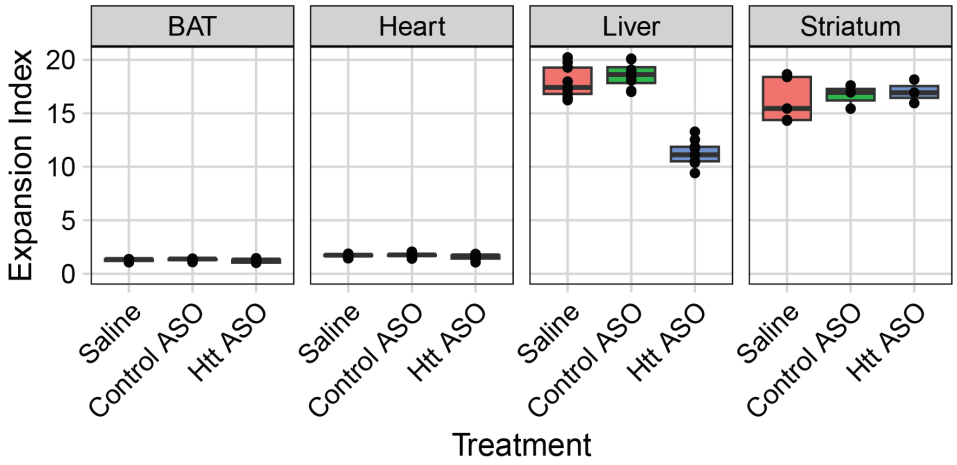
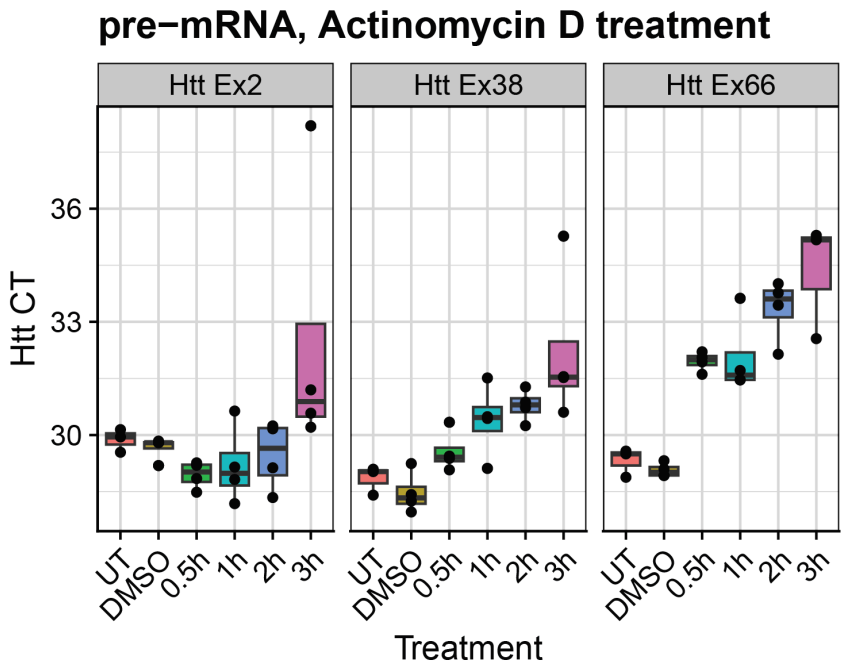
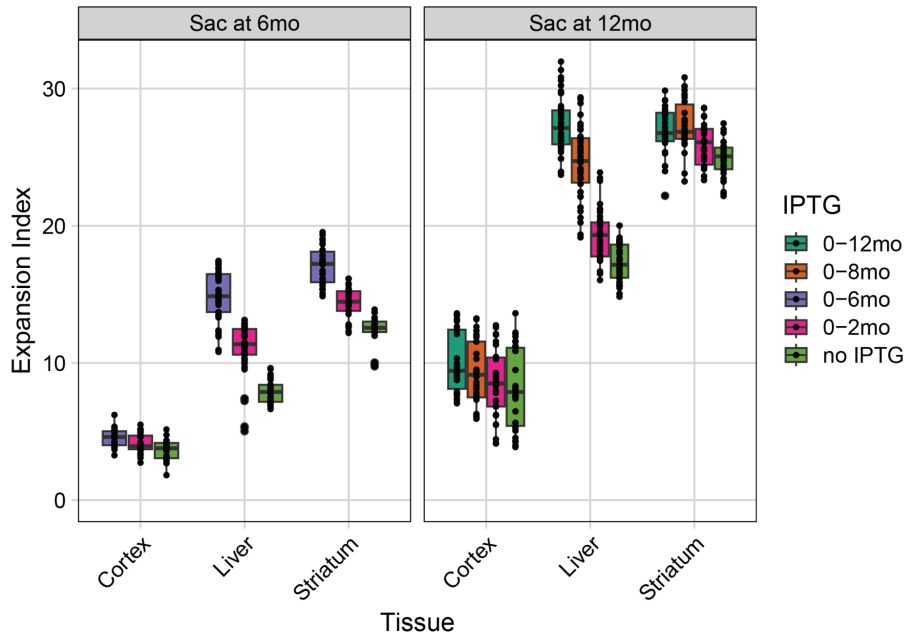
Supplemental Figures and Tables



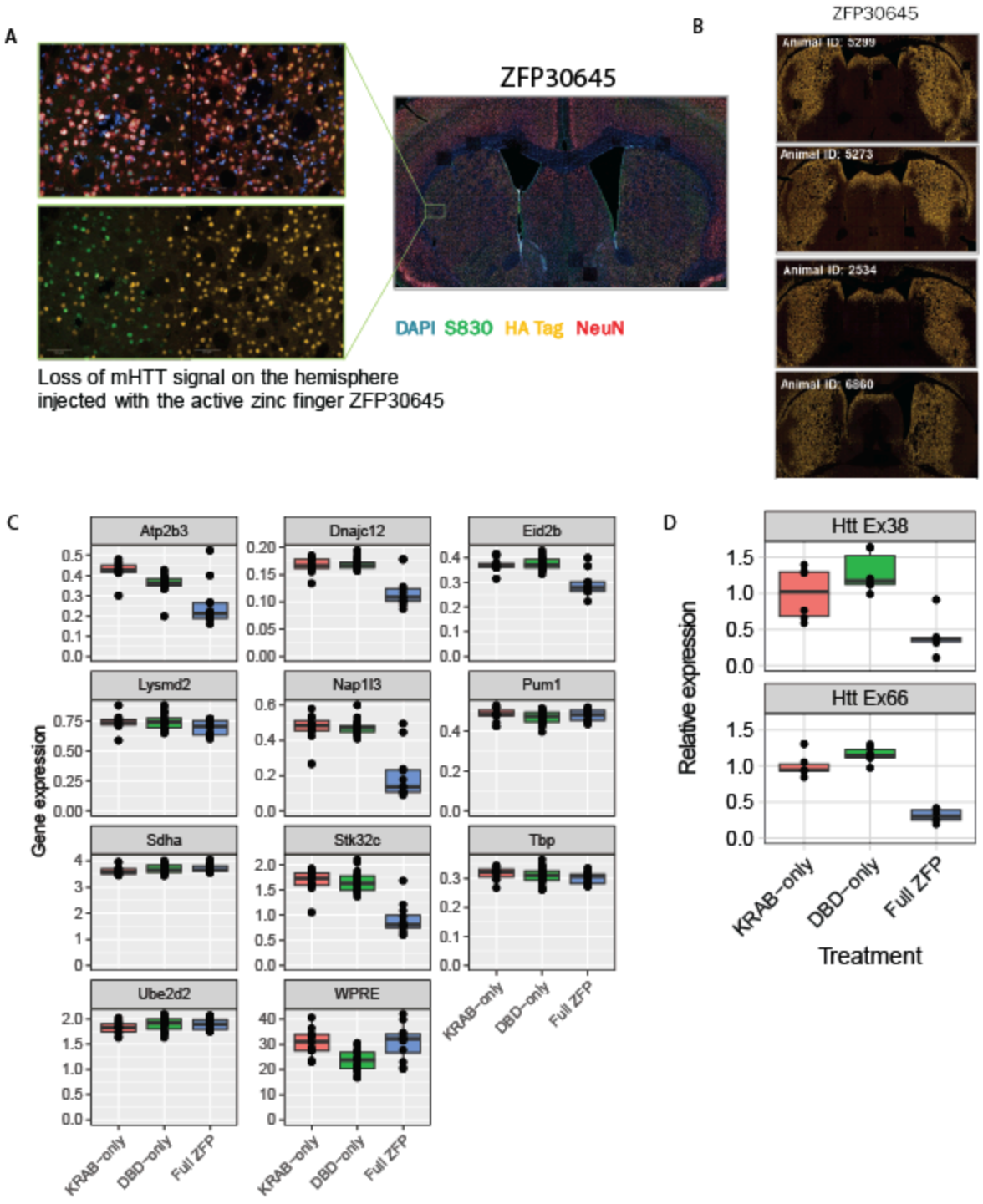
Supplemental Figure 1: Peripheral ASO treatment does not reduce instability in tissues other than liver. Brown adipose tissue (BAT) and heart are stable tissues with very low baseline instability and are not affected by Htt ASO treatment. Striatum is an unstable tissue, but Htt ASO is dosed peripherally and cannot cross the blood-brain barrier, so instability is unaffected. Liver is both unstable and accessible by the ASO, and its instability is markedly reduced by ASO treatment.



Supplemental Figure 2: Actinomycin D treatment leads to robust reductions in *Htt* pre-mRNA. In AML12 cells, pre-mRNA qPCR signal for Htt RNA decreases with increasing lengths of treatment with actinomycin D, a known transcriptional inhibitor.



Supplemental Figure 3: Complete, cross-tissue, LacO dataset. Expansion index decreases with longer windows of *Htt* repression, ie, shorter windows of IPTG treatment. This effect is seen in cortex, liver, and striatum, and in mice sacrificed at both 6 and 12 months of age.



Supplemental Figure 4: Experimental validation of the delta-DBD and delta-KRAB derivative ZFP constructs. A) Immunohistochemical staining showing loss of mHTT in the transduced area. **B)** HA-tag staining showing successful distribution of ZFP into the striatum. **C)** Off-target gene data. **D)** Results of *in vitro* study showing no reduction of transcription in DBD-only construct.

Supplemental Table 1: Raw data underlying all graphs.

Supplemental Table 2: Comparison of inherited CAG sizes across cohorts.