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Parkinsonism and distinct dementia patterns in a family with the MAPT R406W mutation

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Abstract

Background—The Arg406Trp (R406W) missense mutation in the microtubule associated protein-tau gene (*MAPT*) is a known cause of early-onset dementia (EOD). Various dementia phenotypes have been described, including frontotemporal dementia (FTD), FTD with Parkinsonism, and early-onset Alzheimer Disease (EOAD)-like presentations.

Methods—Using whole exome capture with subsequent sequencing, we identified the R406W mutation in a family with multiple individuals with clinically diagnosed EOAD, in a pattern suggesting autosomal dominant inheritance. We clinically re-evaluated all available family members.

Results—Each of the affected individuals had a course meeting clinical criteria for EOAD. Two distinct disease trajectories were apparent: one rapidly progressive, and the other long and gradual. Four of five affected individuals also manifested Parkinsonian symptoms. FTD features were not prominent, and when present, appeared only late in the course of dementia.

Conclusions—The *MAPT* R406W mutation is associated with EOAD-like symptoms and Parkinsonism without FTD, as well as distinct cognitive courses.

Keywords

microtubule associated protein-tau; dementia; early onset Alzheimer's disease; frontotemporal dementia; whole exome sequencing

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1. Introduction

Early-onset dementia (EOD) is defined by memory and cognitive difficulties beginning before age 65, and commonly occurs in a familial pattern. EOD can be divided into presenile dementias, such as frontotemporal dementia (FTD), and senile dementias with early onset (such as early-onset Alzheimer's Disease, or EOAD)¹. The presence of characteristic symptoms guides the diagnosis of early-onset dementia, however due to varied phenotypic expression and frequently overlapping symptoms, the exact diagnosis may not be distinguished without neuropathologic examination².

Genetic investigations have revealed causative mutations for several EOD syndromes. In the case of EOAD, mutations in the *APP*³, *PSEN1*⁴, and *PSEN2*⁵ genes have been pinpointed. Another gene implicated in EOD is the microtubule associated protein-tau (*MAPT*)⁶. The Arg406Trp (R406W) missense mutation in *MAPT* has been associated with various EOD phenotypes including FTD⁷⁻¹²; an illness clinically resembling early-onset (EOAD) with later onset of frontal signs¹³⁻¹⁶; and rapidly-progressing dementia with psychosis¹⁷. Parkinsonian features are infrequently present^{7,12}.

We identified the R406W mutation in a family with multiple individuals with EOD that was clinically indistinguishable from EOAD. The disease occurred in several generations suggesting autosomal dominant inheritance. In order to further elucidate the neuropsychiatric phenotype associated with the mutation, we clinically re-evaluated all available members of the family, updating and confirming evolving clinical signs and symptoms. Each of the clinically affected individuals had a course meeting clinical criteria for EOAD. Two distinct disease trajectories were apparent: one rapidly progressive, and the other following a gradual and long course. Four of five individuals with memory loss also manifested Parkinsonian symptoms. FTD features were not prominent, and when present, appeared only late in the course of dementia.

2. Methods

2.1 Family and clinical data

The family was identified as part of our ongoing genetic studies in dementia. Participants were recruited, enrolled, and sampled according to the Institutional Review Board protocols for the University of Miami. A complete description of the study was provided to the subjects, and written informed consent was obtained. Whole blood was collected from all participants by venipuncture. Affection status was determined by consensus of physicians and clinical staff experienced in clinical dementia research and based on medical records and in-person evaluation. All affected subjects all met NINCDS-ADRDA criteria for the diagnosis of Alzheimer's Disease (AD). Age-at-onset (AAO) was estimated as date of first onset of symptoms as reported by the patient, their informant, or abstracted from the patient's medical records.

All living participants in the family were clinically re-assessed in person following identification of the R406W mutation. Direct evaluation included a neurological examination and neuropsychological measures. Medical records and research study data

were reviewed, including serial physical and neurological examinations, history by family report, cognitive assessments, and instruments assessing symptom domains such as functional impairments, depression, and psychosis. Data on neuropathology and biomarkers such as tau and β -amyloid were not available.

2.2 Molecular analysis

Whole-exome sequencing was performed as part of the research study. Whole blood derived DNA samples of five affected individuals from the family were subjected to whole exome capture using the Sure Select Human All Exon 50 Mb protocol from Agilent Technologies with subsequent sequencing library preparation for massive parallel sequencing on a HiSeq2000 instrument from Illumina. Sequence read alignment and variant calling was performed by applying the BWA/GATK software¹⁸. Variants were filtered to be (1) heterozygous in all five individuals assuming autosomal-dominant inheritance, (2) falling in regions of 100% sharing by identity-of-descent (IBD) previously calculated from genome-wide SNP genotyping data in this family, (3) to be most likely to interfere with protein function (missense, nonsense and splice site changes) (4) in established EOAD genes (*amyloid precursor protein (APP)*, *presenilin 1 (PSEN1)*, *presenilin 2 (PSEN2)*) and EOD genes (*microtubule-associated protein tau (MAPT)*, and *granulin (PGRN)*)¹⁹. Passed filtering variants were validated by Sanger sequencing in five affected and three unaffected family members (two were married-in) with DNA samples available.

APOE-ε genotypes²⁰, *MAPT* H1/H2 haplotypes^{21,22}, and *C9ORF72* repeat expansions^{23,24} have each been shown to contribute to AD risk, phenotypic expression, and/or clinical course of EOD and thus were also examined. Apolipoprotein E (APOE) genotype data were available on all participants and were determined as previously described²⁵. For the *MAPT* H1/H2 haplotype data, SNP rs17650901 was used. This SNP is in perfect linkage disequilibrium with rs1800547, ($r^2=1.0$), which has been previously used to distinguish the H1/H2 haplotypes²⁶. *MAPT* H1/H2 data were available only on affected, sampled individuals (4, 6, 8, 13, 14). The *C9ORF72* repeat copy count was available for affected individuals 4, 6, 8, and 13. Moreover, for all related, sampled individuals in the family (individuals 4, 6, 8, 13, 14, and 15), whole exome data was carefully screened for reported clinical and potentially damaging variants in the following genes related to either dementia and/or Parkinsonism: *SNCA*²⁷, *LRRK2*²⁸, *PRKN*²⁹, *DJI*³⁰, *PINK1*³¹, and *SORL1*³².

3. Results

3.1 Molecular

Molecular applied filtering criteria on whole exome sequencing data exclusively identified the R406W mutation (rs63750424 – C/T) in *MAPT* among the screened early-onset AD genes. Heterozygosity for the R406W mutation was confirmed by Sanger sequencing for all five affected family members with DNA available (4, 6, 8, 13, and 14) as well as one unaffected sampled family member (15). Two married-in spouses (3 and 7), both unaffected, did not carry the mutation.

APOE-ε status was 3/4 for individuals 4 and 13. All other sampled individuals carried the 3/3 genotype. *MAPT* haplotype status was H1/H1 for all sampled, affected individuals. *C9ORF72* sequencing in individuals 4, 6, 8, and 13 revealed a repeat copy count within nonpathogenic range (<30; range: 3–19). No reported clinical or potentially disease-modifying variants in the genes *SNCA*, *LRRK2*, *PRKN*, *DJ1*, *PINK1*, and *SORL1* were detected in this family's whole exome sequencing data.

3.2 Clinical

3.2.1 Overall trends—The pedigree is shown in Figure 1. The pedigree has been altered to protect the identity of the participants. Each of the five affected individuals with DNA available (4, 6, 8, 13, 14) presented with early-onset dementia (range: 48–62 years old). The initial course followed a typical AD pattern, with early forgetfulness, progressive worsening in several areas of cognitive function (for example, short-term memory loss and difficulties with orientation) or activities of daily living, and difficulties with language³³. As the disease progressed, two distinct cognitive trajectories were identified, as measured by the Mini Mental Status Examination (³⁴; see Figure 2). Individuals 6 and 13 manifested a relatively rapid deterioration, while a more benign progression with evidence of long disease duration was seen in individuals 4, 8, and 14.

In addition, four of the five affected individuals developed Parkinsonian symptoms as the course of dementia continued (see Supplemental Table 1). The onset and severity of Parkinsonian symptoms ranged from comorbid Parkinson Disease (PD) with onset of symptoms <5 years into the disease course, to mild Parkinsonian symptoms 17 years after the initial diagnosis of dementia. Symptoms such as early personality, behavior, or language changes, were not present. Later in the course, two individuals showed frontal release signs.

3.2.2 Specific clinical features—The proband, individual 4, had short-term memory loss and calculation difficulties beginning at age 56, and was diagnosed with EOAD. No Parkinsonism, affective symptoms or behavioral changes were present early in disease. Slow functional decline followed, primarily affecting memory and orientation. Language difficulties did not predominate. The participant enrolled in our research study after 12 years of illness, and a research diagnosis of probable AD was assigned. After 17 years of illness, the individual showed abnormal facial expression, bradykinesia, and abnormal speech. Exam at 23 years of disease duration revealed severe dementia with aphasia, Parkinsonism (action and rest tremor, rigidity, flat affect, cogwheeling, and bradykinesia), and frontal release signs (snout, palmomental, grasp reflexes). Her medical history is significant for depression and an operative procedure after >15 years disease duration. Common medical risk factors for dementia (*e.g.*, cardiac or cerebrovascular disease, stroke, diabetes, hypertension) were not present on history or imaging.

Individual 13 experienced the earliest AOO (48 years). A typical dementing pattern, including getting lost and word-finding difficulties, developed but progressed rapidly. Subtle personality changes, including inappropriate joking and disinhibition, appeared 5 years after the onset of memory difficulties. Individual 13 died suddenly 6 years after disease onset. No

Parkinsonian features were noted throughout the course, and the individual's medical history was largely unremarkable.

Individual 6 was clinically diagnosed at 59 years old with EOAD, with symptoms of withdrawal and difficulty adapting to new environments. There was a remote (>30 year) history of several surgeries requiring general anesthesia. Otherwise, the individual was healthy. Symptoms of PD appeared within the first 5 years of illness (flat affect and slow, shuffling gait). PD features progressed to include cogwheel rigidity, hunched posture, and dysphagia, which were responsive to l-methyl dopa. Cognition rapidly declined and the individual was completely aphasic after 7 years. Death occurred after 11 years of illness with clinical and research diagnoses of AD and PD. No autopsy was performed.

Individual 8's clinical course reflected memory difficulties with preserved function for many years. A slight tremor was noted at 15 years of illness. Reassessment at 22 years of illness revealed significant aphasia with mild Parkinsonian features of tremor, masked faces, and slight cogwheeling. Frontal exam was normal. In terms of medical comorbidities, individual 8 had a few risk factors for vascular disease but no evidence of vascular disease.

Individual 14's mild cognitive impairment progressed to amnesia for faces and names. Depression and anxiety developed without personality or behavioral changes. Exam at 7 years disease duration showed very mild asymmetric cogwheeling and slightly hunched posture, with no frontal findings. Individual 14 is in excellent health.

The unaffected family member carrying the mutation (individual 15) demonstrated an unremarkable neurological exam, within no Parkinsonian or frontal features. Despite complaints of difficulty remembering a short list, there was no evidence of functional impairments. Neuropsychological exam revealed mild difficulty with delayed recall and naming politicians.

Individuals 3 and 7 were married-in spouses. Their unaffected status was confirmed by history, neuropsychological testing, and assessments of daily function.

4. Discussion

The presence of the *MAPT* R406W mutation in all affected individuals supports the previously reported association with EOD, and in this case, the phenotype was clinically indistinguishable from EOAD. Generally, published descriptions of individuals with the R406W mutation describe a slowly progressive dementia, with symptoms of frontal dysfunction, but lacking Parkinsonism (see Supplemental Table 2). In contrast to these studies, 4 of the 5 affected individuals carrying the *MAPT* R406W in this family demonstrated Parkinsonian features. The affected individuals did not demonstrate initial frontal signs or symptoms.

Additional early-onset dementias with Parkinsonism exist (reviewed in ³⁵). These include frontotemporal dementia linked to Parkinsonism (FTDP-17), dementia with Lewy Bodies (DLB), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD). In

contrast, mutations in the EOAD genes, *amyloid-beta precursor protein (APP)*, *presenilin 1* and *2 (PSEN1, PSEN2)* are not typically associated with Parkinsonism.

The dementia of FTDP-17 may resemble that of DLB or AD, with motor symptoms including tremor, rigidity, and bradykinesia, and occasionally psychiatric features (hallucinations, delusions). A variety of mutations in *MAPT* are causative for FTDP-17. Indeed, the reports on two other families with both the *MAPT* R406W mutation and Parkinsonism (see Supplemental Table 2) indicate that the diagnosis may be FTDP-17 rather than FTD^{7,8,12,36}.

Unlike AD, marked fluctuations in cognition are seen in DLB, and the presence of recurrent visual hallucinations is a hallmark of the illness³⁷. Parkinsonian features are often more prominent than cognitive degeneration, particularly at disease onset.

Phenotypic variants of PSP include a presentation with PD-like bradykinesia and rigidity³⁸. CBD features include basal ganglia dysfunction (akinesia, postural instability, and tremor) and cortical deficits (alien hand syndrome, apraxia, sensory impairments, aphasia, or dementia)³⁹.

In the *MAPT* R406W mutation, the course of dementia in published descriptions is generally slowly progressive, with gradual functional declines. The serial cognitive exam scores in this family demonstrate two distinct courses of cognitive decline. One is slowly progressive and indolent, similar to previous reports. The other is more rapid and severe. We were unable to identify a simple explanation for this variance. There is no clear association between presence, severity, or AOO of Parkinsonian features and the trajectory of cognitive decline. We did not identify a correlation between co-occurring conditions (stroke, vascular disease, diabetes, exposure to general anesthesia) and the rate of cognitive decline. The *APOE-ε* genotype, *MAPT* H1/H2 haplotype, and *C9ORF72* repeat copy number status did not account for the variance in the rates of cognitive decline. The two individuals, both affected, who carry the *APOE-ε* 3/4 genotype are discordant for disease course, and *MAPT* haplotypes were identical (H1/H1) in all affected individuals. A pathogenic expansion of the *C9ORF72* gene was not detected. Potentially damaging variants were not found in the following genes related to dementia and/or Parkinsonism: *SNCA*, *LRK2*, *PRKN*, *DJI*, *PINK1*, and *SORL1*.

One individual (15) who carries the mutation is unaffected at this time. This individual's current age is less than the age of the latest reported AOO in this family (48–62 years). Continued follow-up examinations are necessary to reveal whether the current complaints of mild memory loss represent early manifestations of EOD, or a more benign process.

An important limitation of the study is the lack of neuropathology data. Diagnosis based on clinical criteria classifies the affected individuals in the currently reported family carrying the *MAP-T* R406W mutation as EOAD, a phenotype that has been previously described^{13–16}. We do not have pathology results for this family. However, neuropathological results are available for individuals in other families carrying the *MAPT* R406W mutation. These reports have been consistent with a neuropathologic diagnosis of FTD. Regardless of clinical presentation, neuropathology on all individuals carrying this

mutation has been uniformly consistent with a diagnosis of FTD. Thus, if tissue were available to be examined, it is possible that the family described in the current report might demonstrate neuropathologic features consistent with a FTD diagnosis. Interestingly, a recent report states that rarely, despite evaluation at a specialty clinic for early-onset dementia, some cases of clinically diagnosed FTD met neuropathologic criteria for Alzheimer's Disease instead⁴⁰.

5. Conclusions

Whole exome sequencing successfully identified the R406W mutation in the *MAPT* gene in individuals affected with EOAD-like symptoms in a single family. Clinical characterization of these individuals reveals an association with Parkinsonism, a lack of association with early frontal dysfunction, and two distinct cognitive courses. Neither co-occurring illnesses nor variant status in EOD- or Parkinsonism-associated genes were correlated with rate of cognitive decline. These data both confirm previous genetic associations and enhance the available data on phenotypes associated with the mutation in *MAPT*. Variability in phenotype, even with the same mutation, may indicate other genetic or environmental factors contribute to disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Legend

- ◆ Early Onset Dementia
- ◇ Clinical Status Unknown
- ◼ R4O6W Known Carrier
- + DNA Available for Testing
- AOO = Age Of Onset
- AOE = Age Of Enrollment

Figure 1.
Family pedigree

Figure 2.
Progression of cognitive change in affected individuals