

# Longitudinal study of neurochemical changes in Q140 mouse model of Huntington's disease

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## INTRODUCTION

The Q140 knock-in mouse model of Huntington's disease (HD) may be a more meaningful model of pathology in human patients because of this model's slow disease progression and selective striatal degeneration. The goal of this study was to investigate metabolic changes in two different brain regions of Q140 and wild type control mice using longitudinal study design starting at 6 weeks of age.

## METHODS

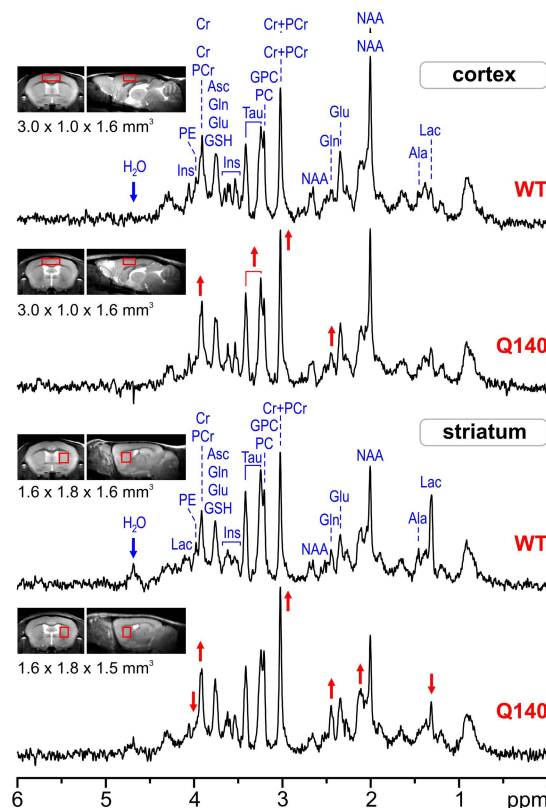
All NMR experiments were performed using a Varian INOVA and Direct Drive console interfaced to a 9.4T magnet equipped with a powerful gradient/shim coil insert (Resonance Research, Inc.) FASTMAP shimming methods were used and spectra were acquired by ultra-short echo-time STEAM (TE = 2 ms, TR = 5 s) with VAPOR water suppression [2]. Spectra were acquired from 3.8 – 4.8  $\mu$ L volumes. Metabolite concentrations were quantified using LCModel with macromolecule spectra included in the basis set. Unsuppressed water signal was used as an internal reference. Q140 mice and WT littermate were obtained from UCLA.

## RESULTS AND DISCUSSION

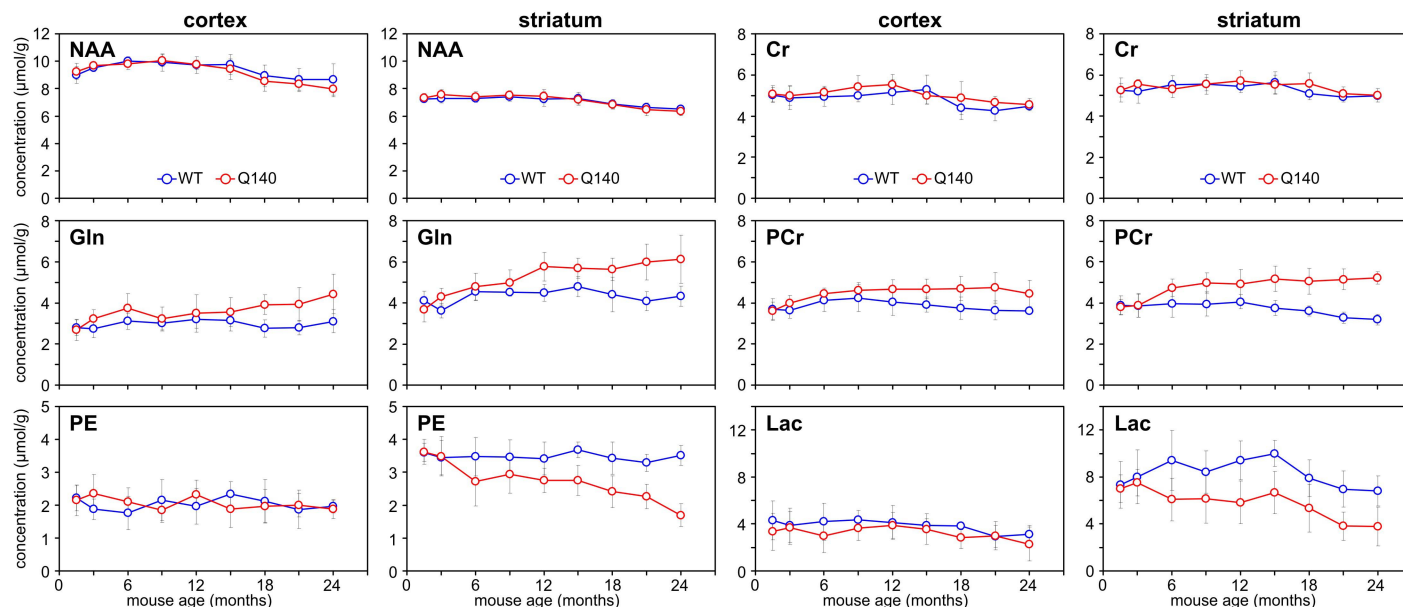
More than 300 spectra were acquired during the lifespan of Q140 and WT mice. Five WT and 4 Q140 mice were eliminated from the study due to extremely high Gln at early age. Routinely achieved spectral quality (Fig. 1) enabled reliable quantification of 16 brain metabolites from each spectrum. Highly significant changes were observed for multiple brain metabolites, including total creatine, glutamine (Gln), phosphoethanolamine (PE), lactate, myo-inositol (Ins) and taurine (Tau). Age dependent changes of selected metabolites are shown in Fig. 2. Metabolite changes were more substantial or exclusively localized in the striatum Gln, phosphocreatine (PCr), Lac and PE. Decrease in NAA and increase in choline compounds, previously reported in R6/2 HD mice [2,3], were not observed. Increase in total Cr, reported in R6/2 mice [2,3], was dominantly caused by increased PCr. Changes in PCr and Lac levels may indicate reduced energy demands in striatum. Reduced PE is most likely linked to the demyelination process. Metabolite changes localized in striatum more closely mimic phenotypes in human HD, which means that knock-in Q140 mouse model might be preferential for studying disease progression and its treatment.

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**REFERENCES:** 1. Tkac I et al., *J Neurochem* 2007; 100, 1397-1406; 2. Tkac I et al., *Magn Reson Med* 1999; 41, 649-656; 3. Tkac I et al., *Proc ISMRM* 2010, abs. 463.



**Fig. 1** In vivo <sup>1</sup>H NMR spectra acquired from the cerebral cortex and striatum of HD Q140 and WT mice at 21 months of age. STEAM, TE = 2 ms. No water signal removal or baseline corrections were applied.



**Fig. 2** Longitudinal changes in concentration of selected brain metabolites measured in the cerebral cortex and striatum of Q140 and WT control mice. Mice were scanned from 6 weeks up to 24 months, totally 288 spectra we analyzed, error bars indicate CD.