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Hereditary Frontotemporal Dementia Linked to the Pathogenic p.L266V Variant of the MAPT Gene in Korea

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Dear Editor,

Frontotemporal dementia (FTD) is a clinically and pathologically heterogeneous disorder presenting mainly with gradual and progressive deterioration in behavior or gradual and progressive language dysfunction.[1] While FTD is primarily a sporadic disease, up to around one-quarter of cases occur due to dominant mutations in major causative genes.[2] The microtubule-associated protein tau (MAPT) gene is one of these genes.[3] More than 60 variants of *MAPT* have been identified as pathogenic.[2] Nevertheless, familial FTD patients carrying pathogenic variants in the MAPT gene have not been reported in Korea. Here we present a case of familial FTD due to the p.L266V variant of *MAPT*.

A right-handed 28-year-old male (III-1 in Fig. 1A) complained of progressive speech difficulties and personality change. When he spoke on the telephone 1 year previously, the listener was not able to understand his inconsistent speech. Six months after the first symptom, agrammatism manifested as the listing of words rather than forming sentences. His mother (II-2) also had presented disorganized behavior and anarthria at the age of 28 years, and had died 5 years after the onset of these symptoms. His uncle (II-3) and grandmother (I-2) had similar symptoms, and both died in their 4th decade of life. The proband was indifferent about his problems and showed emotional lability. He presented stereotypic prosody and frequent inappropriate pausing when speaking. Neuropsychological tests revealed decrements in word fluency, psychomotor speed, inhibitory control ability, and attention, which were compatible with dysfunction of the frontal and temporal lobes. The visuospatial function was intact, and cranial nerve function and motor power of the limbs were normal. Brain magnetic resonance imaging (MRI) showed bilateral atrophy of the frontotemporal lobes and widening of both temporal horns (Fig. 1B and C). There was no evidence of amyloid deposition in amyloid positron-emission tomography. Electromyography to determine the association with motor neuron disease revealed no abnormalities. Considering his clinical history and imaging data, we assumed this case was nonfluent/agrammatic primary progressive aphasia, which is one of the subtypes of FTD.

After obtaining informed consent from his family, we conducted whole-exome sequencing to screen FTD and other dementia-related genes. A missense variant in exon 9 of *MAPT* was identified (NM_005910.5:c.796C>G; p.L266V) (Fig. 1D), which was not present in general population databases (gnomAD and Korean Reference Genome Database).

The compulsiveness of the patient worsened during the follow-up period. He started to show perseverative behavior during daily activities such as eating and toothbrushing. He also showed progressive decrement of verbal output, eventually exhibiting a nonverbal state 3 years later.

In 2003, Kobayashi et al.[4] reported a patient presenting pathogenic tauopathy induced by

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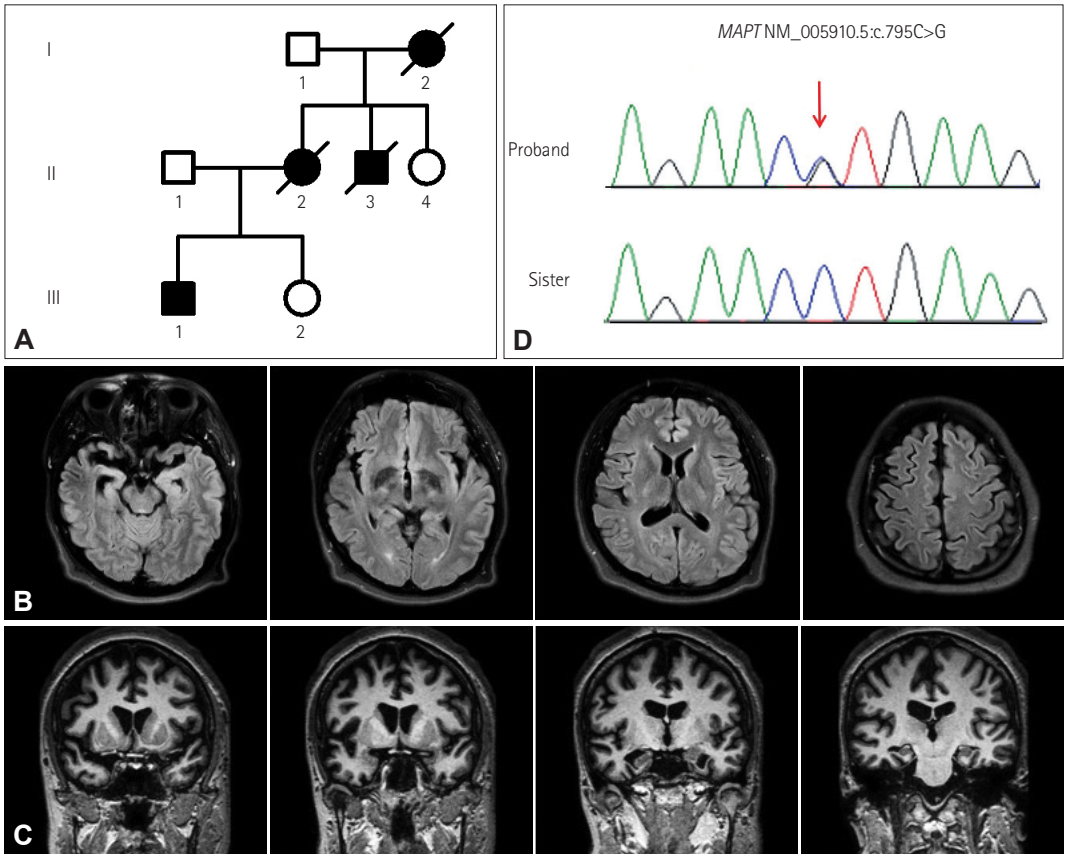

Fig. 1. Clinical information and image finding of the patient. A: Pedigree of the family with hereditary FTD with an autosomal dominant pattern of inheritance. Only the proband (III-1) was confirmed as carrying the p.L266V variant since other affected family members had died. B and C: T2-weighted fluid-attenuated inversion recovery axial MRI images and T1-weighted coronal MRI images of the proband showing bilateral frontotemporal lobe atrophy and widening of both temporal horns. D: Sequencing chromatograms of the proband and his sister. The arrow indicates the c.796C>G (p.L266V) variant. No variant is present in the chromatogram of the proband's sister, FTD: frontotemporal dementia, MAPT: microtubule-associated protein tau, MRI: magnetic resonance imaging.

the p.L266V mutation of *MAPT* for the first time. That patient presented clinical characteristics similar to those of our proband, starting with speech difficulties accompanied with personality change.[4] Microscopic pathology showed basophilic and tau-positive inclusions in neurons and unique tau-positive, argyrophilic astrocytes with thick filaments consisted with both three and four microtubule-binding repeats.[4] It was not possible to confirm the tauopathy in our patient's brain since he was alive. However, his typical clinical course and the presence of several affected family members probably indicate FTD with a genetic predisposition.

Since 1998, numerous *MAPT* variants have been reported for FTD and/or parkinsonism clinically.[2] However, a definite pathogenic *MAPT* variant had not been confirmed in Korea. Kim and colleagues[5,6] reported two novel variants of unknown significance in *MAPT*. To our knowledge, the present patient is the first reported familial FTD case with a pathogenic *MAPT* variant. This case indicates that clinicians should consider gene evaluations of familial FTD.

Author Contributions

Conceptualization: all authors. Data curation: all authors. Formal analysis: all authors. Investigation: all authors. Methodology: all authors. Writing—original draft: all authors. Writing—review & editing: all authors.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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