

Longitudinal DTI reveals presymptomatic white matter changes in YAC128 mouse model of Huntington disease

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Introduction

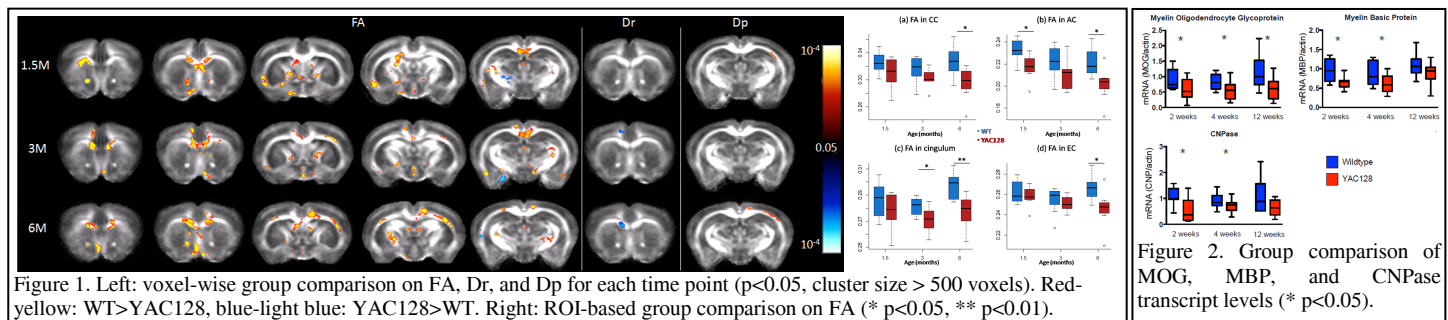
Huntington disease (HD) is an inherited, neurodegenerative disorder with motor, cognitive, and psychiatric deficits¹. The YAC128 mouse model of HD expresses the full-length mutant human huntingtin (*mHTT*) gene². This model recapitulates many aspects of the human disease including progressive neuropathological deficits and provides an opportunity to evaluate candidate therapeutics in preclinical studies³. White matter (WM) atrophy has been reported in diffusion MR studies of early stage HD patients⁴⁻⁶. Myelin-related abnormalities have been suggested by population-specific gene expression profiling of brain tissue from patients with HD⁷. An *in situ* structural study showed decreases in volume of WM rich regions in YAC128 mice⁸. However, whether microscopic WM changes could also be seen at early stage in mouse model is not known. In this work we performed a longitudinal DTI study to monitor microstructural changes in WM in presymptomatic YAC128 mice. In parallel, we performed a longitudinal biochemical analysis to characterize the expression of myelin-related genes in presymptomatic YAC128 mice.

Methods

8 wild-type (WT, 4 males) and 8 YAC128 (4 males) mice of the FVB strain were scanned at 1.5, 3 and 6 months old, on a 7T scanner (ClinScan, Bruker BioSpin, Germany) using 4 channel array coils. The DTI was acquired using a spin echo EPI sequence with 8 averages of 30 diffusion sensitizing directions, $b=1500\text{s/mm}^2$, $TR=10000\text{ms}$, $TE=40\text{ms}$, voxel size= $0.2\times0.2\times0.5\text{mm}^3$. After eddy current distortion and motion correction, fractional anisotropy (FA), radial diffusivity (Dr), parallel diffusivity (Dp) and mean diffusivity (MD) were obtained by weighted least squares tensor fitting⁹. FA images were linearly registered to a mouse FA template¹⁰ and averaged to create time-point specific templates. Individual FA maps were then nonlinearly registered to the corresponding time-point specific template using FSL¹¹. The combined transformation was applied to Dr, Dp, and MD maps. After Gaussian smoothing of 0.2 mm, voxel-wise group comparison was conducted using SPM8¹². T-tests between WT and YAC128 were performed on the mean values over regions of interest (ROIs) defined based on the voxel-wise results. In addition, analysis of myelin-related transcripts in brain tissue from YAC128 and WT mice was conducted in another sets of mice at 2, 4 and 12 weeks old.

Results

YAC128 mice show a significantly lower FA compared to WT mice in the anterior commissure (AC) and corpus callosum (CC) starting from 1.5m, cingulum from 3m, and external capsule (EC) from 6m. YAC128 mice also have a higher Dr in the anterior CC and a lower Dp in the EC relative to WT at all time-points, more significantly at 6m (Fig.1). There is no difference in MD. Assessment of myelin-related transcripts reveals significant deficits in Myelin Oligodendrocyte Glycoprotein (MOG), Myelin Basic Protein (MBP), and 2',3'-Cyclic-nucleotide 3'-phosphodiesterase (CNPase) transcript levels in cortical tissue as early as 2 weeks of age in YAC128 compared to WT mice (Fig.2).



Discussion

Our results indicate progressive microstructural WM alterations in multiple regions in YAC128 mice appearing before detectable motor deficits at 2m¹³, in agreement with studies of patients with HD⁴⁻⁶. Both damage to myelin and axons may contribute to the observed alterations. The early changes detected by DTI and biochemical analysis suggest that WM abnormalities may precede neural degeneration. Image acquisition and analysis of the post-symptomatic stage of the YAC128 model is in progress, which, together with the current presymptomatic results, will provide a complete temporal spatial mapping of the WM alterations of HD. Further biochemical and histological assessments are being performed to corroborate the MRI findings and to delineate the nature of the WM abnormalities observed.

Conclusion

Our results demonstrate progressive WM abnormalities in YAC128 model of HD as early as 2 weeks of age by biochemical analysis and 1.5m of age by DTI. Mapping the dynamic pattern of WM degeneration is important in understanding the neuropathological progression of HD and in preclinical therapeutic trials aiming at the presymptomatic stage of HD.

References

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