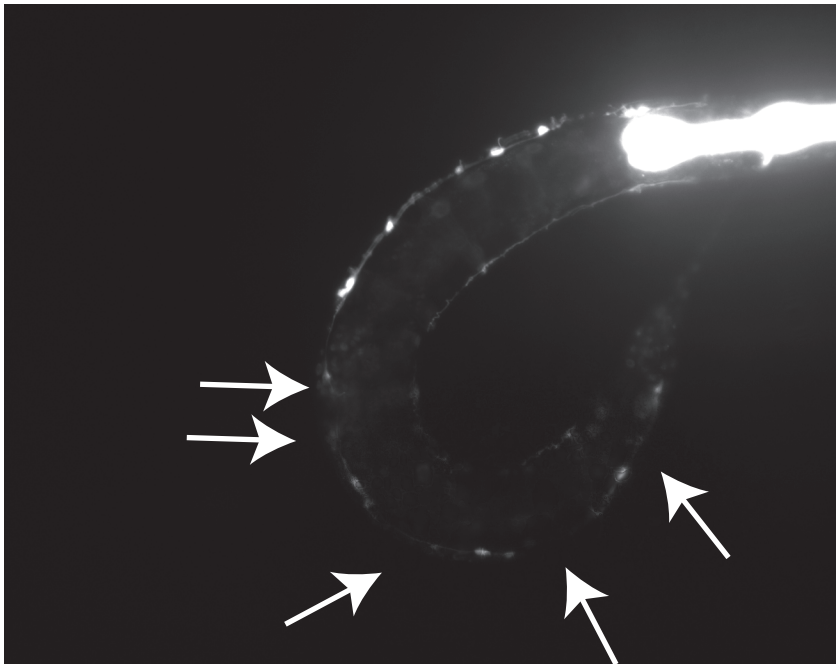
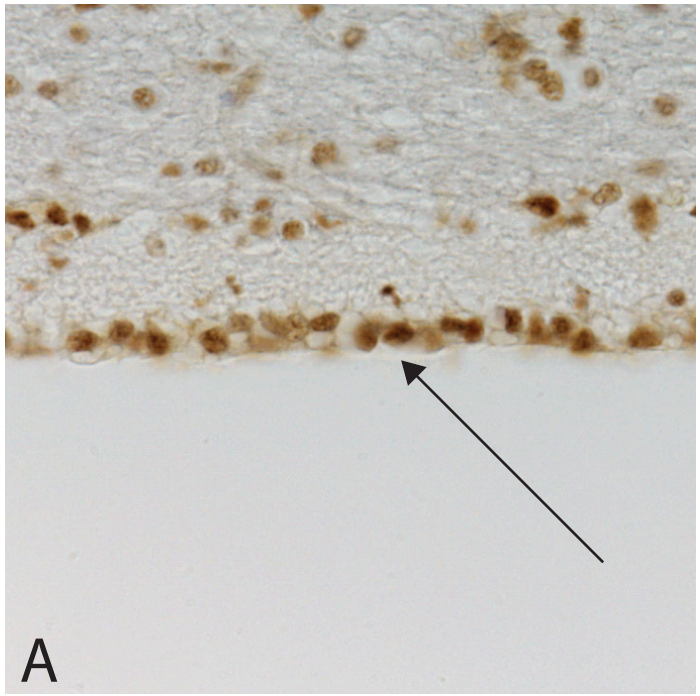
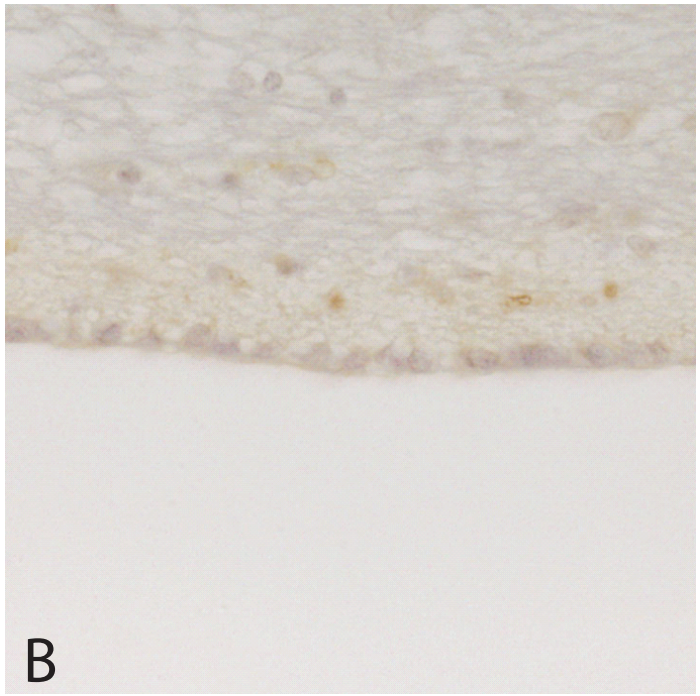


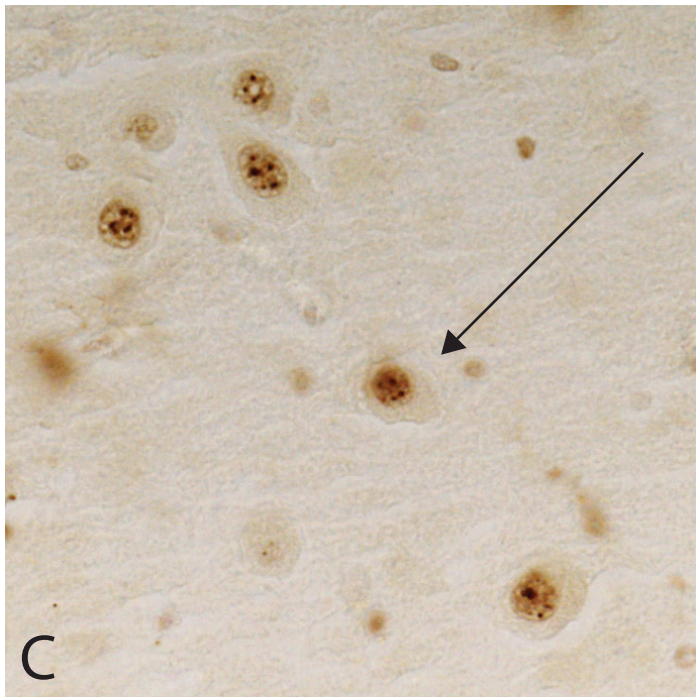
Fig S3

Ependymal Cells





Hippocampal Hilus



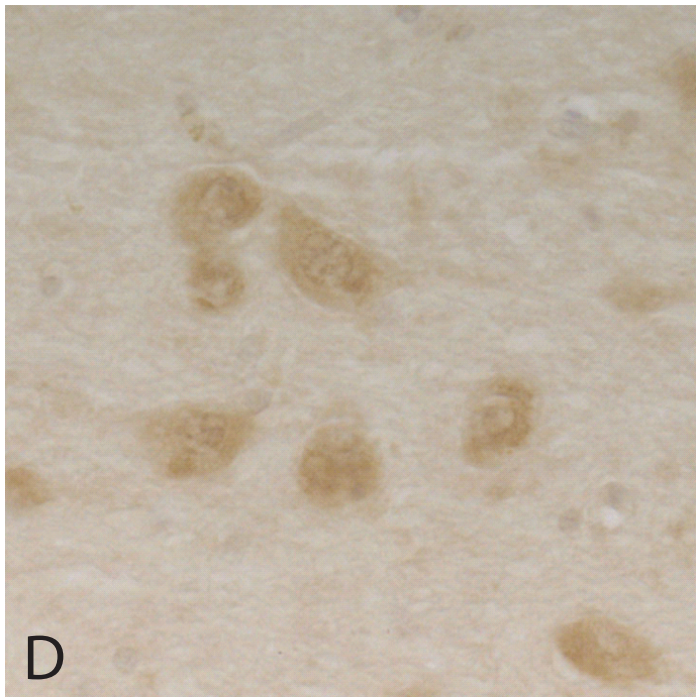
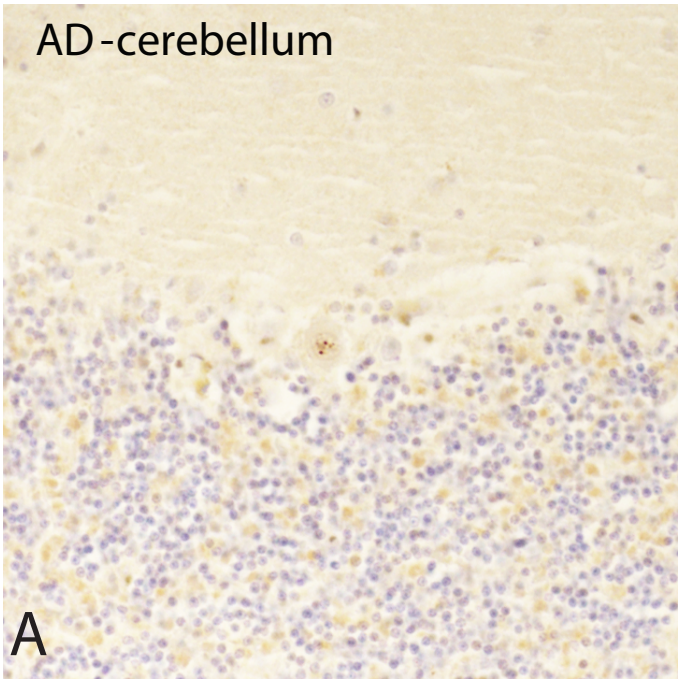


Fig S4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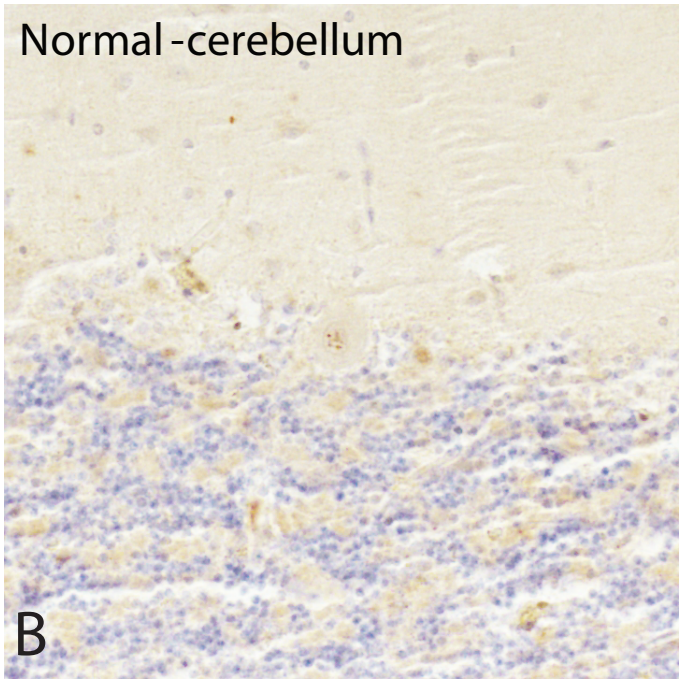
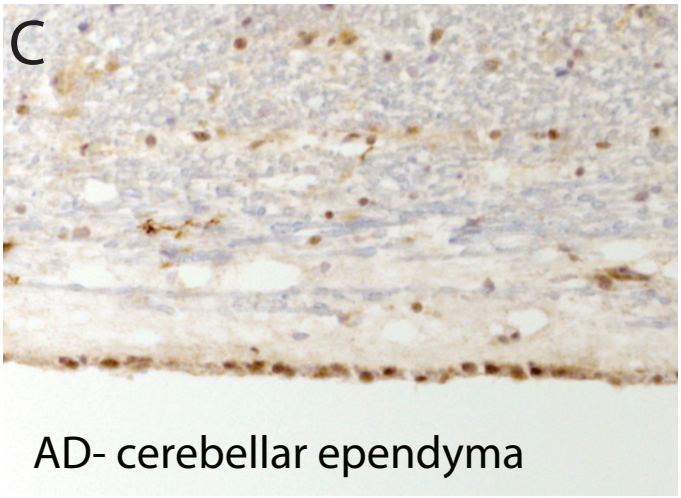
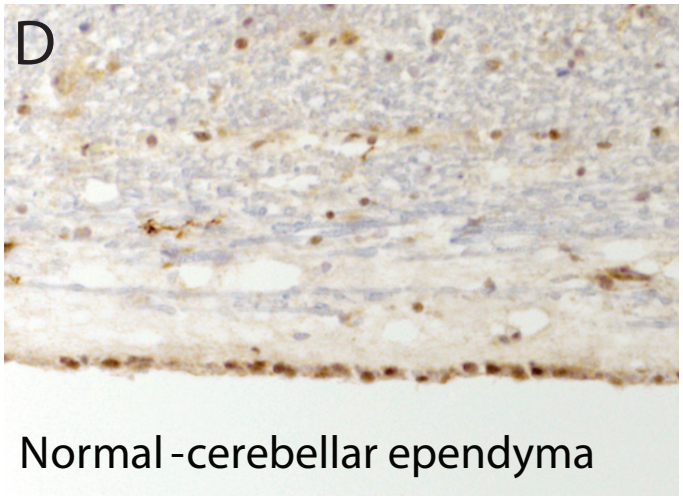
A


Normal-cerebellum
B


C
AD- cerebellar ependyma


D
Normal-cerebellar ependyma

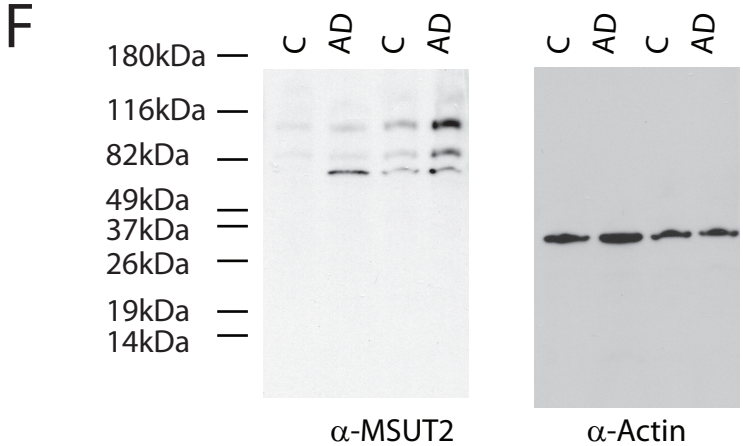

F
C
AD
C
AD
C
AD
C
AD
180kDa
116kDa
82kDa
49kDa
37kDa
26kDa
19kDa
14kDa
α-MSUT2
α-Actin

Fig S5

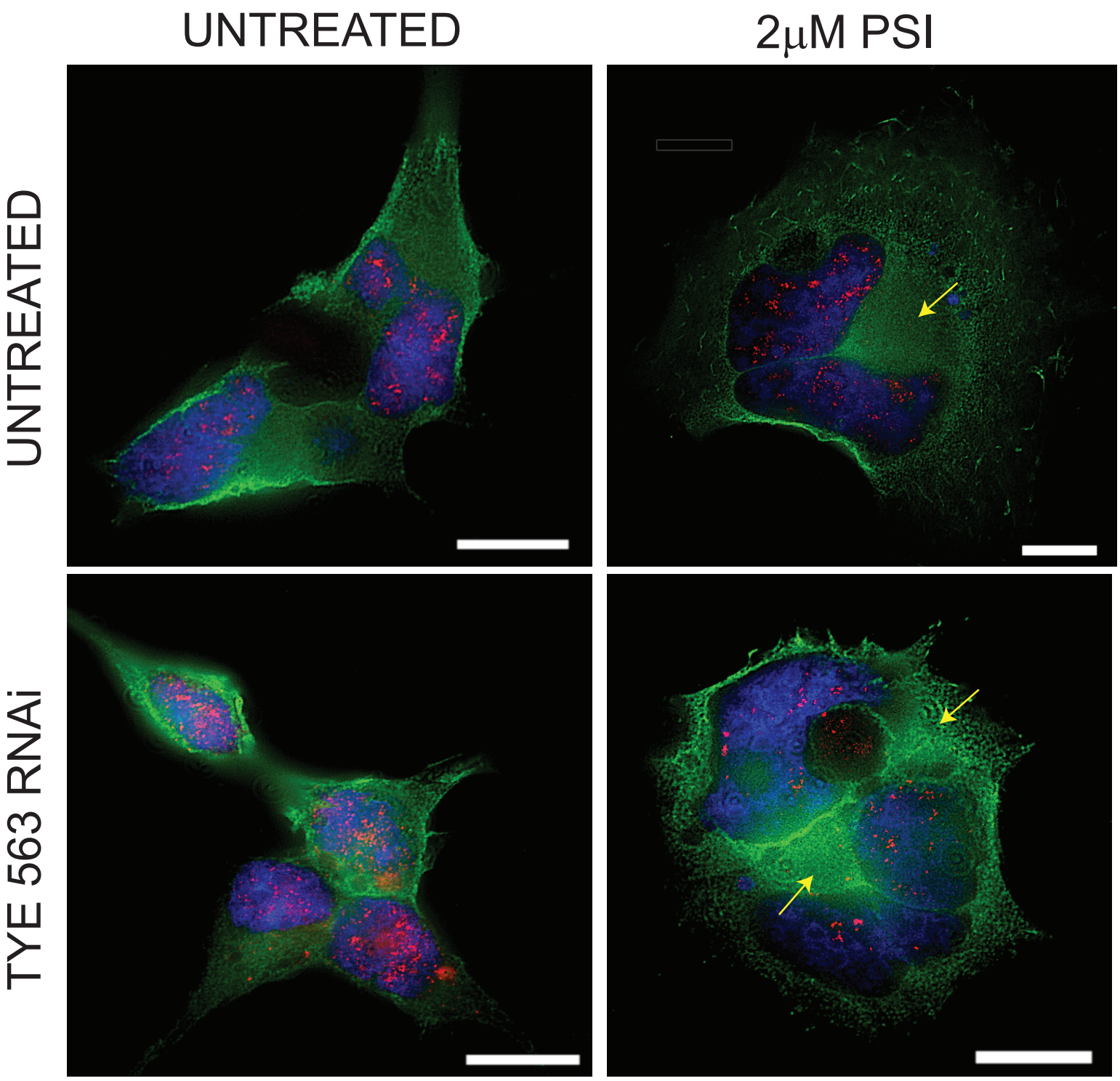


Fig S6