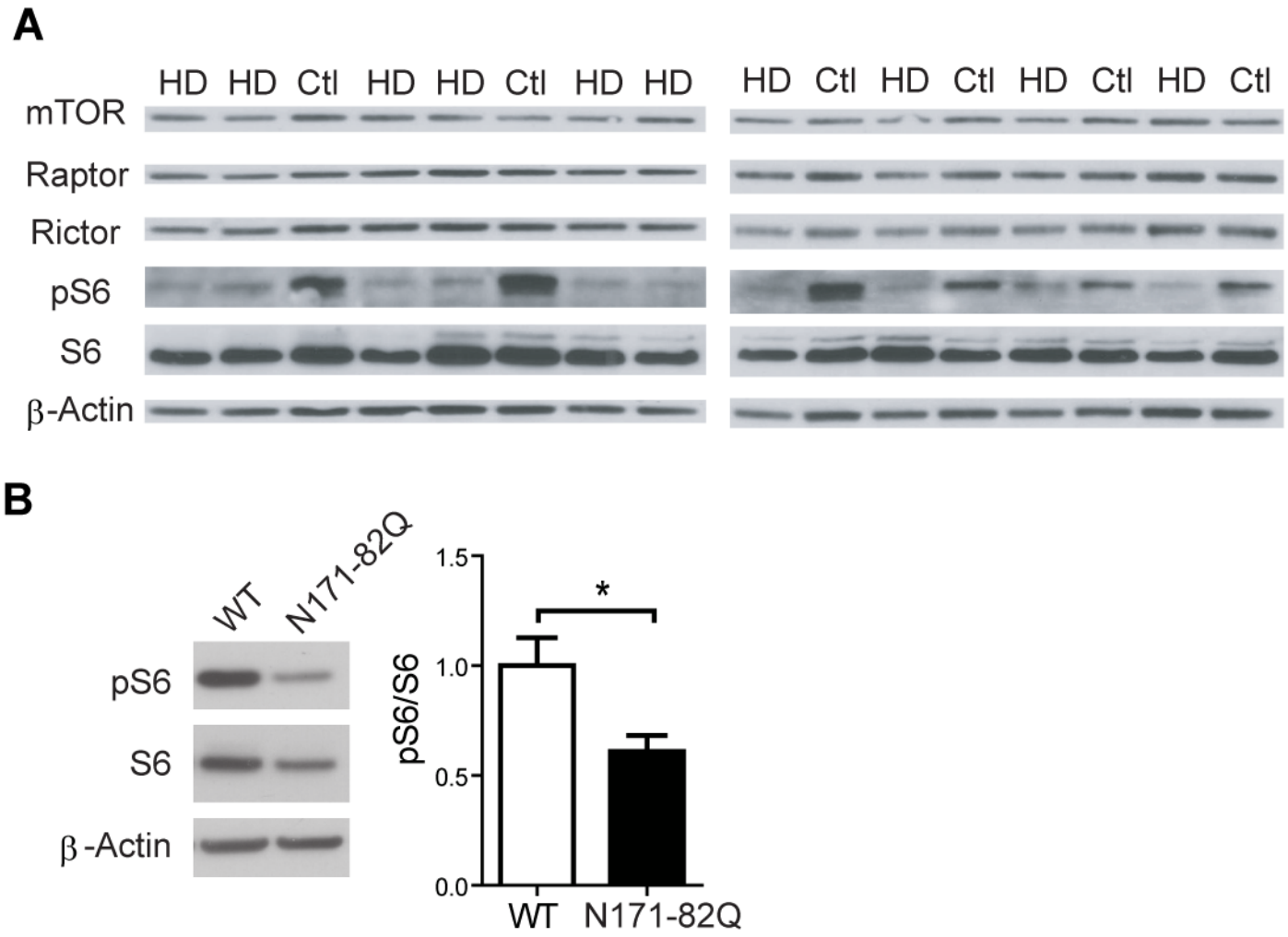


**Figure S1. mTORC1 activity is reduced in HD human and mouse striatum.**
(A) Western blot demonstrates reduced mTORC1 activity (pS6) in the striatum of patients with HD (N=10) compared to unaffected individuals (N=6). β-actin was used as a loading control (related to Figure 1A). (B) Biochemical analysis of endogenous mTORC1 activity (pS6) from14-week-old N171-82Q and WT mouse striatal lysates. β-actin was used as a loading control. Densitometry analysis revealed reduced pS6 level in 14-week-old N171-82Q mice (N=5) compared to age- and sex-matched WT littermates (N=4). Data represent mean $\pm$ SEM.*P<0.05, Student's t-test. Related to Figure 1.

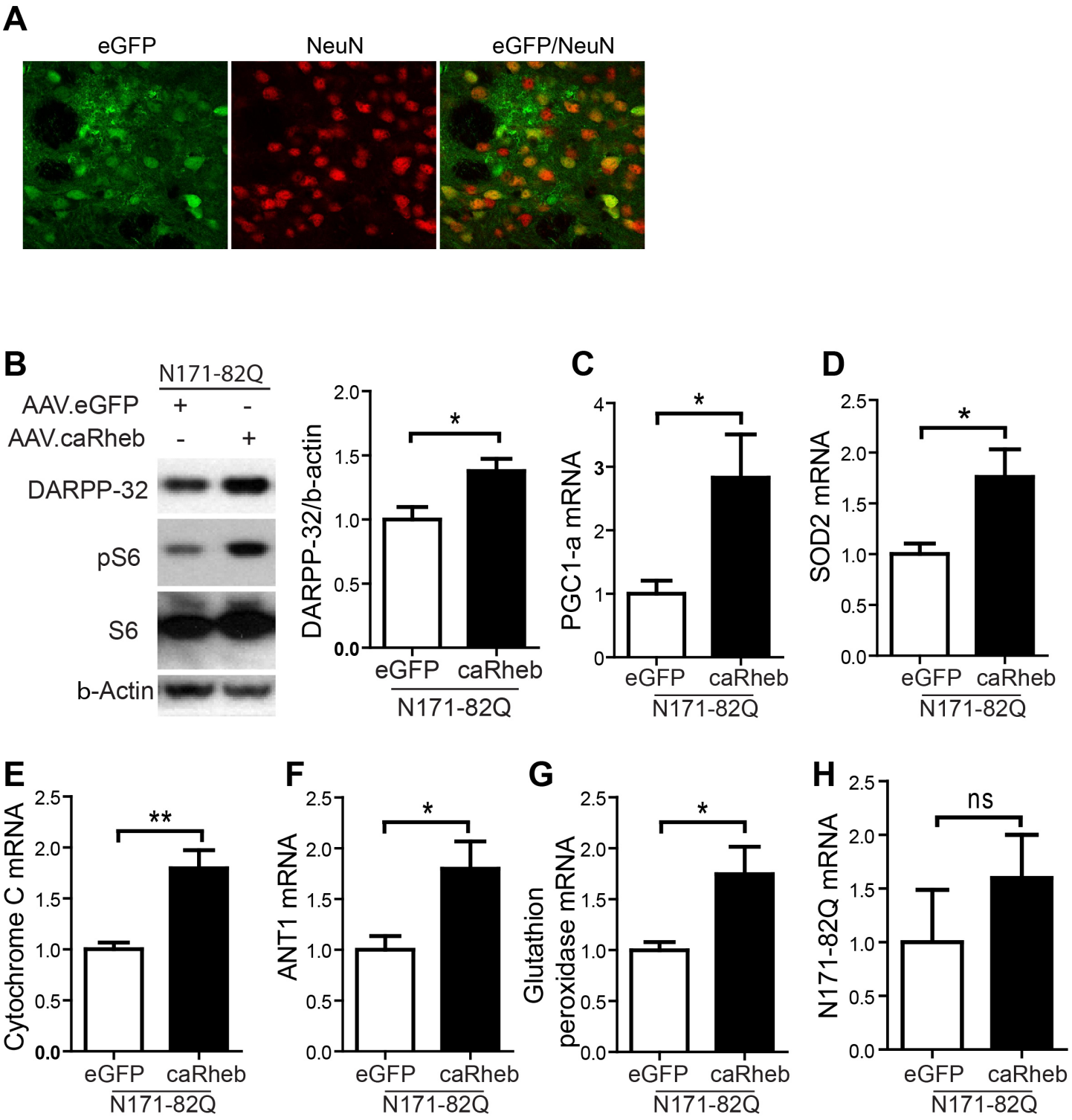


**Figure S2. AAV1 efficiently transduces striatal neurons in mice.**
A representative immunohistochemistry picture of a HD mouse striatum showed robust transduction of neurons (NeuN) in a 18-week-old mouse after AAV1.eGFP injection at 6 weeks of age. See also McBride et al, PNAS: 105(15):5868-73, 2008. (B-H) AAV.caRheb improves metabolism-related deficits in N171-82Q mouse striatum. B) Western blot shows increased pS6 and DARPP-32 levels in striata of N171-82Q mice treated with unilateral injection of AAV.caRheb, compared to AAV.eGFP treated animals. Mice were injected at 10 weeks of age, and tissues were harvested at 13 weeks of age. Right, densitometry quantification of DARPP-32 immunoreactivity (N=4 mice per group; *P<0.05, Student's t-test). (C-H) RT-qPCR analysis of metabolism related genes and the N171-82Q transgene from striatal homogenates of 13 weeks old N171-82Q mice after unilateral injection of AAV.caRheb and contralateral injection of AAV.eGFP at 10 weeks of age (N=4 per group). All genes were normalized to β-actin. Data are mean ± SEM. *P<0.05, **P<0.01, Student's t-test. Related to Figure 2.

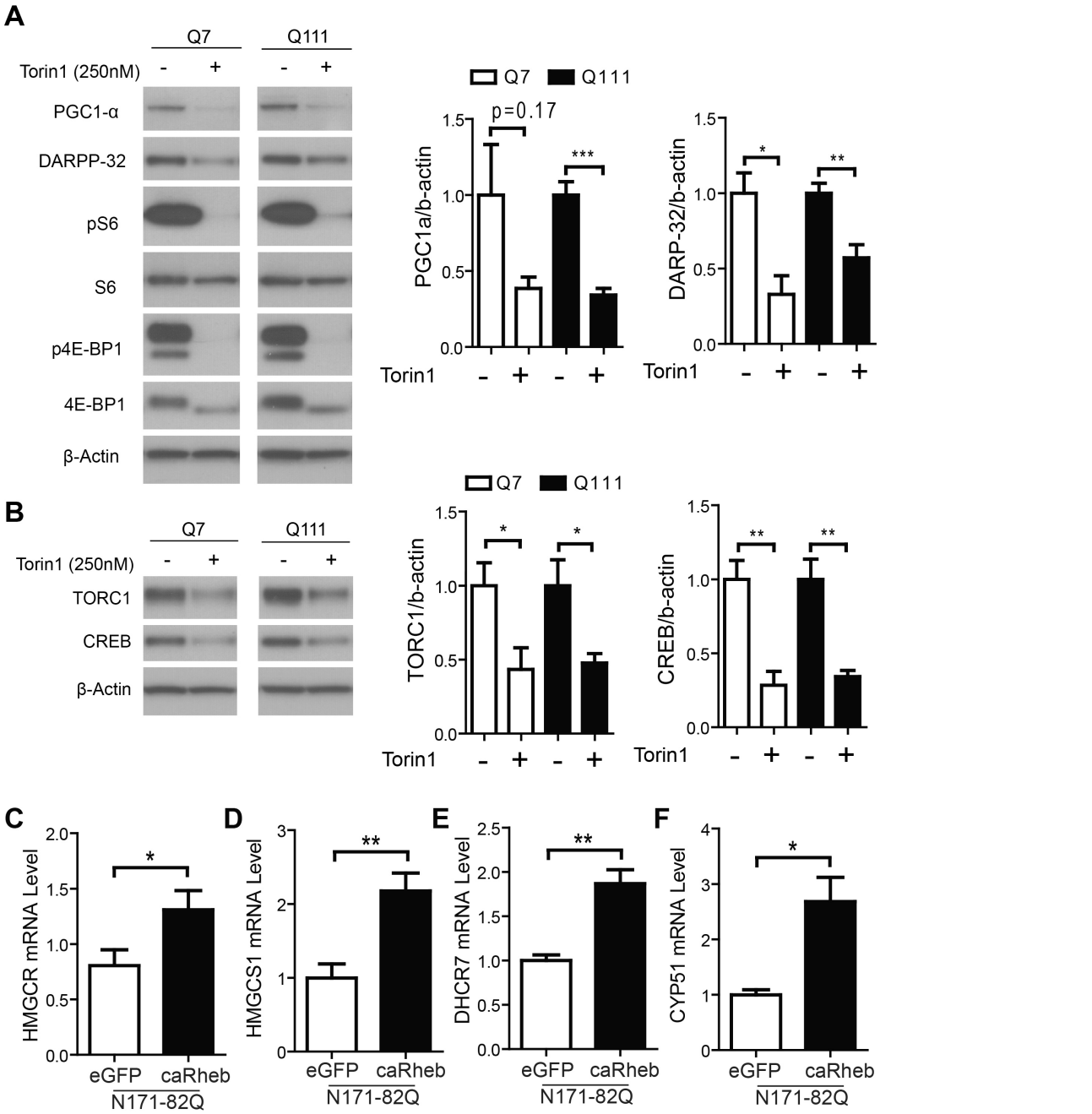


**Figure S3 A,B. Torin1 inhibits metabolism gene expression genes in striatal cell model of HD.** Q7 and Q111 striatal cells grown in normal serum condition were treated with Torin1 or DMSO (control). Total cell extracts were obtained 24 hrs later. (A) Biochemical assessment shows reduced mTORC1 activity (pS6 and p4E-BP1), PGC1-α, and DARPP-32 expression in Q7 and Q111 cells with Torin1 treatment. (B) A representative western blot for CREB and its coactivator, TORC1 24 hours after Torin1 treatment. Densitometry analyses shows Torin1 suppressed TORC1 and CREB levels in Q7 and Q111 cells. Values are percentage of vehicle-treated controls ± SEM of four independent experiments (N=4 per treatment groups). Endogenous β-actin was the loading control.*P<0.05; **P<0.01, Student's t-test. Related to Figure 3.

**C-F. mTOR alters cholesterol biosynthesis gene expression in AAV.caRheb versus AAV.eGFP treated HD transgenic mouse striata.** RT-qPCR analysis of lipogenic genes from striatal homogenates of 13-week-old N171-82Q and WT mice after unilateral injection of AAV.caRheb at 10 weeks of age. Lysates from AAV.eGFP injected contralateral hemispheres served as internal controls (N=4 per group). All genes were normalized to endogenous β-actin. Data represent mean ± SEM. C=Control. *P<0.05, **P<0.01, Student's t-test. Related to Figure 3.

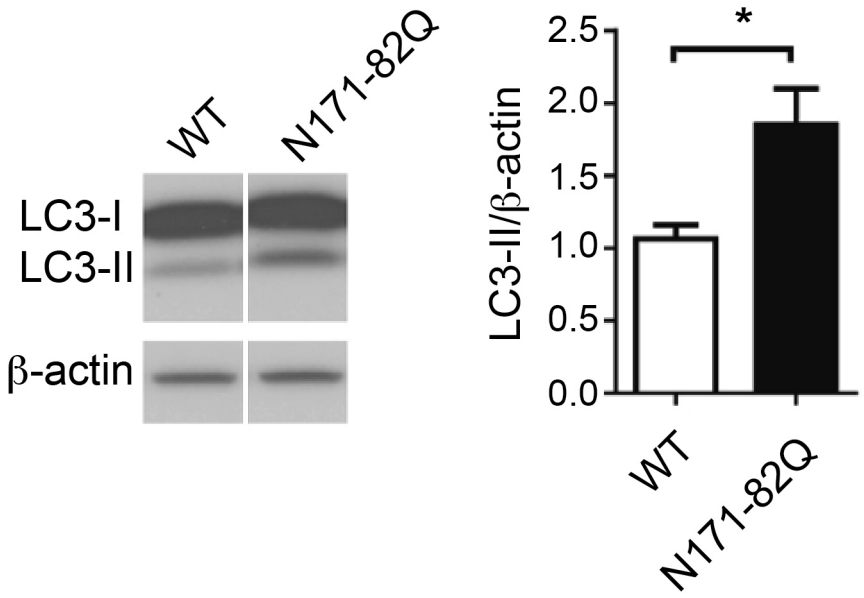


**Figure S4. Basal autophagy is enhanced in N171-82Q mice striata.**
Biochemical assessment of LC3II in striatal lysates from N171-82Q and WT mice after injection of AAV.eGFP at 10 weeks of age. Striata were harvested 3 weeks post-injection. Densitometry analysis revealed increased LC3II levels in the striatum of N171-82Q mice (N=9) compared to WT (N=5). β-actin was used as a loading control. Data are mean $\pm$ SEM.*P<0.05, Student's t-test. Related to Figure 4.

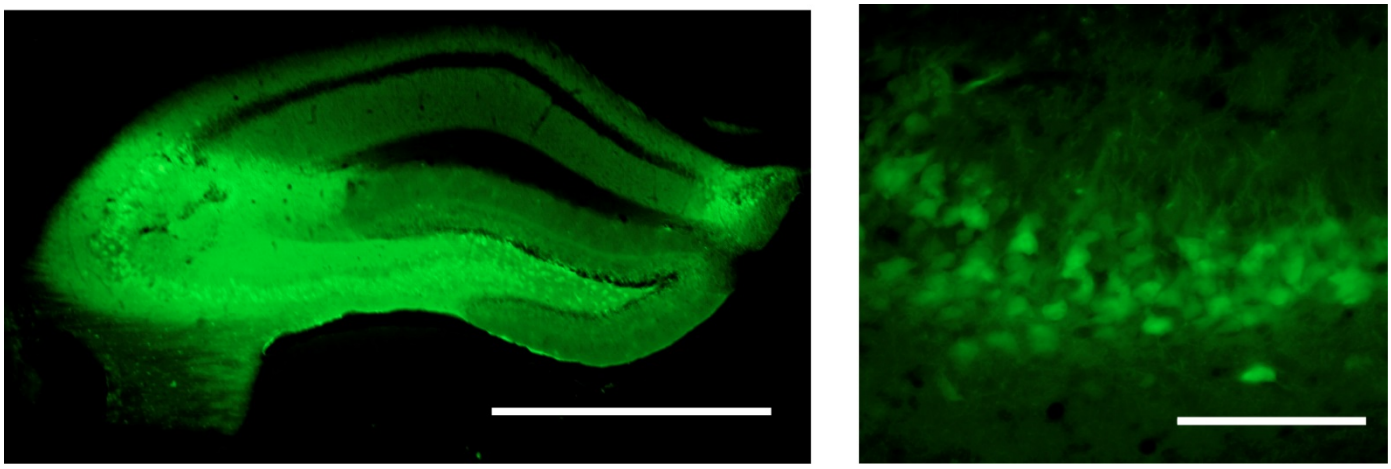

**Figure S5. AAV.eGFP transduction of hippocampus.**
eGFP expression in the hippocampus of N171-82Q mice 2 weeks after AAV1.eGFP injection into the dentate gyrus at 10 weeks of age. Scale bars: 1mm (left), 100 µm (right). Related to Figure 5.

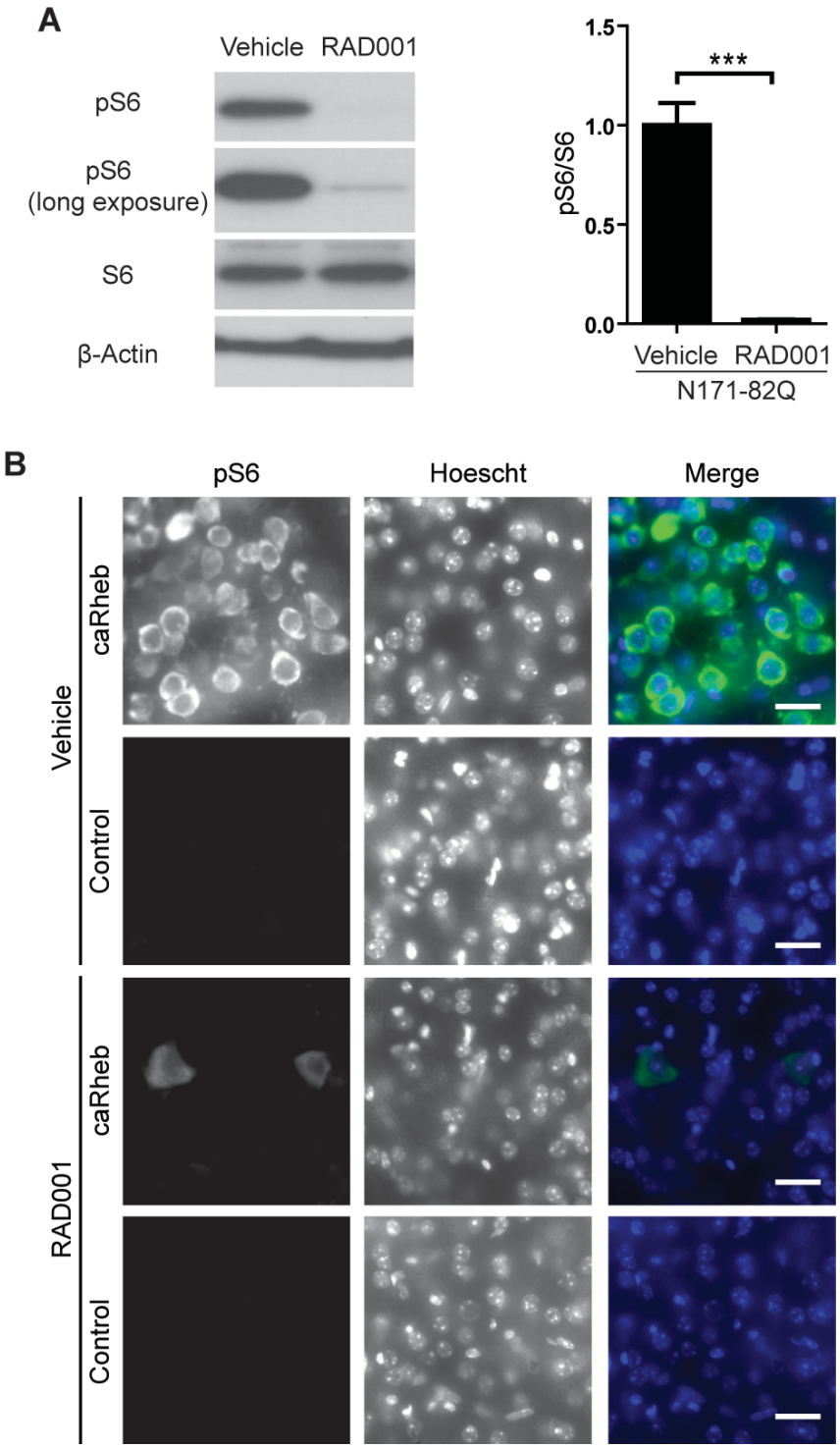


**Figure S6. RAD001 inhibits mTORC1 activity in the striatum of N171-82Q mice.**
(A) Biochemical assessment of mTORC1 activity (pS6) in striatal lysates from N171-82Q mice that received vehicle (2% DMSO) or mTORC1 inhibitor RAD001 (N=3 mice per group). Mice were treated for 2 weeks and striata harvested 24 hours after the last dose. Densitometry analysis of immunoblots of samples from mice. β-actin was used as a loading control. Data represent mean ± SEM. ***P<0.001, Student's t-test. (B) Representative photomicrographs of immunohistochemical staining for pS6 (green) and Hoescht staining (blue), 2 weeks after a single unilateral injection of AAV.caRheb into the striatum of 11-week-old N171-82Q mice. Mice were given vehicle (N=3) or RAD001 (N=4) for 2 weeks. Scale bars: 25 μm. Related to Figure 6.

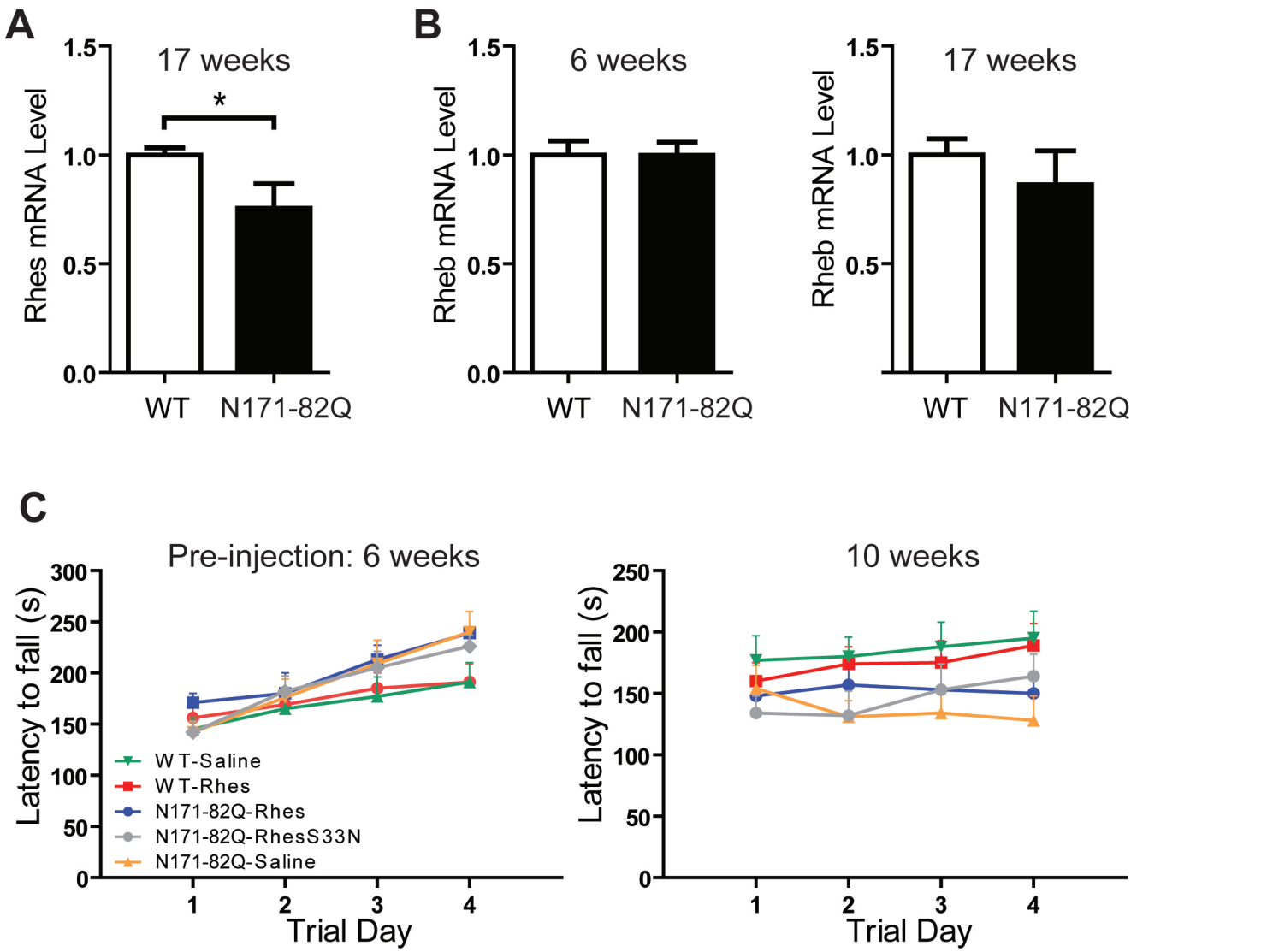


**Figure S7. Rhes expression levels are reduced in HD transgenic mice striata.**
(A) Endogenous striatal Rhes levels in 17-week-old N171-82Q (N=4) and WT mice (N=6). Rhes mRNA abundance was normalized to endogenous β-actin. Data represent mean ± SEM.*P<0.05; Student's t-test. (B) Rheb levels are unchanged in N171-82Q mice striata from 6-week-old N171-82Q (N=5) and WT mice (N=4), and 17-week-old N171-82Q (N=4) and WT mice (N=6). Student's t-test. (C) N171-82Q mice perform indistinguishably from normal at 5 and 10 weeks of age (N=10-14 mice per group). Rotarod data from four consecutive days are shown as latency to fall. Data represent mean ± SEM. One-way ANOVA with Tukey post-hoc test. Related to Figure 7.

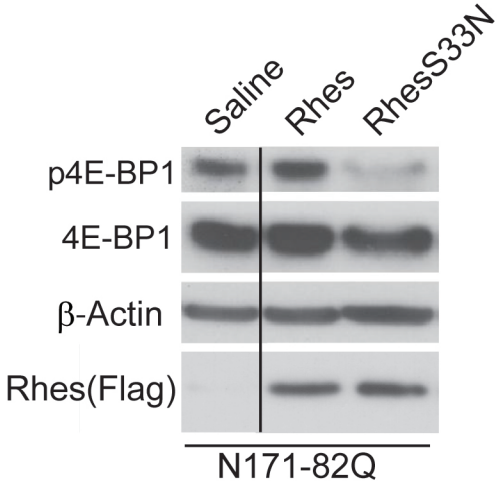


**Figure S8. Transduction of N171-82Q mouse striatum with Rhes and GTPase deficient Rhes S33N.** Representative western blot of mTORC1 activity (p-4E-BP1) and Rhes transgenes (Flag) in N171-82Q mice transduced with AAV.Rhes, AAV.RhesS33N, or saline in the striatum. Mice were injected at 7 weeks of age, and striatal tissues were harvested 3 weeks post-injection. β-actin was used as a loading control. Related to Figure 7.