Case Report

Neurodegenerative Diseases

Neurodegenerative Dis 2011;8:149–152
DOI: 10.1159/000319454

Received: May 20, 2010
Accepted after revision: July 12, 2010
Published online: September 14, 2010

Novel L284R *MAPT* Mutation in a Family with an Autosomal Dominant Progressive Supranuclear Palsy Syndrome

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Key Words
Frontotemporal dementia · Progressive supranuclear palsy · Tau

Abstract
Background: *MAPT* mutations are associated with disorders within the frontotemporal lobar degeneration spectrum. The usual presenting syndrome is behavioural variant frontotemporal dementia, although some patients present with parkinsonism. In a number of these cases the dominant clinical features have been consistent with a progressive supranuclear palsy (PSP) syndrome. ***Objective:*** To describe a family with an autosomal dominant PSP syndrome with a novel L284R mutation in the *MAPT* gene. ***Methods:*** A retrospective case review and genetic analysis of the *MAPT* gene. A literature review of PSP syndromes associated with mutations in the *MAPT* gene. ***Results:*** Multiple members of family DRC292 across different generations had a PSP syndrome with 1 member of the family being found to have a novel L284R mutation in the *MAPT* gene. Behavioural features were also prominent in most cases. A PSP syndrome is only a rare finding associated with *MAPT* mutations and many of these cases have atypical clinical features. ***Conclusion:*** Although rare, *MAPT* mutations should be considered when there is an autosomal dominant family history of a PSP syndrome, particularly of young onset and with prominent behavioural features.

Introduction

Mutations in the *MAPT* gene are causative of neurodegenerative disorders in the frontotemporal lobar degeneration spectrum [1–3]. The majority of patients present with behavioural variant frontotemporal dementia (bvFTD), i.e. personality change and behavioural symptoms, although this may subsequently be associated with parkinsonism. However, some patients have a primary parkinsonian syndrome which can be a corticobasal syndrome or more rarely a progressive supranuclear palsy (PSP) syndrome [4, 5]. Of the 44 pathogenic mutations in MAPT currently described (http://www.molgen.ua.ac.be/FTDMutations/) only 8 have been associated with a PSP syndrome [6–14]. We describe a novel L284R mutation in exon 10 of the *MAPT* gene in a family with an autosomal dominant PSP syndrome.

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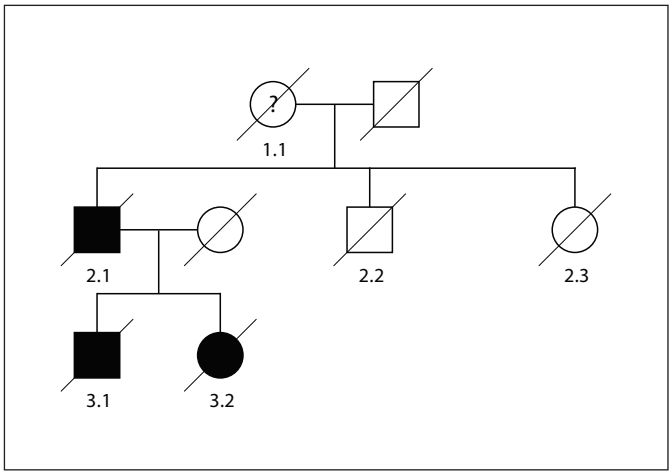

Fig. 1. Family tree of DRC292.

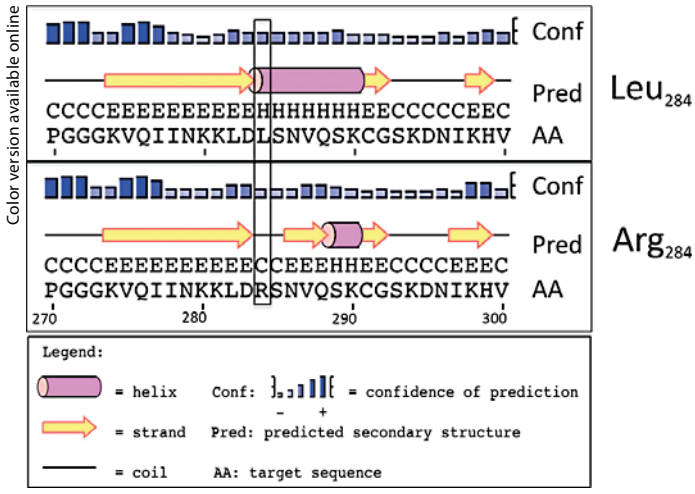

Fig. 2. Secondary structure predictions using PSIPRED (http://bioinf.cs.ucl.ac.uk/psipred/). The non-conservative arginine substitution causes a reduction in the predicted α-helical content (H) of the region containing the residue.

Results

DRC292 is a Caucasian family from the South of England (fig. 1). Little history is available in previous generations of the family, although 1.1 became wheelchair bound in midlife and died at a young age. 2.1 developed problems in the early 40s, in that the family noticed that the eyes had a staring quality and there was increasing difficulty judging distances. From the same time there were multiple falls and shortly afterwards a progressive dementing illness, followed by death at the age of 48 years. 3.1 developed a change in personality (particularly increased obsessiveness) in the mid-40s with falls from around the same time. 3.1 was subsequently diagnosed with PSP and became increasingly immobile and eventually mute, dying at the age of 52 years. 3.2 also developed a personality change at the age of 43 years with apathy and increased irritability as well as worsening memory for recent events and backward falls from around the same time. The neurological examination at the age of 45 years revealed a parkinsonian syndrome with increased tone in all 4 limbs. There was a full range of smooth pursuit eye movements but abnormal saccadic eye movements, particularly in the vertical plane. There was also difficulty with eyelid opening and a dysarthria. 3.2 was diagnosed with PSP at this assessment, deteriorating rapidly from this time with worsening mobility and dying 4 years after onset at the age of 47 years.

Patient 3.2 consented to donate a blood sample to a dementia genetics study investigating autosomal dominant dementia families [15] and was found to have a novel CTT→CGT mutation in exon 10 of the *MAPT* gene causing substitution of a leucine at position 284 with an arginine (L284R; numbering according to 2N4R, the longest CNS isoform of tau). This mutation has not previously been reported, though the same codon is affected by the pathogenic silent L284L mutation (CTT→CTC) which has been reported as causing a frontotemporal lobar degeneration syndrome with behavioural symptoms, executive dysfunction and memory impairment [16, 17]. L284R probably has the same effect as L284L, which affects a predicted A/C-rich splicing enhancer (ACE) and causes a strong shift to exon-10-containing (4R tau) transcripts [16]. However, L284R also causes a non-conservative change from the hydrophobic leucine to the polar, positively charged arginine (fig. 2). It is therefore possible that the mutation has the dual pathogenic effect of increased exon 10 inclusion combined with impaired microtubule binding and/or aggregation due to increased β-sheet content, as seen with the missense mutations. This mechanism may also apply to other exon 10 mutations (N279K, P301L/S, S305N) that have been associated with a clinical and pathological PSP or corticobasal syndrome phenotype [18]. Unfortunately, DNA was not available from other members of the family to investigate whether the mutation segregated with the presence of disease.

Table 1. *MAPT* mutations causing a PSP-like syndrome

Mutation	References	Number	Initial features	AAO years	Duration years	Pathology
R5L	Poorkaj et al. [8]	1	falls, dysarthria, micrographia	62	5	tau 4R>3R
N279K	Delisle et al. [6]	2	parkinsonism, apathy, bradyphrenia	40	7	tau
			attentional problems, apathy	41	N/A	N/A
	Tsuboi et al. [9]	N/A	report of 5 families with parkinsonism/supranuclear palsy	41–45[1]	6–8.5[1]	N/A
ΔN296	Pastor et al. [19]	2	gaze palsy, memory/language problems, emotional lability	38	N/A	N/A
			personality change, parkinsonism	39	3	N/A
	Rossi et al. [11]	1	antecollis, dysarthria, falls, slowing of ocular movements	36	N/A	N/A
P301L	Kaat et al. [14]	1	N/A	N/A	N/A	N/A
G303V	Ros et al. [12]	3	akinetic-rigid syndrome, falls, gaze palsy, dysarthria	37	8	tau 4R>3R
			N/A	41	3	N/A
			N/A	late 30s	N/A	N/A
S305S	Stanford et al. [7]	3	apathy, memory/language problems	53	N/A	N/A
			clumsiness, dysarthria, rigidity	47	4	tau 4R>3R
			dementia, apathy, language problems	49	7	N/A
10+3	Spina et al. [13]	2	postural imbalance, dizziness, stiff neck	N/A	N/A	N/A
10+16	Morris et al. [10]	1	fatigue, apathy, micrographia, falls	40	5	tau

AAO = Age at onset; N/A = not available.
[1] Range of mean values in different families with the same mutation.

Discussion

DRC292 have an autosomal dominant PSP syndrome with early falls and a behavioural syndrome, an onset in the 40s and disease duration around 4–7 years. Reviewing previous descriptions of PSP syndromes associated with *MAPT* mutations (table 1), many of the cases in fact have had a fairly atypical PSP syndrome [7, 9, 19, 20] with a diagnosis of PSP (or atypical PSP) having been given to the patient because of the development of a supranuclear gaze palsy some time during the course of the illness usually in association with falls, parkinsonism and a dementia (usually of the bvFTD type). With this said, however, there are undoubtedly some patients reported who have a more typical PSP syndrome with few early features apart from gaze palsy or falls [11, 12]. Although little information is available in the family reported here, they all appeared to present with early features of a PSP syndrome but also in some cases with behavioural and cognitive features consistent with bvFTD. In summary, a PSP syndrome is a rare manifestation of *MAPT* mutations, but screening should be considered in families where there is an autosomal dominant history of a PSP syndrome, particularly of young onset and when there are accompanying features suggestive of bvFTD.

Acknowledgements

This study was undertaken at the University College London Hospitals/University College London, which received a proportion of funding from the Department of Health's National Institute for Health Research Biomedical Research Centres funding scheme. The Dementia Research Centre is an Alzheimer's Research Trust Coordinating Centre. This study was also funded by the Medical Research Council, UK.

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