Two pathologically-confirmed cases of novel mutations in the *MAPT* gene causing behavioural variant frontotemporal dementia

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INTRODUCTION

Frontotemporal dementia (FTD) is a clinically and pathologically heterogeneous group of neurodegenerative disorders. Around one third of FTD is familial, with the first gene identified as having causative mutations being microtubule-associated protein tau (*MAPT*) in 1998. Since that time 67 *MAPT* mutations have been described (Fig 1), with the majority presenting with clinical features of behavioural change and/or parkinsonism. Other symptoms include semantic impairment and, unlike most other forms of FTD, episodic memory difficulties.

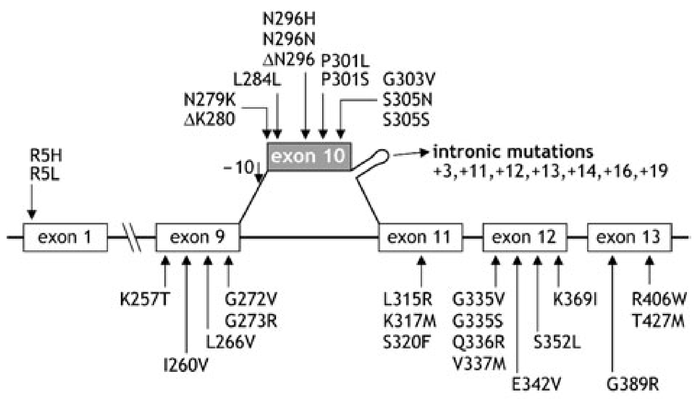

Figure 1: Pathogenic mutations in the MAPT gene [more recently discovered mutations not shown]

In this case series we report two individuals who presented with behavioural variant FTD and were found to have novel pathogenic *MAPT* mutations with subsequent pathological confirmation of a primary tauopathy.

METHODS

Both patients attended the Specialist Cognitive Disorders Clinic at the National Hospital for Neurology and Neurosurgery where they underwent a standard clinical and neuropsychological assessment. Magnetic resonance imaging was performed on a 3T Siemens Trio scanner.

Blood was taken for genetic testing in both patients. Sequencing of exons 1 and 9-13 of the *MAPT* gene was performed initially. Subsequently both samples underwent exome sequencing.

Both patients consented to brain donation at the Queen Square Brain Bank for Neurological Disorders. After death the brains were assessed using standard neuropathological methods, with tissue sections incubated with primary antibodies AT8, Aβ, α-synuclein, TDP-43, 4R tau and 3R tau.

RESULTS

CASE 1

A 46-year-old right-handed gentleman presented with a one year history of behavioural change and impairment of language and cognition. He had become more socially withdrawn and apathetic with poor self-care. He had also become more obsessive with a preference for routines. Over the same time period he had had difficulty with understanding the meaning of words, and had developed difficulties with recognising both faces and familiar places. There was a strong family history of dementia with his mother developing dementia in her 70's, and all but one of her seven siblings also developing a dementia in their 60's or 70's. On examination, his speech was noted to be fluent but empty of content with repeated use of stock phrases. MMSE was 22/30. He was anomic with poor single word comprehension and a surface dyslexia. He slowly deteriorated over the next few years and died at the age of 54.

CASE 2

A 49-year-old right-handed woman presented with a 2-year history of behavioural change, language impairment and poor planning and decision making. She had become more apathetic with a decline in self-care. There was increasing word-finding difficulty with executive dysfunction. The patient's mother died at the age of 70 without dementia but her mother's mother had developed behavioral change in her early 50's without a formal diagnosis of dementia ever made. She died at the age of 70. On examination, speech was fluent but with clear word-finding difficulties. MMSE was 16/30. She deteriorated over the next few years and died at the age of xx.

Both patients underwent neuropsychometry assessment (NT = not tested):

		CASE 1	CASE 2
IQ	Verbal IQ	73	54
	Performance IQ	125	60
Memory	Recognition Memory Test for Words	<5th centile	NT
	Topographical Memory Test	NT	<5th centile
Language	Oldfield Naming Test	6/30	15/30
Visuospatial and perceptual skills	Cube analysis	20/20	20/20
	Incomplete letters	>5th centile	>5th centile
Executive function	Letter fluency (60s)	10	2
	Category fluency (60s)	2	3
	Trail Making Test Part B	25th-50th centile	NT
	Wisconsin Card Sorting Test	NT	<5th centile

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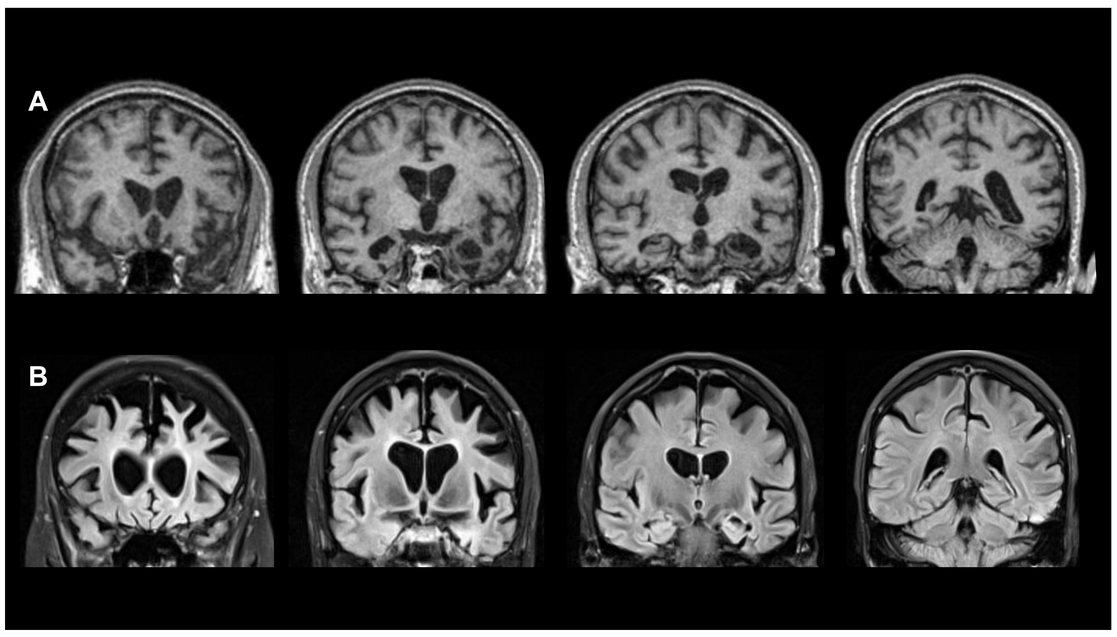

Figure 2: Coronal MRI scans of Case 1 (A) showing asymmetrical (left >right) temporal > frontal lobe atrophy, and Case 2 (B) showing relatively symmetrical frontal > temporal lobe atrophy

Case 1 was found to carry a novel D587V variant in exon 9 of the MAPT gene: NM_001123066.3: c.1760A>T: p.Asp587Val. In the nomenclature of Figure 1 this is known as D252V.

Case 2 was found to carry a novel G724_I727del variant in exon 13 of the MAPT gene: NM_001123066.3: c.2171_2182del: p.Gly724_Ile727del. In the nomenclatures of Figure 1 this is known as G389_I392del.

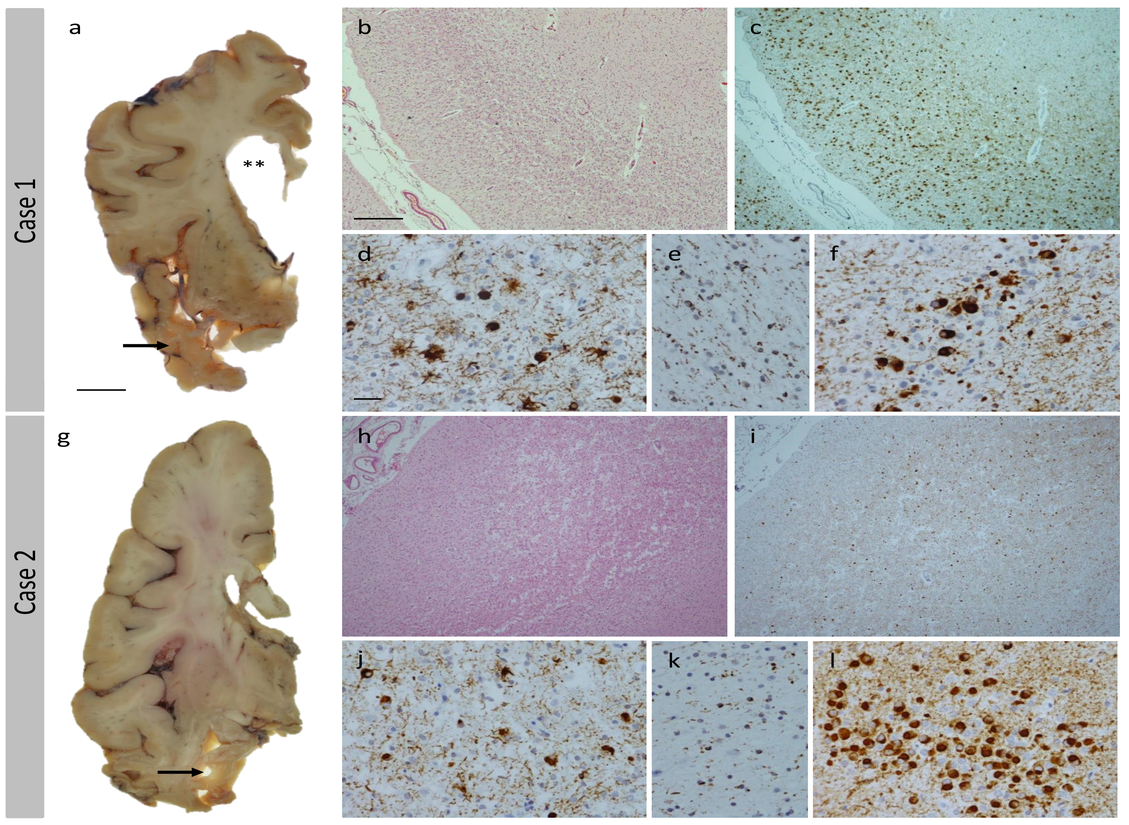

Figure 3: Macroscopic and microscopic neuropathological features of Case 1 (a-f) and Case 2 (g-l). Bar represents 1cm in a and g; 400µm in b, c, h and I; and 30µm in d-f and j-l.

In Case 1 atrophy was most prominent in the anterior temporal and frontal lobes, with severe dilatation of the ventricles (Figure 3a, asterisks, and a blurring between the boundaries of the grey and white matter (Figure 3a, arrow). Microscopically, there was severe neuronal cell loss in the frontal and temporal cortices (Figure 3b). Tau immunohistochemistry revealed a dense network of neuropil threads, pre-tangles, globular inclusions, and neurofibrillary tangles as well as astrocytic tau pathology in the grey matter (figure 3c and d). The white matter contained frequent neuropil threads, scattered coiled bodies and occasional astrocytic inclusions (Figure 3e). The majority of the tau pathology was confirmed to be 3R-tau. Fine 3R-tau positive neuropil threads, globular Pick-body like neuronal inclusions, neurofibrillary tangles and pre-tangles were found in the hippocampus and amygdala (Figure 3f).

In Case 2 there was severe frontal and temporal lobe atrophy with a thin and discoloured cortical ribbon (Figure 3g). Microscopically, there was very severe cortical atrophy in the anterior frontal lobe, middle temporal gyrus and inferior parietal lobes (Figure 3h). 3R-tau positive Pick-body type inclusions were readily seen in the severely atrophic cortical regions, along with a dense meshwork of fine neuropil threads and globose tangles (Figure 3i and j). The frontal, temporal and parietal white matter contained frequent neuropil threads and scattered coiled bodies (Figure 3k). The hippocampus and amygdala were both severely atrophied with 3R-tau pathology evident as Pick-bodies and globose tangles in the residual neurons, along with neuropil threads (Figure 3l).

DISCUSSION

We describe two novel *MAPT* mutations presenting with bvFTD and prominent semantic impairment. Although segregation data is not available for either mutation, both mutations are predicted to be pathogenic, and importantly both are associated with a primary (predominantly 3R) tauopathy at post-mortem.