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Intrafamilial variable phenotype including corticobasal syndrome in a family with p.P301L mutation in the *MAPT* gene: first report in South America

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ABSTRACT

Frontotemporal lobar degeneration is a neuropathological disorder that causes a variety of clinical syndromes including frontotemporal dementia (FTD), progressive supranuclear palsy, and corticobasal syndrome (CBS). FTD associated with parkinsonism occurs frequently as a result of mutations in the *C9orf72* gene and also in the genes coding for the protein associated with microtubule tau (MAPT) and progranulin (GRN) on chromosome 17 (FTDP-17). Herein, we report an Argentinean family, of Basque ancestry, with an extensive family history of behavioral variant of FTD. Twenty-one members over 6 generations composed the pedigree. An extensive neurologic and neurocognitive examination was performed on 2 symptomatic individuals and 3 non-symptomatic individuals. Two different phenotypes were identified among affected members, CBS in the proband and FTD in his brother. DNA was extracted from blood for these 5 individuals and whole-exome sequencing was performed on 3 of them followed by Sanger sequencing of candidate genes on the other 2. In both affected individuals, a missense mutation (p.P301L; rs63751273) in exon 10 of the *MAPT* gene (chr17q21.3) was identified. Among *MAPT* mutations, p.P301L is the most frequently associated to different phenotypes: (1) aggressive, symmetrical, and early-onset Parkinsonism; (2) late parkinsonism associated with FTD; and (3) progressive supranuclear palsy but only exceptionally it is reported associated to CBS. This is the first report of the occurrence of the p.P301L-*MAPT* mutation in South America and supports the marked phenotypic heterogeneity among members of the same family as previously reported.

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1. Introduction

Frontotemporal lobar degeneration (FTLD) refers to a spectrum of rare neurodegenerative disorders characterized by protein accumulation and degeneration of frontal and temporal lobes comprising: the behavioral variant of frontotemporal dementia (bvFTD), the semantic and nonfluent variant of primary progressive aphasia, FTD with motor neuron disease (FTD-MND), progressive supranuclear palsy (PSP), and corticobasal syndrome (CBS).

FTLD shows overlapping symptoms including behavioral and personality changes, language impairment, deficits in executive

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functioning, variable combinations of hyperkinetic or hypokinetic movement disorders (parkinsonism), and/or motor–neuron disease (Baizabal-Carvallo and Jankovic, 2016; Mackenzie and Neumann, 2016; Oeckl et al., 2016; Pottier et al., 2016).

Although PSP and CBS are classified as "tauopathies", characterized by the presence of intracellular aggregates of microtubule-associated protein tau (MAPT), FTD may include underlying tau and TDP-43 pathologies. Nevertheless, PSP, corticobasal degeneration (CBD) and Pick's disease comprise by far the majority of cases of FTLD-tau.

In the last few years, a number of different mutations in the *MAPT*, progranulin (*GRN*), and *C9orf72* have been shown to cause autosomal dominant forms of FTLD (FTD, PSP, and CBS) (Baizabal-Carvallo and Jankovic, 2016; Mackenzie and Neumann, 2016; Oeckl et al., 2016; Pottier et al., 2016). Although no clear genotype-phenotype correlation has been established for all, more than 55 mutations in *MAPT* have classically been assigned as causative of autosomal dominant FTD, PPA and PSP.

Here, we report the results of a genetic study using whole-genome sequencing (WES) in an Argentinean family that includes clinically diagnosed CBS in 1 sibling and FTD in another, with an extensive family history of bvFTD, originally diagnosed as "Pick's-like disease", with an autosomal dominant pattern of inheritance.

2. Patients and methods

2.1. Subjects

This study was approved by the institutional ethics committee. Each subject, from whom blood samples were obtained for genetic testing, provided a written informed consent.

The pedigree consists of 26 family members over 6 generations with 9 affected individuals (Fig. 1). A neurological examination was performed on both living symptomatic individuals (V-1, V-3) and 3 asymptomatic individuals (V-2, V-4, and VI-1).

2.2. Clinical evaluation

Clinical evaluations were conducted at the neuroscience institute (INEBA) (V-1 and V-4) or at the Memory and Aging Center, part of the foundation for the fight against neurologic diseases in children (FLENI) (V-2, V-3, VI-1) in Buenos Aires, Argentina.

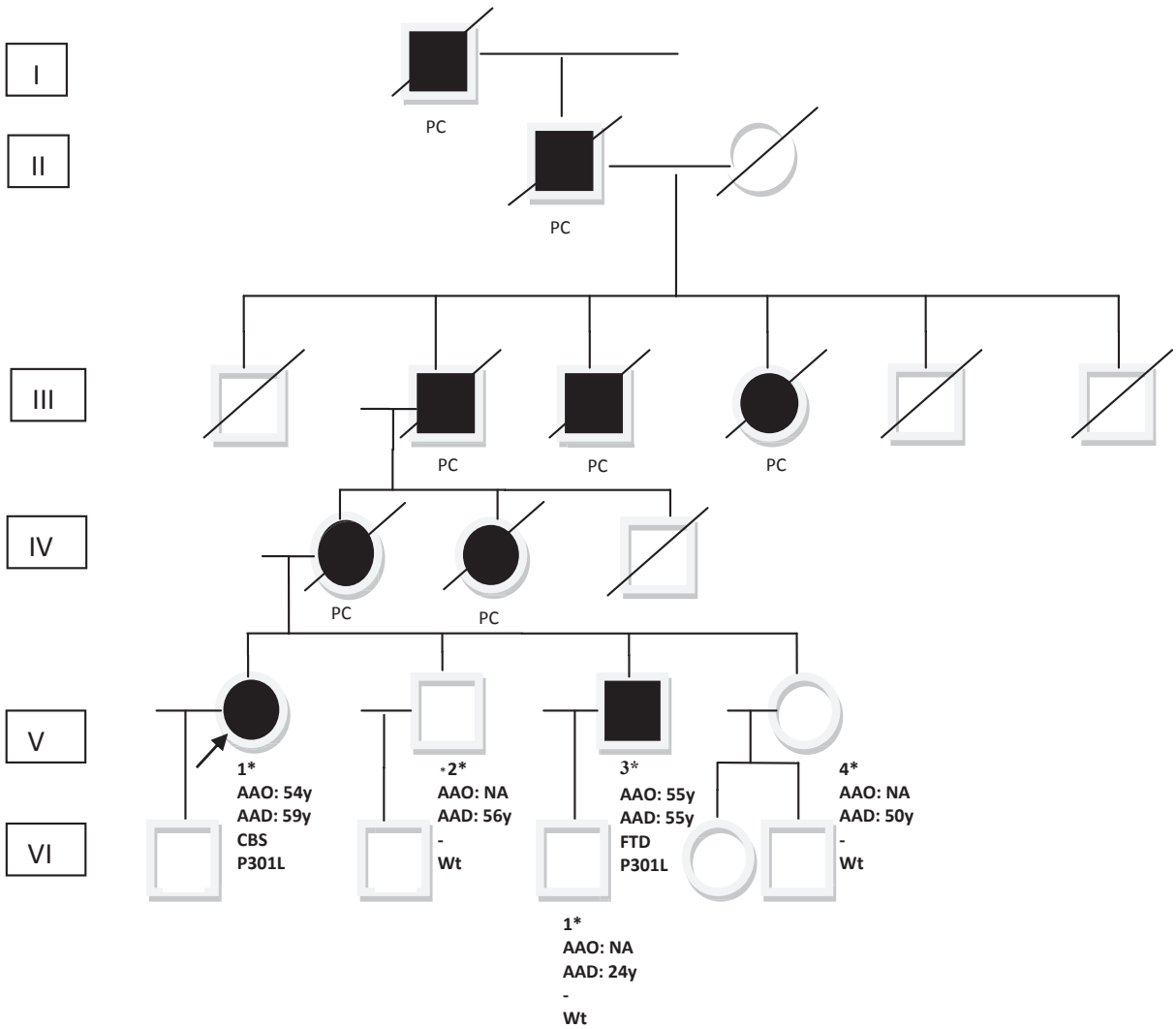

Fig. 1. Pedigree of our family carrying a mutation (p.P301L; rs63751273) in exon 10 of the *MAPT* gene (chr17q21.3). Proband is indicated with an arrow. All affected members are represented in black. Mutation status is shown for all individuals that underwent genetic testing. *Evaluated Individuals and DNA available. ⌀ Deceased individuals. Abbreviations: AO, age at onset; CBS, corticobasal syndrome; E+, affected individuals with positive evaluation; FTD, frontotemporal dementia; P, proband; PC, reported as a Pick's Disease like (bvFTD); Wt, wild type.