Cerebral hypometabolism in carriers of the intron 10 +3 *MAPT* mutation

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Introduction: Multiple systems tauopathy with presenile dementia (MSTD), a form of frontotemporal dementia with parkinsonism-17 (FTDP-17), is a neurodegenerative disorder caused by an (a) to (g) transition at position +3 of intron 10 of the microtubule associated protein tau (*MAPT*) gene. The mutation causes over-expression of 4 repeat (4R) tau isoforms with increased 4R/3R ratio leading to neurodegeneration. Clinically, these patients primarily present with behavior variant FTD (bvFTD), showing disinhibition, and disordered social comportment, as well as impaired executive function, memory, and speech. While altered glucose metabolism has been reported in subjects with sporadic bvFTD, it has yet to be reported in an MSTD sample of this size carrying the intron 10 + 3 mutation. In this study, we used voxel-based analysis to assess brain metabolism using fluorodeoxyglucose (FDG) positron emission tomography (PET) in eleven mutation carriers and eight non-carriers.

Methods: Eleven *MAPT* intron 10 + 3 mutation carriers (5 males; mean age = 48.0 +/- 6.9 years) and eight non-carriers (2 males; mean age = 43.7 +/- 12.0 years) were imaged using FDG PET with standard techniques. Briefly, dynamic PET imaging for 60 minutes followed an intravenous injection of 5-10 mCi of FDG. Scans were then reconstructed using standard techniques, pre-processed for motion correction, and normalized to MNI space. A static FDG image from 30-60 minutes was created from the appropriate frames and normalized to a cerebellar gray matter reference region to create an SUVR image for each participant. These SUVR images were then assessed on a voxel-wise basis for the effect of mutation carrier status, covaried for age at scan and gender and masked using a whole-brain mask. Results were displayed at a voxel-wise threshold of $p < 0.01$ (uncorrected) and minimum cluster size (k) = 50 voxels. SPM8 was used for all pre-processing and voxel-wise statistical analyses.

Results: Eight of the *MAPT* intron 10 + 3 mutation carriers showed mild cognitive impairment at the time of the PET scan (MMSE = 25.3 +/- 2.4), while three *MAPT* intron 10 + 3 carriers were not impaired at the time of scan (MMSE = 28.0 +/- 0.0). Non-carriers had no cognitive impairment at the time of PET scan (MMSE = 27.1 +/- 1.6). Overall, *MAPT* mutation carriers showed lower FDG uptake bilaterally in the hippocampus, parahippocampal gyrus, amygdala, superior parietal lobule, and in the prefrontal cortex compared to non-carriers.

Conclusions: The present findings suggest individuals with the *MAPT* mutation at position +3 of intron 10 show symmetrical glucose hypometabolism relative to non-carriers in the medial temporal lobe, parietal cortex, and frontal cortex. These metabolic changes overlap previously described patterns of neurodegeneration in MSTD patients and are consistent with the characteristics of their cognitive dysfunction.