AAV-mediated delivery of the transcription factor XBP1s into the striatum reduces mutant Huntingtin aggregation in a mouse model of Huntington's disease

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Huntington's disease (HD) is caused by mutations that expand a polyglutamine region in the amino-terminal domain of Huntingtin (Htt), leading to the accumulation of intracellular inclusions and progressive neurodegeneration. Recent reports indicate the engagement of endoplasmic reticulum (ER) stress responses in human HD post mortem samples and animal models of the disease. Adaptation to ER stress is mediated by the activation of the unfolded protein response (UPR), an integrated signal transduction pathway that attenuates protein folding stress by controlling the expression of distinct transcription factors including X-Box binding protein 1 (XBP1). Here we targeted the expression of XBP1 on a novel viral-based model of HD. We delivered an active form of XBP1 locally into the striatum of adult mice using adeno-associated vectors (AAVs) and co-expressed this factor with a large fragment of mutant Htt as a fusion protein with RFP (Htt588 Q95-mRFP) to directly visualize the accumulation o