**Young-onset frontotemporal dementia in a homozygous tau R406W mutation carrier**

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**Abstract**

Microtubule-associated protein tau mutations result in 10–20% of cases of genetic frontotemporal lobar degeneration. Tau mutation carriers typically develop behavioral variant frontotemporal dementia with or without parkinsonism. Unlike most frontotemporal dementia gene mutations, heterozygous R406W tau mutation carriers most often develop clinical Alzheimer’s disease. We report a homozygous tau R406W mutation carrier with behavioral variant frontotemporal dementia who developed symptoms 20 years before mean family symptom onset. Voxel-based morphometry showed frontoinsular, frontal, and mesial temporal cortical atrophy. Homozygous tau R406W mutations appear to accelerate symptom onset and drive a behavioral variant frontotemporal dementia syndrome.

**Introduction**

Frontotemporal dementia (FTD) is a common cause of dementia under the age of 65. The three clinical FTD syndromes include behavioural variant FTD (bvFTD) which presents with early personality and behavioural changes¹ and two language variants, semantic and nonfluent primary progressive aphasia.² Approximately, 40% of patients with a frontotemporal lobar degeneration (FTLD)-spectrum disorder show some family history of neurodegenerative disease,³ with 10% showing an autosomal dominant inheritance pattern.³

Mutations in the microtubule-associated protein tau (MAPT) gene are the first autosomal dominant FTLD genetic mutations identified.⁴ In neurons, MAPT binds to axonal microtubules, promotes microtubule assembly and stabilization, and plays a role in maintaining neuronal integrity and axonal transport. There are currently more than 40 known MAPT mutations, including R406W, with the N279K, P301L, and IVS10+16 being the most commonly observed.⁵ Fourteen percent of FTLD with tau pathology at autopsy show MAPT mutations.⁶ Typically, MAPT mutation carriers present clinically with bvFTD and/or parkinsonian syndromes, including progressive supranuclear palsy (PSP), or corticobasal syndrome (CBS).

In contrast to most MAPT mutation carriers, heterozygous MAPT R406W mutation carriers show early prominent memory symptoms leading to a clinical Alzheimer’s disease (AD) presentation with a later age of onset and slower disease progression.⁴ Most R406W families identified have European ancestry but Japanese kindreds have also been reported.⁷–¹¹ Although most heterozygous R406W carriers show clinical AD, others develop behavioural changes reminiscent of bvFTD later in the disease.
course, and a few have exhibited rapid decline with prominent psychiatric features and parkinsonism. One previous report with limited data describes a homozygous R406W carrier who developed nonfluent speech, behavioural changes, and parkinsonism.

In this report, we provide a detailed description of a man homozygous for the R406W mutation who developed agitation and rigid personality during his early thirties, and memory impairment the following year. Using voxel-based morphometry (VBM), we compared his structural magnetic resonance imaging (MRI) scan to 30 matched healthy controls to delineate atrophy patterns. Clinical details were altered to obscure his identity.

Case Report

A 40-year-old right-handed man presented with a 7-year history of progressive behavioural and cognitive decline. Throughout adolescence and young adulthood, he manifested depression associated with suicidal ideation during stressful times. His first clear behavioural change, however, surfaced around the age of 33 when he became argumentative and exhibited rigidity around dietary preferences. The following year, he began repeating conversations and misplacing objects, and grew disoriented in familiar environments. At the age of 36, behavioural symptoms intensified. He developed persecutory delusions. Obsessions with religious rituals emerged and he perseverated on particular discussion topics. He hugged and kissed strangers. Two years later, his work relationships with clients grew strained and compulsive morning routines made him late for appointments. At the age of 39, he began hoarding garbage. Irritability evolved and his attention declined. He struggled to recognize faces of known individuals. He grew increasingly apathetic, rarely initiating conversations. Six months before presentation, he developed word-finding and comprehension difficulties and speech output greatly diminished.

Both maternal and paternal family history showed dementia and parkinsonism. His parents were consanguineous. One parent showed mild memory changes during the seventh decade, while the other parent developed cognitive decline and behavioural changes during the sixth decade, with parkinsonism emerging later. A grandparent and great-grandparent developed dementia during the seventh decade, and were diagnosed with AD and parkinsonism. No family history of dementia or parkinsonism under the age of 60 was reported.

On examination, he fidgeted and touched the examiner. Speech was hypophonic; he spoke little, but showed grammatical speech. He had masked facies. Square wave jerks were noted with slowed saccade velocity horizontally and vertically. Motor examination revealed normal tone and strength, a mild, high frequency bilateral postural tremor, and mildly slowed repetitive simple movements. Deep tendon reflexes showed symmetric hyperreflexia and Babinski’s sign was absent bilaterally. Snout and jaw jerk reflexes were noted. Gait appeared normal. Clinical diagnosis was consistent with bvFTD.

Neuropsychological battery

Neuropsychological evaluation revealed significant impairments in memory retrieval and recognition, language, working memory and executive function. Visuospatial construction remained intact.

Structural MRI and VBM

T1 MRI brain showed symmetric mesial temporal, frontoinsular and dorsomedial frontal cortical atrophy (Fig. 1A). Using VBM, we compared the patient’s T1 structural MRI scan to a group of 30 healthy controls matched for age (mean 40.7 ± 11.1 years), sex and handedness. VBM showed that he had symmetric bilateral atrophy in MAPT-bvFTD foci in the frontoinsula and mesial temporal structures, including amygdala and hippocampus (pfwe < 0.05). At a more lenient statistical threshold, extensive atrophy in frontoinsula, orbitofrontal, dorsomedial frontal, and dorsolateral prefrontal cortices and striatum emerged.

Genetic testing

Genetic testing revealed a homozygous R406W MAPT mutation. He tested negative for other FTD and AD genetic mutations, including GRN, C9ORF72 repeat expansion, presenilin 1 and 2, and amyloid precursor protein. APOE genotype was E3/E3.

Discussion

We report a homozygous MAPT R406W mutation carrier who developed agitation, personality change and increased rigidity during his early thirties, followed by memory impairment, delusions, obsessive rituals and social disinhibition, leading to a diagnosis of bvFTD. He showed amnestic impairment typical of MAPT mutation carriers, with parkinsonism evolving later during his disease. Compared with his other family members who are presumed heterozygotes, this patient showed symptoms nearly two decades earlier than typically reported for heterozygous R406W carriers. His neuropsychological profile showing executive and language deficits and a relative sparing of visuospatial construction was consistent with bvFTD.
Homozygous R406W carriers appear to develop symptoms at an earlier age compared to heterozygous R406W

Compared to carriers of other MAPT mutations, heterozygous R406W carriers typically show a later age at symptom onset (59.2 ± 5.5 years) with a protracted illness (12.7 ± 1.5 years), and milder frontotemporal atrophy on structural MRI.\textsuperscript{12} Cell culture studies of R406W may reflect its milder presentation in humans. In cell culture, R406W mutated tau protein, does not alter the ability of tau to regulate microtubule dynamics.\textsuperscript{13} Relative to the V337M and P301L mutations, which significantly reduce microtubule assembly initiation and tau binding to microtubules, the R406W mutation shows relatively mild impact on microtubule assembly.\textsuperscript{14,15}

In contrast, our homozygous R406W patient showed symptom onset during the early thirties, more than two decades prior to mean symptom onset in heterozygous R406W. Interestingly, his symptom duration remained within range of that reported in heterozygous R406W carriers. Similarly, the only other report describing a homozygous R406W carrier displayed FTD symptoms (language then behaviour) at 43 followed by parkinsonism;\textsuperscript{7} his siblings also showed FTD features but at a younger age with mean symptom onset at 35 and a disease duration of 7 years, early and rapid compared to heterozygous R406W. Their heterozygous siblings (aged 52 and 60) had a later age at onset and displayed amnesic rather than FTD features. Reports of other homozygous carriers of MAPT mutations in delN296\textsuperscript{16} and S352L\textsuperscript{17} have reported early age of onset during the third...
and fourth decades of life. Overall, earlier age of onset in R406W homozygotes compared with heterozygotes supports a toxic gain of function model of pathogenicity.

The homozygous R406W carrier showed atrophy in bvFTD-targeted brain structures

Heterozygous R406W usually presents with clinical AD, with memory impairments related to hippocampal degeneration as seen in other MAPT mutations. Autopsy studies show that heterozygous R406W show neuronal loss with gliosis and abundant tau-positive neurofibrillary tangles throughout the cortex, hippocampus, amygdala, and brainstem nuclei. The extent to which heterozygous R406W with clinical AD show early preservation of bvFTD-targeted regions, such as the frontoinsular, orbitofrontal, and anterior cingulate cortices, remains unknown.

We found that the homozygous R406W carrier showed atrophy in bvFTD-targeted regions, consistent with his bvFTD clinical presentation. Prominent atrophy emerged in frontoinsular and anterior cingulate cortices, key hubs in a distributed brain network known as the salience network, which degenerates in bvFTD. Additionally, his hippocampal atrophy reflected the memory deficits evolving later in the disease course.

In sum, homozygous MAPT mutations show an age of onset as early as the third or fourth decade. Whether more extensive neuropathological burden explains earlier onset in homozygous R406W remains yet to be determined. Homozygous R406W carriers may be predisposed to clinical bvFTD, rather than a clinical AD phenotype seen in heterozygous R406W carriers, but further studies are needed to affirm this observation. This case underscores the notion that MAPT mutations should be screened in families with an autosomal dominant pattern of clinical AD for which no mutations in known AD genes are found.

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Conflict of Interest

Dr. Geschwind reports grants from NIH, grants from Tau Consortium, during the conduct of the study. Dr. Pressman is funded through the American Brain Foundation. Dr. Lee reports grants from NIH NIA, during the conduct of the study. Bruce L. Miller, MD receives grant support from the NIH/NIA and the Centers for Medicare & Medicaid Services (CMS) as grants for the Memory and Aging Center. As an additional disclosure, He serves as Medical Director for the John Douglas French Foundation; Scientific Director for the Tau Consortium; Director/Medical Advisory Board of the Larry L. Hillblom Foundation; and Scientific Advisory Board Member for the National Institute for Health Research Cambridge Biomedical Research Centre and its subunit, the Biomedical Research Unit in Dementia (UK).

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Supporting Information
Additional Supporting Information may be found in the online version of this article:
Data S1. Supplementary methods.