Microtubule-associated protein tau H2 haplotype is associated with frontotemporal atrophy in cognitively normal elders

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Background: Tau protein is coded by the microtubule-associated protein tau (MAPT). Tau hyperphosphorylation and neurofibrillary tangle formation are associated with several neurodegenerative diseases. The H1 haplotype of MAPT has been associated with late-onset Alzheimer’s disease (AD) and other sporadic tauopathies while the H2 haplotype has been associated with familial frontotemporal dementia (FTD). H2 carriers have been reported to show reduced glucose metabolism in the frontotemporal regions in FTD.

Methods: We analyzed the genetic and imaging data (1.5T 3D MPRAGE T1-weighted MRI) of 27 MAPT H1/H1 and 17 MAPT H1/H2 cognitively normal subjects (Table 1).

Results: Thinner cortex in the left inferior frontal gyrus, the right middle frontal gyrus, the left orbitofrontal and right medial frontal regions, and left temporal pole was significantly associated with H2 haplotype in our 3D regression analyses (left p_corrected=0.045, right p_corrected=0.042, Figure 1). These results were confirmed by the mean cortical thickness comparisons (Figure 2). MAPT H2 carriers showed significantly thinner left entorhinal (p=0.037) and left temporal pole cortex (p=0.013). Trend-level differences were seen in the right medial frontal (p=0.077), right entorhinal (p=0.088), left lateral temporal (p=0.054), and left orbitofrontal (p=0.079) cortices. Figure 3 shows MAPT H2 carriers performed worse on all executive measures; however a trend-level significance was only seen for digit span backwards (p=0.078). Another trend level difference was found for Logical Memory I (p=0.086).

Conclusions: Our findings show that MAPT H2 haplotype is associated with frontotemporal atrophy in cognitively normal elders. Whether MAPT H2 haplotype places subjects at risk for neurodegenerative disorders remains unknown.

Background:

The MRI scans were co-registered to the ICBM53 template using a 9-parameter transformation and bias-field corrected for intensity normalization. The brains were automatically skullstripped in Brainsuite and manually edited for mislabeled brain and nonbrain regions. After 3D hemispheric reconstruction, 38 sulci per hemisphere were traced and averaged across subjects. The cortical surfaces were parameterized, flattened, and warped to align all subjects to a respective average sulcal representation. Three tissue classes (WM, GM, and CSF) were segmented with Brainsuite’s partial volume classifier. The cortical thickness measured from the CSF/GM and GM/WM boundaries was calculated and mapped onto the corresponding cortical hemispheric spatial model. We used linear regression to investigate in 3D the association between cortical thickness and MAPT haplotypes (coded with H1/H1 carriers as 2, H1/H2 as 1, and H2/H2 as 0). 3D statistical significance and correlation coefficient maps were created and adjusted to a respective average sulcal representation. Three tissue classes (WM, GM, and CSF) were segmented with Brainsuite’s partial volume classifier. The cortical thickness measured from the CSF/GM and GM/WM boundaries was calculated and mapped onto the corresponding cortical hemispheric spatial model.

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