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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

Emilia M. Gatto[a,b], **Ricardo F. Allegri**[c,d,e], **Gustavo Da Prat**[b], **Patricio Chrem Mendez**[c], **David S. Hanna**[f,g], **Michael O. Dorschner**[f,g], **Ezequiel I. Surace**[h,d], **Cyrus P. Zabetian**[i,j], and **Ignacio F. Mata**[i,j]

[a]Department of Movement Disorders, Fundación INEBA, Guardia Vieja 4435, Buenos Aires, Argentina

[b]Sanatorio de la Trinidad Mitre, Bartolomé Mitre 2553, Buenos Aires, Argentina

[c]Memory and Aging Center., Instituto de Investigaciones Neurológicas Dr. Raúl Carrea (FLENI), Montañeses 2325, C1428AQK Buenos Aires, Argentina

[d]Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Godoy Cruz 2290, Cdad. Autónoma de Buenos Aires, Argentina

[e]Universidad de la Costa (CUC), Colombia

[f]Department of Psychiatry and Behavioral Sciences, University of Washington, 2815 Eastlake Ave E #200, Seattle, WA 98102, USA

[g]Department of Pathology, University of Washington, 1959 NE Pacific St, Seattle, WA 98195, USA

[h]Laboratorio de Biología Molecular, Instituto de Investigaciones Neurológicas Dr. Raúl Carrea (FLENI), Montañeses 2325, C1428AQK, Buenos Aires, Argentina

[i]Veterans Affairs Puget Sound Health Care System, Seattle, 1660 South Columbian Way Seattle, WA 98108, USA

[j]Department of Neurology, University of Washington/Seattle, 1959 NE Pacific St, Seattle, WA 98195, USA

Abstract

Frontotemporal lobar degeneration (FTLD) is a neuropathological disorder that causes a variety of clinical syndromes including fronto-temporal dementia (FTD), progressive supranuclear palsy

Corresponding Author: Ignacio F. Mata PhD, Address: VA Puget Sound Health Care System, GRECC S-182, 1660 South Columbian Way, Seattle, WA 98108. Telephone Number: (206) 768-5297, Fax: (206) 764-2569, nachofm@uw.edu.

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(PSP) 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 (bvFTD). Twenty one members over 6 generations composed the pedigree. An extensive neurological 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 five individuals and whole-exome sequencing (WES) 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: a) aggressive, symmetrical and early-onset Parkinsonism; b) late parkinsonism associated with FTD and c) PSP 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.

Keywords

FTD; *MAPT*; P301L; Cognition; CBS

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 non-fluent variant of primary progressive aphasia (svPPA and nfvPPA), 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 functioning, variable combinations of hyperkinetic or hypokinetic movement disorders (parkinsonism) and/or motor –neuron disease (Pottier et al. 2016; Mackenzie et al. 2016; Oeckl et al. 2016; Baizabal-Carvallo et al. 2016).

While 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, 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) (Pottier C et al. 2016; Mackenzie IR et al. 2016; Oeckl Pet al. 2016; Baizabal-Carvallo JF 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, primary progressive aphasia (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 one sibling and FTD in another, with an extensive family history of behavioral variant of FTD (bvFTD), originally diagnosed as “Pick’slike 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 (Figure 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 neurological diseases in children (FLENI) (V-2, V-3, VI-1) in Bueno Aires, Argentina.

Personal and family histories were analyzed. Neurologic examination was conducted by neurologists. Symptomatic patients underwent an extensive neuropsychological battery to evaluate the following areas of cognitive domains:

- Orientation: from Mini Mental State Exam (MMSE)
- Attention: digit span (forward and backward) and trail making test A
- Memory: Logical memory from Wechsler Memory Scale, Rey Auditory Verbal Learning Test (RAVLT), and recall from Rey Complex Figure (RCF)
- Language: Boston naming test (BNT), semantic and phonemic verbal fluency
- Visuospatial: from MMSE and copy from Rey Complex Figure (RCF)
- Executive functions: trail making B and verbal fluency

Ancillary test were performed in both symptomatic individuals (brain MRI, PET and SPECT).

2.3. Genetic analyses

First DNA was extracted from blood for the proband (V-1) and two asymptomatic siblings (V-2 and V-4). We performed WES on all 3 individuals following a previously described protocol (Mata et al., 2015). In summary the exome was captured using the Integrated DNA Technologies v1.0 kit (IDT, Coralville, IA) and sequenced with 100-base pair (bp) paired-end reads on a HiSeq2500 (Illumina, San Diego, CA) to achieve a mean coverage of 80–100X. Sequence reads were mapped using the Burrows-Wheeler Aligner and variants were

called using GATK Haplotype Caller. We flagged variants failing to meet the quality thresholds described by the GATK "Best Practices" of QD. We excluded alleles that occurred at a frequency >1 % in the ExAC database (http://exac.broadinstitute.org/). Finally, we used custom software to analyze variants that passed all filters to identify alleles that segregated with disease.

To validate candidate variants and to examine segregation in the family we redrew blood from individuals (V-1, V-2) and added two new family members (V-3, affected and VI-1, healthy). In this case DNA was obtained from peripheral blood leukocytes using the Wizard Genomic DNA Purification Kit (PROMEGA) according to manufacturer's instructions. Fifty nanograms of genomic DNA were used to PCR-amplify exon 10 of the *MAPT* gene (MIM: 157140) using the following forward and reverse primers, respectively: 5′-TGTCACTCATCGAAAGTGGAGG-3′ and 5′-TCCTGAGAGCCCAAGAAGGATT-3′. PCR product clean-up was performed by treatment with ExoSAP-IT reagent (AFFYMETRIX). Bi-directional automatic Sanger sequencing was performed. Electropherograms were analyzed using the Mutation Surveyor software (SOFTGENETICS) and FinchTV (GEOSPIZA).

3. Results

We studied a multigenerational Argentinean family of Basque origin in which 2 individuals (one female and one male) were affected with CBS and FTD, respectively (Figure 1).

Clinical diagnosis of bvFTD described like Pick's disease was reported in 7 deceased patients over 4 generations in whom data was collected by interviews of relatives. All these cases were clinically described as early onset dementia where apathy and disinhibition were the prominent symptoms (Figure 1; cases: I-1, II-1, III-1; III-2, III-3; IV-1, IV-2).

3.1 Clinical description

Case V-1 (Proband)—This 59 year-old woman was referred for asymmetric parkinsonism with mild resting tremor and severe rigidity involving the upper right limb. She was born to a non-consanguineous couple and she has two brothers and one sister.

She was a physician; she first noticed unilateral resting tremor, severe bradykinesia and pain in her right upper limb at the age of 54 years. Micrographia was reported as one of the major complaints. She expressed some concerns about mild memory deficits and she was afraid to be a carrier of a possible genetic disorder since several members of her family, from the maternal side, were clinically diagnosed with Pick's disease.

She was initially misdiagnosed as Parkinson s disease. Levodopa produced a moderated and transient benefit. An initial cognitive assessment, performed at age 56, showed some impairment in attention and executive functions (assessed by Trail Making Test (TMT) A and B). The other cognitive domains were normal

Symptoms progressed and during the next four years the patient exhibited gait disturbance, prominent postural instability (she was prone to fall), myoclonus, focal dystonia with flexor posture and alien limb phenomenon involving upper right limb, as well as, hyperreflexia

involving predominantly the right hemibody, bilateral ankle clonus, and Hoffman's reflex and apraxia. At age 59 she showed marked cognitive impairment involving memory, language, attention and executive domains.

Her family history was relevant as many of her relatives suffered from early onset dementia with prominent behavioral symptoms diagnosed as Pick's disease (now referred as bvFTD), with a suggestive autosomal dominant pattern of inheritance (Figure 1).

Ancillary test results : The thyroid functional analysis, urine and serum copper, vitamin B12 and vitamin E, manganese, ammonium, antiGAD antibody, antiVGKC antibody were all normal or negative. Brain MRI showed bilateral and symmetric putaminal hyperintense T1 signals (Figure 2). FDG PET: diffuse left hemisphere, thalamic, mesencephalic and basal ganglia hypometabolism as well as left motor cortex (Figure 3). ^{18}F-DOPA PET scan left striatal dopaminergic degeneration (Figure 4). Cognitive assessment disclosed a non-amnesic multi-domain mild cognitive impairment. She fulfilled the proposed clinical criteria for possible corticobasal syndrome (CBS): asymmetrical rigidity and dystonia nonresponsive to L–dopa, insidious onset, progressive course and cortical dysfunction (Armstrong et al., 2013).

Proband's brothers (V-2 and V-3) were evaluated at the Memory and Aging Center, (FLENI, Buenos Aires) seeking genetic counseling since they were concerned about their family history.

Case V-2—He was 56 years old at the time of consultation and had come from another Latin American country where he is still living. He did not report any cognitive complaint at the moment he was interviewed and he was worried about his own risk of suffering from the same disease. He added data about the family history and he was willing to undergo cognitive testing, MRI and genetic testing if necessary. Also he confessed he had come to convince his brother (V-3) to seek medical attention. From his point of view, his brother (V-3) seemed a little more distracted and his nephew (VI-1) had reported to him that his father exhibited behavioral problems. Therefore, his main intention was to assist his nephew (subject VI-1) with his brother's medical attention.

He was asked for a blood sample for DNA banking. In addition, a brain MRI and neuropsychological battery test were performed.

The MRI of subject V-2 did not show any overt findings. The cognitive assessment showed some impairments on Rey complex figure (copy and recognition) and TMT A and B. The other cognitive domains were normal. Despite the findings on the cognitive testing, no conclusive diagnosis was made because of the lack of correlation between the clinical exam, the brain MRI and cognitive assessment. Therefore he was cataloged as non-amnestic mild cognitive impairment (MCI). It was suggested to him that annual cognitive assessment should be made and the subject returned to his country of residence.

Case V-3—He was 55 years old at the time of consultation. He is a physician and in the past few years had been working in the International Health Policies but he is currently unemployed. At the time he was interviewed he was living with his son (subject VI-1) and

he was not married. From the initial visit, he seemed an extroverted person. He did not respect the conventional interviewing timeframes. Although it was the first time he had met the physicians from the Memory and Aging Center, he talked to them in a very casual way and sometimes using foul language or even switching between Spanish and English language. He had logorrhea and a tangential speech. Despite his extroverted attitude, he was fully aware of the family circumstances and also reported his own concern on having a neurological disease. However, he did not report any issues regarding his cognitive abilities. In fact, he said he was writing stories and seemed very satisfied and content with his life. Even though he was unemployed and was receiving monthly payments from his brother (V-2), he did not report any financial issues and he looked very comfortable with this situation. He said he was expecting to collect an important amount of money from an old investment he had made in Europe a long time ago. When he was asked about medical condition, he referred he was in a good physical condition but he used to go to a psychiatrist occasionally due to mild anxiety and for that he was taking pregabalin 75 mg once a day. When his brother (V-2) was asked about personality traits of this patient, he responded that his brother had always been a very extroverted person and this was his normal way of behavior. However, he acknowledged he visits his brother very occasionally.

When his son (VI-1) was asked about his father's behavioral changes he added a lot more information. He said his father had lost contact with the rest of the family, that he stays at home almost every day sleeping and was awake during the nights writing. The writing level had decreased substantially and tales became very puerile from his point of view. Also, he added that the story of the money to be collected was not real and although he was financially supported by his brother, he did not account for domestic money issues. Importantly, he reported that his father was abusing alcohol and he always had the same meals. Sometimes his father would wake him up in middle of the night just simply to talk. According to the symptoms reported by his son, subject V-3 was suffering from misjudgments in his financial and social situation, lack of empathy with his son a rest of the family, confabulation, some compulsive behavior (alcoholism) and changes in his daily diet and grooming. Otherwise no hyperorality, hypersexuality or other perseverative behavior was reported nor evidenced.

The cognitive assessment of subject V-3 showed impairments in Logical Memory (immediate and delayed) and total and delayed scores of the Rey auditory learning verbal test (RALVT) with preservation of the recognition phase. Also language, attention and executive domains were impaired. The cognitive profile was compatible with attention and executive disorder. In regard to the brain MRI, there was significant slightly asymmetrical frontal atrophy focally distributed to the frontal lobes whereas the other lobes were preserved. Taken together, these findings were compatible with probable behavioral variant of FTD.

Case VI-1—He was 24 years old at the time of the genetic counseling. He works as a chef in a restaurant and he did not report any cognitive complain about himself. He was convinced that his father was suffering from a neurological disease and he was well-aware of his own risk so he also wanted to undergo genetic testing.

3.2 Genetic studies

We performed WES on the proband (V-1) and two unaffected family members (V-2 and V-4). After filtering out all variants with frequency >1% in the ExAC database or those that failed to meet the quality thresholds of the Genome Analysis ToolKit (GATK) “Best Practices” we ended up with 151 variants not shared between the affected proband and the unaffected family members. We then filtered out those variants with a Combined Annotation Dependent Depletion (CADD; http://cadd.gs.washington.edu/) score < 20 (N=131), thus selecting those included in the 1% more deleterious substitutions in the human genome. Two variants stuck out above the rest, with CADD scores of 38 and 29.

The first one was a G to A substitution in *GRIN3B* (chr19 p13.3) causing an early stop codon, resulting in premature termination of the protein (Trp575*; rs112116006). This variant, although rare in Europeans, is a common SNP in Latinos (MAF >6%).

The second variant, with a CADD score of 29, was a C to T transition in exon 10 in the *MAPT* gene (chr17q21.3, MIM: 157140), which causes a nonsynonymous proline to leucine change at codon 301 (p.P301L; rs63751273). Mutations in this gene has been previously shown to cause several neurodegenerative disorders including FTD, Parkinson’s disease, PSP and multiple system atrophy (Hodges et al., 2016 ; Tang et al., 2016). *MAPT*-p.P301L is located in a highly conserved region of the gene, and affects only the 4-repeat tau isoforms since exon 10 is spliced out in the 3-repeat isoform. This mutation is considered pathogenic and has been found in approximately 32 FTD families worldwide.

We then genotyped this variant in all remaining available family members, including the proband (to confirm the variant) using Sanger sequencing. The same variant was also found in the other affected sibling (V-3).

Together, these data support co-segregation of this mutation with the disease

Discussion

We report the first Argentinean family with a pathogenic variant (p.P301L; rs63751273) in exon 10 of the *MAPT* gene causing a heterogeneous neurological phenotype including both CBS and bvFTD. Positive family history in FTLD has been identified in 30–50% of cases (Gasca-Salas et al., 2016), with an autosomal dominant pattern of inheritance in ~10– 20% of them (Sieben A, et al, 2012; Chow et al., 1999). Among all forms of FTLD, mutations in the *GRN*, *MAPT* and *C9orf72* genes account for approximately 17% of the cases (Majounie et al., 2012), with *GRN* and *MAPT* accounting for approximately 5–20% of all familial FTLD (Rademakers et al., 2012). In all these cases a great clinical heterogeneity is reported including bvFTD (in some cases associated with motor neuron disease); primary progressive aphasias (PPAs, with three variants nonfluent agrammatic, logopenic and semantic); PSP-variant Steele-Richardson Olszewski syndrome; and the CBS (Coyle-Gilchrist et al., 2016). However, CBS and PSP combined were present in only 8.6% of FTLD (Ioannidis et al., 2012; Ghetti et al., 2015; Gasca-Salas et al., 2016).

To date, more than 55 mutations have been identified in the *MAPT* gene causing autosomal dominant forms of FTD and parkinsonism, with a wide clinical heterogeneity mainly consistent of typical bvFTD (Ghetti et al., 2015; Irwin et al., 2016). Despite having some risk associations with *MAPT* variants (Jung et al., 2012; Rossi et al. 2008; Wischik et al., 2015) pathogenic *MAPT* mutations are an unusual cause of CBS thus making it hard to define a clear genotype-phenotype correlation.

In 1998 a mutation in the *MAPT* gene, p.P301L, was described in several families with FTD and parkinsonism (Hutton et al., 1998; Dumanchin et al., 1998). In 1999, Bugiani et al., reported an Italian family with a different mutation in the same amino acid, p.P301S, that presented with the same phenotype of our family, CBS in some siblings and FTD in others highlighting the intrafamilial variability (Bugiani et al., 1999). Moreover, as in our proband case, brain MRI showed Ti weight hyperintensity in caudate, thalami and putamen (Buggiani et al., 1999).

Kouri et al. reported a new *MAPT* causing mutation in exon 13 (p.N410H), in a family with not only clinical diagnosed but also neuropathological findings meeting the diagnostic criteria for CBD (Kouri et al., 2014; Donker Kaat et al., 2009; Irwin et al., 2015; Baizabal-Carvallo et al., 2016). Recently, Marshall et al reported a novel heterozygous mutation, p.C291R, with an unusual clinical presentation characterized by progressive apraxia of speech and CBS (Marshall et al., 2015). Although in this family apraxia of speech was the dominant sign, CBS is also known to overlap PPA and FTD and word finding difficulties can be a presenting symptom in CBS (Jung et al., 2012).

Adding to the complex heterogeneity, a p.G389R amino acid substitution in *MAPT* gene has been reported in a clinically sporadic patient with CBS (Rossi et al., 2008).

Some authors mention some concerns about the true MAPT-CBS association because in many cases a neuropathological confirmation is not available or failed to meet pathologic criteria for CBD (Kouri et al., 2014; Wszolek et al., 2003). An illustrative case showed a MAPT mutation (p.I260V) in exon 9 with differential FTD phenotype and CBD neuropathology (Grover et al. 2003).

Among different *MAPT* mutations, p.N279K and p.P301L, not only can cause specific phenotypes but also can show different pathophysiological mechanisms. The p.N279K mutation shows abnormally premature developmental 4R tau expression, including changes in the 3R:4R isoform ratio while the p.P301L *MAPT* mutation shows thicker processes which contain 4R tau and alpha-synuclein and abnormal mitochondrial retrograde transport (Iovino M et al., 2015).

On the other hand, newly performed CBS genome-wide association studies (GWAS) showed that genes other than *MAPT* increase the risk of CBS, among them *MOBP* appears as an interesting gene to explore the link between neuronal and oligodendrocyte pathology in CBS (Kouri et al., 2015).

In contrast, intronic and exonic mutations that affect exon 10 splicing and lead to an overproduction of four-repeat tau tend to be associated with a parkinsonism plus predominant phenotype (Ghetti et al., 2015).

As was mentioned above, FTD, PPA, CBS and PSP should be regarded as a clinically and biologically cohesive spectrum and some authors continue to validate the historically eponymic term of Pick's complex, although the neuronal inclusions exhibit distinct differences. These observation could explain the clinical diagnosis of Pick's disease that was mentioned for deceased siblings in our family (Kertesz A., 2003; Ikeda et al. 2002)

This report has several strengths defined by the fact that is a first family in our country, with a pathogenic variant in *MAPT* and variable phenotype in several members of the same kindred. Moreover, a rare phenotype (CBS) contributes to support the variable spectrum associated with *MAPT* mutations. The identification and report of families with a *MAPT* mutation give us the opportunity to investigate potential biomarkers, also in very early stage of the disease. Interestingly, the analysis of carriers and non-carriers from a four-generation French-Canadian family segregating p.P310L showed a frontal executive and attentional tasks dysfunction even in presymptomatic individuals (Rademakers et al., 2004). This neuropsychological dysfunction was early described in the proband and his affected brother.

We cannot ignore some weakness such as the lack of pathological confirmation of CBS diagnosis and the scarce objective information of all generations with a recall bias and different historical classification of previously called Pick's.

In summary, our findings contribute to support the high phenotypic variability among families and also, within the same family with the same *MAPT* mutation. This observation underscores the concept that other environmental or genetic factors could modify the phenotype.

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Highlights

- We found the p.P301L-*MAPT* mutation in a family with behavioral variant of FTD (bvFTD)
- This family included clinically diagnosed CBS in one sibling and FTD in another
- First report of p.P301L mutation in the Tau gene in South America
- This supports the high phenotypic heterogeneity in p.P301L-*MAPT* mutation carriers

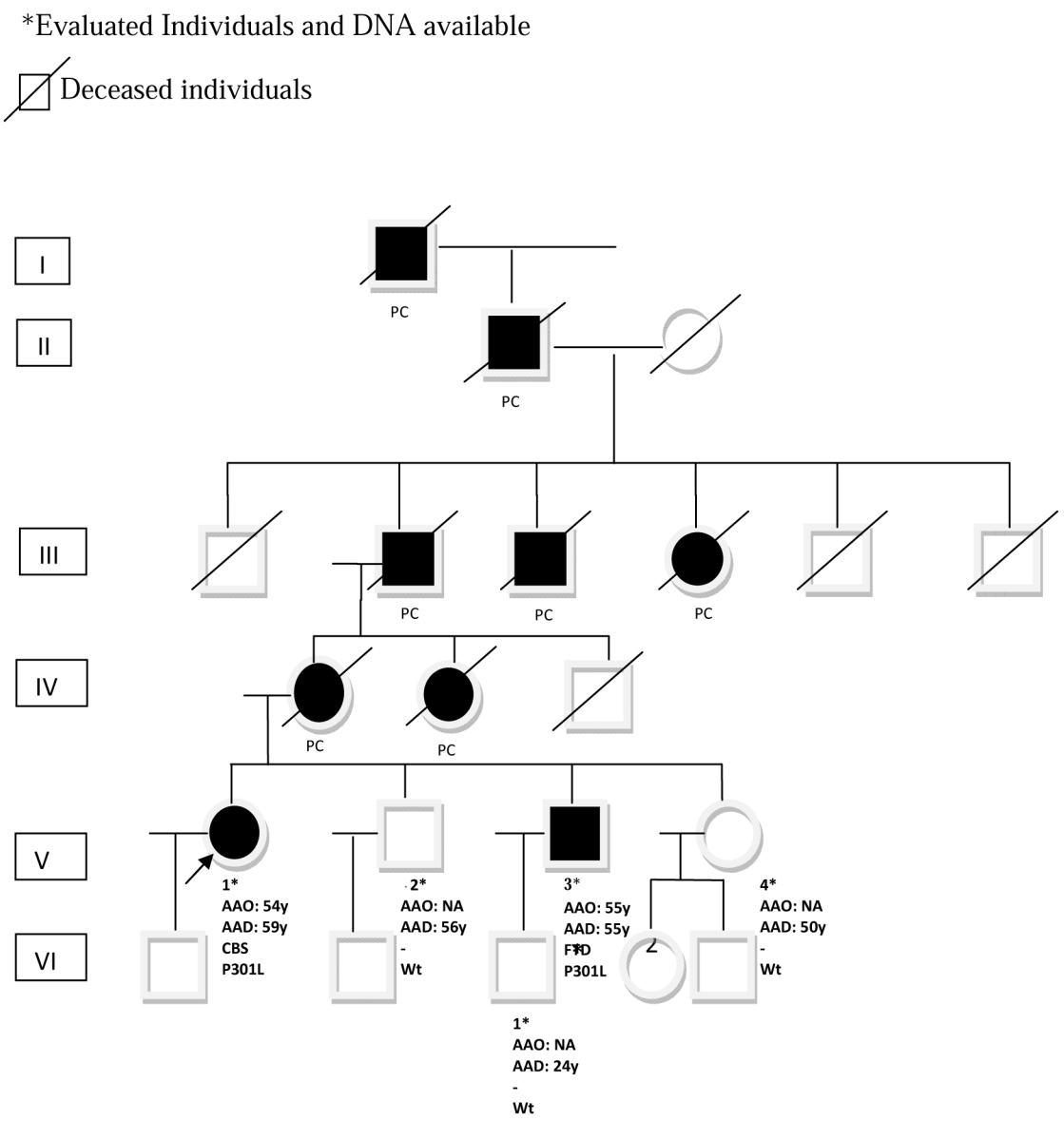

Figure 1.

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. AO= Age at onset.P= proband. E+ = affected individuals with positive evaluation CBS= Corticobasal Syndrome; FTD= Frontotemporal Dementia; PC = Reported as a Pick's Disease like (bvFTD). Mutation status is shown for all individuals that underwent genetic testing (Wt = wild type).

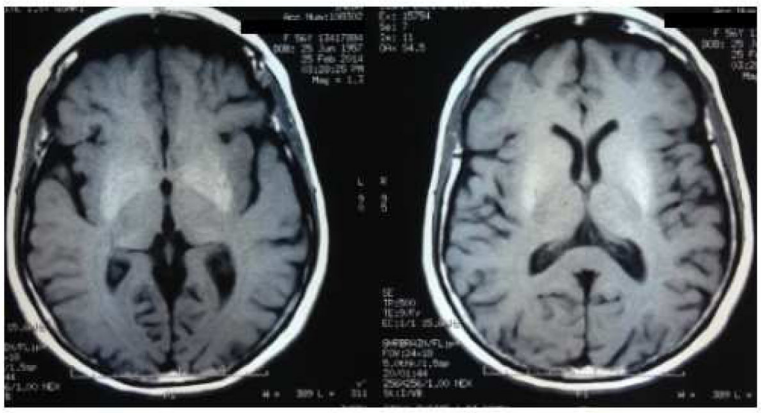

Figure 2.
Brain MRI from proband (V-I) showing bilateral and symmetric putaminal hyperintense T1 signals

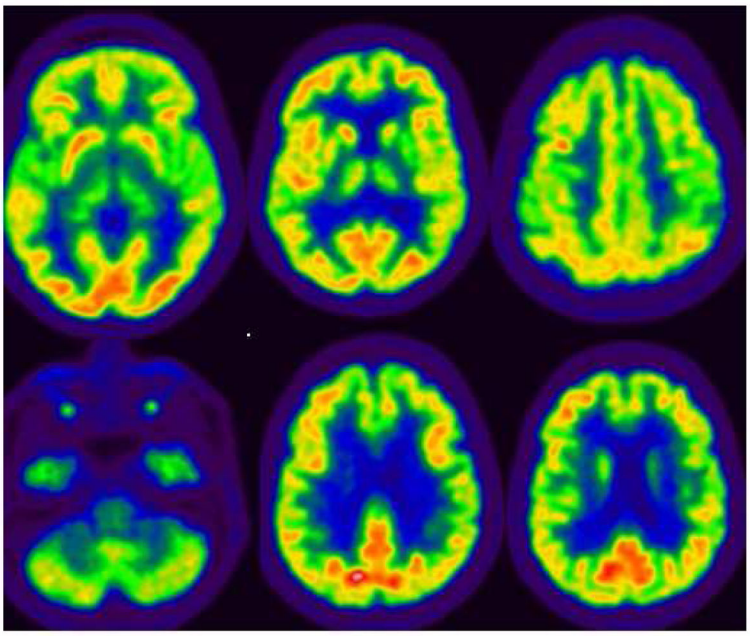

Figure 3.
FDG PET from proband (V-I) showing diffuse left hemisphere, thalamic, mesencephalic and basal ganglia hypometabolism as well as left motor cortex

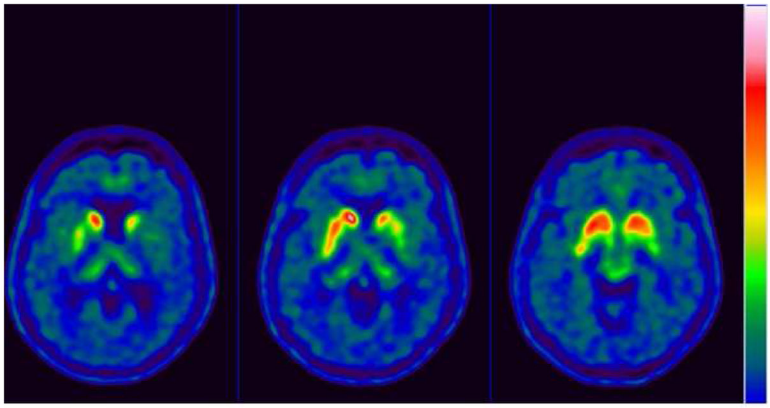

Figure 4.
^{18}F-DOPA PET scan left striatal dopaminergic degeneration from proband (V-I).