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*Systematic Review*

# Dissecting the Clinical Heterogeneity and Genotype-Phenotype Correlations of *MAPT* Mutations: A Systematic Review

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**Abstract**

**Background**: Microtubule-associated protein tau (*MAPT*) mutations are one of the main causes of genetic Frontotemporal dementia (FTD) and are characterised by high clinical heterogeneity. A behavioural variant of FTD is the principal phenotype, but other rarer phenotypes are described, mostly reported as single cases. In this review, we provide an overview of the clinical phenotypes associated with *MAPT* mutations in order to define their characteristics and explore genotype-phenotype correlations. **Methods**: We performed systematic bibliographic research on the Pubmed database, focusing on articles published between 1998 and 2022. We analysed the clinical phenotype of 177 patients carrying *MAPT* mutations, focusing on the rarest ones. We performed a narrative synthesis of the results. **Results**: Regarding language phenotypes, the most frequent were the non-fluent variant and the semantic variant of Primary Progressive Aphasia (nfvPPA, svPPA), approximately in the same proportion. Almost 20% of the whole group of patients present a clinical phenotype belonging to the corticobasal syndrome-progressive supranuclear palsy (CBS-PSP) spectrum. While no clear genotype-phenotype correlation could be identified, some mutations were associated with a specific phenotype, while others gave origin to multiple clinical pictures and mixed phenotypes. **Conclusions**: A high clinical heterogeneity exists in FTD associated with *MAPT* mutations without a clear phenotype-genotype correlation in most cases. However, some characteristics can be helpful to drive genetic testing. Deep phenotyping of patients, together with functional studies of single mutations, particularly those associated with atypical phenotypes, are necessary to better understand the biological mechanisms underlying this clinical variability.

**Keywords:** *MAPT*; FTD; primary progressive aphasia; AD; CBS; PSP; phenotypes

## 1. Introduction

Frontotemporal dementia (FTD) refers to a group of disorders characterised by striking clinical and pathological heterogeneity. Up to 40% of FTD are inherited forms caused by mutations in the progranulin (*GRN*), in the chromosome 9 open reading frame 72 (*C9orf72*) or in the microtubule-associated protein tau (*MAPT*) gene in most cases. The latter is responsible for approximately 5–10% of all familial FTD cases [1]. Almost 90 pathogenic *MAPT* mutations have been discovered so far (Human Gene Mutation Database, https://digitalinsights.qiagen.com/products-overview/clinical-insights-portfolio/human-gene-mutation-database/; [2]), causing different effects on tau protein, with alteration of: (i) tau affinity for microtubules, leading to microtubule destabilisation; (ii) tau aggregation properties; (iii) the physiological proportion of 4R and 3R tau isoforms [3]. The clinical phenotypes associated with FTD are highly heterogeneous, with some differences between the three main genetic forms [4]. In *MAPT* mutation, the age at onset is usually earlier than in *GRN* and *C9orf72* mutations and wide phenotypic variability, in terms of age of onset, clinical presentation and features of pathological tau deposits in the brain [1], is evident. The most common phenotype is the behavioural variant (bvFTD), while primary progressive aphasia (PPA) is less frequently described. bvFTD is characterised by progressive atrophy in the frontal and temporal lobes, causing behavioural, cognitive and personality alterations. PPAs include a heterogeneous group of diseases mainly affecting language. Depending on the brain area involved, symptoms vary from progressive loss of meaning and single-word comprehension deficits (semantic variant of PPA) to slow, effortful, hesitant and distorted speech (non-fluent variant of PPA). In addition, other phenotypes such as Corticobasal Syndrome (CBS), Progressive Supranuclear Palsy (PSP) and amnestic syndrome consistent with Alzheimer's disease (AD-like) are associated with *MAPT*. CBS is characterised by asymmetric motor signs (rigidity, tremor, dystonia, and myoclonus) and is often associated with apraxia, cortical sensory deficits and alien limb phenomena. PSP affects body movements, causing early loss of balance, difficulty in walking or swallowing, slurred speech and eye movement impairment. AD-like phenotypes caused

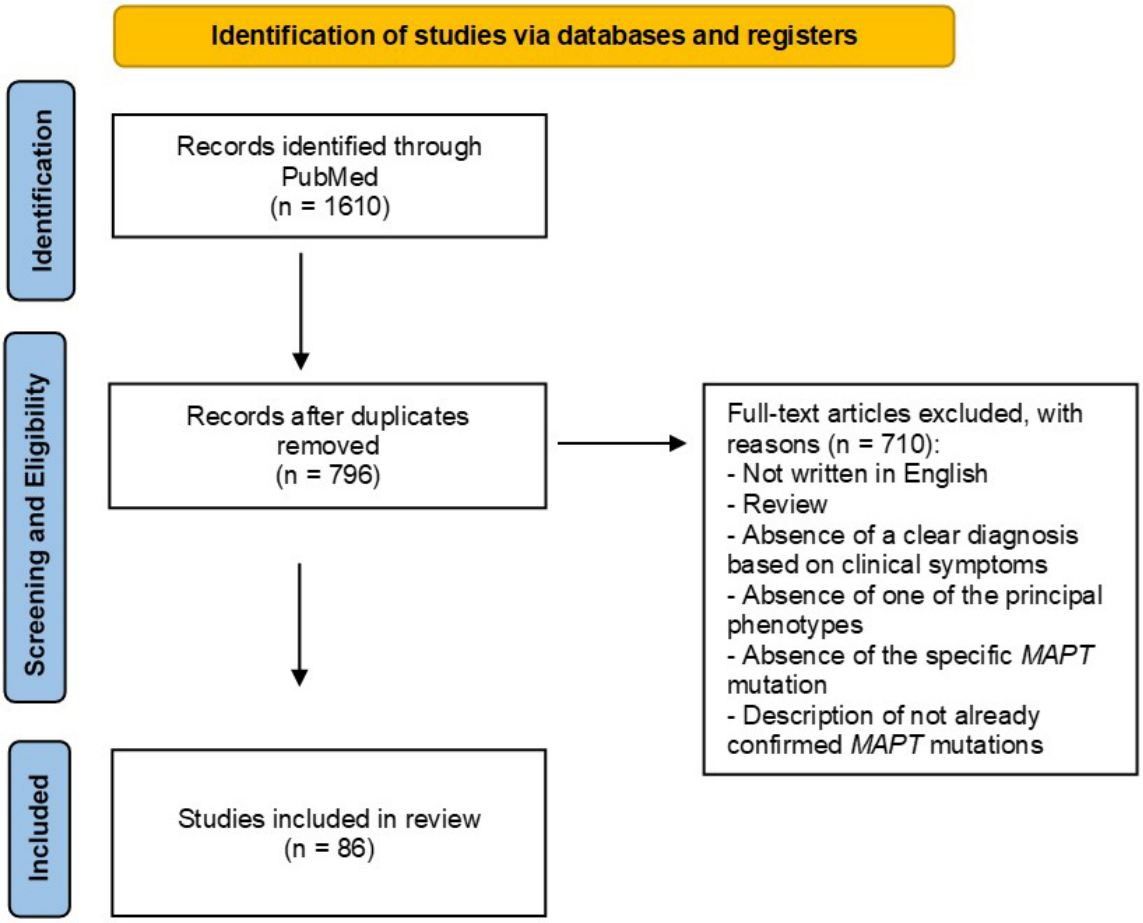


**Fig. 1. PRISMA flow-chart of the Pubmed search.** *MAPT*, microtubule-associated protein tau.

by *MAPT* mutations are usually characterised by predominantly episodic memory deficits at onset. In this review, we provide an overview of the clinical phenotypes associated with *MAPT* mutations, focusing on the rarest ones and on those belonging to the Frontotemporal Lobar Degeneration (FTLD) spectrum, trying to better define their characteristics and to explore genotype-phenotype correlations.

## 2. Materials and Methods

We conducted systematic bibliographic research on the Pubmed database. The search focused on articles published between 1998 (the year of the discovery of the *MAPT* gene) and 2022. We applied the following terms of search: (MAPT) AND (FTD), (MAPT) AND (frontotemporal dementia), (MAPT) AND (FTDP-17), (MAPT) AND (bvFTD), (MAPT) AND (behavioural variant), (MAPT) AND (PPA), (MAPT) AND (primary progressive aphasia), (MAPT) AND (svPPA), (MAPT) AND (semantic variant), (MAPT) AND (semantic dementia), (MAPT) AND (nfvPPA), (MAPT) AND (non-fluent variant), (MAPT) AND (lvPPA), (MAPT) AND (logopenic variant), (MAPT) AND (phenotype), (MAPT) AND (PSP), (MAPT) AND (progressive supranuclear palsy), (MAPT) AND (CBD), (MAPT) AND (CBS), (MAPT) AND (corticobasal syndrome) and (MAPT) AND (corticobasal degeneration). The Title/Abstract filter was used (see PRISMA flow-chart, Fig. 1)

Since we primarily focused on the FTLD spectrum, we did not include the terms “AD” or “Alzheimer Disease” in our research. The few articles that included these terms that we found were described here because they were somehow included in an FTLD cohort or accidentally found while studying FTLD patients.

We found a total of 1610 articles. All the articles not written in English, the reviews and the studies without a clear description of the clinical phenotypes and/or without a formal diagnosis were excluded. We also excluded articles that did not specify the *MAPT* mutation or that described just haplotypes or risk factors or variants with uncertain significance (Fig. 1).

Where possible, the current bvFTD, PPAs, PSP and corticobasal degeneration (CBD) criteria [5–8] were applied retrospectively.

We selected 86 articles, including 177 patients. Among them, 28 patients showed one of the PPAs diagnosis (including semantic variant and non-fluent variant), 23 had PSP phenotype, 12 CBS phenotype, 30 had AD-like pheno-

type, and 84 were diagnosed with bvFTD. Some of these papers are listed in different groups, as the same article often comprises patients with different disease phenotypes. We analysed the clinical data of the patients, including age at onset, familial history, neuroimaging data and *MAPT* mutations. We compared the ages at onset between groups by using ANOVA with Bonferroni correction. A narrative synthesis of the results has been performed. All *MAPT* mutations were reported referring to the NCBI Reference Sequence Database (RefSeq) transcript NM_005910.6.

## 3. Results

### *3.1 Primary Progressive Aphasias (PPAs) Phenotypes*

#### 3.1.1 General Overview

We identified 21 articles describing 28 patients with different linguistic phenotypes (Table 1, Ref. [9–29]), including two patients recently reported by our group [19,27]. Ten patients had the clinical diagnosis of nfvPPA (35.71%) and ten subjects of svPPA (35.71%). Six patients exhibited clinical symptoms consistent with the right temporal variant of FTD (rtvFTD) (21.43%). In three of them, we revised the diagnosis on the basis of the recent rtvFTD criteria [30]. Two patients had a clinical diagnosis characterised by linguistic symptoms plus other non-verbal symptoms (7.14%): one patient with Primary Progressive Apraxia of Speech and one subject with a Primary Progressive Anarthria or Apraxia of Speech. In the whole PPA group, familial history was reported as positive in 23 cases (82.14%). Age at onset varied between 24 and 69, with a mean age of onset of 51.68 (±11.62).

#### 3.1.2 Non-Fluent Variant of Primary Progressive Aphasia

Ten patients of our series had the diagnosis of nfvPPA. The average age at onset was 51.7 years (±15.74). One patient had a very early age at onset, before 30 years [21]. The main symptoms at onset were verbal production deficits with non-fluent, hesitant, and stuttering speech, anomia and difficulties in word finding. Two patients presented behavioural changes; one patient had concomitant Apraxia of Speech (AOS), suggesting a slow evolution to CBS, and one patient presented signs of CBS. V363I *MAPT* mutation was found in two distinct articles [17,18], while the other mutations were isolated case reports. nfvPPA associated with AOS was found in association with the V363I mutation [18]; this patient's phenotype was characterised by progressive difficulties in speech production (hesitant, stuttering, non-fluent), followed by apraxia of speech (dysprosodia) and bradykinesia, articulatory difficulties and mild buccofacial apraxia. All these characteristics suggested a progression to CBS. CBS features were reported in another patient with nfvPPA linked to the R5H *MAPT* mutation [15] who presented non-fluent speech and expression difficulties (word finding, naming deficits, stuttering and hesitant speech) at onset, followed by mask face, right-hand apraxia, bradykinesia, rigidity and stimulus-sensitive myoclonus on his right-hand and forearm. Two studies reported behavioural changes associated with prominent non-fluent aphasia linked to G389R and S305I *MAPT* mutations [22,25].

#### 3.1.3 Semantic Variant of Primary Progressive Aphasia

Ten patients had the diagnosis of svPPA; the main symptoms at onset were language deficits (anomia and word finding) and memory disturbances. Average age at onset was 48.3 (±9.33). Three *MAPT* mutations were associated with this phenotype: the P301L in three patients belonging to the same family, the G389R in one case and Q336H in another patient. Predominant anterior temporal lobe atrophy was described in all svPPA patients.

#### 3.1.4 Right Temporal Variant of Frontotemporal Dementia

Interestingly, the diagnosis of rtvFTD was found in six patients. The mean age at onset was 53 years (±6.19), and the main symptoms at onset were memory disturbances, familiar faces identification deficits and behavioural disturbances. *MAPT* mutations related to the right temporal variant of FTD were: V363I, P332S, R406W, S352L and P301L. Two brothers shared the P332S mutation. Remarkably, their mother carried the same mutation and presented Primary Progressive Anarthria or a Progressive Apraxia of Speech [11]. At Magnetic resonance imaging (MRI), predominantly right frontotemporal or temporal atrophy was found in three patients [10,29]; the other three patients, two of them belonging to the same family, showed bilateral and symmetric temporal and frontal atrophy, barely consistent with the recently published criteria [30]. Their clinical description highlighted initial memory deficits and prosopagnosia signs followed by typical semantic deficits.

#### 3.1.5 Primary Progressive Aphasia-Plus Phenotypes

Two patients showed a PPA-plus phenotype, in which language disturbances were present but not predominant. These two subjects presented Primary Progressive Apraxia of Speech or Anarthria [11,21] linked to P332S and K317N *MAPT* mutations. The first report [11] was the mother of the two subjects carrying the same mutation and who developed right temporal variant FTD. Her first symptom was a modification in her voice followed by orofacial apraxia, brisk face reflexes and hypernasal dysarthria; across the 25 years of illness, the patient had never manifested cognitive or behavioural modifications. The subject of the second paper [21] presented with difficulty in expression and production of sounds. Over time, the patient developed PSP-like symptoms, such as vertical gaze palsy, axial rigidity, backward falls and apraxia of eyelid opening. We also found one CBS case with nfvPPA signs at onset carrying the V363I *MAPT* mutation; even though the main diagnosis was actually CBD, the patient showed unspecified primary progressive aphasia, left-sided parkinsonism and CBS [31].

**Table 1. Primary Progressive Aphasias (PPA) phenotypes.**

| Phenotype | Age at onset | Symptoms/deficit at onset | Other symptoms/deficits | MRI atrophy | Family history | *MAPT* mutation | Reference |
|---|---|---|---|---|---|---|---|
| svPPA | 46 | word-finding, semantic | N.A. | bilateral frontotemporal | y | P301L | [9] |
| svPPA | 69 | word-finding, semantic | N.A. | bilateral frontotemporal | y | P301L | [9] |
| svPPA | 43 | word-finding, semantic | N.A. | bilateral frontotemporal | y | P301L | [9] |
| rtvFTD | 46 | prosopoagnosia | memory, behavioural disorders | right temporopolar | n | V363I | [10] |
| Primary Progressive Anarthria or AOS | 60 | dysarthria, orofacial apraxia | N.A. | N.A. | y | P332S | [11] |
| rtvFTD | 50 | memory, attention, anomia | N.A. | bilateral frontotemporal | y | P332S | [11] |
| rtvFTD | 49 | memory, prosopoagnosia, depression | semantic | bilateral anterior temporal pole | y | P332S | [11] |
| svPPA | 38 | memory, anomia | semantic, behavioural disorders | bilateral frontotemporal | y | G389R | [12] |
| svPPA | 46 | word-finding, naming | behavioural disorders | anterior temporal pole > left | y | P301L | [13] |
| svPPA | 53 | semantic | N.A. | N.A. | y | P301L | [13] |
| svPPA | 48 | semantic | behavioural disorders | N.A. | y | P301L | [13] |
| nfvPPA | 65 | non-fluent aphasia and parkinsonism | anxiety, cognitive decline | bilateral cortical | y | K298E | [14] |
| nfvPPA + CBD | 60 | word-finding, naming, stuttering | parkinsonism, right-hand apraxia, stimulus-sensitive myoclonus | frontotemporal > left | y | R5H | [15] |
| nfvPPA | 31 | N.A. | N.A. | frontotemporal > left | y | L266V | [16] |
| nfvPPA | 69 | stuttering | N.A. | NA | y | V363I | [17] |
| nfvPPA + AOS (later CBS) | 55 | AOS | bradykinesia | left frontal | n | V363I | [18] |
| svPPA | 47 | loss of semantic knowledge | N.A. | N.A. | y | P301L | [19] |
| nfvPPA | 54 | naming, prosopoagnosia | N.A. | left temporal | y | P301L | [20] |
| PPA + AOS | 69 | naming, disprosodia | parkinsonism, lower motor neuron disease | N.A. | y | K317N | [21] |
| svPPA | 56 | memory, anomia, comprehension, surface dyslexia | seizures | frontotemporal > left | y | P301L | [22] |
| nfvPPA | 24 | memory, agrammatism, AOS | behavioural disorders | frontotemporal > left | n | G389R | [23] |
| nvfPPA | 57 | naming | N.A. | left temporal | n | D177V | [24] |
| nfvPPA | 37 | non-fluent aphasia | behavioural disorders | N.A. | N.A. | S305I | [25] |
| nfvPPA | 65 | word-finding, dysartria | N.A. | N.A. | y | G304S | [26] |
| svPPA | 37 | semantic, judgment | N.A. | left temporopolar | y | Q336H | [27] |
| rtvFTD | 59 | memory deficits, behavioural changes | prosopagnosia and atypical parkinsonism | frontotemporal | y | S352L | [28] |
| rtvFTD | 52 | episodic memory deficits, depression, apathy | anomia and several behavioural problems | bilateral temporal; right > left | y | R406W | [29] |
| rtvFTD | 62 | behavioural changes (inappropriate, neglectful of other feelings, gluttonous) | prosopagnosia, single-word comprehension deficit and object naming, then familiar face recognition | marked anterior temporal pole; right > left | y | P301L | [29] |

MRI, Magnetic resonance imaging; y, yes; n, no; N.A., not available. >, atrophy is more pronounced in the specified hemisphere. svPPA, semantic variant primary progressive aphasia; nfvPPA, non-fluent variant primary progressive aphasia; rtvFTD, right temporal variant frontotemporal dementia; AOS, apraxia of speech; CBS, corticobasal syndrome; CBD, corticobasal degeneration.

### 3.2 Corticobasal Syndrome Phenotypes

We identified 12 patients with CBS phenotype (Table 2, Ref. [31–38]). Mean age at onset was 48.82 years (±13.67). Relatively "pure" CBS was found in seven patients (58.33%); the other five had mixed phenotypes. Among them, three patients showed associated signs of PSP over the course of the disease (CBS-PSP). One patient exhibited a corticobasal syndrome-apraxia of speech (CBS-AOS) phenotype, with apraxia of speech as the first symptom. Lastly, one patient had CBS associated with PPA, presenting with unspecified primary progressive aphasia symptoms (possibly nfvPPA) [31]. In general, in CBS cases, the main symptoms at onset were asymmetric signs of parkinsonism—rigidity, dystonia, clumsiness, tremor—and gait disturbances. As already mentioned, one patient presented with AOS and two patients presented associated aphasia and memory impairment [31,36]. MRI showed a general asymmetry of the atrophic areas involved, mainly the fronto-parietal region. The two most frequent *MAPT* mutations were P301T and P301S (both 25%), followed by the V363I mutation (16.67%). The other four cases were characterised by isolated and different *MAPT* mutations [35–38].

Casseron and colleagues [33] reported two cases of P301S mutation found in a large family with a diagnosis of CBD. Both patients had an age of onset in their late 30s. The patient described by Bugiani and colleagues [32] had, in turn, a very early age of onset (27 years-old) and presented asymmetric symptoms from the beginning. Interestingly, his father was diagnosed with schizophrenia and neuropathologically showed frontotemporal atrophy with widespread neuronal tau inclusions. Erro and colleagues [34] reported three cases carrying another mutation at the same codon, the P301T, with an older age of onset and, in one case, with speech difficulties at the beginning. Most patients in this group had a positive family history of neurodegenerative/psychiatric diseases (83.33%).

### 3.3 Progressive Supranuclear Palsy Phenotypes

We found 23 patients with PSP phenotype, whose mean age at onset was 43.09 (±5.96) (Table 3, Ref. [18,34,39–52]). Nine of them (39.13%) had an age at onset before or at 40 years. A diagnosis of "pure" PSP was found in the majority of cases (86.96%), considering that one patient specifically diagnosed with PSP-RS was considered part of these typical presentations. Besides these, we identified two atypical PSPs associated with CBS features [46] and one PSP associated with Primary Lateral Sclerosis [34]. According to the diagnosis, the main symptoms at onset were postural instability with falls, abnormal gait movements and parkinsonism. Authors also described memory and attention disturbances in two cases [39]: forgetfulness, word-finding, altered behaviour [46] and personality changes [48]. There wasn't a specific MRI pattern, but a general diffuse cerebral atrophy was often reported. Mesencephalic atrophy was described in only two patients. In seven articles (fourteen patients), an MRI description wasn't available. Family history was positive in most patients (82.61%).

The most frequent *MAPT* mutation associated with the PSP phenotype was N279K (39.13%), followed by the N296del and the S285R mutations (both 13.04%). The other eight cases were characterised by different *MAPT* mutations. *MAPT* N279K mutation was described in Japanese families [43,44]. Comparing their phenotypic characteristics with sporadic PSP patients, Ogaki and colleagues [43] found that the visual grasping symptom could be a sign specifically related to the presence of a *MAPT* mutation.

Pastor and colleagues [46] described two patients with atypical PSP linked to the N296del *MAPT* mutation. This mutation could be a risk factor for Parkinson's disease [46] in the homozygous state and, interestingly, even in the heterozygous state [50].

Two *MAPT* mutations at the same residue, V363I and V363A, are associated respectively with CBS [31] and PSP phenotypes [18]. In the latter study, the PSP patient had a mixed diagnosis of CBS, PPA and left-sided parkinsonism, with complete anarthria and severe dysphagia in the advanced stage.

### 3.4 Alzheimer's Disease-Like Phenotypes

We identified 15 articles describing 30 patients with an AD-like phenotype at onset linked to a *MAPT* mutation (Table 4, Ref. [9,18,27,53–64]). One patient has been previously reported by our group [27]. The mean age at onset was 55.73 (±6.5). The most frequent AD phenotype was the 'classical' AD type, which included those patients diagnosed with 'AD' or 'probable AD' (60%). Most patients (76.67%) presented with memory impairment at onset, in some cases associated with behavioural disorders. These included personality changes, depression, restlessness, anxiety, suspiciousness, irritability and childish behaviours. Seven patients developed behavioural alterations (23.33%). Interestingly, nine patients developed parkinsonism during the disease course (30%). From a neuroradiological point of view, the most atrophic brain areas were bilateral medial temporal lobes and the hippocampi, according to the current criteria [65].

The R406W *MAPT* was the most frequent mutation with AD-like phenotype (76.67%). Two patients carried the P301L *MAPT* mutation. All the remaining patients (23.33%) carried rarer mutations. The almost totality of the AD-like group was characterised by a positive family history of neurodegenerative diseases (96.67%). It's worth mentioning the only article describing a phenotype consistent with posterior cortical atrophy (PCA) [18]: a 54-year-old woman who developed difficulties in recognising faces and visuospatial impairment at the age of 51 and carried the V363I mutation.

**Table 2. Corticobasal Syndrome phenotypes.**

| Phenotype | Age at onset | Symptoms/deficit at onset | Other symptoms/deficits | MRI atrophy | Family history | *MAPT* mutation | Reference |
|---|---|---|---|---|---|---|---|
| CBS | 70 | right-sided dexterity impairment, slowed gait, imbalance | dysarthria, asymmetric parkinsonism, apraxia, right-sided neglect | biparietal | y | V363I | [31] |
| CBS-PPA | late 50s | left-sided parkinsonism and aphasia | N.A. | N.A. | n | V363I | [31] |
| CBS | 27 | left arm dystonia and rigidity | N.A. | right parieto-frontal | y | P301S | [32] |
| CBS/PSP | 38 | slowness, writing disability | N.A. | bilateral frontal | y | P301S | [33] |
| CBS/PSP | 38 | psychomotor slowness, gait and posture disorder | N.A. | bilateral frontal | y | P301S | [33] |
| CBS | 68 | Right-hand clumsiness | language, depression, mood changes | left parieto-temporal | y | P301T | [34] |
| CBS | 49 | gait instability | lack of motor coordination in the right-hand | mild frontotemporal | y | P301T | [34] |
| CBS | 43 | speech difficulties and cognitive decline | motor difficulties > right-hand | left posterior parietal | y | P301T | [34] |
| CBS | 54 | asymmetric parkinsonism at right, micrographia | memory deficits | bilateral symmetric putaminal hyperintense signals | y | P301L | [35] |
| CBS/PSP | 63 | memory and mood | N.A. | N.A. | y | N410H | [36] |
| CBS-AOS | 47 | speech difficulty | AOS, orofacial apraxia and dysphagia | left posterior frontal lobe | y | C291R | [37] |
| CBS | 40 | clumsiness and tremor of the left-hand | stiffness, movement slowness, speech impairment, cognitive disturbances | right fronto-parietal | n | G389R | [38] |

y, yes; n, no; N.A., not available; CBS, corticobasal syndrome; PPA, primary progressive aphasia; PSP, progressive supranuclear palsy; AOS, apraxia of speech.

**Table 3. Progressive Supranuclear Phenotype phenotypes.**

| Phenotype | Age at onset | Symptoms/deficit at onset | Other symptoms/deficits | MRI atrophy | Family history | MAPT mutation | Reference |
|---|---|---|---|---|---|---|---|
| PSP | 40 | behavioural, memory and attention disturbances | N.A. | diffuse cortico-subcortical in late-stage | n | N279K | [39] |
| PSP | 41 | behavioural, attention disturbances | N.A. | normal | y | N279K | [39] |
| PSP + PLS | 45 | gait disturbance | N.A. | asymmetric frontotemporal, left hippocampus. mesencephalic | y | P301T | [34] |
| PSP | 40 | dystonia and supranuclear gaze palsy | N.A. | normal | y | S285R | [40] |
| PSP | 41 | gait unsteadiness | N.A. | N.A. | y | S285R | [40] |
| PSP | 40 | fatigue and micrographia | N.A. | N.A. | n | IVS 10+16C>T | [41] |
| PSP | 48 | cognitive decline, changes in speech | gait and postural disturbances, vertical supranuclear gaze palsy | left frontal and temporal | y | IVS10+3G>A | [42] |
| PSP | 40 | unstable gait, behavioural change, memory problems | N.A. | unremarkable | y | N279K | [43] |
| PSP | 41 | shuffling gait, bradykinesia | N.A. | N.A. | y | N279K | [43] |
| PSP | 43 | difficulty in walking | N.A. | N.A. | y | N279K | [43] |
| PSP | 46 | difficulty speaking and breathing | gait disturbances, limb bradykinesia | N.A. | n | S285R | [44] |
| PSP | 42 | parkinsonism, personality changes, postural tremor | micrographia, shuffling gait | N.A. | y | N279K | [44] |
| PSP | 44 | Right-hand clumsiness and oscillopsia | horizontal pendular nystagmus | N.A. | y | N279K | [44] |
| PSP-RS | 40 | bradykinesia, resting tremor at right-hand | smaller voice and handwriting | frontal and temporal | y | N279K | [45] |
| Atypical PSP | 38 | forgetfulness, word-finding problems, and slowness | N.A. | mild diffuse cerebral atrophy | y | DelN296 | [46] |
| Atypical PSP | 39 | altered behaviour and parkinsonism, and progressive clumsiness of his left limbs | N.A. | mild diffuse cerebral atrophy | y | DelN296 | [46] |
| PSP | 62 | gait disorder, postural instability, dysarthria, micrographia | N.A. | unspecified cerebral atrophy | N.A. | R5L | [47] |
| PSP | 43 | personality changes | memory, backward falls | N.A. | y | L284R | [48] |
| PSP | 37 | akinetic-rigid syndrome, gait disturbance, falls | micrographia, dysarthria, no upgaze, apraxia of eyelid | N.A. | y | G303V | [49] |
| PSP | 36 | antecollis, dysarthria, postural instability, slowing of ocular movements, increased deep tendon reflex | N.A. | N.A. | y | DelN296 | [50] |
| PSP | 56 | diplopia due to oculomotor dysfunction with supranuclear ophthalmoparesis | N.A. | midbrain and mesencephalon | y | V363A | [18] |
| PSP | 41 | leg stiffness and en-bloc turning | bradykinesia, instability, hypomimia, vertical supranuclear gaze palsy | mild temporal | y | N279K | [51] |
| PSP | 48 | dystonia of the left arm, slurring of speech | writing with right-hand difficulties, walking up and downstairs | mild over the cerebrum vertex | y | S305S | [52] |

y, yes; n, no; N.A., not available; PSP, progressive supranuclear palsy; CBS, corticobasal syndrome; PLS, primary lateral sclerosis; PSP-RS, progressive supranuclear palsy Richardson syndrome.

**Table 4. Alzheimer's Disease phenotypes.**

| Phenotype | Age at onset | Symptoms/deficit at onset | Other symptoms/deficits | MRI atrophy | Family history | *MAPT* mutation | Reference |
|---|---|---|---|---|---|---|---|
| AD | 59 | memory | parkinsonism | bilateral temporo-frontal | n | P301L | [9] |
| AD | 46 | memory | parkinsonism | N.A. | y | P301L | [9] |
| AD | 56 | memory, loss and calculation difficulties | parkinsonism | N.A. | y | R406W | [53] |
| AD | 59 | withdrawal and difficulty adapting to new environments | parkinsonism | N.A. | y | R406W | [53] |
| AD | 62 | memory | parkinsonism | N.A. | y | R406W | [53] |
| AD | 48 | topographical disorientation, word-finding difficulties | N.A. | N.A. | y | R406W | [53] |
| AD | 58 | mild cognitive impairment progressing to amnesia for faces and names | parkinsonism | N.A. | y | R406W | [53] |
| AD | 55 | memory | N.A. | hippocampal | y | R406W | [54] |
| AD | 56 | memory | N.A. | bilateral medial temporal lobes | y | R406W | [55] |
| AD | 45 | memory, disorientation, loss of interest | N.A. | N.A. | y | R406W | [55] |
| AD | 51 | memory | N.A. | temporal medial lobes, hippocampus and parahippocampal | y | R406W | [55] |
| AD | 68 | memory | behavioural | medial temporal lobe | y | R406W | [56] |
| AD | 59 | memory | behavioural | frontotemporal | y | R406W | [57] |
| AD | 56 | memory, disorientation | depression, verbal perseveration | bilateral temporal | y | IVS10+16C>T | [58] |
| AD | 49 | memory, disorientation | falls, stiff neck, occasional choking | N.A. | y | IVS10+16C>T | [59] |
| AD | 40 | memory, irritability | depression | N.A. | y | Q351R | [60] |
| AD | 65 | memory | N.A. | bilateral temporal | y | R406W | [61] |
| AD | 65 | memory | N.A. | cortical and central | y | R406W | [61] |
| AD | 52 | prosopoagnosia | N.A. | bilateral medial temporal | y | R406W | [61] |
| AD | 55 | memory, personality change, depression | behavioural | N.A. | y | R406W | [62] |
| AD | 62 | memory, personality change, anxiety | behavioural | hippocampal and medial temporal lobe atrophy | y | R406W | [62] |
| AD | 60 | memory, restlessness | behavioural | hippocampal and medial temporal lobe atrophy | y | R406W | [62] |
| AD | 54 | memory, personality change, childish behaviour, irritability | behavioural | hippocampal and medial temporal lobe atrophy | y | R406W | [62] |
| AD | 56 | memory, childish behaviour | behavioural | hippocampal and medial temporal lobe atrophy | y | R406W | [62] |
| PCA | 51 | prosopoagnosia | visuospatial deficits | right parietal and temporal regions | y | V363I | [18] |
| AD | 59 | memory | N.A. | bilateral, medial temporal lobe and hippocampi | y | R406W | [63] |
| AD | 65 | memory | N.A. | medial temporal | y | Q336H | [27] |
| AD | 53 | prosopoagnosia | behavioural, language, parkinsonism | medial temporal lobe and parahippocampal | y | R406W | [64] |
| AD | 58 | memory | behavioural, AOS | N.A. | y | R406W | [64] |
| AD | 50 | dyscalculia, social withdrawal, lack of initiative | behavioural, language, parkinsonism | medial temporal hippocampus > left, parahippocampal | y | R406W | [64] |

y, yes; n, no; N.A., not available. >, atrophy is more pronounced in the specified hemisphere. AD, Alzheimer's Disease; PCA, posterior cortical atrophy.

**Table 5. Overall summary of phenotypes.**

| Phenotype | N° of patients | Positive family history | Mean AAO |
|---|---|---|---|
| PPA | 28 | 82.14% | 51.68 (±11.62) |
| nfvPPA | 10 | 60%* | 51.7 (±15.74) |
| svPPA | 10 | 100% | 48.3 (±9.33) |
| rtvFTD | 6 | 83.33% | 53 (±6.19) |
| PPAOS/Primary Progressive Anarthria | 2 | 100% | 64.5 (±6.36) |
| bvFTD | 84 | 71.43%* | 47.62 (±10.85) |
| PSP | 23 | 82.61% | 43.09 (±5.96) |
| CBS/CBD | 12 | 83.33% | 48.82 (±13.67) |
| AD-like | 30 | 96.67% | 55.73 (±6.5) |

AAO, age at onset; PPAOS, Primary Progressive Apraxia of Speech.

*some articles did not specify a family history of disease.

### *3.5 Behavioural Variant of Frontotemporal Dementia (bvFTD)*

We identified 84 patients with bvFTD phenotype at onset (**Supplementary Table 1**, Ref. [16,20,43,66–95]). More than half of patients had a family history of dementia (71.43%), considering that several papers did not specify this information (25%). The mean age at onset was 47.62 (±10.85), and 18 patients (21.43%) were younger than 40 years old, 15 of them with positive family history. Most of the patients (28.57%) carried the IVS10+16C>T *MAPT* mutation, followed by the P301L (14.28%) and the P397S mutation (7.14%). The most frequent phenotype was "typical" bvFTD (90.48%); eighteen patients (21.43%) presented parkinsonism, and fourteen patients had speech disturbances during the course of the disease (16.67%). Brain MRI showed, in most cases, atrophy of bilateral frontal and temporal regions. Notably, in 10 patients, the atrophy was mainly on one side; among them, the majority showed a left-predominant atrophy, consistent with the presence of speech impairment (70%). Four patients who showed a primary diagnosis of bvFTD had remarkable semantic features [68,83,88]. Even though the authors did not make a PPA diagnosis, their main MRI patterns involved bilateral anterior temporal lobe atrophy, with less marked frontal lobe involvement. Moreover, they showed naming deficits, reduced verbal fluency, poor single-word comprehension and general semantic deficits. These phenotypes were linked to P397S, S356T and D252V *MAPT* mutations.

### *3.6 Clinical-Genetic Correlations in the Whole Cohort*

A general overview of the whole cohort is reported in Table 5. Using ANOVA, we compared ages at onset between groups, and we only found a significant difference between AD and all other phenotypes ($p < 0.05$) (nfvPPA, svPPA, rtfFTD and PPAOS or Primary Progressive Anarthria are intended as part of the great PPA group). The age at onset in the AD group was higher than in the others. Conversely, the age at onset also differed between bvFTD and PSP/CBS subgroups and between PPAs and CBS ($p < 0.05$). We did not find any difference between bvFTD and PPAs ($p > 0.05$). In Fig. 2 and in **Supplementary Table 2**, all the *MAPT* mutations that we found associated with different clinical phenotypes were reported.

Notably, some of the mutations are associated with multiple phenotypes, in particular CBS, PPA and bvFTD. The P301L appears to be a cross-group mutation, as it was found at least once in every phenotype group except for the PSP group. IVS10+16C>T mutation was the most frequent in bvFTD patients. In general, the PSP group shares fewer mutations with the other phenotypes, with most patients carrying the N279K mutation. Similarly, almost all AD carry the R406W *MAPT* mutation, shared with only one rtvFTD patient and with one bvFTD.

## 4. Discussion

In this review, we analysed the clinical phenotypes of patients carrying the *MAPT* mutations reported in the literature between 1998 and 2022 to delineate possible clinical-genetic correlations, paying particular attention to the rarest clinical presentations such as PPAs, atypical parkinsonism and AD-like phenotypes.

Among the entire group of patients included in this review, 52.54% carried a phenotype rarer than bvFTD: AD-like phenotype (16.95%), followed by the PPAs group (15.82%), which may reflect the fact that atypical phenotypes are more fully characterised in the literature than the classical ones.

Interestingly, considering all patients, seven had an onset before their 30s, most of them with a diagnosis of bvFTD, in agreement with previous findings on very early age at onset FTD, in which most of the subjects present the bvFTD phenotype [96]. In this review, we extend the findings of very early onset FTD to other phenotypes, with 18 *MAPT* patients with PPAs and PSP/CBS having age at onset at or before their 40s. Early age at onset does not have a clear link with specific mutations.

Regarding the language phenotypes, we found almost the same number of patients with svPPA and nfvPPA, while logopenic variant was absent. An almost equal ratio of svPPA and nfvPPA was found in *MAPT* mutations in one

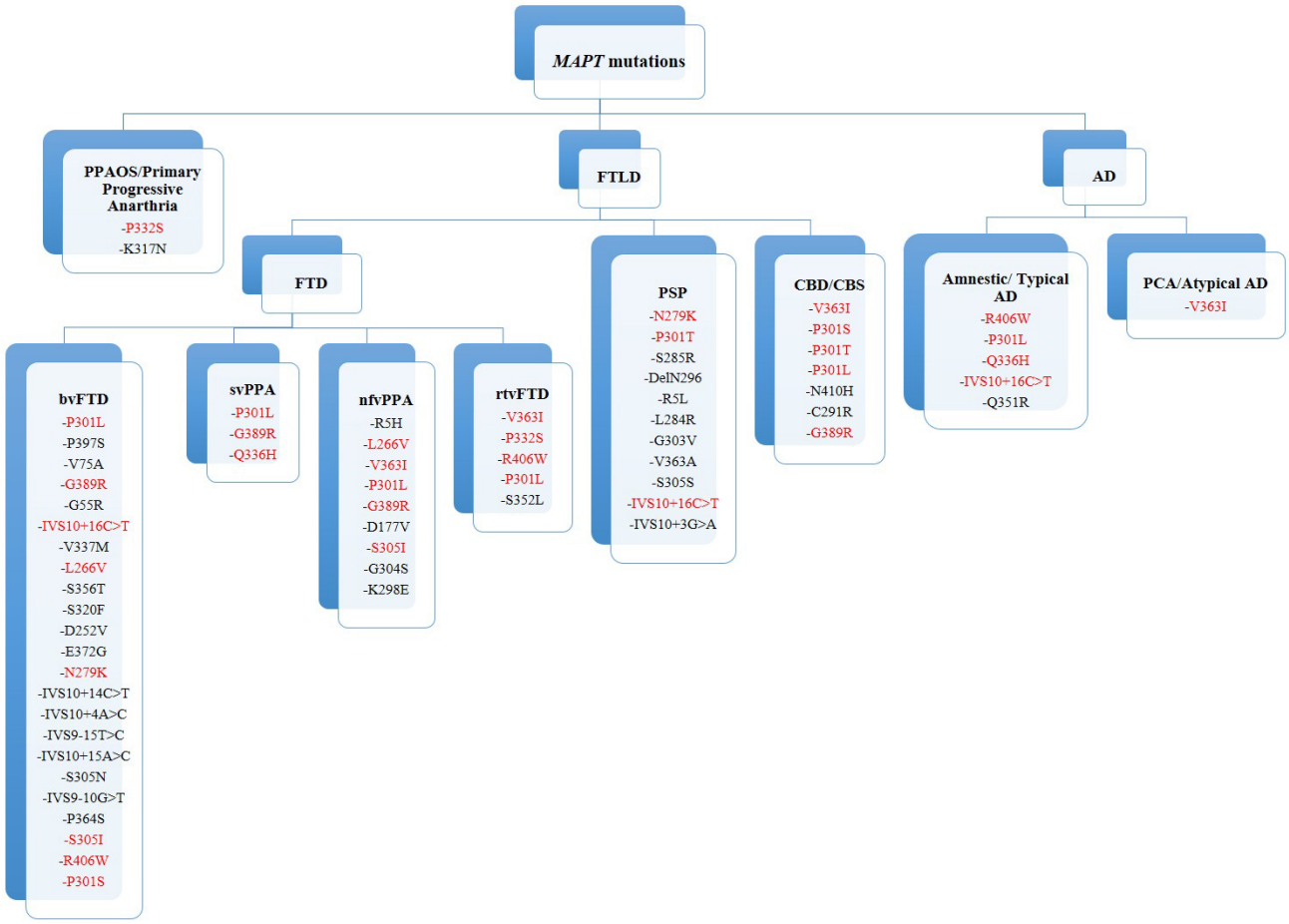


**Fig. 2. *MAPT* mutations and phenotypes.** In red: *MAPT* mutations associated with different phenotypes. FTLD, frontotemporal lobar degeneration; FTD, frontotemporal dementia; bvFTD, behavioural variant frontotemporal dementia; svPPA, semantic variant primary progressive aphasia; nfvPPA, non-fluent variant primary progressive aphasia; rtvFTD, right temporal variant frontotemporal dementia; PPAOS, primary progressive apraxia of speech; PSP, progressive supranuclear palsy; CBD/CBS, corticobasal degeneration or syndrome; AD, Alzheimer's disease; PCA, posterior cortical atrophy.

of the largest worldwide cohorts of genetic FTD [4]. This result differed from genetic TDP-43 proteinopathies, where the predominant language phenotype was the logopenic variant in a large cohort of *GRN* carriers [97] and the nfvFTD in *C9orf72* expansion [4,98]. Unlike *MAPT* patients, svPPA is exceptional in these other two genetic forms of FTD [97]. This result suggests a relative homogeneity of pathology for the semantic phenotype with a major vulnerability of the temporal anterior lobe for tau accumulation [99].

Another difference with TDP43 genotypes is that the mean age at onset in PPA patients by our review is earlier than PPA linked to *C9orf72* expansion and *GRN* mutations reported in the literature [97].

Interestingly, although the criteria for rtvFTD have only recently been defined, we identified at least six patients whose clinical presentation was consistent with this phenotype. RtvFTD is rarer than the left variant and represents a "unique", usually considered sporadic and associated with TDP-43 pathology [100]. The recognition of this clinical entity has become even more important as the involvement of the right temporal lobe seems to be associated with a more widespread neurodegeneration than in patients with main involvement of the left temporal lobe and a shorter survival, possibly linked to a diagnostic delay [101]. RtvFTD has also been associated, although rarely, with *GRN* mutations, suggesting that these two genes should be tested first.

Among the PPA group, we classified five patients as "PPA-plus" because of other neurological symptoms associated, mainly parkinsonism, myoclonus and dystonia. Conversely, we could not classify patients as mixed PPAs, a diagnostic category largely represented in PPA, because of the lack of a detailed neuropsychological assessment in several cases.

Considering the overall group of PPA, the most frequent *MAPT* mutation was the P301L. This is the most frequent mutation worldwide, and it is found to be linked to bvFTD phenotypes [4]. In our review, P301L was also found associated with svPPA, with one case of nfvPPA, with

one rtvFTD and one CBS. The rarer V363I mutation has been found in four PPA cases, half of them also characterised by CBS signs. This mutation has also been described in bvFTD [102], showing high heterogeneity in its clinical presentation. Some authors hypothesise that the rare presence of this mutation in the general population can be due to an incomplete penetrance and late disease onset [31].

In this paper, we included a large number of patients with PSP and CBS phenotypes, usually defined as sporadic; genetic PSP has also been associated with mutations in parkinsonism-related genes [103,104] and very rarely with *C9orf72* and *GRN* mutations. PSP patients from our review had a mean age at onset earlier than that observed in sporadic forms or in PSP associated with other FTD genes [105], and almost 40% of PSP linked to *MAPT* had a very early age at onset, before their 40s, an important feature that can lead to suspect a *MAPT* mutation in PSP phenotypes. Among patients with CBS phenotype, relatively "pure" CBS was found in more than 50% of patients, while the others showed mixed clinical symptoms, classifiable as PSP-CBS according to MDS criteria [106]. Therefore, we could suggest that co-occurrence of PSP and CBS features and early age at onset may orient the diagnosis toward a genetic tauopathy.

We identified 30 patients with an AD-like phenotype presenting with memory deficits but later developing behavioural modifications with or without parkinsonism, thus orienting the diagnosis towards FTD. The *MAPT* mutation more frequently associated with this phenotype was the R406W, but we also found two patients carrying P301L, two IVS10+16C>T, one V363I, one Q336H and one carrying Q351R mutations. As expected, age at onset in the AD group was significantly higher than in all other groups, with almost the totality of patients with onset after 50's. While in the R406W mutation, a mixed 3R/4R pathology is often described, similarly to AD, in AD-like cases with different mutations, the pathology is not specified, and thus a mixed proteinopathy cannot be excluded.

Several mutations are associated with multiple phenotypes, showing no clear genotype-phenotype correlation. However, some mutations are predominantly associated with atypical forms such as AD-like presentations or parkinsonisms (Fig. 2). However, a positive family history, the presence of other associated symptoms, and an early age of onset may be suggestive of a MAPT mutation.

*MAPT* mutations can have different impacts on tau protein, altering its ability to promote microtubule assembly, affecting its aggregation properties or determining the ratio between 4R and 3R isoforms [107], such as mutations associated with PSP and CBS phenotypes that often lead to 4R pathology, similarly to sporadic cases (see **Supplementary Fig. 1**). However, the mechanisms by which the mutations can give origin to different clinical forms are not known yet. A recent interesting study on iPS cells showed that one of the more frequent mutations associated with parkinsonism (N279K) has an impact on mitochondrial functions at variance with other mutations [108]. This suggests that the clinical variability could be explained by mutation-related specific biological mechanisms that need to be further explored.

Our review has several limitations. First, the research terms included the name of the diseases and of the gene but not every single symptom or tau pathology. In addition, some papers lacked detailed clinical descriptions and neuropsychological assessment. However, to include the majority of articles, we searched in depth in the reference list of every paper and, in some articles written before the appearance of current clinical criteria, we deduced the diagnoses based on clinical description. In addition, due to the heterogeneity of the clinical phenotypes, except for age at onset, we did not perform a metanalysis of the results but a narrative descriptions, and we discussed the results in light of previous findings on other genetic forms. Despite these limitations, we could provide an overview and an update of clinical-genetic associations of the cases described in the literature, analysing the phenotypes of a large number of *MAPT* patients. We underlined the high clinical heterogeneity of FTD associated with *MAPT* mutations without clear phenotype-genotype correlations in most cases. Deep phenotyping of patients, together with the study of the pathogenetic mechanisms of single mutations, particularly those associated with atypical phenotypes, are necessary to better understand the biological basis of the clinical and neuropathological phenotypic variability of neurodegenerative diseases associated with *MAPT* mutations.

## Availability of Data and Materials

All data underlying the results are available as part of the article.

## Author Contributions

CV and EP acquisition of data, analysis and interpretation of data, drafting the manuscript. PC conception and design, analysis and interpretation of data, drafting the manuscript. GR and GG, analysis and interpretation of data and reviewing it critically for important intellectual content. SP conception and design, analysis and interpretation of data drafting the manuscript. AR acquisition of data, analysis and interpretation of data, reviewing it critically for important intellectual content. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity. All authors give final approval of the version to be published.

## Ethics Approval and Consent to Participate

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## Supplementary Material

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