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The *MAPT* p.A152T variant is a risk factor associated with tauopathies with atypical clinical and neuropathological features

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Abstract

Microtubule-associated protein tau *(MAPT)* mutations have been shown to underlie frontotemporal dementia and a variety of additional sporadic tauopathies. We identified a rare p.A152T variant in *MAPT* exon 7 in two (of eight) patients with clinical presentation of parkinsonism and postmortem finding of neurofibrillary tangle pathology. Two siblings of one patient also carried the p.A152T variant, and both have progressive cognitive impairment. Further screening identified the variant in two other cases: one with pathologically confirmed corticobasal degeneration and another with the diagnosis of Parkinson's disease with dementia. The balance of evidence suggests this variant is associated with disease, but the very varied phenotype of the cases with the mutation is not consistent with it being a fully penetrant pathogenic mutation. Interestingly, this variation results in the creation of a new phosphorylation site that could cause reduced microtubule binding. We suggest that the A152T variant is a risk factor associated with the development of atypical neurodegenerative conditions with abnormal tau accumulation.

Keywords: MAPT; Parkinsonism; Corticobasal degeneration; Genetics; Postencephalitic parkinsonism

1. Introduction

Tau belongs to the family of the microtubule-binding proteins (*MT*) (Witman et al., 1976) and is encoded by the MT-associated protein tau (*MAPT*) gene located on chromosome 17 (17q21) (Andreadis et al., 1992). *MAPT* mutations have been linked to a variety of neurodegenerative diseases with abnormal tau accumulation, and mainly to frontotemporal dementia (FTD) (Hutton et al., 1998) but also to other sporadic tauopathies, including progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and various disorders with more unusual tau pathology (Conrad et al., 1997; Höglinger et al., 2011; Momeni et al., 2009). Recently, an A152T variation in *MAPT* exon 7 was identified in a patient who had dementia and unclassifiable tauopathy (Kovacs et al., 2011). With this background, we determined to sequence the *MAPT* gene in our small series of cases with indeterminate tauopathies (eight cases). Here, we report two patients with atypical parkinsonian disorder and abnormal tau accumulation at postmortem, both of whom were identified to carry the A152T variation. We then screened a larger series of tauopathy cases for this mutation (PSP and CBD) and some cases with idiopathic Parkinson's disease to determine the nature of the phenotype that seemed to be associated with this variant and found an additional case with CBD as well as a case of Parkinson's disease in which there was prominent tangle pathology.

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2. Methods

All subjects in this report had provided written consent to perform neuropathological and genetic studies. The access to clinical records and pathological material at the Queen Square Brain Bank (QSBB) has generic ethical approval from a London Multi-Centre Research Ethics Committee under a license from the Human Tissue Authority.

2.1. Neuropathology

After postmortem the brains were divided midsagittally. One half brain was immediately frozen and stored at −80 °C, whereas the other half was immersed and fixed in 10% neutral formalin for 3 weeks. Tissue blocks were processed using standard protocols. We performed hematoxylin and eosin, Luxol fast blue/cresyl violet, Congo red staining on 7-μm-thick sections and also used the modified Bielschowsky and Gallyas silver impregnation methods. Immunohistochemistry with antibodies to phospho-tau (AT8 clone recognizing Ser202/Thr205), 3-repeat (3R) and 4-repeat (4R) tau isoforms (de Silva et al., 2003), ubiquitin, p62, TAR DNA-binding protein-43 (TDP-43), and α-synuclein was also carried out using a standard avidin-biotin method.

2.2. Patients from unclassified tauopathy series

In our initial DNA-sequencing study, we sequenced the entire *MAPT* gene open reading frame in eight cases that had received a clinical diagnosis of postencephalitic parkinsonism (PEP) or clinical parkinsonism with unclassifiable tauopathy at postmortem. PEP is a rare clinical entity characterized by the development of parkinsonism after the development of encephalitis (Geddes et al., 1993). Initial postmortem studies indicated PEP in case 1, described later in the article, and was previously reported as such (Geddes et al., 1993). The original neuropathological investigation did not reach a conclusive diagnosis in case 2, which had been categorized as "parkinsonism associated with unclassifiable neurofibrillary tangle pathology".

2.3. Genetic analysis

Genomic DNA was extracted from brain tissue of the eight archival cases. In these cases, the *PARK2* and *LRRK2* genes had also been previously fully sequenced without finding any changes. Three of these eight cases have been previously reported (case 5, 7, and 8) (Geddes et al., 1993). After the p.A152T mutation was found in exon 7 in two of these cases, additional screening of this exon was carried out in blood-derived DNA of the three siblings of case 1 (two suffering from dementing illnesses and one unaffected), and in 150 neuropathologically defined control subjects and 133 1958 Wellcome Trust blood donor control subjects. At this stage, the occurrence and frequency of this variant in public databases were also assessed.

2.4. Statistical analysis

Fisher exact tests were conducted using an online tool research.microsoft.com/enus/um/redmond/projects/mscompbio/FisherExactTest/. A p-value less than 0.01 was considered statistically significant.

2.5. Secondary screening

After we had identified the variant in the unclassified tauopathy cases described earlier and failed to find the variant in control subjects, we screened for the mutation by sequencing *MAPT* exon 7 in DNA derived from the brains of the QSBB archival collection, including 114 cases with PSP (Pittman et al., 2004), 8 cases with CBD (Houlden et al., 2001), and 48 cases with idiopathic Parkinson's disease, all of which had received pathological confirmation of their diagnoses.

3. Results

3.1. Primary sequencing

3.1.1. Genetics

Among the eight cases subjected to primary genetic analysis, two cases (25%) reported earlier were identified to carry a heterozygote nonsynonymous variant in exon 7 (rs143624519, c.454G<A, p.A152T) (accession numbers NM_005910.5 and NP_005901.2, respectively) (Fig. 1A and 1B). This variant was also found in the two sisters of case 1, who are both developing progressive cognitive impairment, but this variant was absent in the third unaffected sister. All patients are Caucasian and of Northern European descent. This variant is present with a frequency of 19 in 3510 (0.54%) individuals of European American origin (19 in 7020 alleles) in the publically available database from the National Heart, Lung, and Blood Institute (NHLBI) "Grand Opportunity" Exome Sequencing Project (GO-ESP) (Exome Variant Server, NHLBI ESP, Seattle, WA [URL: evs.gs.washington.edu/EVS/] [accessed on 01/2012]). We additionally screened 150 neuropathologically confirmed control subjects from the UK and 133 belonging to the 1958 Wellcome cohort and did not find this variant. The Fisher exact test used to compare both allele and genotype frequencies between the clinically diagnosed PEP and the ESP cohort gave a two-tailed p-value of < 0.01 for allele and genotype frequencies. A search through two publically available databases (1000 genomes and National Institute of Environmental Health Sciences (NIEHS) Environmental Genome Project, Seattle, WA [URL: evs.gs.washington.edu/niehsExome/] [accessed on 03/2012]) revealed similarly low frequencies of the A152T variant (Supplementary Table 1) (1000 Genomes Project Consortium, 2010). This variant has been reported more frequently in Alzheimer's disease (AD) patients than in control subjects (Cruchaga et al., 2012).