

Figure Legends

Figure S1. Viral spread and co-transduction. (A, B) Coronal sections are shown from a mouse injected unilaterally with a mixture of mHDx-1-lentivirus and VL12.3-AAV were stained for Htt (green) and iAb (red). (A) Sections from three different anterior/posterior levels show a similar extent of spread for the two viruses. (B) Confocal images show co-localization of mHDx-1 and VL12.3 with more cells being VL12.3-positive than mHDx-1-positive, indicating co-transduction of cells and greater transduction efficiency for AAV. Scale bar = 50 μ m. (C) Coronal sections are shown from an R6/2 mouse injected with AAV-GFP on postnatal day 3 and sacrificed at 10 weeks of age. Three different anterior/posterior levels show striatal spread equivalent to, or better than, that seen for adult injections. (D) A coronal section from a BACHD mouse injected with AAV-GFP at 2 months of age and sacrificed at 6 months of age shows hippocampal transgene expression. Numbers indicate mm from bregma.

Figure S2. Happ1 treatment improves beam-crossing performance in four HD mouse models. Time to cross the center 80 cm of a square 1 m long, and 28 mm, 12 mm or 6 mm wide (indicated by the different sizes of open boxes in each panel) beam was measured. (A-C) Male R6/2 and wt littermates were tested weekly, and Happ1 treatment improves, while VL12.3 treatment degrades performance. (D-F) Male N17182Q and wt littermates were tested every other week and Happ1 treatment improves performance. (G-I) Male YAC128 and wt littermates were tested monthly, and Happ1 treatment improves performance. (J-L) Male and female BACHD mice were tested monthly, and Happ1 treatment improves performance. Asterisks indicate a significant difference between GFP- and iAb-treated mutants. *= $p < .05$, **= $p < .01$, ***= $p < .001$

Movie S3. Happ1 treatment improves climbing performance in YAC128 mice. Mice were placed at the bottom of a vertical wire mesh tube and observed for 5 minutes. The time when all four feet were off the ground was scored as climbing time. Both the GFP-treated wt mouse on the left and the Happ1-treated YAC128 mouse on the right spend a significant amount of time climbing the wire mesh and often climb to the top to investigate the roof. The GFP-treated YAC128 mouse in the middle investigates and rears frequently, but spends significantly less time climbing than the others and does not climb to the top.

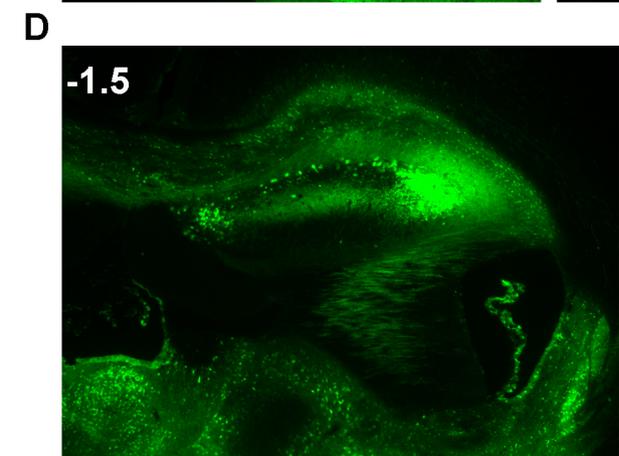
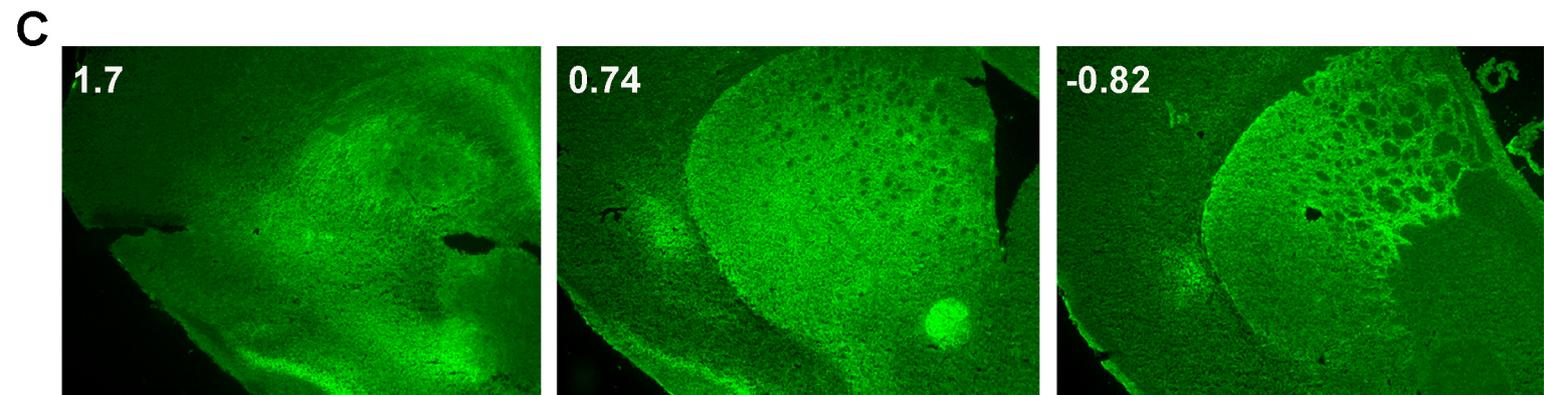
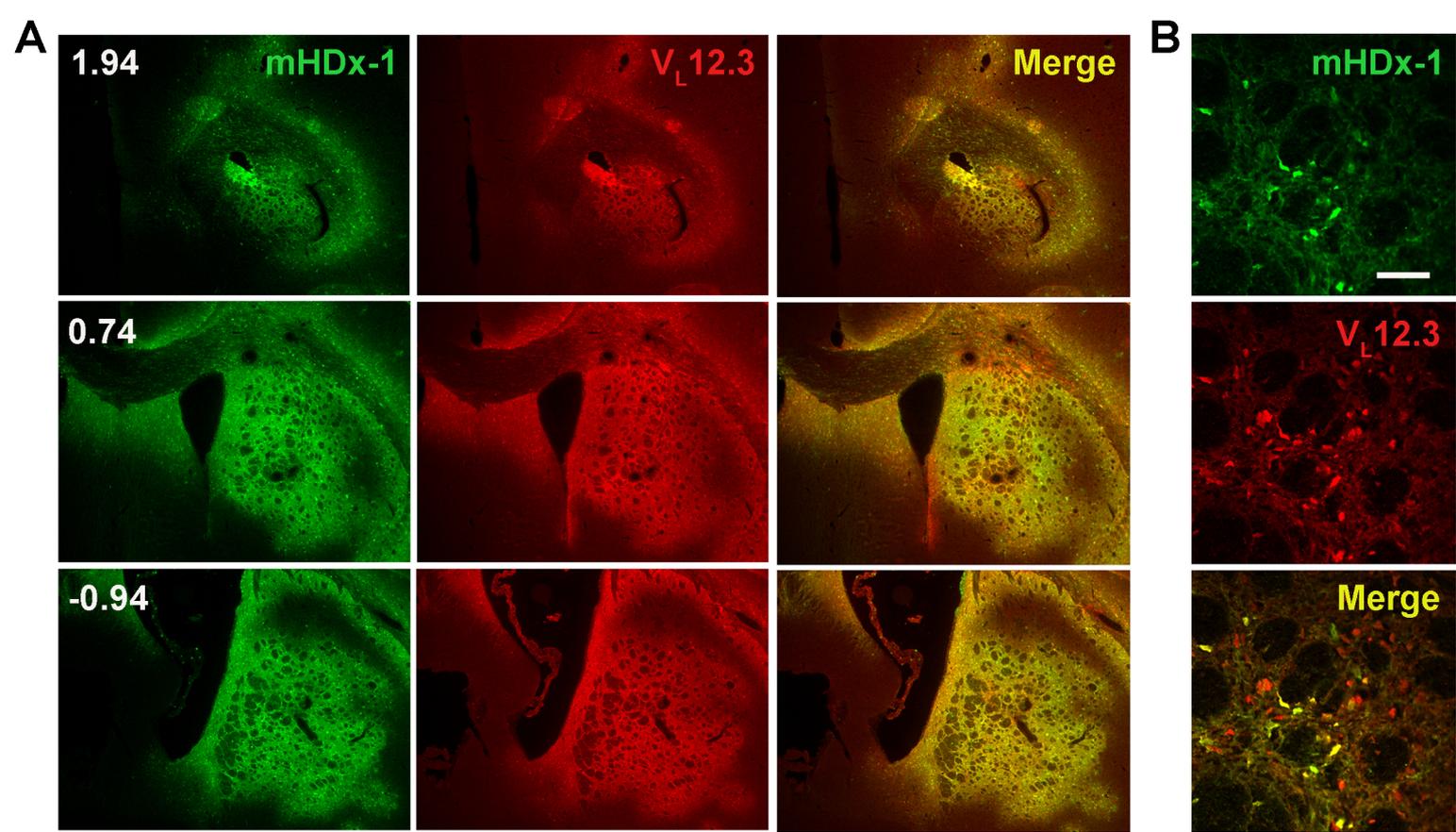
Figure S4. Happ1 treatment improves clasping and body weight in N171-82Q mice. (A, B) The GFP-treated N171-82Q mouse (left) displays forelimb and hind limb clasping and reduced body weight while the Happ1-treated N171-82Q mouse (right) displays greater limb extension and normal body weight.

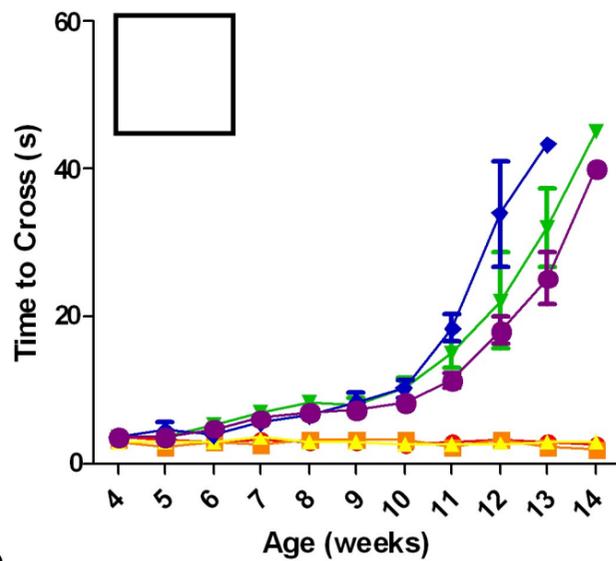
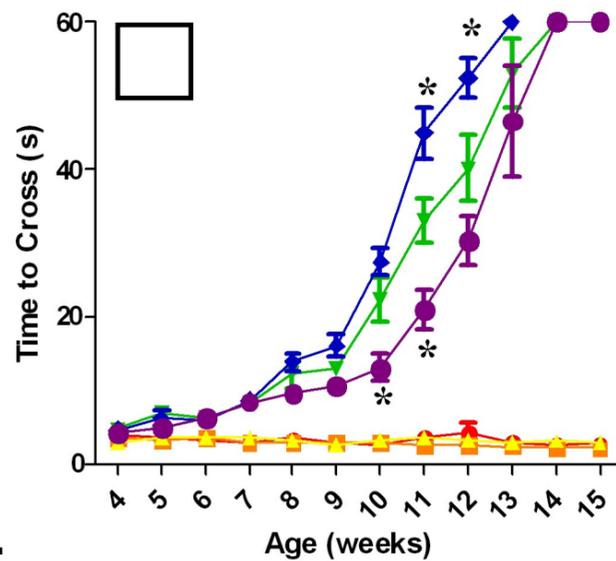
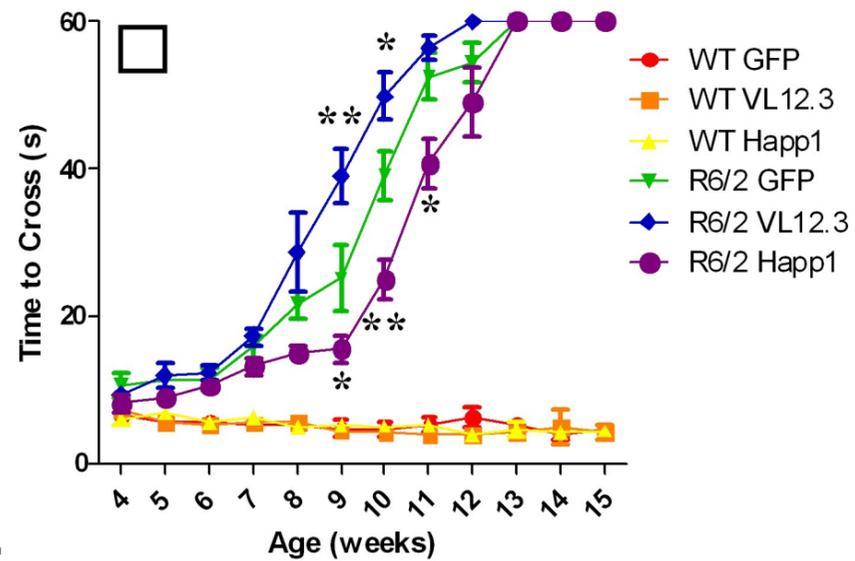
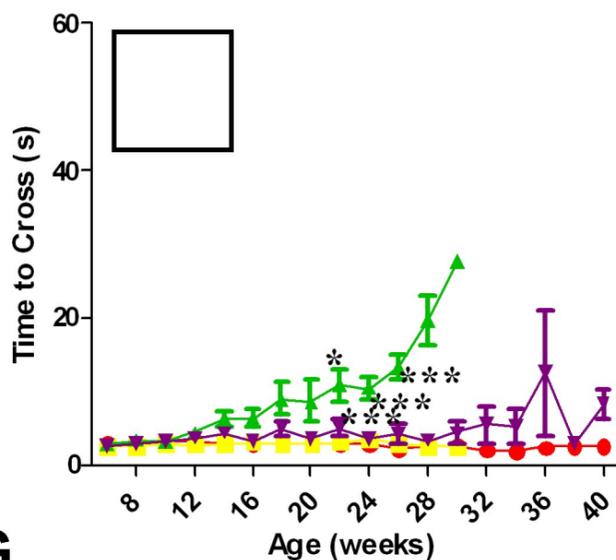
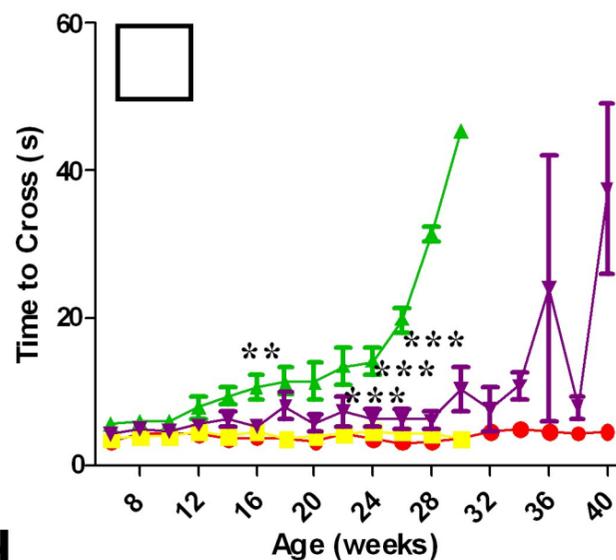
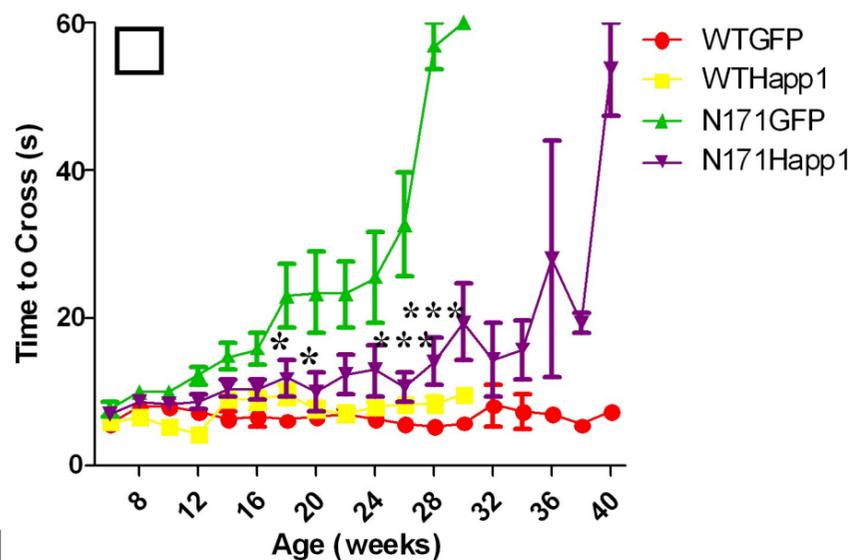
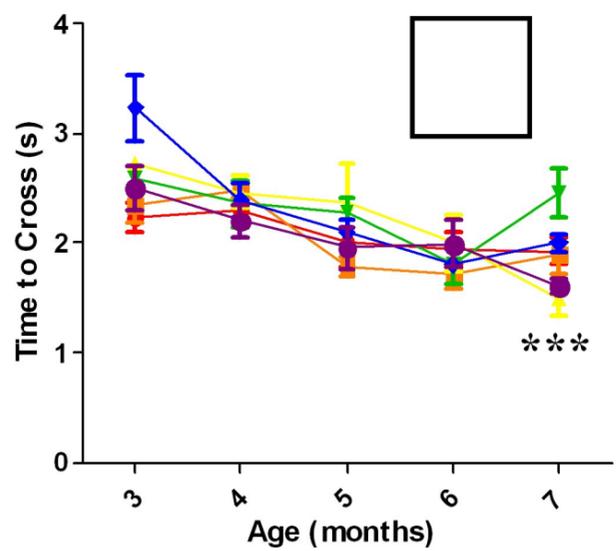
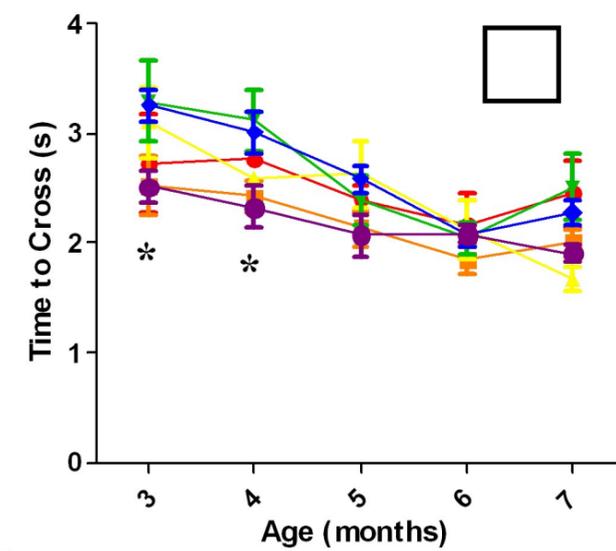
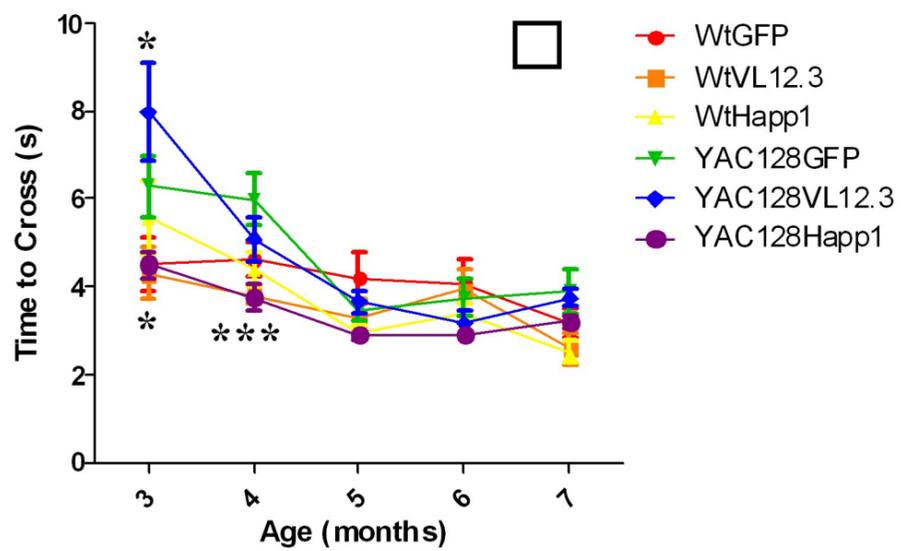
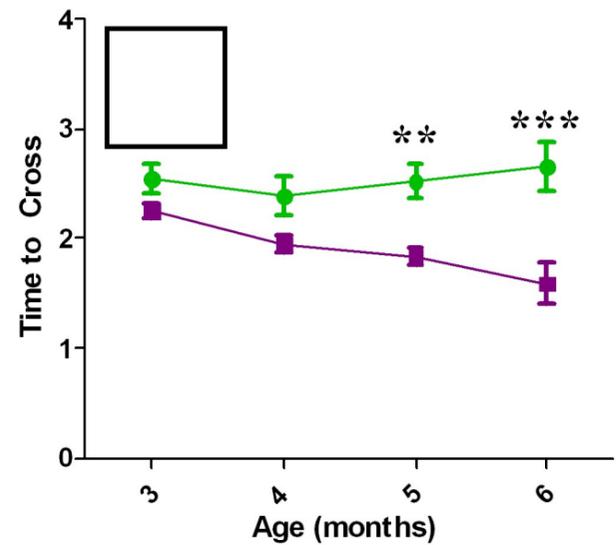
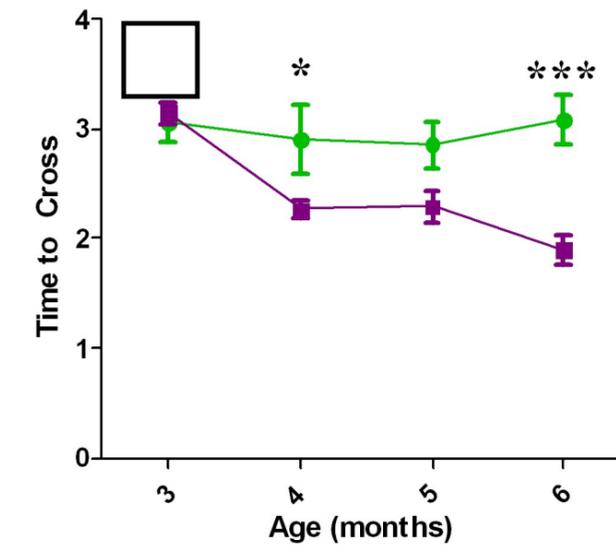
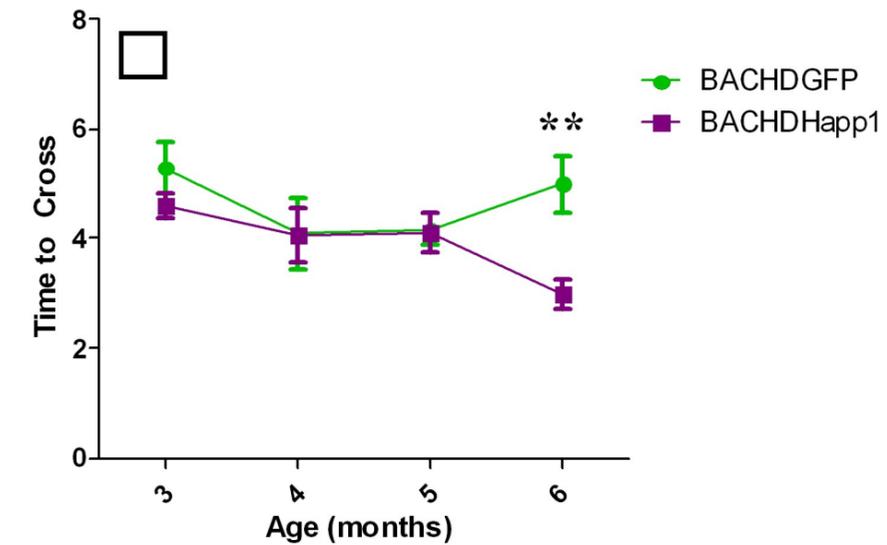
Figure S5. VL12.3 or Happ1 decrease Htt aggregation in the lentiviral and R6/2 HD models. Three sections each of (A) 6 weeks post-surgery mHDx-1-lentivirus-injected and (B) 10 week-old R6/2 brains were stained for Htt with MW8 antibody. Following GFP-AAV injection in both models, the majority of the Htt is aggregated, although some diffuse staining in neurons is seen (arrows in left panel A). With injection of VL12.3 or Happ1, there is a reduction in aggregated Htt and an increase in diffuse Htt staining. In the presence of Happ1, total Htt staining appears to be reduced.

Figure S6. A summary of motor behavior results is presented.

Figure S7. A summary of cognitive behavior results is presented.

Figure S8. A summary of neuropathological results is presented.



A**B****C****D****E****F****G****H****I****J****K****L**

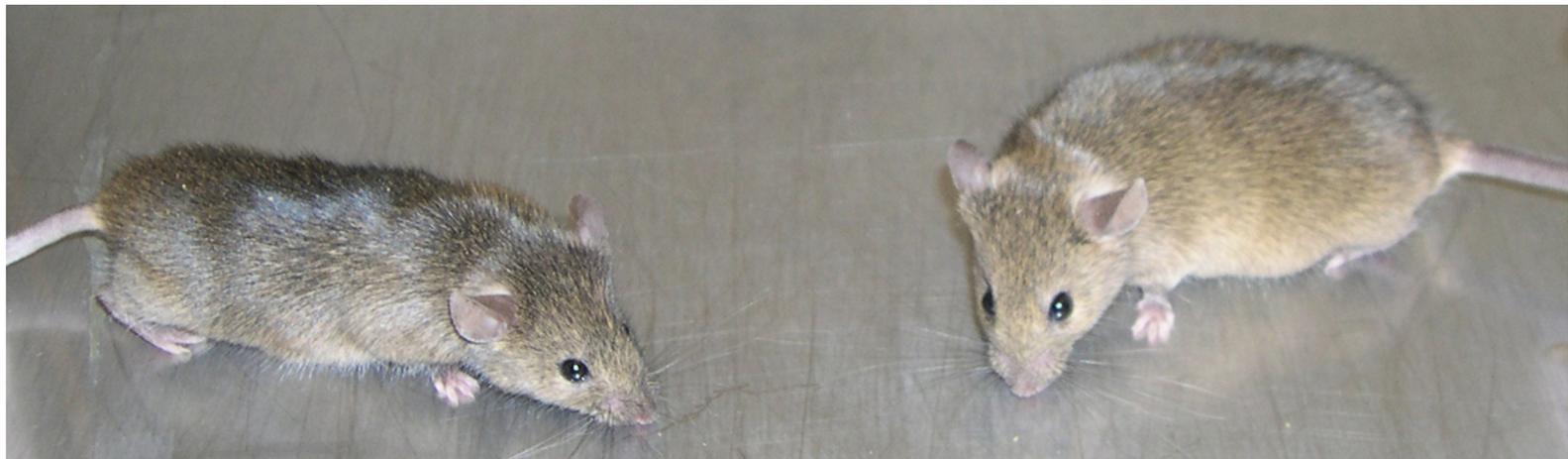
A N171-82Q GFP

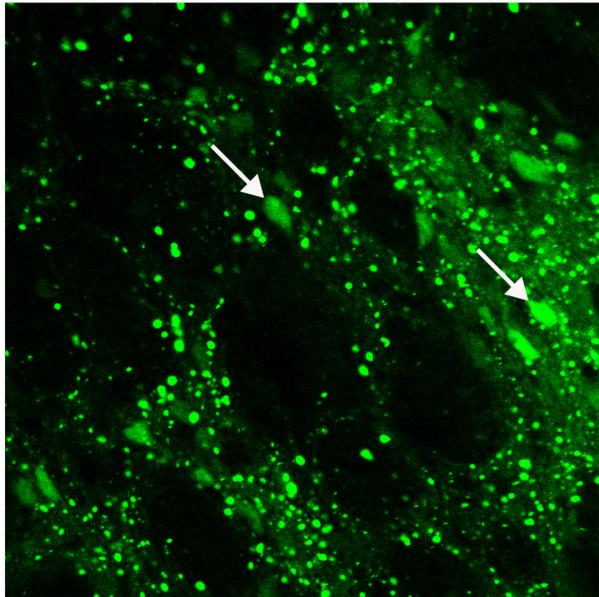
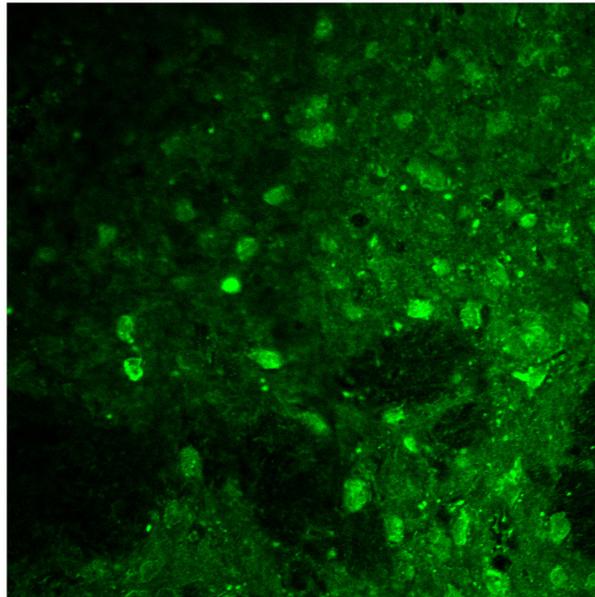
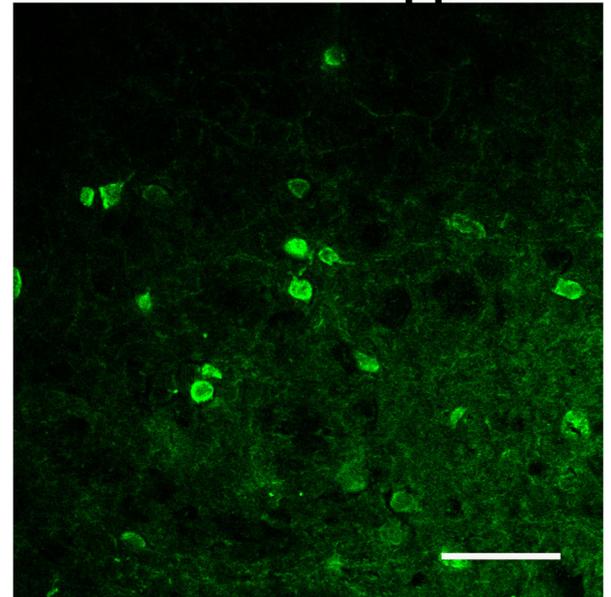
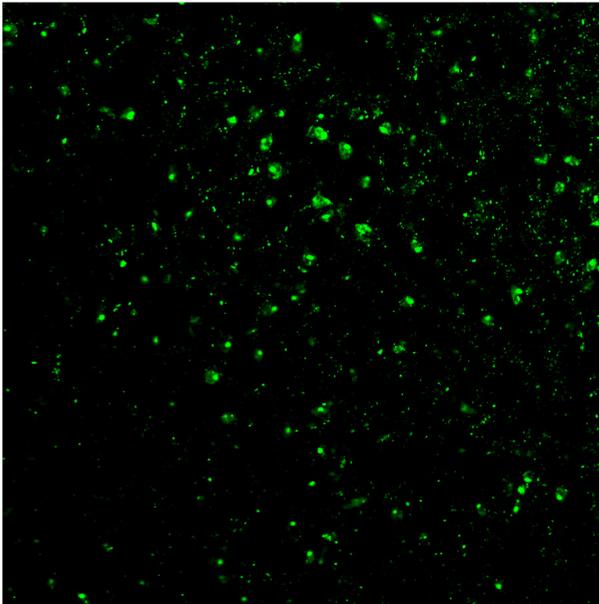
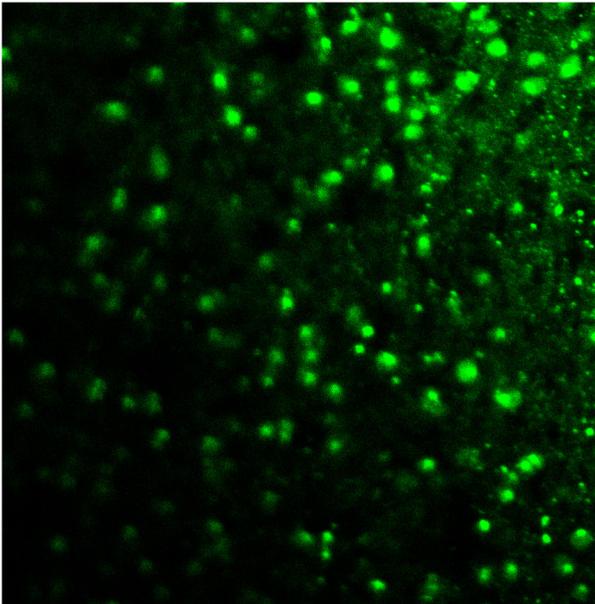
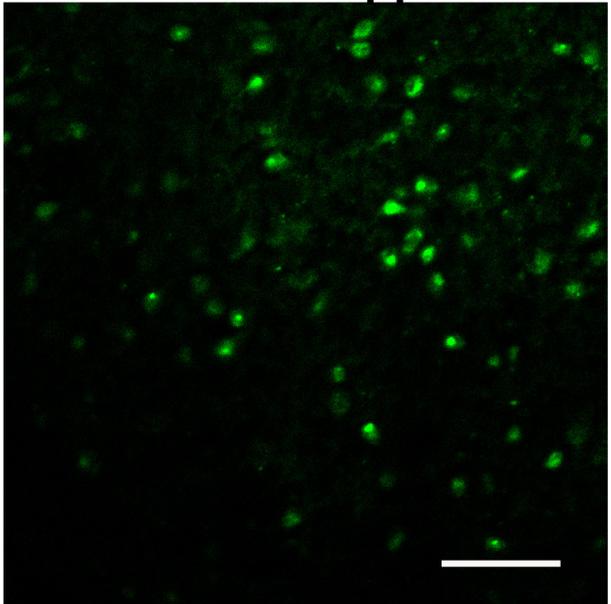


A N171-82Q Happ1



B



A**mHDx-1+GFP****mHDx-1+VL12.3****mHDx-1+Happ1****B****R6/2+GFP****R6/2+VL12.3****R6/2+Happ1**

	Amphetamine-induced rotation	Rotarod	Beam crossing	Climbing	Clasping
mHDx-1 lentivirus	Happ1 + V _L 12.3 +	ND	ND	ND	ND
R6/2	ND	Happ1 + V _L 12.3 -	Happ1 + V _L 12.3 -	ND	ND
N171	ND	Happ1 +	Happ1 +	ND	Happ1 +
YAC	ND	Happ1 + V _L 12.3 =	Happ1 + V _L 12.3 =	Happ1 +	ND
BAC	ND	Happ1 +	Happ1 +	Happ1 +	ND

+, improved; -, declined; =, no effect; ND, not determined

	Open field	Novel object location	Novel object preference
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YAC

Happ1 +
V_L12.3 =

Happ1 +
V_L12.3 =

Happ1 +
V_L12.3 =

BAC

Happ1 +

Happ1 =

Happ1 =

+, improved; =, no effect

	Neuron loss	DARPP-32 loss	Aggregation	Inclusions	Ventricles
mHDx-1 lentivirus	Happ1 + V_L12.3 +	Happ1 + V_L12.3 +	Happ1 + V_L12.3 +	ND	ND
R6/2	ND	Happ1= V_L12.3 -	Happ1 + V_L12.3 +	Happ1 + V_L12.3 =	Happ1 + V_L12.3 =
N171	ND	ND	ND	ND	ND
YAC	ND	ND	ND	ND	Happ1 + V_L12.3 =
BAC	ND	ND	ND	ND	Happ1 +

+, improved; -, declined; =, no effect; ND, not determined