**Expanding and exploring the MAPT p.V363I mutation phenotype: an overlapping of progressive supranuclear palsy - corticobasal syndrome - posterior cortical atrophy**

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**Introduction**

Mutations in the microtubule-associated protein tau gene (MAPT) have heterogenous clinical and pathological manifestations, and their pathogenicity is based on two different mechanisms: missense and splicing mutations, leading to aggregates of insoluble filaments of tau1. In this letter, we describe the atypical phenotype of a patient carrying the rare variant p.V363I MAPT mutation and explore the clinical presentation through a multimodal imaging biomarkers approach.

**Case report**

A 49-year-old woman presented with a two-year history of progressive slowed gait, visuospatial difficulties, left-sided rigidity, and dexterity impairment. She worked as a primary school teacher when she felt difficulties watching the students and driving her car. Family history was unremarkable. Her neurologic examination demonstrated asymmetric left-sided bradykinesia and rigidity, with left upper limb dystonia (video, segment 1). Cranial nerve examination showed vertical supranuclear gaze palsy, more prominent to upgaze than downgaze, and slowed horizontal saccades (video, segment 2). She had bilateral upper limb ideomotor apraxia, worse on the left arm (video, segment 3), and presented all Balint syndrome components, simultanagnosia, optic ataxia, and oculomotor apraxia, more prominent on the left (video, segment 4). Moreover, she demonstrated a left spatial hemineglect (video, segment 4). There were no behavioral or personality disturbances.

Considering the findings, she was clinically diagnosed with probable corticobasal syndrome (CBS)2 in overlap with probable progressive supranuclear palsy (PSP)3. Also, she fulfilled the criteria for posterior cortical atrophy (PCA)4. A comprehensive laboratory and imaging investigation was performed. Laboratory findings were normal. Brain magnetic resonance imaging (MRI) disclosed atrophy at the brainstem and right parietooccipital regions, and Fluorodeoxyglucose(FDG)-PET showed an asymmetric hypometabolism at the right striatum, frontal and parietooccipital lobes. She had a negative cortical amyloid deposition at Pittsburgh Compound-B(PIB)-PET (figure). A commercial genetic panel (Invitae, San Francisco, CA) identified that she was heterozygous for a mutation in the MAPT gene, variant p.V363I (rs63750869; c.1087G>A:NM\_005910.5).

**Discussion**

Different phenotypes have been associated with autosomal-dominant MAPT mutations at the V363 codon, including behavioral, cognitive, and parkinsonian syndromes1,5. The p.V363I variant is a missense mutation located in the MAPT microtubule-binding domain, previously confirmed as pathogenic and a cause of tauopathy and corticobasal degeneration pathology5.

Clinical syndromes previously related to the p.V363I variant were semantic dementia6, primary progressive aphasia1, behavioral variant frontotemporal dementia7, CBS5, and PCA1, and some had both motor and cognitive syndromes at presentation5. However, this variant has only been described in a small number of nine patients5, and has not been previously related to PSP, although another mutation in the same residue (p.V363A) had a single case with a PSP clinical presentation5. Moreover, none of them displayed PSP, CBS and PCA overlapping on the same subject.

The absence of family history reinforces prior studies that suggested incomplete penetrance for this mutation1. Additionally, imaging findings are congruent with the clinical presentation and previous case reports5. Also, we were able to exclude Alzheimer’s disease co-pathology, a possible cause of PCA presentation.

Finally, we described a patient with the p.V363I MAPT variant presenting a unique PSP-CBS and PCA phenotype, which might aid in the understanding of the phenotypic heterogeneity and genetic underpinnings of this rare mutation.

**References**

1. Rossi, G. *et al.* Different mutations at V363 MAPT codon are associated with atypical clinical phenotypes and show unusual structural and functional features. *Neurobiol. Aging* **35**, 408–417 (2014).

2. Armstrong, M. J. *et al.* Criteria for the diagnosis of corticobasal degeneration. *Neurology* **80**, 496–503 (2013).

3. Höglinger, G. U. *et al.* Clinical diagnosis of progressive supranuclear palsy: The movement disorder society criteria. *Mov. Disord.* **32**, 853–864 (2017).

4. Sebastian J. Crucht *et al.* Consensus classification of posterior cortical atrophy. *Alzheimer’s Dement.* **13**, 870–884 (2017).

5. Ahmed, S. *et al.* MAPT p.V363I mutation A rare cause of corticobasal degeneration. *Neurol. Genet.* **5**, (2019).

6. Bessi, V. *et al.* Semantic dementia associated with mutation V363I in the tau gene. *J. Neurol. Sci.* **296**, 112–114 (2010).

7. Anfossi, M. *et al.* MAPT V363I variation in a sporadic case of frontotemporal dementia: Variable penetrant mutation or rare polymorphism? *Alzheimer Dis. Assoc. Disord.* **25**, 96–99 (2011).