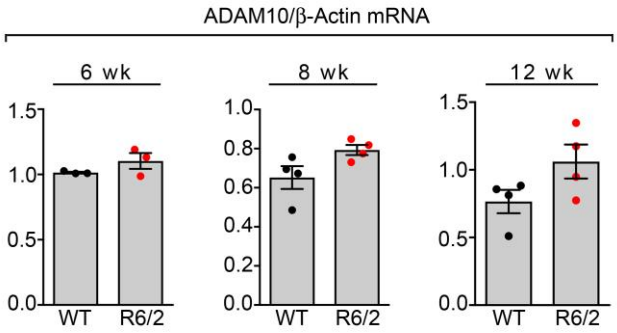
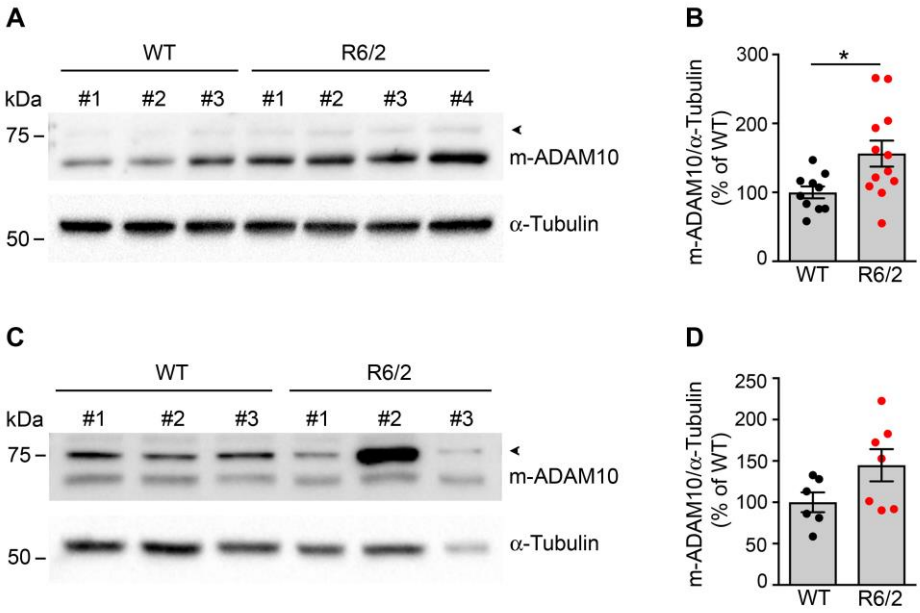
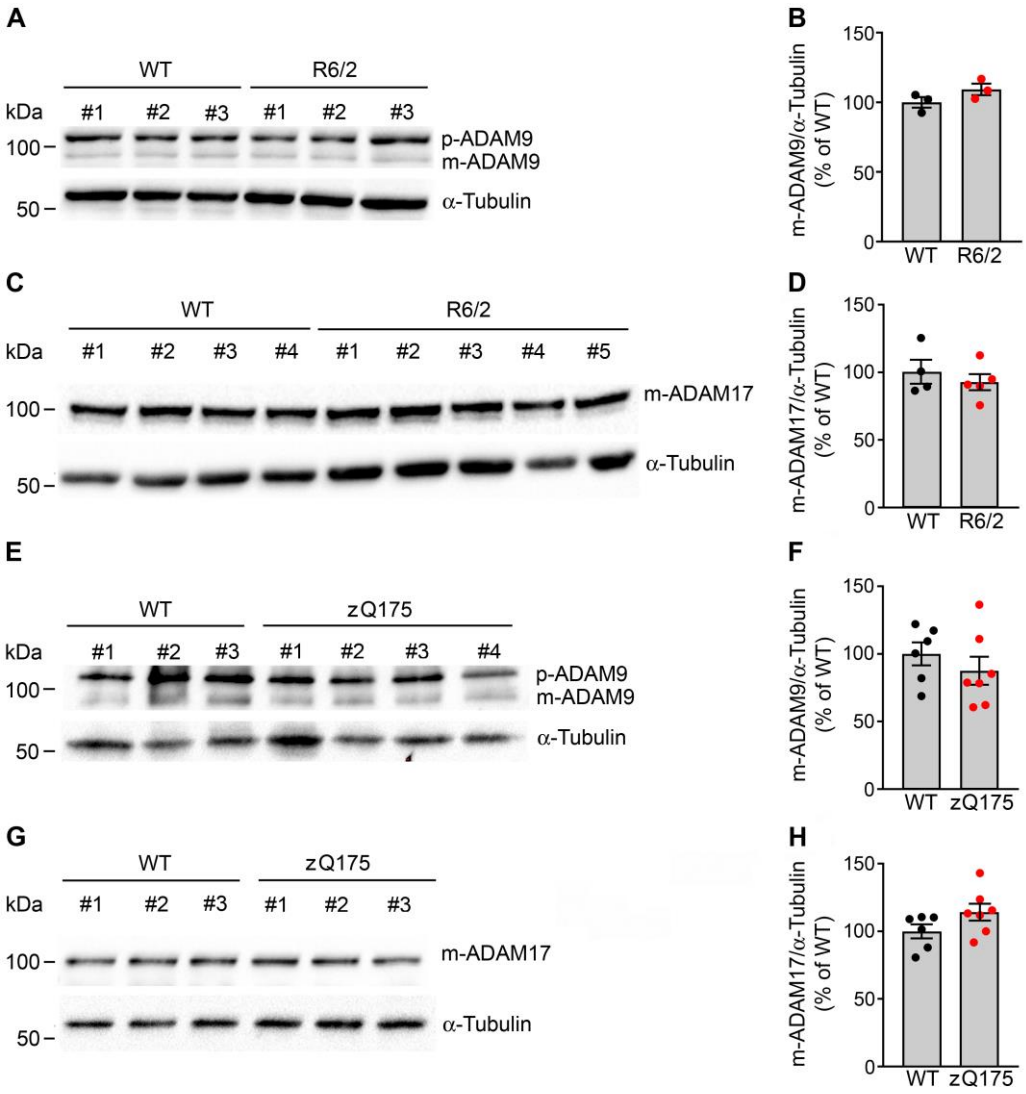


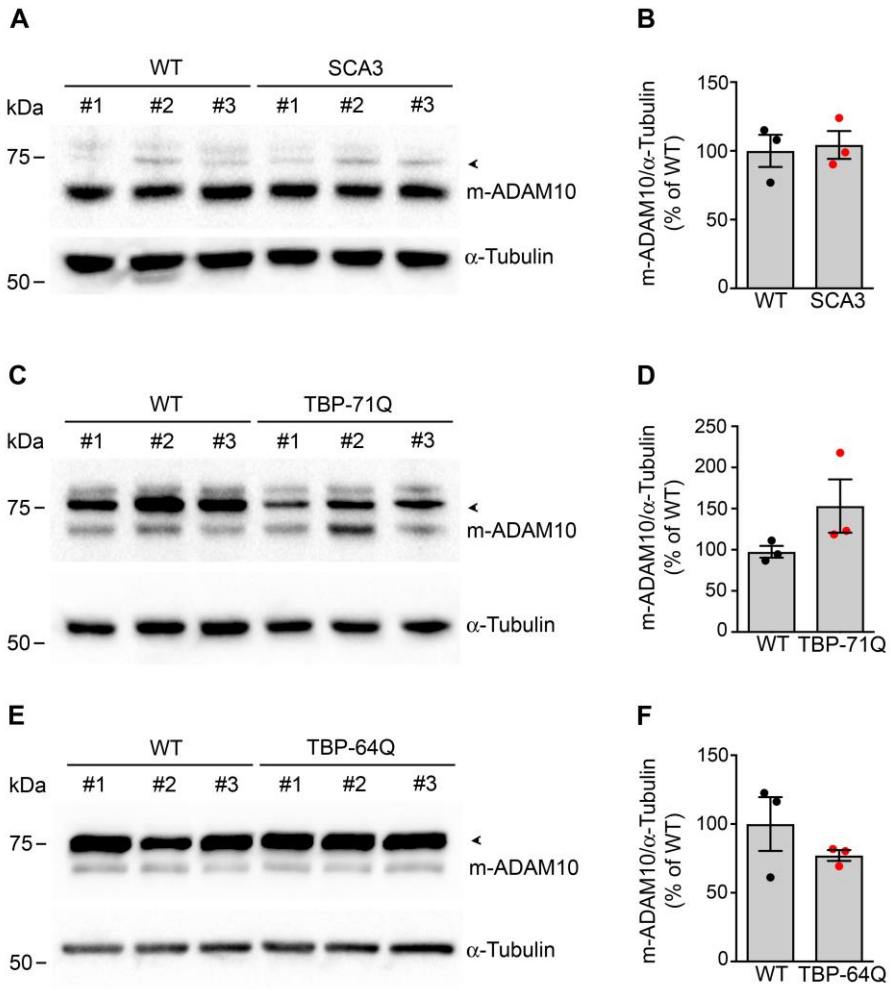
Supplementary Figure 1. **ADAM10 mRNA levels in the striatum of WT and R6/2 mice.** ADAM10 mRNA levels were determined in the striata of WT and R6/2 mice at 6, 8 and 12 wk of age by qRT-PCR and normalized to the level of β-Actin mRNA. Data are represented as the mean ± SEM and were analysed by unpaired *t* test. 6 wk: n=3 mice/genotype; 8 wk: n=4 mice/genotype; 12 wk: n=4 mice/genotype.



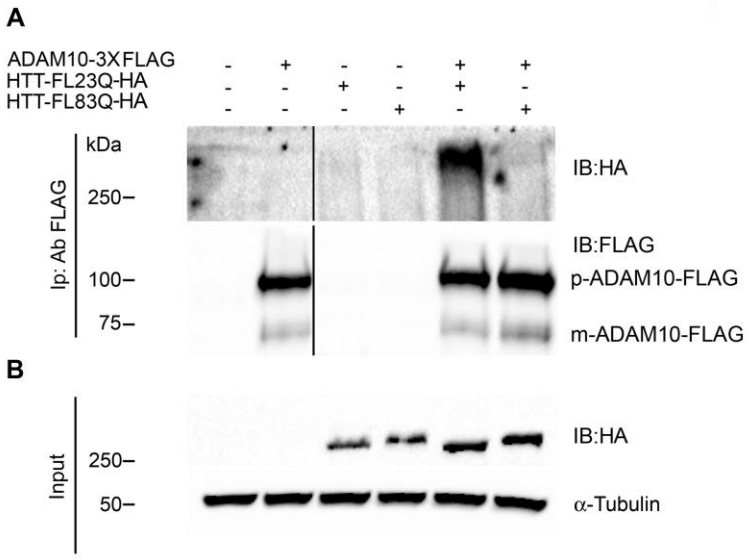
Supplementary Figure 2. m-ADAM10 in the cortex and cerebellum of WT and R6/2 mice. (**A**) Representative Western blot for mature ADAM10 (m-ADAM10) in the cortices of WT and R6/2 mice at 9 wk of age. (**B**) Quantification of data presented in **A**. n=10-12 mice/genotype were tested. *P<0.05, unpaired *t* test. (**C**) Representative Western blot for m-ADAM10 in cerebellum from WT and R6/2 mice at 10 wk of age. (**D**) Quantification of data presented in **C**. n=6-7 mice/genotype were tested. In **A** and **C** α-Tubulin, loading control. Data are presented as mean ± SEM. Arrowheads, nonspecific band.



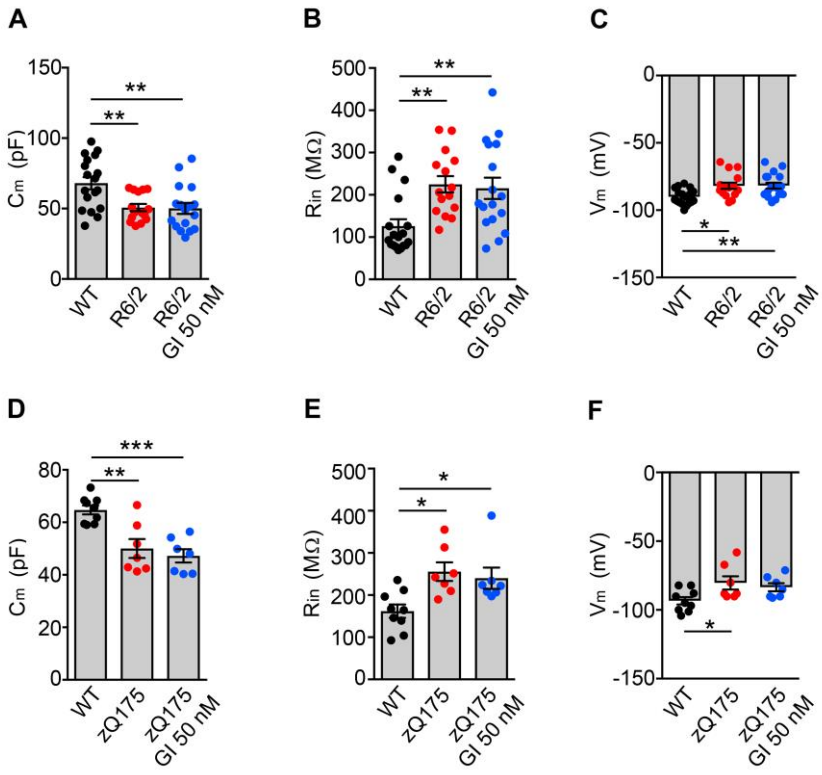
Supplementary Figure 3. Mutant HTT does not affect striatal m-ADAM9 and m-ADAM17 levels. (**A**) Representative Western blot for p-ADAM9 (zymogen) and m-ADAM9 (active form of ADAM9) in striata from WT and R6/2 mice at 8 wk of age. (**B**) Quantification of data presented in **A**. n=3 mice/genotype. (**C**) Representative Western blot for the active form of ADAM17 (m-ADAM17) in WT and R6/2 mice at 8 wk of age. (**D**) Quantification of data presented in **C**. n=4-5 mice/genotype. (**E**) Representative Western blot for p-ADAM9 and m-ADAM9 in striata from WT and heterozygous zQ175 mice at 54 wk of age. (**F**) Quantification of data presented in **E**. n=6-7 mice/genotype. (**G**). Representative Western blot for m-ADAM17 in WT and heterozygous zQ175 mice at 54 wk of age. (**H**) Quantification of data presented in **G**. n=6-7 mice/genotype. In **A**, **C**, **E** and **G** α-Tubulin, loading control. Data are represented as mean ± SEM and were analysed by unpaired *t* test.



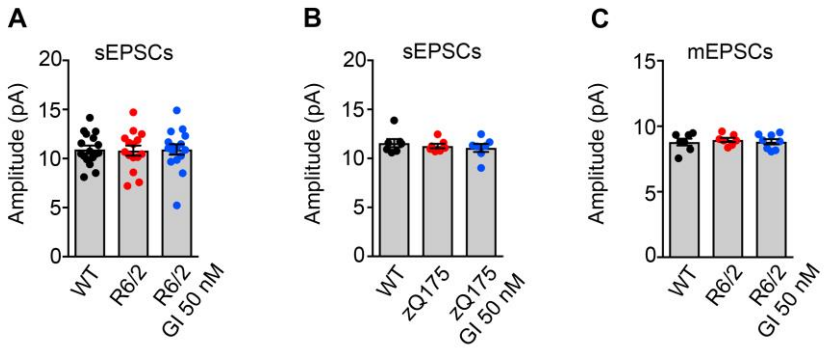
Supplementary Figure 4. **m-ADAM10 levels in cerebellum of rodents affected by SCA3 and SCA17** (**A**) Representative Western blot for m-ADAM10 in cerebellum from WT and symptomatic SCA3 mice. (**B**) Quantification of data presented in **A**. n=3 mice/genotype. (**C**) Representative Western blot for m-ADAM10 in cerebellum from WT and symptomatic TBP-71Q mice (affected by SCA17). (**D**). Quantification of data presented in **C**. n=3 mice/genotype. (**E**) Representative Western blot for m-ADAM10 in cerebellum from WT and symptomatic TBP-64Q (SCA17) rats. (**F**) Quantification of data presented in **E**. n=3 rats/genotype. In **A**, **C**, **E** α-Tubulin, loading control. Data are represented as mean ± SEM. Significance was determined by unpaired *t* test. Arrowheads, nonspecific band.



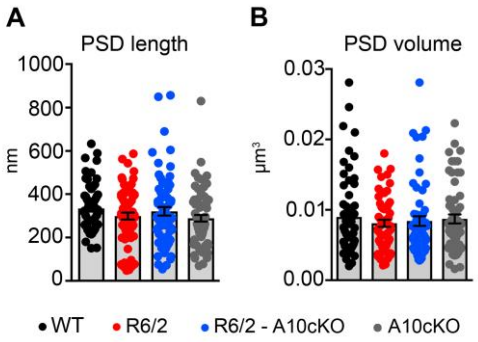
Supplementary Figure 5. **Co-immunoprecipitation analysis of ADAM10 and HTT in HEK293T cells.** (**A**) HEK293T cells were transfected with HTT-FL23Q-HA or HTT-FL83Q-HA and ADAM10-3XFLAG. Whole protein lysates were immunoprecipitated with anti-FLAG antibodies and the resulting blot was probed for HA (top panel) and FLAG (bottom panel). Lanes were run on the same gel but were noncontiguous. (**B**) Western blot for HA on input samples. α-Tubulin, loading control. One of n=2 replicates is shown.



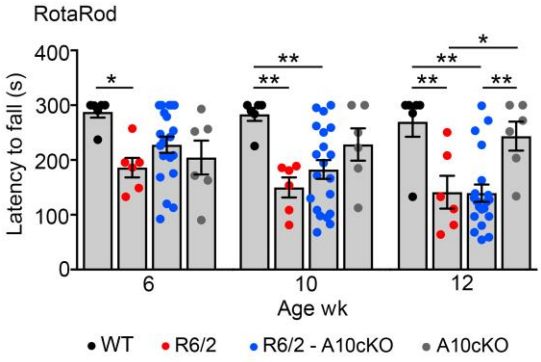
Supplementary Figure 6. Treatment with GI254023X does not rescue passive and firing properties of R6/2 and zQ175 MSNs. (**A-C**) Membrane capacitance (C_m), input resistance (R_{in}), and membrane resting potential (V_m) of MSNs in acute brain slices from WT and R6/2 mice at 11 wk of age after GI254023X treatment (50 nM for 45 minutes). WT (n=18); R6/2-untreated (n=15); R6/2-GI254023X (n=17). (**D-F**) C_m, R_{in}, and V_m in MSNs from WT and heterozygous zQ175 mice at 54 wk of age after GI254023X treatment (50 nM for 45 minutes). WT (n=9); zQ175-untreated (n=7); zQ175-GI254023X (n=7). Data are represented as mean ± SEM. *P<0.05, **P<0.001, ***P<0.001, One-way ANOVA with Bonferroni's post hoc test.



Supplementary Figure 7. sEPSC and mEPSCs amplitude is not affected in HD mice before and after treatment with GI254023X. (**A**) sEPSCs amplitude of MSNs in acute brain slices from WT and R6/2 at 11 wk of age. WT (n=17); R6/2-untreated (n=15); R6/2-GI254023X (n=16). (**B**) sEPSCs amplitude of MSNs in acute brain slices from WT and heterozygous zQ175 mice at 54 wk. WT (n=7); zQ175-untreated (n=7); zQ175-GI254023X (n=7). (**C**) mEPSCs amplitude of MSNs in acute brain slices from WT and R6/2 mice at 11 wk of age. WT (n=7); R6/2-untreated (n=7); R6/2-GI254023X (n=8). In A-C brain slices have been treated with GI254023X 50 nM for 45 minutes. Data are represented as mean ± SEM and were analysed by One-way ANOVA with Bonferroni's post hoc test.



Supplementary Figure 8. Morphometric analysis of post-synaptic density (PSD) length and volume in WT, R6/2, R6/2-A10cKO, and A10cKO mice. In **A** and **B**, 60 PSDs were analysed in n=3 mice/genotype at 13 wk of age. Data are represented as mean ± SEM and were analysed by One-way ANOVA with non parametric Dunn's multiple comparison test.



Supplementary Figure 9. ADAM10 heterozygous deletion in the forebrain does not rescue motor defects in R6/2 mice. RotaRod performance for WT (n=6), R6/2 (n=6), R6/2-A10cKO (n=20) and A10cKO (n=6) mice at 6, 10, and 12 wk of age. Data are presented as mean ± SEM. *P<0.05, **P<0.01 in One-way ANOVA with Newman Keuls post hoc test.

Supplementary Table 1. Cell membrane properties of MSNs from WT and R6/2 at 11 wk of age and from WT and heterozygous zQ175 mice at 54 wk of age. GI254023X was administered at the concentration of 50 nM for 45 minutes. Data represent mean ± SEM. *P<0.05; **P<0.01; ***P<0.001 vs WT, One-way ANOVA with Bonferroni's post hoc test.

	C_m (pF)	R_{in} (MΩ)	V_m (mV)
WT (n=18)	68.0±4.3	126±16	-90.2±1.3
R6/2 (n=15)	50.7±2.6**	225±19**	-81.9±2.3*
R6/2 + GI254023X [50 nM] (n=17)	50.1±3.9**	216±25**	-81.7±2.1**
WT (n=9)	64.7±1.7	162±16	-93.4±2.7
zQ175 (n=7)	50.0±3.6**	256±22*	-80.3±4.8*
zQ175 + GI254023X [50 nM] (n=7)	47.2±2.5***	240±25*	-83.5±3.0

Supplementary Table 2. Spontaneous EPSCs recorded from MSNs of WT and R6/2 mice at 11 wk of age and from WT and heterozygous zQ175 mice at 54 wk of age. GI254023X was administered at the concentration of 50 nM for 45 minutes. Data represent mean ± SEM. *P<0.05; ***P<0.001 vs WT; ##P<0.01 vs R6/2; # P<0.05 vs zQ175, One-way ANOVA with Bonferroni's post hoc test.

	Frequency (Hz)	Amplitude (pA)
WT (n=17)	3.32±0.24	10.93±0.39
R6/2 (n=15)	1.21±0.09***	10.81±0.51
R6/2 + GI254023X [50 nM] (n=16)	2.00±0.12***##	10.92±0.53
WT (n=7)	3.51±0.33	11.56±0.42
zQ175 (n=7)	1.63±0.09***	11.26±0.23
zQ175 + GI254023X [50 nM] (n=7)	2.50±0.20*#	11.07±0.41

Supplementary Table 3. Miniature EPSCs recorded from MSNs of WT and R6/2 mice at 11 wk of age. GI254023X was administered at the concentration of 50 nM for 45 minutes. Data represent mean ± SEM. ***P<0.001 vs WT; # P<0.05 vs R6/2, One-way ANOVA with Bonferroni's post hoc test.

	Frequency (Hz)	**Amplitude (pA)**
WT (n=7)	2.21±0.22	8.79±0.26
R6/2 (n=7)	0.66±0.06***	8.96±0.16
R6/2 + GI254023X [50 nM] (n=8)	1.27±0.13***#	8.82±0.20