



## MAPT-Related Frontotemporal Dementia

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### Summary

#### Clinical characteristics

The spectrum of clinical manifestations of *MAPT*-related frontotemporal dementia (*MAPT*-FTD) has expanded from its original description of frontotemporal dementia and parkinsonian manifestations to include changes in behavior, motor function, memory, and/or language. A recent retrospective study suggested that the majority of affected individuals have either behavioral changes consistent with a diagnosis of behavioral variant FTD (bvFTD) or, less commonly, a parkinsonian syndrome (i.e., progressive supranuclear palsy, corticobasal syndrome, or Parkinson disease). Fewer than 5% of people with *MAPT*-FTD have primary progressive aphasia or Alzheimer disease. Clinical presentation may differ between and within families with the same *MAPT* variant. *MAPT*-FTD is a progressive disorder that commonly ends with a relatively global dementia in which some affected individuals become mute. Progression of motor impairment in affected individuals results in some becoming chairbound and others bedbound. Mean disease duration is 9.3 (SD: 6.4) years but is individually variable and can be more than 30 years in some instances.

#### Diagnosis/testing

The diagnosis of *MAPT*-FTD is established in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *MAPT* identified by molecular genetic testing.

#### Management

*Treatment of manifestations:* There is no cure for *MAPT*-FTD. Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This can involve multidisciplinary care that often includes a neurologist, specially trained nurses, speech-language pathologist or therapist, physical therapist, occupational therapist, nutritionist, psychiatrist/psychologist, social worker, and genetic counselor.

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*Surveillance:* To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, routine evaluations by multidisciplinary specialists are recommended.

## Genetic counseling

*MAPT*-FTD is inherited in an autosomal dominant manner. Most individuals diagnosed with *MAPT*-FTD have an affected parent with the clinical features of FTD and/or parkinsonism; however, because of the late onset and relatively rapid course of the disease, the affected parent often dies before onset of the disease in the offspring. A proband with *MAPT*-FTD may have the disorder as the result of a *de novo* pathogenic variant; such variants have been reported but are thought to be rare. Once the *MAPT* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

## Diagnosis

No consensus clinical diagnostic criteria for *MAPT*-related frontotemporal dementia (*MAPT*-FTD) have been published. However, diagnostic criteria for features of FTD including behavioral changes [Rascovsky et al 2011] ([full text](#)), corticobasal degeneration [Armstrong et al 2013] ([full text](#)), progressive supranuclear palsy [Höglinger et al 2017] ([full text](#)), and primary progressive aphasia [Gorno-Tempini et al 2011] ([full text](#)) have been published.

## Suggestive Findings

*MAPT*-FTD **should be suspected in** individuals with the following clinical features, neuroimaging findings, and family history.

### Clinical features

- Age at onset ranges from 17 to 82 years; mean age of onset is 49.5 (SD: 10.0) years [Moore et al 2020].
- The most common initial manifestations are:
  - Behavioral changes consistent with a diagnosis of behavioral variant FTD (bvFTD) [Rascovsky et al 2011];
  - Parkinsonian features suggestive of either corticobasal syndrome [Armstrong et al 2013] or progressive supranuclear palsy [Höglinger et al 2017].
- Less common initial presentations include:
  - An amnesic presentation (which may be diagnosed as Alzheimer disease);
  - A language presentation (consistent with one of the primary progressive aphasia syndromes) [Gorno-Tempini et al 2011].

### Neuroimaging findings

- **CT and MRI.** While both brain CT and MRI can show the atrophy patterns seen in *MAPT*-FTD, MRI shows greater detail. The hallmark feature is atrophy of the frontal and temporal lobes, which is often symmetric, but can be asymmetric.

A recent study showed at least two patterns of atrophy:

- A "temporal" type in which atrophy initially predominantly involved the hippocampus, amygdala, anteromedial temporal cortex, and insula;
  - A "frontotemporal" type in which atrophy involved both the frontal lobe and temporal lobe more laterally than observed in the "temporal" type [Young et al 2021].
- **Additional neuroimaging studies approved in the US**

- **Beta amyloid positron emission tomography (PET) scan** to help differentiate Alzheimer disease (with beta amyloid accumulation) from *MAPT*-FTD
- **Fluorodeoxyglucose (FDG) PET scan** to help differentiate non-genetic causes of dementia involving the frontal lobes

**Family history** is consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations). Of note, diagnoses may vary in affected family members; for example, one family member may be diagnosed with bvFTD while another family member is diagnosed with a parkinsonian syndrome. Other family members (particularly in prior generations) may have received a diagnosis of an unspecified dementia, Alzheimer disease, or Parkinson disease.

Absence of a known family history does not preclude the diagnosis.

## Establishing the Diagnosis

The diagnosis of *MAPT*-FTD is **established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *MAPT* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *MAPT* variant of uncertain significance does not itself establish or rule out the diagnosis of this disorder.

Because the phenotype of *MAPT*-FTD is indistinguishable from many other inherited disorders with frontotemporal dementia, recommended molecular genetic testing approaches include use of a **multigene panel** or **comprehensive genomic testing**.

Note: Single-gene testing (sequence analysis of *MAPT*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

- **A neurodegenerative disease, dementia, or frontotemporal dementia multigene panel** that includes *MAPT* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click [here](#). More detailed information for clinicians ordering genetic tests can be found [here](#).

- **Comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click [here](#). More detailed information for clinicians ordering genomic testing can be found [here](#).

**Table 1.** Molecular Genetic Testing Used in *MAPT*-Related Frontotemporal Dementia

Gene <sup>1</sup>	Method	Proportion of Proband with a Pathogenic Variant <sup>2</sup> Detectable by Method
<i>MAPT</i>	Sequence analysis <sup>3</sup>	>99% <sup>4</sup>
	Gene-targeted deletion/duplication analysis <sup>5</sup>	<1% <sup>4, 6, 7</sup>

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on variants detected in this gene.

3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exonic or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click [here](#).

4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]

5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single exon deletions or duplications.

6. To date, only one individual with FTD has been described with a partial deletion of *MAPT*, encompassing exons 6 to 9, resulting in both loss of function as well as gain of toxicity of the truncated tau protein product [Rovelet-Lecrux et al 2009].

7. To date, only ten individuals with FTD and a duplication of *MAPT* have been described [Wallon et al 2021].

## Clinical Characteristics

### Clinical Description

The spectrum of clinical manifestations of *MAPT*-related frontotemporal dementia (*MAPT*-FTD) has expanded from its original description of frontotemporal dementia and parkinsonian manifestations to include changes in behavior, motor function, memory, and/or language (see Table 2).

A recent retrospective study suggested that the majority of affected individuals have either behavioral variant FTD (bvFTD) or, less commonly, a parkinsonian syndrome (i.e., progressive supranuclear palsy, corticobasal syndrome, or Parkinson disease). Fewer than 5% of people with *MAPT*-FTD have primary progressive aphasia or Alzheimer disease [Moore et al 2020]. Of note, however, in this retrospective study many affected individuals had received only a diagnosis of an unspecified dementia. Furthermore, clinical presentation may differ between and within families with the same *MAPT* variant.

**Table 2.** *MAPT*-Related Frontotemporal Dementia: Frequency of Select Features

Feature	Frequency of Feature	Comment
Behavioral changes	+++	Meeting criteria for bvFTD <sup>1</sup>
Parkinsonism	++	Parkinsonian features incl diagnosis of atypical parkinsonism syndromes (CBS <sup>2</sup> or PSP <sup>3</sup> )
Language impairment	+	Most commonly semantic impairment (often co-occurring w/behavioral change) but non-fluent aphasia can occur in rare cases <sup>4</sup>
Memory impairment	+	Amnesic presentation can occur; memory problems can also co-occur w/behavioral change.

+++ = most common, ++ = common, + = less common

bvFTD = behavioral variant frontotemporal dementia; CBS = corticobasal syndrome; PSP = progressive supranuclear palsy

1. Rascovsky et al [2011]

2. Armstrong et al [2013]

3. Höglinger et al [2017]

4. Gorno-Tempini et al [2011]

**Age of onset.** A recent worldwide observational study suggested that age of onset may be before that of the other two major genetic causes of FTD (*C9orf72*-FTD and *GRN*-FTD), with the mean age of onset being 49.5 (range:

17-82) years and the average age of death being 58.5 (range: 24-93) years. Mean disease duration is 9.3 (SD: 6.4) years, but duration is individually variable and can be more than 30 years in some instances [Moore et al 2020].

**Behavioral manifestations.** The most common presentation in *MAPT*-FTD is bvFTD. Affected individuals present with progressive changes in personality and behavior, including core changes in three of the following six areas [Rascovsky et al 2011]:

- Early behavioral disinhibition
- Early apathy or inertia
- Early loss of sympathy or empathy
- Early perseverative stereotype or compulsive/ritualistic behavior
- Hyperorality or dietary change
- Neuropsychological profile of executive function difficulties with relative sparing of memory and visuospatial symptoms

**Motor manifestations.** Parkinsonian features, a common finding in individuals with *MAPT*-FTD, can occur before or after behavioral changes; however, as the disease progresses most individuals have both findings. Individuals can present with an unspecified parkinsonism that does not meet diagnostic criteria for any particular disorder. However, individuals can also fit diagnostic criteria for atypical parkinsonian disorders corticobasal syndrome [Armstrong et al 2013] and progressive supranuclear palsy (Richardson syndrome) [Höglinger et al 2017].

Some individuals with *MAPT*-FTD can also receive a diagnosis of Parkinson disease [Im et al 2015, Valentino et al 2020].

Progression of motor impairment in affected individuals results in some becoming chairbound and others bedbound.

**Memory impairment.** Episodic memory impairment, unusual for FTD, occurs quite commonly in individuals with *MAPT*-FTD. This can present either along with behavioral change or as the primary and predominant manifestation. Memory impairment can lead to an initial diagnosis of Alzheimer disease.

**Language impairment.** In *MAPT*-FTD, a primary language presentation is less common; however, affected individuals often develop semantic impairment, most commonly co-occurring with behavioral change. On the rare occasion that it is the first manifestation, the presumed diagnosis may be semantic-variant primary progressive aphasia [Gorno-Tempini et al 2011, Moore et al 2020]. Rarely, affected individuals have presented with a nonfluent variant primary progressive aphasia [Munoz et al 2007, Villa et al 2011, Moore et al 2020].

*MAPT*-FTD is a progressive disorder that commonly ends with a relatively global dementia in which some affected individuals become mute.

**Neuropathology.** The neuropathologic hallmark of *MAPT*-FTD is presence of tau protein deposits in neurons and glia. Tau deposits typically involve the cerebral cortex, white matter, subcortical regions, and brain stem nuclei. A variety of different pathologic findings can be seen with some *MAPT* variants associated with predominantly four-repeat tau inclusions, some with predominantly three-repeat tau inclusions, and some with a mix of three- and four-repeat inclusions. This last group often has paired-helical filament tau inclusions similar to those seen in Alzheimer disease [Ghetti et al 2015, Forrest et al 2018].

## Genotype-Phenotype Correlations

The following genotype-phenotype correlations have been observed [Moore et al 2020]:

- The common variants p.Pro301Leu and c.915+16C>T usually present with bvFTD.
- The variant p.Asn279Lys usually presents with a parkinsonian syndrome.

- A sizeable minority of individuals with the variant c.915+16C>T present with a parkinsonism syndrome.
- The less common variants p.Leu284Arg, c.853A>C, c.887\_889delATA, p.Gly303Val, c.915T>C, and p.Lys317Met can present with a parkinsonian syndrome.
- The variants p.Val337Met, p.Gln351Arg, and p.Arg406Trp in particular may present with episodic memory problems, and in some individuals this can be the initial presentation, with a phenotype similar to Alzheimer disease.

## Penetrance

*MAPT*-FTD is commonly thought to be a fully penetrant disorder. However, occasional reduced penetrance may exist in some families with specific *MAPT* variants (e.g., p.Leu315Arg, p.Val363Ile and p.Gly389Arg), and may be age related.

## Nomenclature

*MAPT*-FTD may also be referred to as *MAPT*-related tauopathy.

*MAPT*-FTD was previously referred to as frontotemporal degeneration with parkinsonism linked to chromosome 17 (FTDP-17).

## Prevalence

The prevalence of *MAPT*-FTD is unclear. A recent epidemiologic study in the UK suggests that prevalence of all FTD is 11:100,000 [Coyle-Gilchrist et al 2016]. In the authors' experience, genetic FTD accounts for ~30% of all FTD; thus the prevalence of genetic FTD is estimated to be 3.3:100,000. Based on the recent large retrospective study of genetic FTD [Moore et al 2020], *MAPT*-FTD accounts for about 25% of genetic FTD, resulting in an estimated prevalence of *MAPT*-FTD of 0.8:100,000.

## Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *MAPT*.

A 17q21.31 deletion that includes *KANSL1* and *MAPT* is associated with [Koolen-de Vries Syndrome](#) (KdVS). KdVS is characterized by developmental delay / intellectual disability, neonatal/childhood hypotonia, dysmorphisms, congenital malformations, and behavioral features.

## Differential Diagnosis

The clinical characteristics of *MAPT*-related frontotemporal dementia (*MAPT*-FTD) significantly overlap with those of other conditions, including FTD of unknown cause, genetic FTD (e.g., *GRN*- and *C9orf72*-related FTD), FTD spectrum disorders (e.g., corticobasal syndrome and progressive supranuclear palsy), as well as non-FTD spectrum disorders (Parkinson disease, Alzheimer disease, and Huntington disease). This clinical overlap makes it difficult to predict which family has *MAPT*-FTD by clinical presentation alone.

Around 30% of individuals with FTD have familial FTD (i.e., a positive family history of dementia, usually with autosomal dominant inheritance). Table 3 lists the most common genes associated with familial FTD.

Note: On rare occasions individuals with *MAPT*-FTD may be seen initially by psychiatrists for mental health issues that resemble schizophrenia. However, schizophrenia typically initially manifests in the teenage years to age 30 years, while onset of *MAPT*-FTD is typically between ages 30 and 60 years.



**Table 3.** Genes of Interest in the Differential Diagnosis of *MAPT*-Related Frontotemporal Dementia

Gene(s)	DiffDx Disorder	Clinical Features of DiffDx Disorder			
		Onset	Disease duration	Pathology	Comment
<b>Familial FTD: Most commonly involved genes</b>					
<i>C9orf72</i>	<i>C9orf72</i> -ALS/FTD	Mean: 58.2 yrs; range: 20-91 yrs <sup>1</sup>	Mean: 6.4 yrs; range: 0-36 yrs <sup>1</sup>	TDP-43 pathology in wide neuroanatomic distribution, w/particular involvement of extramotor neocortex, hippocampus, & lower motor neurons	May be diagnosed as bvFTD, ALS, FTD/ALS, or PPA. <sup>2</sup> Parkinsonism can develop as disease progresses. Rarely a Huntington disease-like phenotype is seen. Heterogeneity in clinical presentation is common w/in families. Phenotypes may overlap w/disease progression. <i>C9orf72</i> is involved in ~5%-10% of all FTD. <sup>3</sup>
<i>GRN</i>	<i>GRN</i> -FTD	Mean: 61.3 yrs; range: 25-90 yrs <sup>1</sup>	Mean: 7.1 yrs; range: 0-27 yrs <sup>1</sup>	TDP-43 pathology in neocortex & striatum; widespread & often asymmetric atrophy in frontal, temporal, &/or parietal lobes; characteristic parietal involvement	Most common presentation is bvFTD. Can also present as PPA, CBS, atypical PD, or (very rarely) ALS. May be misdiagnosed as AD. <i>GRN</i> is involved in ~5%-10% of all FTD. <sup>3</sup>
<b>Familial FTD: Less commonly involved genes (&lt;5% of all FTD)<sup>3</sup></b>					
<i>CCNF</i>	<i>CCNF</i> -FTD/ALS (OMIM 619141)	Mean: 55.3 yrs; range: 42-66 yrs	Mean: 2.5 yrs; range: 1-54 yrs	TDP-43 type 1 pathology	Assoc w/ALS, FTD/ALS, or PLS
<i>CHCHD10</i>	<i>CHCHD10</i> -related disorders	Approximately 50 yrs	1-27 yrs	Pathology not yet available	Presentation is highly variable; assoc w/ALS, FTD, cerebellar ataxia, & myopathy.
<i>CHMP2B</i>	<i>CHMP2B</i> -FTD	Typically in late 50s Mean: 57 yrs; range 46-70 yrs	3-20+ yrs	Neuropathology assoc w/ ubiquitin- & p62-positive inclusions, & TDP-43-, MAPT-, & FUS-negative inclusions	Usually presents w/ bvFTD but parkinsonism can be seen as disease progresses
<i>FUS</i>	<i>FUS</i> -ALS ± FTD <sup>2</sup> (OMIM 608030)	Onset frequently <35 yrs Median: 39 yrs; range: 11-80 yrs	Median: 2.1 yrs	FUS pathology in neuronal cytoplasm & dendrites. Severe caudate atrophy may differentiate FTLD-FUS from FTLD-Tau & FTLD-TDP.	Assoc w/ALS & occasionally FTD/ALS or bvFTD
<i>OPTN</i>	<i>OPTN</i> -ALS ± FTD <sup>2</sup> (OMIM 613435)	Mean: 51.9 yrs; range: 23-83 yrs	Range: 1-24 yrs	<i>OPTN</i> -positive cytoplasmic inclusions in CNS	Assoc w/ALS & occasionally FTD/ALS
<i>SQSTM1</i>	<i>SQSTM1</i> -ALS/FTD <sup>2</sup> (OMIM 616437)	Range: 48-73 yrs	Range: 2-29 yrs	TDP-43 pathology	Assoc w/ALS, bvFTD, ALS/FTD, &/or PDB <sup>4</sup>

Table 3. continued from previous page.

Gene(s)	DiffDx Disorder	Clinical Features of DiffDx Disorder			
		Onset	Disease duration	Pathology	Comment
<i>TARDBP</i>	ALS or ALS w/FTD (See <a href="#">TARDBP-ALS</a> .)	41-60 yrs Range: 29-77 yrs	Range: 2-4 yrs	TDP-43 inclusions in upper & lower motor neurons & cortex; can be assoc w/focal temporal lobe atrophy	Assoc w/ALS & occasionally FTD/ALS or bvFTD; more rarely can cause PPA
<i>TBK1</i>	<i>TBK1</i> -ALS/FTD <sup>2</sup> (OMIM <a href="#">616439</a> )	Mean: 63.3 yrs; range: 56-70 yrs	Range: 1-10+ yrs <sup>1</sup>	TDP-43 pathology; can be assoc w/focal temporal lobe atrophy	Can cause bvFTD, PPA, CBS, FTD/ALS, ALS; assoc w/1%-2% of all FTD
<i>TIA1</i>	<i>TIA1</i> -ALS ± FTD (OMIM <a href="#">619133</a> )	Mean: 58.9 yrs; range: 28-86 yrs	1-11 yrs	TDP-43 type B pathology in extramotor neocortex, motor cortex, spinal cord	Assoc w/ALS w/or w/o bvFTD
<i>TUBA4A</i>	<i>TUBA4A</i> -ALS/FTD (OMIM <a href="#">616208</a> )	Median: 65.5 yrs; range: 59-70 yrs	Median: 7 yrs; range: 6-11 yrs	TDP-43 pathology	Assoc w/ALS & occasionally FTD/ALS or bvFTD
<i>UBQLN2</i>	<i>UBQLN2</i> -ALS/FTD (OMIM <a href="#">300857</a> )	Mean: 42 yrs; range: 16-71 yrs	Mean: 4 yrs; range: 1-15+ yrs	TDP-43-positive inclusions	Assoc w/ALS & occasionally FTD/ALS. X-linked inheritance.
<i>VCP</i>	<a href="#">Inclusion body myopathy w/Paget disease of bone &amp;/or FTD (IBMPFD)</a>	Mean: 40 yrs; range: 35-66 yrs	Mean: 6 yrs after dementia diagnosis	Numerous intranuclear & rare neuronal cytoplasmic inclusions; dystrophic neuritis seen in neuropathology; TDP-43 type D pathology	Adult-onset proximal & distal muscle weakness (clinically LGMD <sup>5</sup> ), early-onset PDB, & FTD. Can also present as ALS.
<b>Non-FTD spectrum disorders</b>					
<i>HTT</i>	<a href="#">Huntington disease</a>	Range: 35-44 yrs	Median:15-18 yrs	Degeneration of neurons in caudate, putamen, & cerebral cortex	Behavioral & psychiatric manifestations of <i>MAPT</i> -FTD can be confused w/ those of HD.



Table 3. continued from previous page.

Gene(s)	DiffDx Disorder	Clinical Features of DiffDx Disorder			
		Onset	Disease duration	Pathology	Comment
<i>APP</i> <i>PSEN1</i> <i>PSEN2</i> <sup>6</sup>	Early-onset familial Alzheimer disease (See <a href="#">Alzheimer Disease Overview</a> .)	<i>APP</i> : usually 40s & 50s (range: 30-65 yrs) <i>PSEN1</i> : usually 40s or early 50s (range: 30s-early 60s) <i>PSEN2</i> : 40-75 yrs	<i>PSEN1</i> : relatively rapid progression over 6-7 yrs is common. <i>PSEN2</i> : mean: 11 yrs	β-amyloid plaques, intraneuronal neurofibrillary tangles (containing tau protein), & amyloid angiopathy	Can sometimes present w/prominent behavioral syndrome similar to bvFTD, particularly <i>PSEN1</i> -related Alzheimer disease, & therefore may be confused w/ <i>MAPT</i> -FTD

AD= Alzheimer disease; ALS = amyotrophic lateral sclerosis; bvFTD = behavioral variant FTD; CBS = corticobasal syndrome; CNS = central nervous system; DiffDx = differential diagnosis; FTD = frontotemporal dementia; FUS = fused in sarcoma; HD = Huntington disease; LGMD = limb-girdle muscular dystrophy; PD = Parkinson disease; PDB = Paget disease of bone; PLS = primary lateral sclerosis; PPA = primary progressive aphasia

1. Moore et al [2020]
2. See [Amyotrophic Lateral Sclerosis Overview](#).
3. Greaves & Rohrer [2019]
4. Paget disease of bone (PDB) involves focal areas of increased bone turnover that typically leads to spine and/or hip pain and localized enlargement and deformity of the long bones.
5. Muscle weakness progresses to involve other limb and respiratory muscles; cardiac failure and cardiomyopathy have been observed in later stages of IBMPFD.
6. It is likely that pathogenic variants in other genes causative of early-onset familial Alzheimer disease will be identified because kindreds with autosomal dominant familial Alzheimer disease with no known pathogenic variants in *PSEN1*, *PSEN2*, or *APP* have been described (see [Alzheimer Disease Overview](#)).

## Management

No clinical practice guidelines for *MAPT*-related frontotemporal dementia (*MAPT*-FTD) have been published.

## Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *MAPT*-FTD, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. *MAPT*-Related Frontotemporal Dementia: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
<b>Neurologic</b>	Complete neurologic exam & assessment of behavioral change	There are no validated rating scales for clinical use in FTD, but common scales used in research incl the CDR plus NACC FTLD <sup>1</sup> & the FTD Rating Scale. <sup>2</sup>
<b>Cognitive function</b>	Neuropsychologic exam	Evaluate extent & profile of cognitive disturbance

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
<b>Musculoskeletal / Activities of daily living</b>	Orthopedics / physical medicine & rehab / PT eval	To incl assessment of: <ul style="list-style-type: none"> <li>• Muscle tone; joint range of motion; posture; mobility; strength, coordination, &amp; endurance; pain; bedsores</li> <li>• Need for adaptive devices</li> <li>• Footwear needs</li> <li>• PT needs</li> <li>• Need for assistive walking devices (e.g., cane, walker, walker w/wheels, walker w/seat, wheelchair)</li> </ul>
	OT eval	To assess: <ul style="list-style-type: none"> <li>• Fine motor function (e.g., hands, feet, face, fingers, &amp; toes)</li> <li>• Home adaptations for ADL &amp; safety</li> </ul>
	Eval of driving safety	In case of cognitive impairment & impaired judgement, driving safety should be evaluated.
<b>Psychiatric illness</b>	History of psychiatric illness	Attention to possible alcohol or drug abuse
		Referral for psychiatric eval as needed
<b>Dysarthria</b>	For those w/dysarthria: speech/language eval	Referral for speech therapy as needed
<b>Dysphagia</b>	For those w/frequent choking or severe dysphagia, assess nutritional status & aspiration risk.	Consider involving a gastroenterology/nutrition/feeding team, incl formal swallowing eval.
<b>Genetic counseling</b>	By genetics professionals <sup>3</sup>	To inform affected persons & their families re nature, MOI, & implications of <i>MAPT</i> -FTD to facilitate medical & personal decision making
<b>Family support &amp; resources</b>	Assess need for: <ul style="list-style-type: none"> <li>• Community or online resources;</li> <li>• Social work involvement for parental support;</li> <li>• Home nursing referral.</li> </ul>	<ul style="list-style-type: none"> <li>• Early discussion of advanced care planning is warranted.</li> <li>• The affected individual's perspective &amp; burden must be taken into account for clinical decision making.</li> <li>• The presence of cognitive impairment may raise ethical concerns.</li> </ul>

ADL = activities of daily living; CDR = Clinical Dementia Rating®; FTD = frontotemporal dementia; FTLD = frontotemporal lobar degeneration; MOI = mode of inheritance; NACC = National Alzheimer's Coordinating Center; OT = occupational therapy; PT = physical therapy

1. Miyagawa et al [2020]

2. Mioshi et al [2010]

3. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

## Treatment of Manifestations

There is no cure for *MAPT*-FTD. Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This can involve multidisciplinary care that often includes a neurologist, specially trained nurses, speech-language pathologist or therapist, physical therapist, occupational therapist, nutritionist, psychiatrist/psychologist, social worker, and genetic counselor (see Table 5).

**Table 5.** MAPT-Related Frontotemporal Dementia: Treatment of Manifestations

Manifestation/ Concern	Treatment	Considerations/Other
<b>Parkinsonism</b>	PT, levodopa trial	Note: Because of psychiatric levodopa side effects, use only when functional impairment is significant. The majority of affected persons do not show a significant response to levodopa.
<b>Psychiatric/ behavioral manifestations</b>	Environmental, behavioral, & physical interventions	To minimize occurrence & consequences of undesired behaviors
	Counseling	For those w/affective disorders or to support affected person &/or caretakers
	SSRIs	For those w/affective disorders or disinhibition & challenging behaviors, pharmacologic therapy is the first-line approach.
	Atypical antipsychotics	<ul style="list-style-type: none"> <li>When severe manifestations (agitation, aggressiveness, psychosis) are refractory to SSRIs, often a temporizing measure is used until persons become more apathetic.</li> <li>Note: Risk of iatrogenic extrapyramidal syndrome</li> </ul>
<b>Dysarthria</b>	By speech-language pathologist or therapist	Use of augmentative communication devices
<b>Dysphagia</b>	Continuous eval & therapy	Consider safe swallowing techniques & diet modifications; possible need for gastrostomy tube.
<b>Sialorrhea</b>	Anticholinergic medications, salivary gland botulinum toxin injections, or radiotherapy	Note: Anticholinergic medication can affect cognition.
<b>Family/caregiver support/resources</b>	Psychosocial support & education via caregiver & patient support groups	To ↓ stress & burden on caregivers

PT = physical therapy; SSRIs = selective serotonin reuptake inhibitors

## Surveillance

**Table 6.** MAPT-Related Frontotemporal Dementia: Recommended Surveillance

System/Concern	Evaluation	Frequency
<b>Neurologic</b>	Neurologic exam for new manifestations &/or response to medications	At each visit
<b>Mobility / Activities of daily living</b>	Physical medicine & rehab / PT & OT	Per treating clinician
<b>Cognitive function</b>	Rapid screening tools, incl tests of verbal fluency	At each visit
<b>Psychiatric/behavioral manifestations</b>	Medical history, neurologic exam	
<b>Dysarthria</b>	Eval by speech-language pathologist	Per treating clinician
<b>Dysphagia</b>	Medical history	At each visit
<b>Sialorrhea</b>		
<b>Bladder function</b>		
<b>Family/caregiver support/resources</b>	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	

## Evaluation of Relatives at Risk

See [Genetic Counseling](#) for issues related to testing of at-risk relatives for genetic counseling purposes.

## Therapies Under Investigation

Search [ClinicalTrials.gov](#) in the US and [EU Clinical Trials Register](#) in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

## Genetic Counseling

*Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.*

## Mode of Inheritance

*MAPT*-related frontotemporal dementia (*MAPT*-FTD) is inherited in an autosomal dominant manner.

## Risk to Family Members

### Parents of a proband

- Most individuals diagnosed with *MAPT*-FTD have an affected parent with the clinical features of frontotemporal dementia (FTD) and/or parkinsonism; however, because of the late onset and relatively rapid course of the disease, the affected parent often dies before onset of the disease in the offspring.
- A proband with a *MAPT*-FTD may have the disorder as the result of a *de novo* pathogenic variant. *De novo* *MAPT* pathogenic variants have been reported but are thought to be rare [Ando et al 2020].
- If the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.
- The family history of some individuals diagnosed with *MAPT*-FTD may appear to be negative because of failure to recognize the disorder in family members (e.g., a psychiatric disorder not diagnosed at the time as FTD), early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

**Sibs of a proband.** The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is affected or is known to have a *MAPT* pathogenic variant, the risk to the sibs of inheriting the pathogenic variant is 50%.

- *MAPT*-FTD is almost completely penetrant; thus, heterozygous sibs are extremely likely to develop manifestations during their lifetime. Although a strong correlation exists between individual age at onset and both parental and mean family age of onset [Moore et al 2020], the phenotype in affected family members may vary (e.g., bvFTD in one family member and parkinsonism in another family member).
- If the *MAPT* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism. Presumed parental germline mosaicism was reported by Boeve et al [2005], who determined that neither parent of two affected sibs was heterozygous for the *MAPT* pathogenic variant found in the affected offspring.

**Offspring of a proband.** Each child of an individual with *MAPT*-FTD is at a 50% risk of inheriting the *MAPT* pathogenic variant.

**Other family members.** The risk to other family members depends on the status of the proband's parents: if a parent has the *MAPT* pathogenic variant, the parent's family members may be at risk.

## Related Genetic Counseling Issues

### Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

### Predictive testing (i.e., testing of asymptomatic at-risk individuals)

- Predictive testing for at-risk relatives is possible once the *MAPT* pathogenic variant has been identified in an affected family member.
- Potential consequences of such testing (including but not limited to socioeconomic changes and the need for long-term follow up and evaluation arrangements for individuals with a positive test result) as well as the capabilities and limitations of predictive testing should be discussed in the context of formal genetic counseling prior to testing.

### Predictive testing in minors (i.e., testing of asymptomatic at-risk individuals age <18 years)

- For asymptomatic minors at risk for adult-onset conditions for which early treatment would have no beneficial effect on disease morbidity and mortality, predictive genetic testing is considered inappropriate, primarily because it negates the autonomy of the child with no compelling benefit. Further concern exists regarding the potential unhealthy adverse effects that such information may have on family dynamics, the risk of discrimination and stigmatization in the future, and the anxiety that such information may cause.
- For more information, see the National Society of Genetic Counselors [position statement](#) on genetic testing of minors for adult-onset conditions and the American Academy of Pediatrics and American College of Medical Genetics and Genomics [policy statement](#): ethical and policy issues in genetic testing and screening of children.

In a family with an established diagnosis of *MAPT*-FTD, it is appropriate to consider testing of symptomatic individuals regardless of age.

## Prenatal Testing and Preimplantation Genetic Testing

Once the *MAPT* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider decisions regarding prenatal testing to be the choice of the parents, discussion of these issues is appropriate. For more information, see the National Society of Genetic Counselors [position statement](#) on prenatal testing in adult-onset conditions.

## Resources

*GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click [here](#).*

- **Association for Frontotemporal Degeneration (AFTD)**  
**Phone:** 866-507-7222  
**Email:** [info@theaftd.org](mailto:info@theaftd.org)  
[www.theaftd.org](http://www.theaftd.org)
- **CurePSP**  
3rd Floor  
**Phone:** 800-457-4777; 347-294-2873 (CURE)  
**Email:** [info@curepsp.org](mailto:info@curepsp.org)  
[www.psp.org](http://www.psp.org)
- **FTD Talk**  
United Kingdom  
**Email:** [j.rohrer@ucl.ac.uk](mailto:j.rohrer@ucl.ac.uk)  
[www.ftdtalk.org](http://www.ftdtalk.org)
- **National Institute of Neurological Disorders and Stroke (NINDS)**  
PO Box 5801  
Bethesda MD 20824  
**Phone:** 800-352-9424 (toll-free); 301-496-5751; 301-468-5981 (TTY)  
[Frontotemporal Dementia Information Page](#)
- **Rare Dementia Support**  
United Kingdom  
**Email:** [contact@raredementiasupport.org](mailto:contact@raredementiasupport.org)  
[www.raredementiasupport.org](http://www.raredementiasupport.org)
- **ARTFL-LEFFTDS Longitudinal Frontotemporal Lobar Degeneration - Registry**  
[www.allftd.org](http://www.allftd.org)
- **FTD Prevention Initiative - Registry**  
[www.thefpi.org](http://www.thefpi.org)
- **Genetic Frontotemporal Dementia Initiative - Registry**  
[www.genfi.org](http://www.genfi.org)

## Molecular Genetics

*Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.*



**Table A.** MAPT-Related Frontotemporal Dementia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
<i>MAPT</i>	17q21.31	Microtubule-associated protein tau	alsod/MAPT genetic mutations MAPT database	MAPT	MAPT

Data are compiled from the following standard references: gene from [HGNC](#); chromosome locus from [OMIM](#); protein from [UniProt](#). For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click [here](#).

**Table B.** OMIM Entries for MAPT-Related Frontotemporal Dementia ([View All in OMIM](#))

157140	MICROTUBULE-ASSOCIATED PROTEIN TAU; MAPT
172700	PICK DISEASE OF BRAIN
600274	FRONTOTEMPORAL DEMENTIA; FTD
601104	SUPRANUCLEAR PALSY, PROGRESSIVE, 1; PSNP1

## Molecular Pathogenesis

Tau protein, encoded by *MAPT*, is a microtubule-binding protein believed to be involved in assembly and stabilization of microtubules. Alternative mRNA splicing of *MAPT* in the human adult brain produces six isoforms of the tau protein that differ by either (1) the presence or absence of exons 2 or 3 in the amino-terminal half or (2) the presence or absence of exon 10 in the carboxy-terminal half. Exclusion of exon 10 leads to the production of three-repeat isoforms, whereas inclusion of exon 10 leads to four-repeat isoforms. While the expression levels of three-repeat and four-repeat isoforms are similar in normal adult human cerebral cortex, expression levels may change in neurodegenerative tauopathies.

**Mechanism of disease causation.** *MAPT* pathogenic variants alter the relative production of tau isoforms, resulting either in changes in how microtubules assemble or in the propensity of tau to aggregate.

**Table 7.** Notable *MAPT* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_005910.6 NP_005901.2	c.837T>G	p.Asn279Lys	See Genotype-Phenotype Correlations.
	c.851T>G	p.Leu284Arg	
	c.887_889delATA	p.Asn296del	
	c.902C>T	p.Pro301Leu	
	c.908G>T	p.Gly303Val	
	c.944T>G	p.Leu315Arg	See Penetrance.
	c.950A>T	p.Lys317Met	See Genotype-Phenotype Correlations.
	c.1009G>A	p.Val337Met	
	c.1052A>G	p.Gln351Arg	
	c.1087G>A	p.Val363Ile	See Penetrance.
	c.1165G>C	p.Gly389Arg	See Genotype-Phenotype Correlations.
c.1216C>T	p.Arg406Trp		
NM_005910.6	c.853A>C <sup>1</sup>	--	
	c.915T>C <sup>1</sup>	--	
	c.915+16C>T	--	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

*GeneReviews* follows the standard naming conventions of the Human Genome Variation Society ([varnomen.hgvs.org](http://varnomen.hgvs.org)). See [Quick Reference](#) for an explanation of nomenclature.

1. Nucleotide change is predicted to disrupt splicing [Tubeuf et al 2020].

## Chapter Notes

### Author Notes

Jonathan Rohrer is a Professor of Neurology at the Dementia Research Centre in the Queen Square UCL Institute of Neurology as well as a Consultant Neurologist at the National Hospital for Neurology and Neurosurgery. He is also a Clinical Co-Investigator at the UK Dementia Research Institute. After a Natural Sciences degree at the University of Cambridge he went on to study medicine at the University of Oxford and UCL. He started as a Wellcome Trust Clinical Research Fellow in 2005 at UCL, where he first began to study frontotemporal dementia (FTD) including the neuroimaging of genetic FTD, and completed his [PhD](#) in 2010. Dr Rohrer then became an NIHR Clinical Lecturer, during which time he started the [Genetic Frontotemporal Dementia Initiative](#), GENFI, an international multicenter cohort study of presymptomatic genetic FTD. The research of his team focuses on the development of novel biomarkers in FTD and clinical trials for genetic forms of FTD through the [FTD Prevention Initiative](#). Details about Dr Rohrer's work and about FTD more generally can be found at [FTD Talk](#).

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