LETTER

Main Title:

The Q351R *MAPT* mutation is associated with a mixed 3R/4R tauopathy and a slowly progressive cognitive, behavioural and parkinsonian syndrome.

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Introduction

We have previously reported the initial clinical and imaging findings of a woman with a novel *MAPT* Q351R mutation[1,2]. We continued to assess her following these case reports until she died and have now analysed her brain at post-mortem. Her case was of unique interest due to the novelty of the mutation and its clinical features[1], as well as the strong binding seen on flortaucipir PET imaging[2] which was suggestive of a very specific pathological finding, that of a mixed 3R/4R tauopathy, similar to that seen in other *MAPT* mutations (V337M and R406W)[3,4], and consistent with the same type of paired helical filament tau pathology seen in Alzheimer's disease. She is the first patient with this mutation to come to autopsy and we report the findings in this study.

Methods

A patient with a Q351R mutation was seen over a 20 year period, during which time she was assessed clinically, and with repeated MR brain imaging (eleven scans in total) as well as flortaucipir PET imaging. In this report, her MR imaging is compared against a cohort of 43 healthy individuals (all female; mean age 61.5 years-old, range 49.7 to 68.5 years-old). All participants gave their consent to take part. At the time of death her brain was donated to the Queen Square Brain Bank for Neurological Disorders and underwent post mortem analysis.

Results

Clinical history

She presented to a specialist cognitive neurology clinic at 49-years-old with a 4-year history of amnestic symptoms and mild behavioural change, mainly in the form of apathy. Neurological exam was normal but her initial neuropsychological assessment showed the presence of episodic and semantic memory impairment with other cognitive domains intact[1]. Following this, there was a slow progression of cognitive and behavioural symptoms over the next 20 years, with increasing forgetfulness and apathy, as well as prominent disinhibition, change in appetite and musicophilia. In addition, 13 years into her

illness, she developed parkinsonism with bradykinesia, rigidity, and both resting and postural tremor. She was still living at home and was able to attend research appointments until the age of 67-years-old. She died at the age of 69-years-old, 24 years into her illness.

Brain imaging

MR imaging throughout the course of her illness showed slowly progressive atrophy with a whole brain atrophy rate over the whole course of the illness of 0.7% year (Fig 1a). The pattern of involvement was initially dominated by focal medial temporal atrophy affecting the amygdala and anterior more than posterior hippocampus. Over time there was progressive cortical involvement also, affecting the temporal and insular cortices and later the frontal and anterior cingulate cortices. Striatal atrophy, particularly ventrally, was seen later in the condition as well (Fig 1b, Fig 1c). In contrast, posterior cortical regions were relatively spared. Flortaucipir PET imaging showed strong binding of the tracer[2] similar to that seen in both Alzheimer's disease (AD) and a small subgroup of *MAPT* mutations (R406W and V337M) (Fig 1d).

Pathology

The brain weighed 1,079g. There was marked cerebral atrophy in a frontotemporal distribution, which was most severe in the anterior medial temporal lobes. Histological examination confirmed frontotemporal lobar degeneration with prominent involvement of mesial temporal lobe structures. Tau immunohistochemistry showed extensive deposition of hyperphosphorylated tau, mostly as neurofibrillary tangles, neuropil threads and small dot-like deposits. The tau pathology was most severe in the temporal lobe where there was a gradient, in that the superior temporal gyrus was the least affected region while the fusiform and parahippocampal gyri together with the amygdala and hippocampus showed the most severe changes (Fig 1e). Tau-positive threads, neurites and dot-like deposits were frequent in the temporal white matter, but these were sparse in the frontal white matter. Tau deposition also affected the basal ganglia (ventral > dorsal striatum), brainstem (midbrain > pons

> medulla) and, to a lesser extent, the dentate nucleus. Differential tau immunohistochemistry demonstrated that the pathological tau forming the inclusions contained both 3-repeat and 4-repeat tau isoforms. In addition, there was mild deposition of the amyloid-β peptide in cerebral cortices, corresponding to Thal phase 1 cerebral amyloid pathology and mild cerebrovascular disease (hyaline arteriolosclerosis).

Discussion

This patient had a 24-year long illness characterized by a slowly progressive cognitive and behavioural disorder that was dominated initially by amnestic symptoms and only mild personality change. MR imaging revealed focal volume loss in the anteromedial temporal lobes, followed later by insula and orbitofrontal involvement as well as the ventral striatum, with tau PET imaging localising to these regions as well. Post-mortem analysis confirmed mixed 3R/4R tau pathology with neurofibrillary tangles, most prominent in the medial temporal lobes, as predicted by tau PET[2,3,4].

In summary, the novel Q351R *MAPT* mutation appears to be associated with a similar clinical, radiological and pathological phenotype to nearby mutations (V337M/R406W)[3,4,5]. This case, now complete with post-mortem pathology, highlights the importance of considering *MAPT*-associated frontotemporal dementia in people with slowly progressive amnestic and behavioural syndromes[5], even when tau biomarkers (e.g. tau PET imaging) may support the more common diagnosis of AD.

References

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Figure

Figure 1a – Longitudinal whole brain volume change over time in the patient in comparison to a group of cross-sectional brain volumes from a cohort of age- and sex-matched healthy individuals. TIV = total intracranial volume.

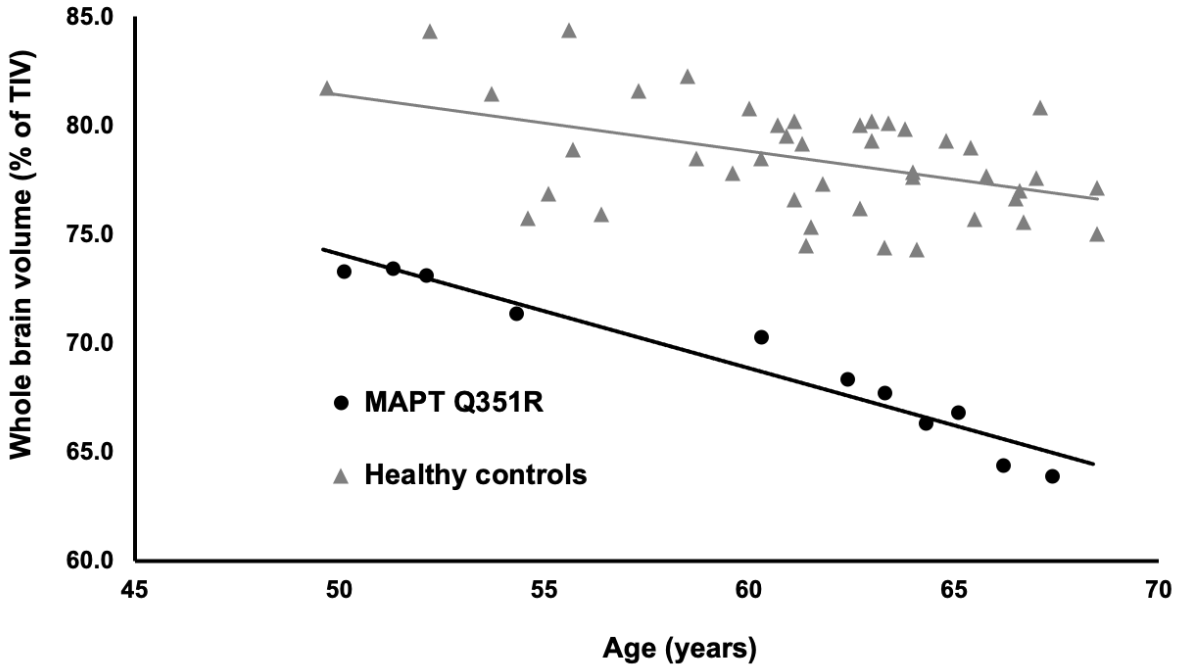

Figure 1b – Coronal T1-weighted MR images from the patient's eleven scans registered to the baseline image, starting at 5 years into symptoms until 22 years from symptom onset.

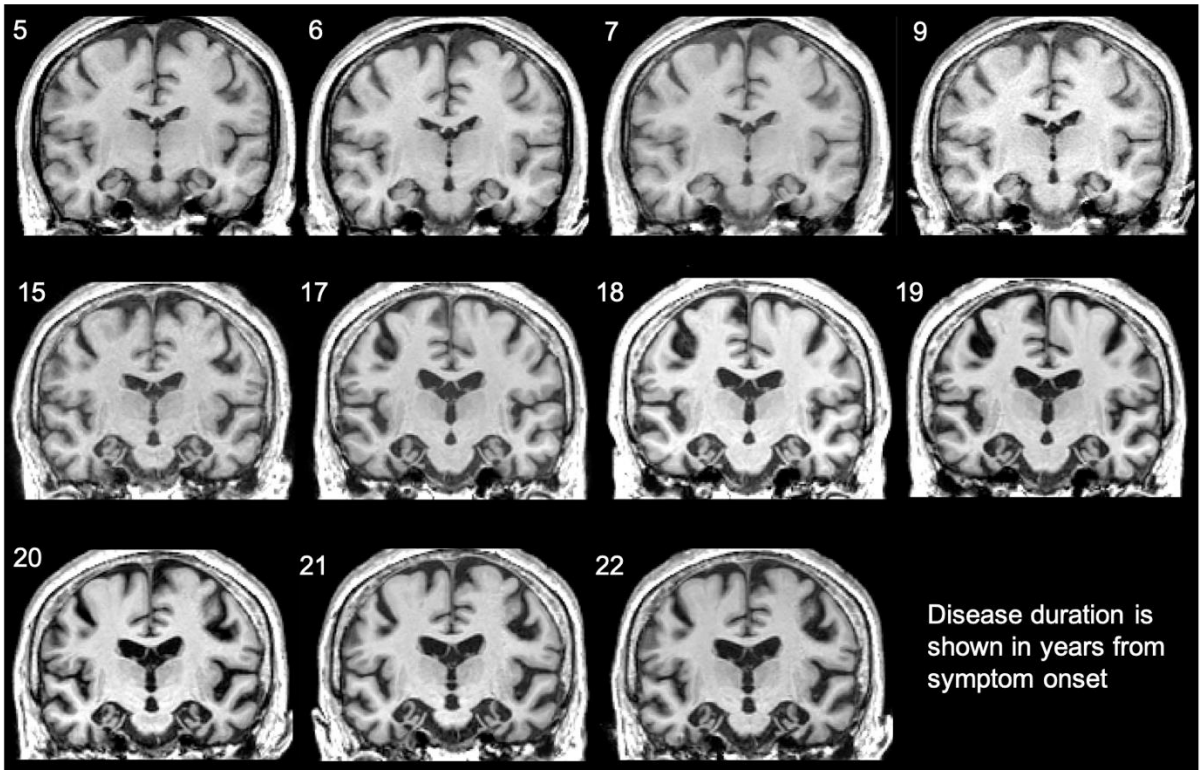

Figure 1c – Patterns of regional brain volume loss in the patient identifies focal medial temporal lobe atrophy early on in the illness. Measures are derived from parcellation of volumetric MRI brain scans using the geodesic information flow (GIF) algorithm. The values are expressed as the percentage of the mean volume of a cohort of age- and sex-matched healthy individuals with increasing darkness of green representing more atrophy (smaller brain volume). R = right, L = left.

Disease duration from symptom onset	Frontal cortex		Insular cortex		Ventral striatum		Dorsal striatum		Anterior cingulate cortex		Temporal cortex		Amygdala		Hippocampus		Parietal cortex		Posterior cingulate cortex		Occipital cortex	
	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L
~5 years	90	91	80	84	89	92	96	98	93	81	80	74	62	58	63	68	97	97	96	96	92	96
~10 years	89	90	73	73	89	92	87	90	88	75	78	73	54	55	59	60	99	100	91	90	91	97
~15 years	88	85	74	69	84	89	93	95	82	87	77	74	51	49	57	54	95	91	94	100	96	97
~20 years	83	83	68	62	82	86	88	89	77	83	72	70	50	46	55	53	90	87	90	99	95	95

Figure 1d – Flortaucipir PET imaging performed at the age of 65-years-old, 20 years into the ilness, shows focal anteromedial temporal lobe tracer uptake as well as insula and orbitofrontal cortex involvement.

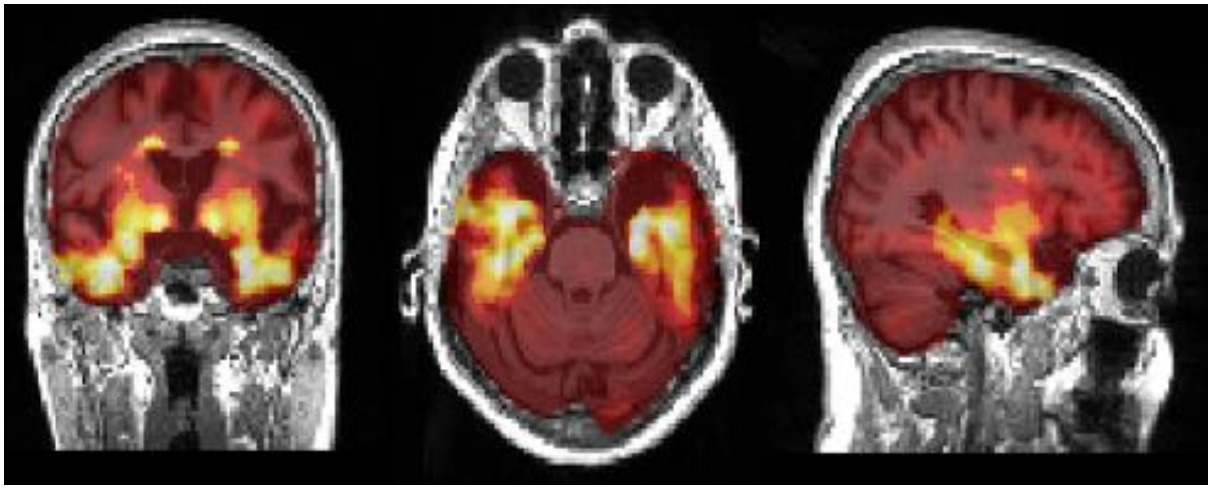

Figure 1e. A) Deposition of hyperphosphorylated tau in all areas of the temporal lobe was significant, with the medial temporal lobe structures showing the most severe involvement (Hipp = hippocampus, PHG = parahippocampal gyrus, FUS = fusiform gyrus). Accordingly, all hippocampal subregions, including CA1 (B) were affected by severe neurofibrillary tangle and neuropil thread pathologies and many of the granule cell neurons of the dentate fascia (C) possessed neurofibrillary tangles. The tau pathology was also severe in the parahippocampal gyrus (D, E) and fusiform gyrus (F). (A-F: tau immunohistochemistry, AT8 antibody. B and C: obj. 20; E: obj. 10; D and F: obj. 2)