

Original Research Article

## Evidence for a Common Founder and Clinical Characteristics of Japanese Families with the *MAPT* R406W Mutation

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### Key Words

Amnesic syndrome · Familial dementia · Founder effect · FTDP-17 · *MAPT* mutation

### Abstract

**Background/Aim:** Mutations in *MAPT* cause frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17). Patients with the *MAPT* R406W mutation were reported to show phenotypic heterogeneity in different ethnic backgrounds. We here report the clinical and genetic characteristics of Japanese families with the R406W mutation. **Methods:** We examined the clinical and neuroimaging features of 6 patients from three families with the R406W mutation. We determined the genotypes of intragenic *MAPT* single-nucleotide polymorphisms (SNPs) and the flanking microsatellite markers to search for a common founder. **Results:** The initial symptom was memory loss with the average age at onset being 54 years. Anterograde amnesia with episodic memory impairment was the predominant phenotype. Behavioral and personality changes or parkinsonism is not a prominent feature. A brain MRI study revealed marked atrophy of the medial temporal lobe. Genetic analysis of SNPs and microsatellite markers revealed that the affected members of the three families share common genotypes. **Conclusion:** The findings of the affected members in this study, which corroborate previously reported findings of European families, suggest that the R406W mutation may represent a phenotype of predominant anterograde amnesia in FTL-17. Our genetic data suggest that a founder effect may account for some families with the R406W mutation.

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## Introduction

Mutations in the microtubule-associated protein tau gene (*MAPT*) cause an inherited neurodegenerative disease, i.e. frontotemporal dementia (FTD) with parkinsonism linked to chromosome 17 (FTDP-17) [1]. More than 100 families with FTL-17 have been described worldwide. It has been demonstrated that phenotypic presentations in patients with FTDP-17 vary considerably [2]. The phenotype of FTDP-17 can be generally divided into two subtypes: FTD- and parkinsonism-predominant phenotypes [3]. Memory impairment occurs less frequently as the primary presenting feature, and only in a few cases of FTDP-17, the phenotype of predominant memory disturbance is similar to that in Alzheimer's disease (AD) [4, 5].

The R406W mutation in exon 13 of *MAPT* was previously described in different ethnic backgrounds [6–12]. The patients with the R406W mutation showed a relatively late onset age with an average of 56 years. In the families from Western countries, the patients were reported to exhibit a phenotype resembling AD with early memory impairment [8–10, 12]. In a Dutch family, FTD-like symptoms such as personality changes in addition to initial memory impairment were reported [6]. Moreover, in a previous study, a Japanese patient with the R406W mutation with early disease onset (47 years) and rapidly progressive FTD-like psychiatric symptoms was reported [13]. These reports suggest that phenotypic variation may also be present in the families with the R406W mutation.

To further clarify the clinical characteristics of patients with the R406W mutation, we here report the clinical and neuroimaging features of three unrelated Japanese families with the R406W mutation. We also performed genetic analysis to determine the possibility of a common founder in these families.

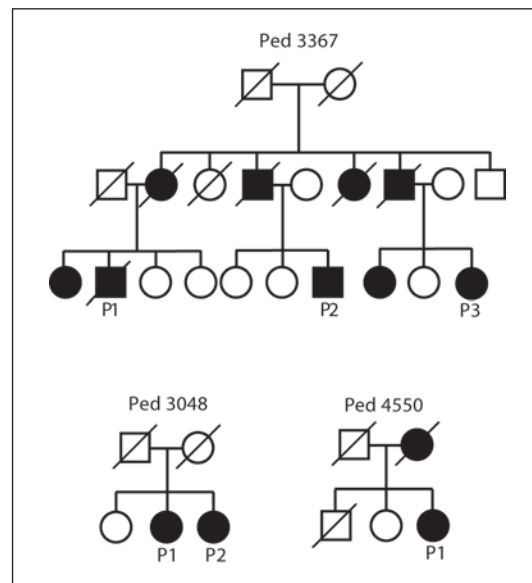
## Methods

### *Patients*

Mutational analysis of two pedigrees with the R406W mutation, Ped 3367 and Ped 3048, were previously described [11, 14]. We found a new family (P4550) with the R406W mutation. In this family, the proband's mother died in her 60s with the clinical diagnosis of AD. The family trees are shown in figure 1. Although these families all reside in the Niigata Prefecture, Japan, family records revealed no shared surname and no geographical connections; thus, they are considered to be apparently unrelated. Six patients from three pedigrees were neurologically examined by board-certified neurologists. Six patients were examined by brain MRI and 3 by single photon emission computed tomography (SPECT). CSF samples were obtained from 2 patients; tau and phosphorylated tau (p181 tau) were quantified using a commercially available enzyme immunoassay kit (Innogenetics, Belgium), as previously described [15]. Written informed consent was obtained from all the patients or their caregivers. This study was approved by the Institutional Review Board of the Niigata University School of Medicine.

### *Molecular Genetic Analysis*

Genomic DNA was extracted from peripheral blood leukocytes by a standard procedure. Mutational analysis was performed by sequencing both strands of all PCR-amplified coding exons and flanking intronic sequences of *MAPT*, *APP*, *PSEN1*, *PSEN2*, and *PRGN*, as previously reported [11]. The *APOE* genotype was determined by restriction enzyme digestion of PCR products using *Hha*1.



**Fig. 1.** Pedigrees of families with the *MAPT* R406W mutation. Circle = Female; square = male; slash through the symbol = deceased individual; black symbol = affected individual.

To determine whether the three families with the R406W mutation share a common founder, we determined the genotypes of six single-nucleotide polymorphisms (SNPs) in *MAPT* and the six flanking microsatellite markers on chromosome 17q21 in the affected individuals. Information on SNP genotypes can be retrieved from [www.ncbi.nlm.nih.gov/projects/SNP](http://www.ncbi.nlm.nih.gov/projects/SNP) or <http://snp.ims.u-tokyo.ac.jp/>. The microsatellite markers spanning ~1.3 Mb containing the *MAPT* region include D17S930, D17S1861, D17S1804, D17S920, D17S693, and D17S1859. The SNP genotypes were determined by direct sequencing of the PCR products amplified using appropriate primer pairs. Allele sizes of the microsatellite markers were determined by PCR amplification using fluorescently labeled primers. All the primer sequences are available on request.

## Results

### *Clinical Characteristics*

The clinical characteristics of the 6 patients with the R406W mutation are summarized in table 1. The age at onset of the patients was  $54 \pm 7$  years (mean  $\pm$  SD; range: 46–68 years). These patients commonly showed insidious onset of memory disturbance such as repetition of questions and difficulties in remembering appointments and names. Anterograde amnesia including a decline in episodic memory was the primarily presenting feature in all patients, resulting in impairment in ability to work and perform daily activities. The Mini-Mental State Examination (MMSE) score at a mean disease duration of 10 years was  $17 \pm 6$  (range: 9–25). Behavioral and personality changes were not noted by these patients or their caregivers in the early course of the disease. Mild personality changes and disinhibition, such as restlessness and garrulousness, were observed in 3 patients with a long duration of the disease (Ped 3367-P3; Ped 3048-P2, and Ped 4550-P1). Neurological examination of these patients revealed no motor signs of parkinsonism. The clinical diagnosis of early-onset AD was suspected in these families prior to genetic investigation.

Detailed neuropsychological tests were performed on 1 patient (Ped 3367-P1) at the age of 56 years, who was alert and cooperative on examination. His speech output was not disturbed, and there were no features of echolalia, verbal stereotype, or perseverations. The

**Table 1.** Clinical characteristics of the patients with the *MAPT* R406W mutation

	Ped 3367-P1	Ped 3367-P2	Ped 3367-P3	Ped 3048-P1	Ped 3048-P2	Ped4550-P1
Age at onset, years	51	47	50	56	54	68
Age at examination, years	56	48	67	73	67	77
Duration of disease, years	5	1	17	17	13	9
MMSE score	25	22	9	14	17	16
Dementia stage	CDR 1	CDR 0.5	CDR 2	CDR 2	FAST 5	CDR 2
Initial symptom	memory loss	memory loss	memory loss	memory loss	memory loss	memory loss
Memory impairment	+++	+++	+++	+++	+++	+++
Personality changes	–	–	+	–	–	+
Disinhibition	–	–	+	–	+	+
Parkinsonism	–	–	–	–	–	–
CSF tau level, pg/ml	282	116	n/a	n/a	n/a	n/a
CSF p181 tau level, pg/ml	80	74	n/a	n/a	n/a	n/a
<i>APOE</i> typing	3*4	3*4	2*3	3*3	3*3	2*3

CDR = Clinical dementia rating scale; FAST = functional assessment stage; n/a = data not available; grading of severity of clinical features: – = absent, + = mild, ++ = moderate, +++ = severe.

MMSE score was 25/30. Assessment using the Wechsler Adult Intelligence Scale III yielded a verbal IQ of 97, a performance IQ of 90, and a full IQ of 93. In the Wechsler Memory Scale-Revised test, the patient showed low index scores in the delayed recall subtest (score: <50) and general memory subtest (score: 65), whereas his index score in the attention/concentration subtest (score: 98) was normal. His frontal assessment battery score [16] was 16/18. The clinical assessment of attention consisting of the visual cancellation task, memory updating test, paced auditory serial addition test, position Stroop test, and continuous performance test [17] yielded normal results.

#### *Molecular Genetic Analysis*

Mutational analysis of *APP*, *PSEN1*, *PSEN2*, *MAPT*, and *PGRN* revealed that 6 patients from three pedigrees carry a R406W mutation in *MAPT*. To examine whether these families share a common founder haplotype, we determined the genotypes of intragenic *MAPT* SNPs and the flanking microsatellite markers. All the affected individuals from the three pedigrees with the R406W mutation shared common genotypes of intragenic *MAPT* SNPs (A-C-C-C-A-delT) and the flanking microsatellite markers (105-105-238-100-95-183 at D17S930-D17S1861-D17S1804-D17S920-D17S693-D17S1859; table 2). The estimated frequency of the disease-associated haplotype constructed by *MAPT* SNPs and the microsatellite markers (105-105-238-A-C-C-C-A-T-delT-100-95-183) in control subjects from the same population was 3.3% (n = 60). All the subjects were homozygous for the H1 haplotype, as previously reported [18].

#### *Neuroimaging Findings*

The brain structure was evaluated by MRI in 6 patients. All the affected subjects showed a similar structural change of severe atrophy mainly involving the medial temporal lobe (fig. 2a–i). Mild cortical atrophy may be observed without apparent hemisphere predominance. Parenchymal signal changes were absent.

We investigated regional cerebral blood flow (rCBF) patterns in 3 patients by SPECT. The patients in the early stage of the disease did not show a prominent decrease in rCBF. In

**Table 2.** Shared genotypes of *MAPT* SNPs (in bold) and microsatellite markers in three R406W families

Microsatellite marker/SNP	Distance from <i>MAPT</i> <sup>a</sup> /location in <i>MAPT</i>	Ped 3367 P1		Ped 3367 P2		Ped 3367 P3		Ped 3048 P1		Ped 4550 P1	
D17S930	1,147	105	<b>105</b>	105	<b>105</b>	103	<b>105</b>	105	<b>105</b>	105	<b>105</b>
D17S1861	1,063	107	<b>105</b>	103	<b>105</b>	105	<b>105</b>	105	<b>105</b>	103	<b>105</b>
D17S1804	855	238	<b>238</b>	238	<b>238</b>	238	<b>238</b>	238	<b>238</b>	236	<b>238</b>
rs242557	intron 1	G	<b>A</b>	G	<b>A</b>	G	<b>A</b>	G	<b>A</b>	G	<b>A</b>
rs63750222	exon 4A	C	<b>C</b>	C	<b>C</b>	C	<b>C</b>	C	<b>C</b>	C	<b>C</b>
rs2258689	exon 6	T	<b>C</b>	T	<b>C</b>	T	<b>C</b>	T	<b>C</b>	C	<b>C</b>
rs2435211	intron 6	T	<b>C</b>	T	<b>C</b>	C	<b>C</b>	T	<b>C</b>	C	<b>C</b>
rs2435200	intron 9	G	<b>A</b>	G	<b>A</b>	G	<b>A</b>	G	<b>A</b>	A	<b>A</b>
pR406W	exon 12	C	<b>T</b>	C	<b>T</b>	C	<b>T</b>	C	<b>T</b>	C	<b>T</b>
rs5820605	exon 14	T	–	T	–	–	–	T	–	–	–
D17S920	423	100	<b>100</b>	100	<b>100</b>	102	<b>100</b>	102	<b>100</b>	102	<b>100</b>
D17S693	575	99	<b>95</b>	95	<b>95</b>	99	<b>95</b>	99	<b>95</b>	95	<b>95</b>
D17S1859	1,425	181	<b>183</b>	177	<b>183</b>	177	<b>183</b>	181	<b>183</b>	177	<b>183</b>

<sup>a</sup> Distance from *MAPT* (in kb) was calculated on the basis of the latest human assembly GRCh37.p2 (www.ncbi.nlm.nih.gov/projects/genome/assembly/grc/human/index.shtml).

the patient with a long disease course of 17 years at the age of 67 years (Ped 3367-P3), the decreased rCBF in the bilateral temporal lobes and the cingulate gyrus of the anterior and posterior portions was visualized by *N*-isopropyl-*p*-[<sup>123</sup>I]iodoamphetamine (<sup>123</sup>I-IMP) SPECT using three-dimensional stereotactic surface projection (3D-SSP; fig. 2j) [19].

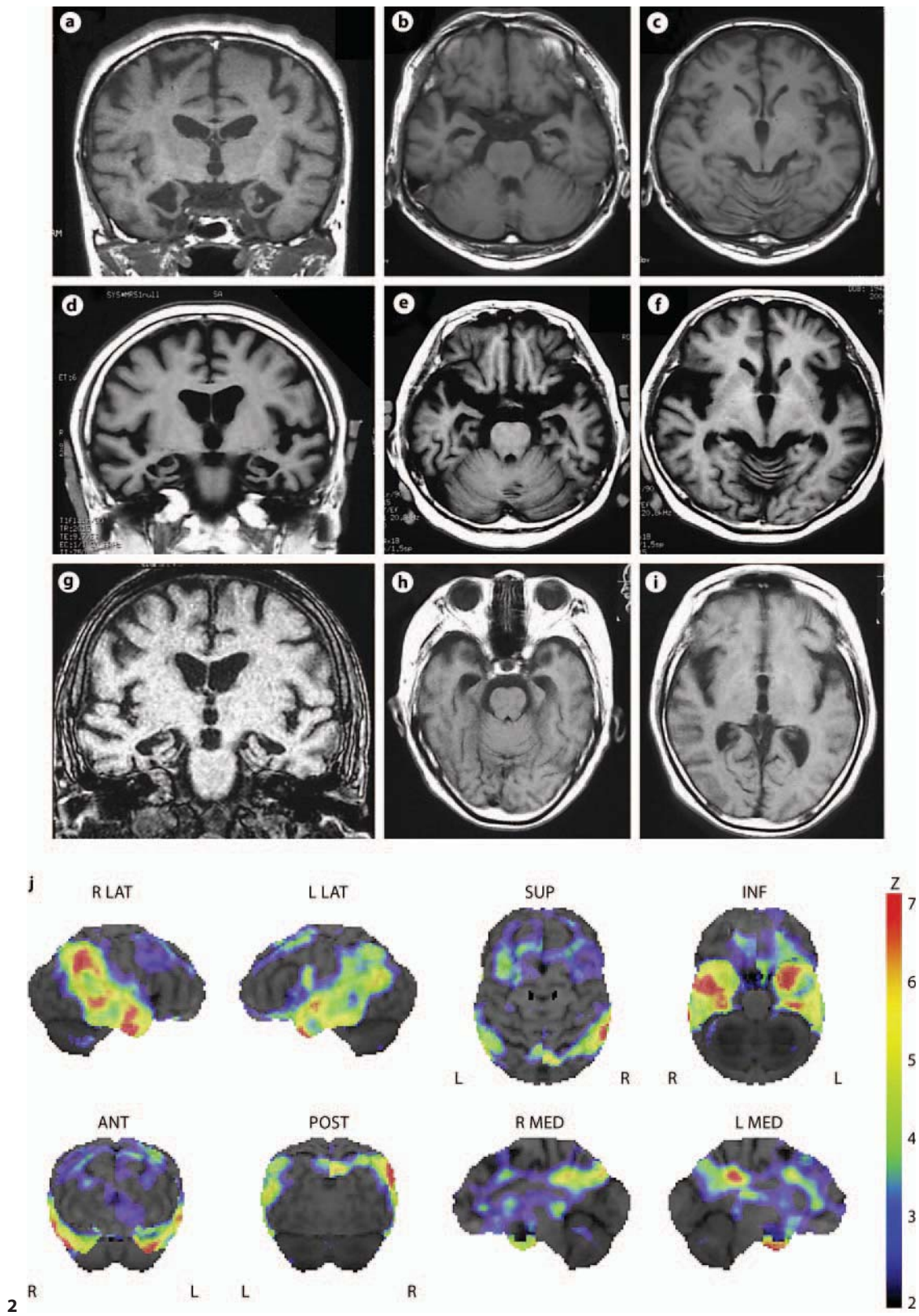
#### CSF Analysis

We were able to determine the total and phosphorylated p181 tau levels in the CSF of 2 patients (Ped 3367-P1 and Ped 3367-P2; table 1). The average total tau level in the patients with the R406W mutation is slightly higher than that in our control subjects (157 ± 65 pg/ml, n = 24) and lower than that in patients with AD (555 ± 248 pg/ml, n = 31) [15]. p181 tau was higher than that in the controls (29 ± 10 pg/ml, n = 21) and comparable to that in patients with AD (86 ± 39 pg/ml, n = 31).

#### Discussion

The three families with the *MAPT* R406W mutation presented in this study showed relatively uniform clinical characteristics as follows: (1) presenile insidious onset of memory loss, (2) predominant early clinical features of anterograde amnesia, (3) relatively spare behavioral and personality changes or parkinsonism, (4) slow progression of disease, and (5) prominent atrophy of the medial temporal lobe involving the hippocampus. These clinical characteristics were similarly observed in Western families with the R406W mutation [8–10, 12], suggesting that the predominant symptom of memory impairment with slowly progressive disease may be a cardinal clinical presentation of the R406W mutation irrespective of the ethnic background. However, it should be noted that different clinical features suggestive of FTD were also observed in a few patients with the R406W mutation [6, 13].

The phenotype of prominent memory disturbance was occasionally noted in patients with *MAPT* mutations in introns 10 and 16 and P301L [4, 5, 20]. Similar to our patients, these



patients were misdiagnosed as having AD prior to genetic or pathological analysis. Prominent early memory impairment is characteristic of AD and is an exclusion criterion for the diagnosis of FTD [21]. It remains unclear how some *MAPT* mutations lead to the phenotype of memory disturbance reminiscent of AD. In the case of R406W families, this phenotype may be explained by the prominent involvement of the hippocampus, which is considered the pathological substrate for memory impairment. Indeed, in the R406W patients in this study severe atrophy was noted in the hippocampus on MR images (fig. 2). This notion is supported by previous neuropathological studies showing that neuronal loss and gliosis are observed together with tau-positive neurofibrillary tangles and neuronal threads in the medial temporal lobe including the hippocampi [6, 7, 12, 13, 22].

Genetic analysis of the intragenic *MAPT* SNPs and the flanking microsatellite markers demonstrated that the three families with the R406W mutation in this study shared the same genotypes. This finding raises the intriguing notion that they may share extended chromosomal segments around the tau locus and have a common founder among their ancestors even though they are apparently unrelated pedigrees. This notion is supported by the observation that the frequency of the disease-associated haplotype in the general population is as low as 3.3%. The similarity of the phenotype observed in our families may be explained by the possibility that these families may represent a single extended R406W pedigree. In contrast to our findings, three families from Western Europe have been reported to carry different haplotypes among families [8], arguing against the founder effect; thus, the R406W mutation in these families seems to arise independently. Taken together, although the founder effect of the R406W mutation is responsible for the occurrence in some families, the same mutation may also occur independently in different kindreds.

In conclusion, findings on our and previously described cases suggest that the R406W mutation occurs pan-ethnically and may represent a peculiar phenotype of predominant anterograde amnesia of FTDP-17 in addition to two well-known core phenotypes of FTDP-17: the FTD- and parkinsonism-predominant phenotypes. Because anterograde amnesia is the prototypical presentation of AD, using solely the clinical diagnostic criteria in the families with the R406W mutation failed to properly identify the pathological substrate of their disease. A similar AD-like phenotype exhibiting anterograde amnesia was reported in a family with a mutation (c.154delA) in *PGRN* [23], another causative gene for FTLD. On the other hand, some *PSEN1* mutations responsible for early-onset familial AD may cause the FTD-like phenotype [24, 25]. Comprehensive mutational analysis of genes including *PSEN1*, *PSEN2*, *APP*, *MAPT*, and *PGRN* would be necessary for familial dementia with a broad spectrum of overlapping clinical phenotypes.

**Fig. 2.** Representative T<sub>1</sub>-weighted MR images of 3 patients: Ped 3367-P1 at the age of 56 years (a–c); Ped 3367-P3 at the age of 67 years (d–f), and Ped 4550-P1 at the age of 77 years (g–i). Coronal images revealed marked atrophy of the medial temporal lobe including the hippocampus and parahippocampal gyrus (a, d, e). On axial images, an enlarged inferior horn of the lateral ventricles was observed (b, e, h). Atrophic change in the frontal lobe is less noticeable (c, f, i). j Decreased rCBF by <sup>123</sup>I-IMP SPECT with 3D-SSP in Ped 3367-P3 at the age of 67 years. After global normalization to the mean blood flow for the entire brain, rCBF in the patient was compared with that in normal controls by the Z test. Color-coding represents the statistical significance (Z score) of the decrease in rCBF. Decreases in rCBF were observed in the bilateral temporal lobes as well as in the cingulate gyrus of anterior (ANT) and posterior (POST) portions. L = Left; R = right; INF = inferior; LAT = lateral; MED = medial; SUP = superior.

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