INTRODUCTION
Mutations in the microtubule associated protein Tau (MAPT) gene have been linked with frontotemporal dementia (FTD), but little is known of the progression of neurodegeneration in early presymptomatic carriers. We aimed to identify the presence of early brain changes in MAPT mutation carriers.

METHODS
3T MRIs from 84 MAPT mutation carriers from the Genetic FTD Initiative (GENFI) with 77 age-matched non-carrier cognitively normal controls were included. We divided presymptomatic carriers into two groups based on their expected years to symptom onset (EYO) categorized as 'late' (within 10 years of expected onset) and 'early' (more than 10 years from expected onset) (Table). A voxel-based morphometry (VBM) analysis was performed to compare 26 symptomatic carriers with 41 age-matched controls to identify regions of interest (ROIs) which were atrophic in the symptomatic stage. Following this, we used the automated Geodesic Information Flow algorithm (Cardoso et al., 2015) to extract the volumes for these ROIs in all 84 carriers and 77 controls (Figure 1). Manual segmentation of the hypothalamus was performed following the criteria described in (Bocchetta et al., 2015) to extract hypothalamic volumes (Figure 2). We computed w-scores for each ROI from a linear regression model carried out on the controls adjusting for the effect of age, gender, total intracranial volume and scanner type. A w-score of <1.28 (corresponding to the 10th percentile) was considered as 'abnormal'.

Table. Demographics by group. *One subject excluded from VBM analysis due to a cerebellar artefact. Early presymptomatic carriers were classified as within 10 years of expected age of onset.

RESULTS
Seven structures were identified from the VBM analysis as significantly atrophic in symptomatic carriers, including the nucleus accumbens, amygdala, hippocampus, orbitofrontal cortex, temporal pole, anterior insula and hypothalamus (Figure 3). We found that 14% of early presymptomatic carriers had an abnormal w-score for the nucleus accumbens and hippocampus, with 20% of the group having an abnormal orbitofrontal cortex w-score. 36% of the late group showed abnormal amygdala and temporal pole scores, whilst 27% of the group had abnormal hippocampal scores, 32% had an abnormal anterior insula score and 9% having an abnormal hypothalamus score. The percentages in the symptomatic group were much higher with the hippocampus and temporal pole showing abnormal w-scores in 83% of cases, in 93% for the anterior insula, 56% for the orbitofrontal cortex, and 48% for the hypothalamus (Figure 4).

CONCLUSION
Abnormal limbic regions are a frequent feature in presymptomatic MAPT mutation carriers, showing early structural changes before symptom onset. Further investigations of the associated cognitive and white matter changes are ongoing.

Acknowledgements: The Dementia Research Centre is supported by Alzheimer’s Research UK, Alzheimer’s Society, Brain Research UK, the Wolfson Foundation. This work was supported by the NIHR Queen Square Dementia BRIU, UCLH BRC, UWENC Clinical Research Facility, UK DRI, MRC UK GENFI grant, Italian Ministry of Health, Canadian Institutes of Health Research, Bluefield Project and JPN DGENFI-PROX grant. MB is supported by the Alzheimer’s Society and the UK DRI. JDR is an MRC Clinician Scientist and has received funding from the NIHR Rare Diseases Translational Research Collaboration, Bluefield Project and Association for Frontotemporal Degeneration.