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【 CASE REPORT 】

Clinical and Genetic Study of the First Japanese FTDP-17 Patient with a Mutation of +3 in Intron 10 in the *MAPT* Gene

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Abstract:
Frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17) with mutations in the *MAPT* gene is a hereditary neurodegenerative tauopathy with various clinical phenotypes. We herein report the first Japanese patient with FTDP-17 caused by an IVS10+3G>A mutation in the *MAPT* gene, which is linked to an H1M haplotype. The present study suggests that the IVS10+3G>A mutation in the *MAPT* gene can have originated from a non-Caucasian population. In the disease course, myoclonus and respiratory failure can be observed. This study may expand on the clinical and genetic findings for FTDP-17 with mutations in the *MAPT* gene.

Key words: FTDP-17, *MAPT*, IVS10+3G>A mutation, non-Caucasian, H1M haplotype

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Introduction

Frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17) comprises a group of heterogeneous neurodegenerative tauopathies characterized by behavioral and personality disturbances, cognitive impairment and motor dysfunction as cardinal symptoms (1). The majority of FTDP-17 families have mutations in the *MAPT* gene (2), which is inherited in an autosomal-dominant manner (3). The *MAPT* gene encodes the microtubule-associated protein tau, which is involved in microtubule assembly and stabilization, neuronal polarity and axonal transport in the brain (4). *MAPT* consists of 16 exons and encodes 6 human brain isoforms of tau protein with 3 or 4 microtubule-binding repeat domains (3R and 4R) (5). By 2015, 53 pathogenic *MAPT* mutations had been reported in approximately 150 families from Asia, Australia, Europe and both North and South America (1). Among them, 16 *MAPT* pathogenic mutations in 29 Japanese FTDP-17 families have been reported (6). Multiple system tauopathy with presenile dementia (MSTD), which has previously been found in one American kindred of European ancestry, is an inherited disease caused by a G to A transition at position +3 in intron 10 of *MAPT* (7, 8). The IVS10+3G>A mutation in the *MAPT* gene results in the overproduction of tau isoforms with 4 microtubule-binding repeats (5). The first reported MSTD family is the most well-studied kindred with this mutation (9). However, while the IVS10+3G>A mutation in the *MAPT* gene has been reported in four Caucasian families, it has never been found in a non-Caucasian population.

We herein report the first Japanese patient with a heterozygous IVS10+3G>A mutation in the *MAPT* gene.

Case Report

The pedigree consists of 22 Japanese family members across 4 generations, with 4 affected individuals. The proband (Figure A, III-1) is a 50-year-old woman who was the elder sister in her family. She presented with marked deterioration in her memory function at 48 years of age. At 49 years of age, the patient exhibited gait disturbance, limb

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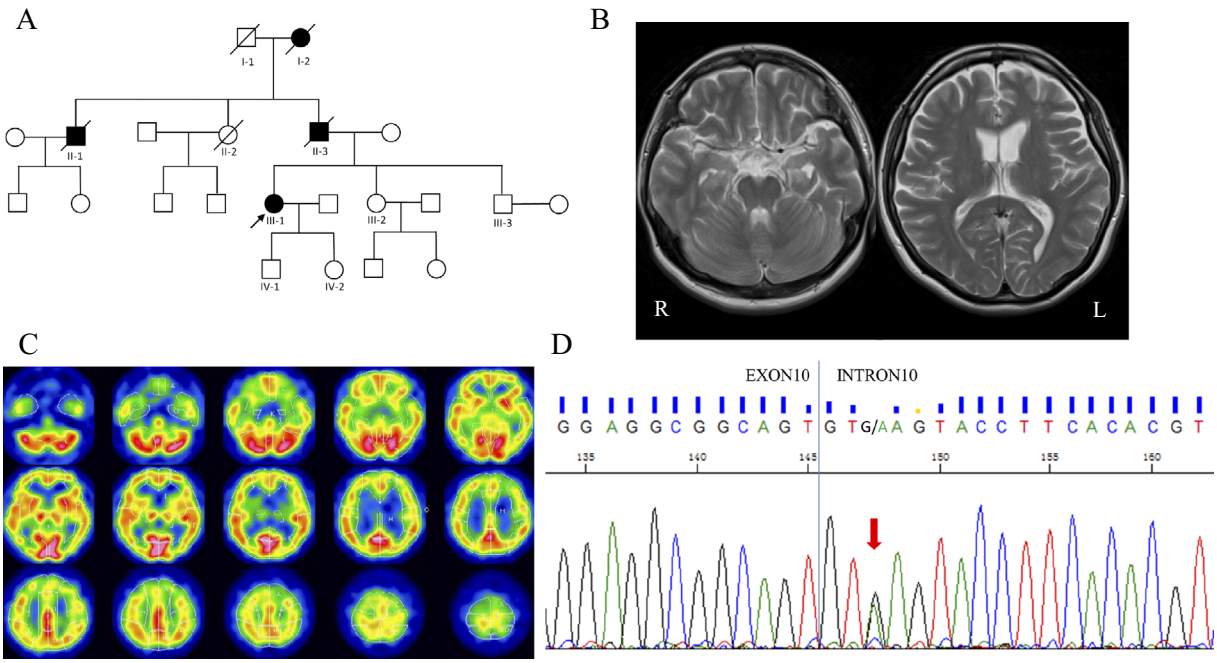

Figure. **(A) Pedigree of the present FTDP-17 family. The proband is indicated (arrow). Squares indicate men, while circles indicate women; slashes indicate deceased individuals, while shaded (black) symbols indicate individuals with symptoms of FTDP-17, including both genetically evaluated and unevaluated individuals, and unshaded symbols indicate individuals without symptoms of FTDP-17. (B) Brain MRI of the proband showed mild cerebral atrophy in the left frontal and temporal lobes. R: right, L: left. (C) Brain SPECT of the proband showed decreased perfusion in the bilateral frontal lobes. (D) A sequence analysis revealed the IVS10+3G>A mutation in the *MAPT* gene in the proband. The red arrow indicates the IVS10+3 nucleotide.**

bradykinesia and postural instability with frequent falling. Later, she developed vertical supranuclear gaze palsy and neck rigidity. She gradually lost facial animation, and bulbar syndrome appeared.

She presented with difficulty eating, speaking and breathing. A neurological examination revealed upward gaze palsy, dysarthria and dysphagia. She showed increased muscle tone in all four limbs as well as the neck and muscles of mastication. As a consequence, she had difficulty opening her mouth. She also showed myoclonus in the right upper limb and neck. The tendon reflexes were exaggerated in the upper limbs, and positive Babinski signs were noted. No muscle weakness or cerebellar, sensory or autonomic dysfunction was detected. She exhibited decreased fluency and agrammatism of speech at 48 years of age. At that time, the patient's Mini-Mental State Examination (MMSE) score was 23/30. On an examination two years later, she showed total loss of speech output. As a result, no detailed testing of the cognitive function was possible. She became bedridden, and feeding via a percutaneous gastrostomy tube was begun six months previously. Hypercapnic respiratory failure appeared at night, and non-invasive positive pressure ventilation (NIPPV) was conducted. There were no significant abnormalities in laboratory serologic tests. Brain magnetic resonance imaging (MRI) showed mild cerebral atrophy in the left frontal and temporal lobes (Figure B). Brain ^{99m}Tc-ethyl cysteinate dimer-single-photon emission computed tomography showed a perfusion decrease in the bilateral frontal lobes (Figure C).

The proband's father (Figure A, II-3) had been employed as a house painter until 44 years of age, when he was laid off due to frequent mistakes. At the same time, changes in his behavior and personality were noted. Subsequently, he developed memory deficits, bradykinesia and gait disturbance. At that time, he was diagnosed with 'early-onset Alzheimer's disease'. The patient's condition gradually deteriorated, and he developed dysarthria, dysphagia and marked muscular hypertonia. At 49 years of age, he was bedridden and required gastrostomy. He died of pneumonia at 50 years of age.

The proband's grandmother (Figure A, I-2) suffered from a similar illness that remained undiagnosed until her death at 50 years of age. She presented with memory deficits and gait disturbance, similar to the proband. She was bedridden for several years before death. The age of onset was not clear.

Only limited information was available on the proband's uncle (Figure A, II-1), who moved to another town early in life. One of the relatives recalled he had worked normally until 50 years of age, when he developed a rare illness like 'dementia'. Soon after, he burned to death in an accident.

No other family members were known to be affected in this pedigree. While the proband's aunt (Figure A, II-2) died of cholangiocarcinoma at 50 years of age, the proband's

Table. **Mutation Analysis of the *MAPT* gene of the Proband-ideogram.**

Mutation	Rs1467967	Rs242557	Rs3785883	Rs2471738	Del-in9	IVS10+3	Rs7521
Proband	G/G	A/A	G/G	C/C	H1H1	G/A	G/G

Haplotype nomenclature is assigned as previously reported (10). Alleles for the SNPs defining the haplotypes are given in the 5' to 3' order as follows: rs1467967, rs242557, rs3785883, rs2471738, Del-in9, rs7521.The order of "GAGCH1G" indicates H1M haplotype.

younger sister (49 years of age; Figure A, III-2), younger brother (43 years of age; Figure A, III-3) and both her children (Figure A, IV-1 and IV-2) have not shown any neurological or psychiatric abnormalities thus far. Concerning ethical issues, we did not examine her younger sister, younger brother or children genetically or clinically, as they had not developed any symptoms at the point of the examination.

We carried out whole-exome sequencing of genomic DNA from the proband. The genomic DNA was isolated from peripheral blood leukocytes using standard methods. Exome capture was performed with a SureSelect Human All Exon V6+UTR (89Mb) Kit (Agilent Technologies, Santa Clara, USA). Paired-end sequencing was carried out on a HiSeq2500 (Illumina, San Diego, USA) using a HiSeq SBS Kit V4 (Illumina), which generated 100-bp reads. The reference databases utilized included hg19 (GRCh37) (http://genome.ucsc.edu), HGMD (https://portal.biobase-international.com), ExAC (http://exac.broadinstitute.org), GnomAD (http://gnomad.broadinstitute.org) and dbSNP (https://www.ncbi.nlm.nih.gov/SNP). We examined variants of a total of 488 genes known to be responsible for or associated with Alzheimer disease (AD), progressive supranuclear palsy (PSP), frontotemporal lobar degeneration (FTLD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS) (Supplementary material). Through this analysis, we identified a G to A transition at position +3 in intron 10 of *MAPT* (IVS10+3G>A) and ruled out mutations in other causative genes. We then examined exon 10 and its flanking intronic sequence in the *MAPT* gene in the proband via polymerase chain reaction (PCR). On Sanger sequencing, we reconfirmed this IVS 10+3G>A mutation in intron 10 of the *MAPT* gene, which was in a heterozygous state in the proband (Figure D). The haplotype associated with the mutation was identified by the presence or absence of the 238-bp deletion in intron 9 (del-In9) and by genotyping 5 single-nucleotide polymorphisms (SNPs) (rs1467967, rs242557, rs3785883, rs2471738 and rs 7521) (10). The insertion of the del-In9 tags the H1 haplotype, and its deletion tags the H2 haplotype. The five haplotypes tagging SNPs allow further division of the H1 haplotype into subtypes. Polymerase chain reaction primer pairs (available on request) were designed and used to amplify each SNP of interest. On Sanger sequencing, we identified the *MAPT* diplotype of the proband as H1M/H1M (Table).

Discussion

In addition to the American MSTD family, three other sets of kindred have been identified in British, Italian and Italian-Polish families with the identical IVS10+3G>A mutation in the *MAPT* gene (11-15). The clinical signs and symptoms reported in these cases show some phenotypic heterogeneity. The major symptoms presented in the American MSTD family were disinhibition, early short-term memory loss and superior gaze palsy. The predominant feature in the British family was generalized deterioration in the cognitive function with choreiform-like movements. The predominant clinical signs in the Italian kindred were changes in speech, behavioral and social conduct and cognitive decline. The predominant clinical signs in the Italian-Polish family were behavioral abnormalities, bulbar syndrome, aphasia and damage to the cardiovascular system. Parkinsonian symptoms were a consistent clinical feature in members of all four families. Although there were a few subtle differences in the pathological findings among the four sets of kindred with the IVS10+3G>A mutation, clinical imaging or postmortem assessment of the four families consistently revealed marked neurodegeneration in the medial temporal and frontal regions (9).

In this paper, we describe the clinical, neuroimaging and genetic features of a woman from a Japanese family with the IVS10+3G>A mutation in the *MAPT* gene. At least the proband's father and grandmother had suffered a similar illness in this family. They all presented with predominant clinical signs of cognitive decline, bradykinesia and gait disturbance, and all were bedridden for several years before their death. In the proband, the first signs of disease were observed at 48 years of age, and her deterioration was very rapid, progressing to respiratory failure within only 2 years. In contrast, the proband's father showed symptoms at 44 years of age, and the disease duration was 6 years, which is consistent with the age of onset and disease duration for the first reported MSTD kindred (mean age of onset: 49 years; mean duration: 11 years) (6). Furthermore, the proband also presented with rather complicated symptoms, such as myoclonus and respiratory failure, that were absent in her father. Neither of these two symptoms was reported in the four sets of Caucasian kindred mentioned above. However, clinical variability can be seen in individuals with the same *MAPT* mutation, even within the same family (16). The predominant clinical signs of the proband are changes in speech, cognitive decline, generalized bradykinesia and rigidity and superior gaze palsy, which most closely resemble those of the first MSTD family and have therefore contributed to the main clinical picture of atypical PSP.

The diverse clinical presentations in families with this

mutation suggest that additional genetic factors may influence the phenotypic expression of the disease (11). There are two main haplotypes in *MAPT*: H1 and H2. Several SNPs throughout the *MAPT* gene are in complete linkage disequilibrium (LD) and largely tag the H1 and H2 haplotypes (17). The H1-specific SNPs in the *MAPT* genomic region allow for further division of the H1 haplotype into subtypes (18). The analysis of diplotypes associated with the mutation in the proband showed that the IVS10+3G>A mutation was in the haplotype H1M background. The different haplotypes around the mutation might account for the different phenotypes. The synergistic effects of the H1M haplotype and the IVS10+3G>A mutation in the proband might have played a role in the clinical presentation of rapid deterioration, with respiratory failure and myoclonus.

Interestingly, the H2 haplotype is absent in the Japanese population (19) and is thought to be exclusively Caucasian in origin (20). To date, the IVS10+3G>A mutation in the *MAPT* gene has only been reported in Caucasian populations. Our findings show that, unlike the H2 haplotype, the IVS10+3G>A mutation in the *MAPT* gene can develop independently in different parts of the world. In the disease course, myoclonus and respiratory failure can be observed. This study may expand on the clinical and genetic findings for FTDP-17.

The present clinical and genetic study was approved by the institutional review board of Yamanashi University, and written informed consent was obtained from the patient.

The authors state that they have no Conflict of Interest (COI).

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