



# Module 1: What is frontotemporal dementia?

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## Dementia

*Dementia* is an umbrella term which refers to a syndrome of progressive loss of brain function. There are a number of causes of dementia. Some cases are caused by general diseases in the body which affect brain function, but most are caused by pathological processes occurring directly within the brain itself. *Alzheimer's disease* (AD), a process which occurs directly within the brain, is the most common and recognised cause of dementia and typically occurs in people over 65 years of age. *Frontotemporal lobar degeneration* (FTLD) is another, somewhat less common form of brain disease and typically occurs in people under 65 years of age. This leads to a clinical dementia syndrome known as *frontotemporal dementia* (FTD).

It is important to distinguish between *early onset* (also known as *younger onset*) *dementia*, which generally refers to dementia beginning before age 65, and *early stage dementia*, which refers to the beginning of a dementia process regardless of age at onset.

Each type of dementia begins in a different way, with characteristic patterns of symptoms reflecting the affected region(s) of the brain. Alzheimer's disease, for example, typically begins deep within the medial (middle) aspects of the temporal lobes, causing prominent early memory loss as the structures used for memory are affected. Individuals with Frontotemporal dementia tend to show a very different pattern of symptoms reflecting early involvement of regions situated toward the front of the brain, the frontal lobes and frontal (or *anterior*) parts of the temporal lobes.

Different forms of dementia also tend to progress at different rates. Many are characterised by a very slow decline over a number of years. Some progress more quickly with changes becoming evident from month to month. In rare cases, changes may be apparent from week to week. Ultimately, however, all forms of dementia cause significant disability and seriously affect the individual's ability to function independently in the community.



## Frontotemporal dementia (FTD)

### ***Epidemiology: prevalence, causes and risk factors***

Frontotemporal dementia is a younger onset dementia and is one of a few forms of dementia that tend to occur in relatively young individuals, typically aged between 45 and 65 years [1]. A small proportion experience symptom onset at 70 years or older [2]. Another small group may experience very early symptom onset, with the youngest documented onset occurring at 21 years of age [3].

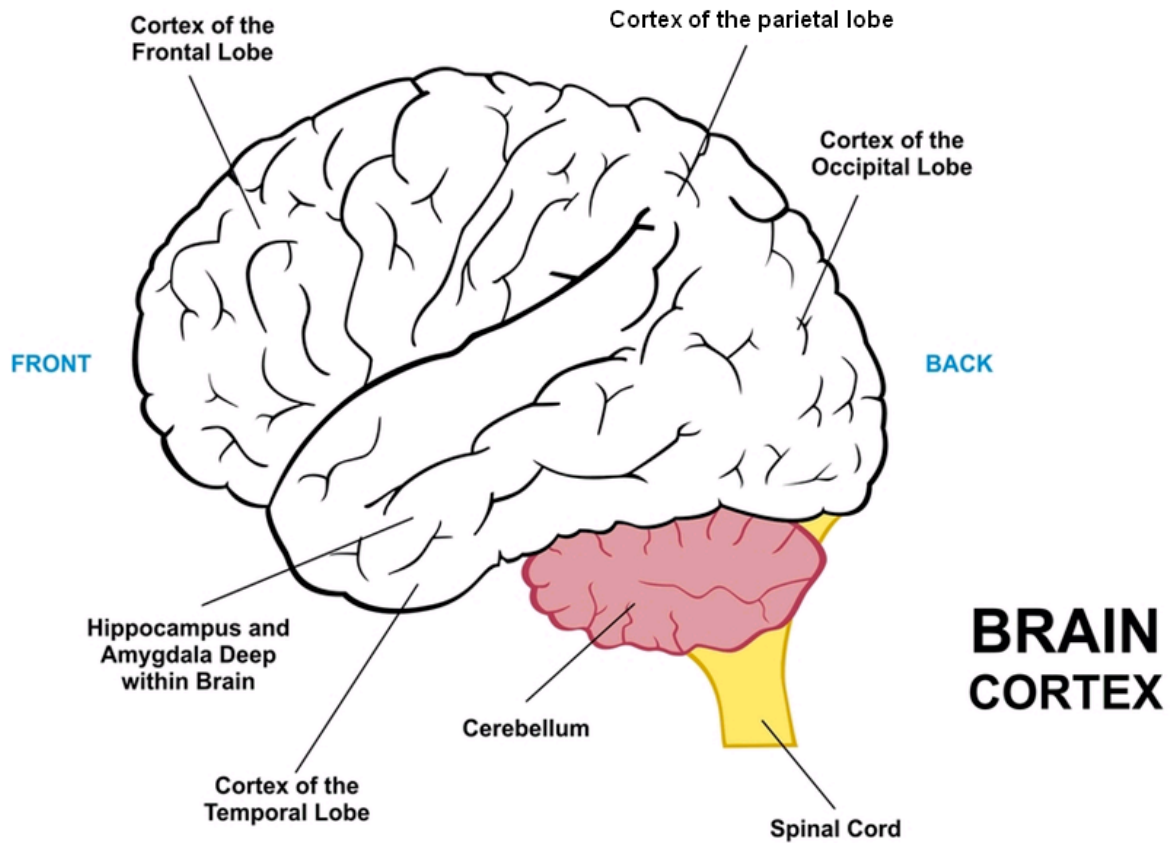
Frontotemporal dementia is estimated to be the second most common cause of dementia in younger people after Alzheimer's Disease [4].

The estimated prevalence rates vary due to differences in the samples and populations used in different studies, with estimates of the incidence per 100,000 people ranging from 15-50. Based on these incidence estimates, between 3,000 and 10,000 Australians are currently estimated to be affected by Frontotemporal dementia.

Patterns of sex differences are variable amongst scientific reports, possibly due to small sample sizes [5]; thus, it is not clear that incidence differs between men and women.

The cause of the majority of Frontotemporal dementia (FTD) cases is currently unknown. There are genetic causes in about one third of people, and it can run in families (see *Genetics*). Most often it occurs in individuals with no family history of FTD or even of dementia.

Environmental factors clearly linked to FTD have not been identified, but some studies have suggested an unproven association with *vascular risk factors* (a group of risk factors associated with stroke and heart disease) such as diabetes, smoking, and hypertension.



**Figure 1.** Regions of the brain

### ***Brain involvement***

The frontal and anterior temporal lobes of the brain are the most affected sites in frontotemporal dementia or FTD (see Figure 1.).

The **frontal lobes** subserve many important psychological and cognitive functions, including personality, social graces, reasoning, problem solving, and the emotional aspects of our interpersonal interactions. Some aspects of language production are also subserved by the frontal lobes.

When an individual suffers degenerative **damage to the frontal lobes**, they may begin to behave in bizarre or inappropriate ways, display a lack of empathy, have difficulty engaging socially, and/or have difficulty communicating. People with FTD who exhibit these symptoms may initially be referred to psychiatric services due to the nature of their presentations [6]. These symptoms of FTD can be particularly distressing for families because initial changes may seem to be under the control of the individual.



It is important for family and friends to understand that while the behaviour of the affected individual may appear deliberate, it is actually an involuntary symptom of the specific brain structures being affected by the disease.

The frontal parts or **anterior aspects of the temporal lobes** are responsible for knowledge and understanding of words, concepts, and faces. When there is dysfunction in this region of the brain, people may lose their ability to appreciate the meaning of words and objects and may become unable to recognise faces and body language that helps them distinguish various emotional and non verbal cues. The temporal lobes are also important for language, and disruption to this region may result in complex communication difficulties.

In **typical Alzheimer's disease**, the middle parts or **medial aspects of the temporal lobes** are initially affected. This area is critical for the formation of new memories. Thus, the dementia associated with AD tends to be characterised by an early decline in recent/short term memory skills, specifically rapid forgetting.

This area of the brain is not characteristically affected in FTD, resulting in a dementia syndrome that does not include prominent recent memory difficulties. It is important to note however, that memory is a complex cognitive skill involving other basic skills such as attention and concentration. Thus, some people with FTD may demonstrate apparent memory difficulties, despite relative preservation of the medial temporal lobes structures. This is because people with FTD will often not be able to concentrate and attend to information sufficiently for this information to be held and stored in memory.

### ***Clinical Categories of Frontotemporal dementia (FTD)***

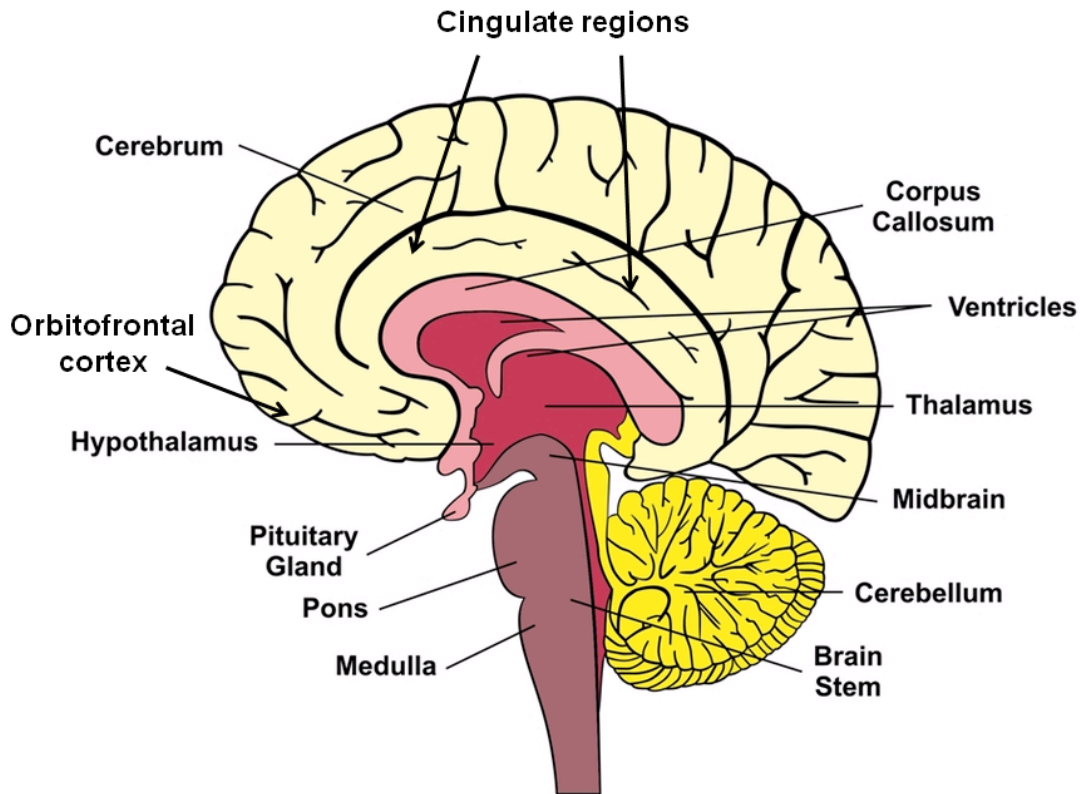
FTD categories are defined by the initial presenting symptoms, which reflect the regions of the brain that are first affected. Within each category are specific subtypes characterised by early clustering of specific symptoms. All are characterised by insidious onset and progressive decline, though the rate of decline varies by subtype.

#### **Behaviour onset FTD**

***Behavioural variant FTD (bvFTD)***; also known as frontal variant (fvFTD) is typically characterised by early behaviour changes including a decline in social interpersonal conduct, impaired regulation of behaviour, reduced emotional reactivity, loss of insight, decline in personal fastidiousness and hygiene, distractibility, dietary changes, and repetitive behaviour [7, 8]. Mental rigidity and inflexibility are also characteristic, leading to a reduced ability to adapt to new situations [8]. Those familiar with individuals who develop bvFTD often describe an apparent change in their friend or family member's general personality, habits, behaviour, or emotional responses.



This “change” often represents an exaggeration or enhancement of previous personality traits. For example, meticulous, methodical people can become overly obsessive and rigid; normally talkative people can become extremely garrulous. However, sometimes this change can be a true departure from their pre-morbid nature.



**Figure 2.** A view through the middle of the brain showing deep cortical and subcortical structures.

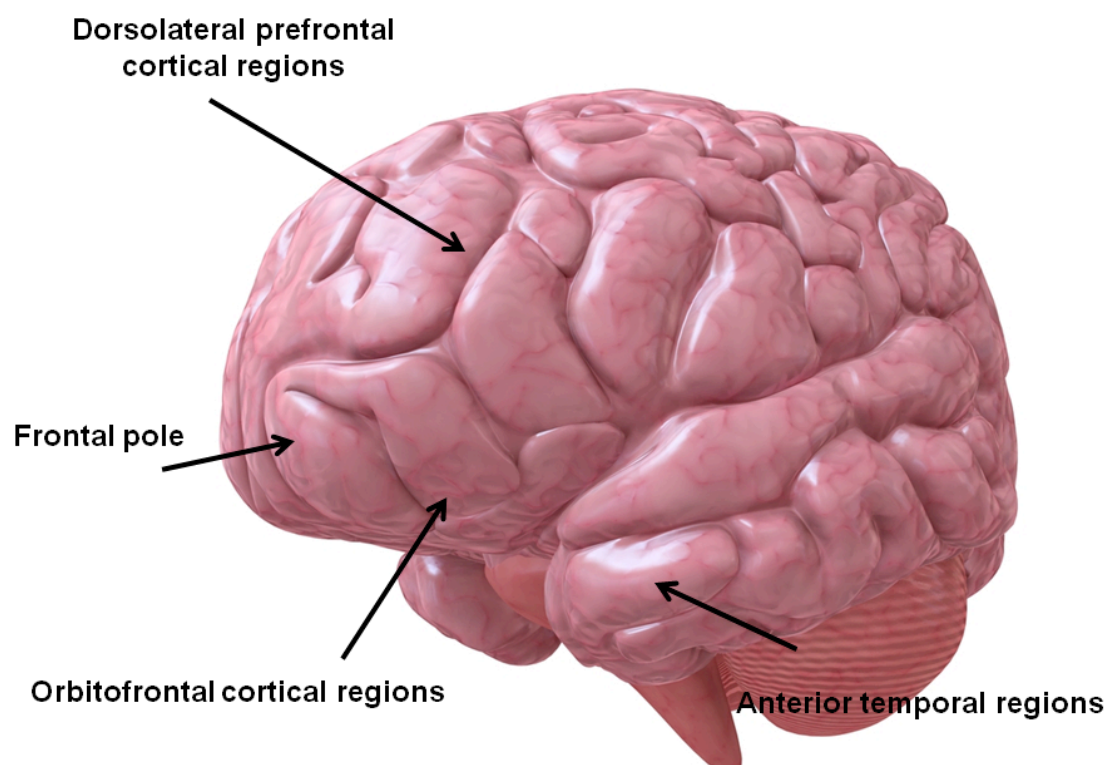
Three subtypes of bvFTD have been described [9] and their clinical symptoms may be predictive of underlying molecular neuropathology [10] (see Figure 4), though symptoms also frequently coexist across these categories [2, 11]:

1. The *Apathetic* subtype typically involves a decrease in physical activity and emotional blunting, reduced motivation, less interest in once enjoyable pursuits, and increasing social isolation. The apathetic presentation tends to be associated with extensive frontal lobe involvement extending into the dorsolateral prefrontal cortex and cingulate cortex.



2. The *Disinhibited* subtype is characterised by difficulty regulating personal behaviours and overactivity, restlessness, fatuous behaviour, impulsivity, and social inappropriateness. Involvement of the orbitomedial frontal and anterior temporal regions of the brain is associated with a disinhibited presentation.
3. The *Stereotyped-compulsive* subtype is characterised by distinctive motor stereotypies (repetitive, ritualised behaviours) and muscular rigidity. Changes to deep brain structures known as the basal ganglia may be evident, along with variable regions of the cortex, often of the temporal rather than frontal lobe [9].

*Other search terms:* Note that in some research and clinical circles, the term FTD is used to refer specifically to bvFTD.



**Figure 3.** An oblique three-dimensional view of the brain showing the different parts of the frontal lobes affected by FTD.





## **Language onset FTD**

When language impairment is the initial presenting symptom, one of three clinical diagnoses is usually assigned according to the specific speech and language impairments identified [12].

**1. Progressive non-fluent aphasia (PNFA)** is a syndrome of expressive language decline characterised by grammatical difficulties in language production and/or effortful, halting speech with speech sound errors. It is also known as the non-fluent variant of FTD (nfvFTD) [12]. This can be associated with specific difficulty initiating or sequencing speech production, known as *apraxia of speech*. Apraxia of speech can also occur alone. Comprehension of grammatically complex sentences may also be impaired.

Individuals with PNFA tend to retain their knowledge of the meaning of individual words and objects. Because receptive language abilities (such as the ability to comprehend verbal information and generally understand the meaning of language) and insight into their condition are preserved in the early stages, people with PNFA may be susceptible to frustration and depression in the early stages of the disease.

Atrophy or dysfunction of the language-dominant (usually left) posterior fronto-insular region is typically seen on neuroimaging in PNFA [12]. (The insula is an island of cortex hidden below the overlying folds of the frontal, parietal and temporal lobes.) This clinical subtype tends to be associated with tau-positive neuropathology [2] (see *Pathology*) and tends to have a later onset of symptoms and/or later diagnosis than other forms of FTD [5, 13].

**2. Semantic dementia (SD)** is a syndrome associated with a pervasive breakdown in the individual's general knowledge store, ultimately resulting in a complete loss of semantic knowledge or memory. Semantic knowledge or memory refers to factual information that we learn over time, especially the meanings of words, objects, and concepts. As a result of breakdown in the semantic system, patients experience impaired understanding of single words (due to loss of word or object knowledge, especially those which are not commonly used or seen) and difficulty finding words. In contrast to individuals with PNFA, grammar and motor components of speech production and the ability to repeat sentences remain intact; thus, speech still sounds fluent and effortless but may be missing names or seem "empty" in content [12]. Difficulties recognizing familiar faces (or other exemplars within a class) may also occur. Patients may also show behavioural changes similar to bvFTD [14]. It is also termed the semantic variant of FTD (svFTD)[12].

Neuroimaging in SD tends to reveal bilateral abnormalities in the ventral (lower) and lateral (outer) anterior temporal regions which are usually worse on the left [12, 15]. SD is typically associated with ubiquitin-positive, TDP-43-positive pathology [2, 10] (see *Pathology*).





Language-onset FTD syndromes may also be accompanied by early behavioural changes as seen bvFTD [16], especially in SD [14, 17].

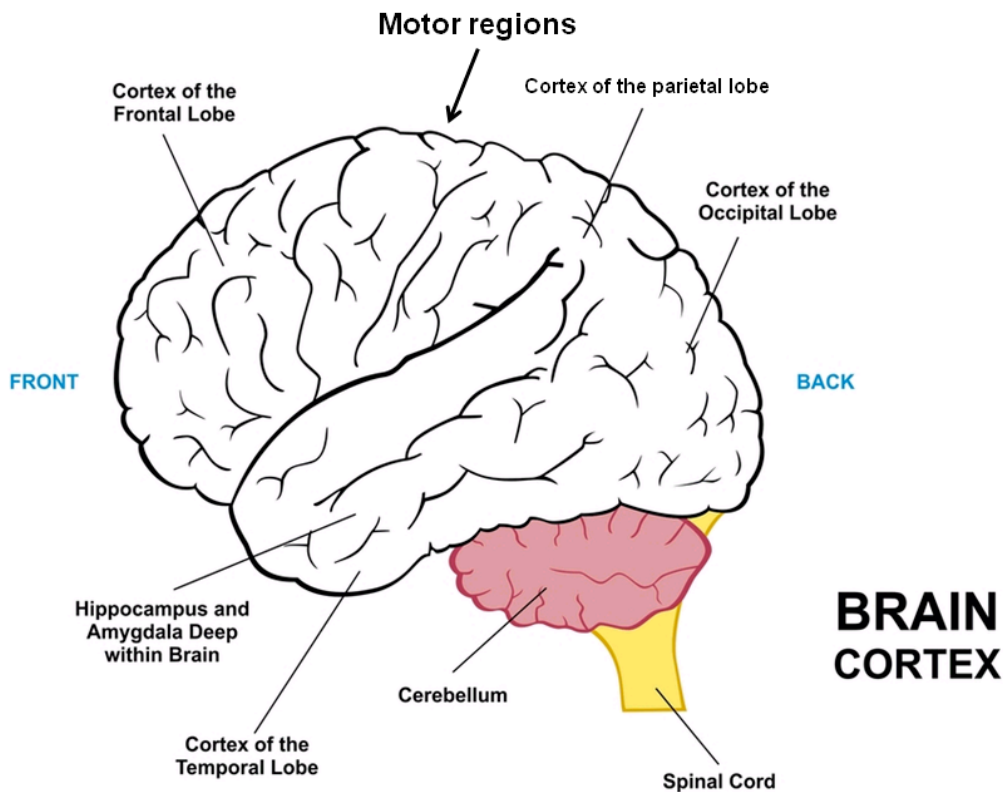
**3. Progressive logopenic aphasia** is a syndrome of slow or interrupted speech output, impaired word finding in spontaneous speech, and impaired repetition of sentences and phrases (rather than single words). Difficulties using the correct speech sounds (or *phonemes*) may also be present. Intact abilities include understanding of individual words and objects, and the grammar and motor aspects of speech.

Imaging abnormalities in this condition are found in the region of the left temporo-parietal junction [12]. Progressive logopenic aphasia is often discussed in articles about Frontotemporal dementia (FTD) as this is indeed a dementia that begins in the temporal lobes. However, logopenic aphasia is almost always caused by Alzheimer's pathology, not the pathology generally associated with FTD and thus is considered an atypical language-onset variant of Alzheimer's Disease [2, 18] (see Figure 2). For this reason, it will not be discussed in great detail throughout this toolkit.

*Other search terms:* When researching language onset FTD, it is useful to know that in some research and clinical circles, all patients who present with a language-onset dementia are said to have *Primary Progressive Aphasia* (PPA). Cases of PPA are then subcategorised as PPA-agrammatic (i.e., PNFA), PPA-semantic (i.e., SD), or logopenic PPA. In other circles, the term PPA is only used to refer specifically to PNFA.

### **Frontotemporal dementia (FTD) syndromes with movement disorders**

A number of disease processes affecting the movement pathways can also lead to the syndrome of FTD. These are subdivided neurologically into abnormalities of pyramidal (relating to voluntary movements controlled by the pyramidal cells of the brain's primary motor centre) and extrapyramidal (relating to involuntary aspects of movement controlled by deeper regions of the brain) motor function. Pyramidal dysfunction is usually manifested by weakness. Extrapyramidal dysfunction is associated with many of the symptoms of Parkinson's disease, including tremor, stiff movements and muscles, and abnormal or involuntary movements, particularly of the muscles that move the eyes.



**Figure 4.** Brain regions with the motor cortical regions identified.

FTD may co-occur with the following movement-related conditions, among others:

1. ***FTD with parkinsonism linked to chromosome 17 (FTDP-17)*** is an inherited condition caused by known genetic mutations [19]. It may be characterised by parkinsonian symptoms such as rigidity, tremor, and slowness of movement together with symptoms of FTD.
2. ***Corticobasal syndrome (CBS)*** is characterised by atrophy and/or dysfunction in diverse regions of the brain, both cortical and subcortical, which are involved both in motor control and cognition. It results in a syndrome of asymmetric Parkinsonism with limb apraxia (difficulty performing purposeful, coordinated movements), alien limb phenomenon (the sensation that one's limb is detached from the body or not under one's own control), falls, and muscular jerks known as myoclonus. Accompanying deficits often include PNFA, apathy, and other cognitive and behavioural changes associated with FTD [17, 20].



3. ***Progressive supranuclear palsy syndrome (PSPS)*** is a motor syndrome caused by sub cortical brain dysfunction, and is characterised by slowness of movement, impaired tone in the muscles of the trunk (axial dystonia), falls, swallowing difficulties, and vertical gaze palsy (especially early voluntary difficulty moving the eyes downward). Cognitive and behavioural difficulties include slowed thinking, reduced speed of information processing, and other changes associated with FTD [20].

Most people with FTD syndromes do not experience significant movement or motor problems. Motor symptoms can develop in the later stages of the illness regardless of onset type, however, highlighting the clinico-pathological overlap amongst these conditions.

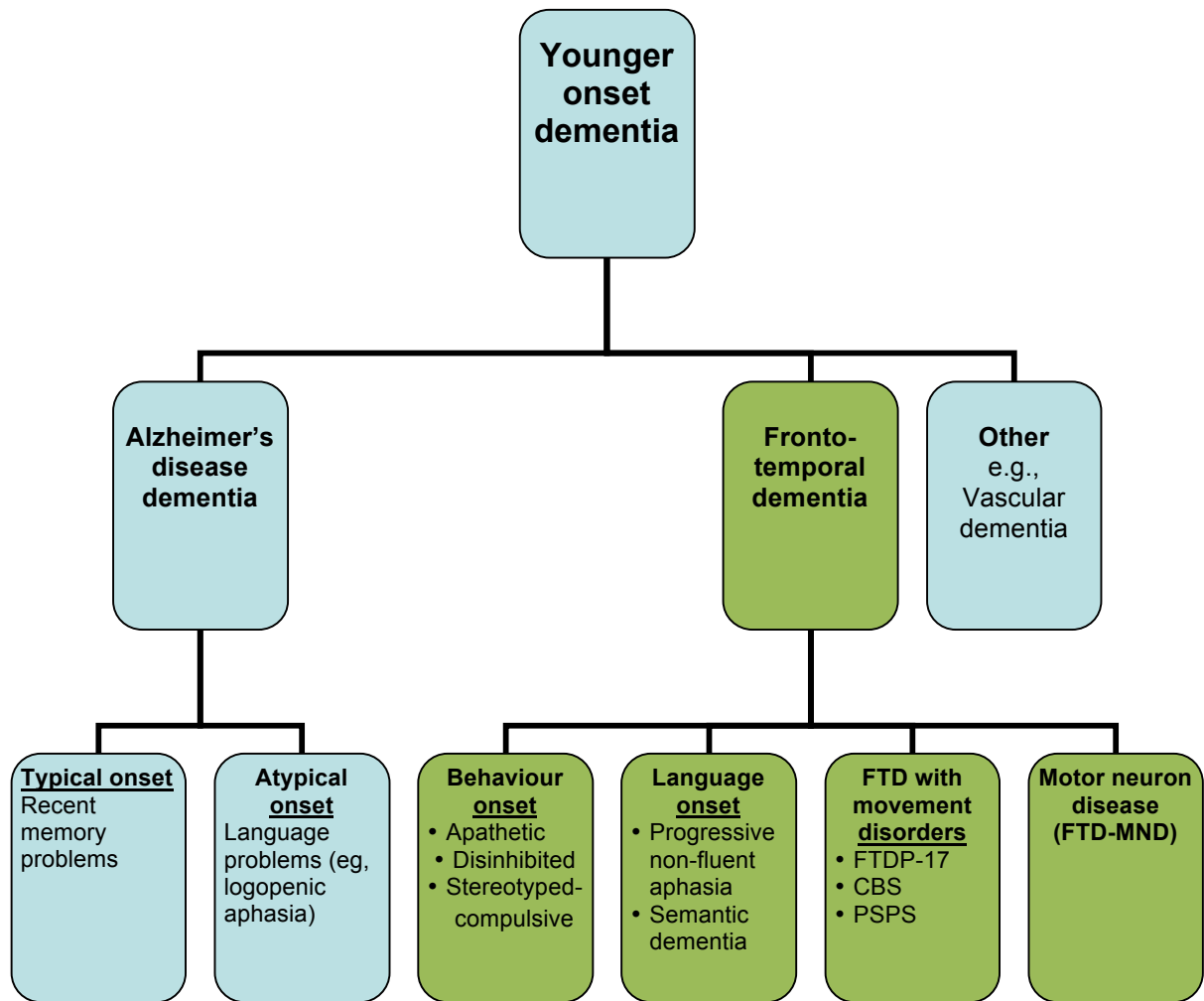
### **Rarer diseases with FTD features**

*Progressive subcortical gliosis (PSG)*, is a rarer condition that is considered to be part of the FTD spectrum of conditions. It is characterized by mixed FTD-like features involving the behavioural, personality and cognitive impairments of bvFTD, but often with language and cortico-basal syndrome or other deficits, and extensive degeneration of white matter on imaging studies. Both males and females are affected, and it may have a rapidly deteriorating course over months rather than years. It is usually sporadic without a family history, but genetic forms also occur. Cases that have been examined pathologically seem more likely to be associated with changes in the *tau* protein [21].

### **Overlap between motor neuron disease and FTD**

*Motor neuron disease (MND)*, also known as *amyotrophic lateral sclerosis (ALS)* (or *Lou Gehrig's disease* in North America), is known as *FTD-MND* when it co-occurs with FTD [22]. It is associated with degeneration of upper (in the brain) and/or lower (in the body) motor neurons, resulting in muscular wasting, weakness, and muscular twitches (fasciculations), especially in the upper extremities and tongue [23]. The condition may be familial (genetic) or sporadic. Cognitive and behavioural symptoms in patients with FTD-MND tend to include symptoms of bvFTD and the syndrome of PNFA [22]. While psychotic symptoms are rare in FTD, up to 50% of patients with the FTD-MND subtype may have delusions [24]. These may suggest specific mutations on chromosome 9 (see C9ORF72 mutations in the *Genetics* section). In FTD-MND, the clinical syndrome can begin with either motor or cognitive/behavioural symptoms, which appear to occur along a continuum.

Figure 2 provides a visual representation of the clinical categories of Frontotemporal dementia (FTD) and how these relate to other forms of younger onset dementia.



**Figure 5.** The major forms of younger onset dementia and their clinical subtypes. FTDP-17: FTD with Parkinsonism linked to chromosome 17; CBS: Corticobasal syndrome; PSPS: Progressive supranuclear palsy syndrome.

**Table 1**

*Summary of the common clinical symptoms associated with different subtypes of FTD.*

Category	Clinical subtype	Common symptoms
<b>Behaviour</b>	Apathetic	Decreased physical activity, emotional blunting, reduced motivation, social withdrawal
	Disinhibited	Overactivity, restlessness, fatuous behaviour, impulsivity, social inappropriateness
	Stereotyped-compulsive	Repetitive and ritualised behaviours, muscular rigidity
<b>Language</b>	Progressive non-fluent aphasia	Expressive language difficulties with effortful, halting speech and grammatical problems
	Semantic dementia	Loss of knowledge of word and object meaning, difficulty finding words
<b>Movement disorders and MND</b>	FTDP-17	Rigidity, tremor, slowness of movement together with symptoms of dementia
	CBS	Asymmetric limb apraxia, alien limb, falls, and myoclonus with slowed thinking and other symptoms of FTD
	PSPS	Slow movement, impaired muscle tone, falls, and eye movement difficulties together with slow thinking and other symptoms of FTD
	FTD-MND	Muscular wasting, weakness, and fasciculations together with PNFA and behavioural symptoms of FTD

### ***Clinical symptoms***

Many FTD cases do not fit neatly into one of the above categories. FTD is a highly idiosyncratic disorder, and each person's symptoms are dependent on his or her unique personality, life experiences, and degree and location of brain involvement. Variable phenotypes may even be seen in families with heritable FTD [15]. Thus, clinical categories which are designed to facilitate communication about the disorders amongst physicians and scientists may not accurately capture the subtleties of all cases [12].



Consequently, this toolkit focuses on the individual symptoms with which an affected individual may present, and on management techniques suited to these individual symptoms.

A broad range of symptoms that have been described in FTD are listed below in alphabetical order [1, 7, 9, 17, 25-28]. It is important to note that some people experience only a handful of the symptoms listed, while others experience many of them. Some symptoms may represent a distinct change from the well person, and others may represent an exaggeration of premorbid personality characteristics or other tendencies. Symptoms may also emerge, fluctuate, and/or disappear over time. A particularly distressing symptom may be problematic throughout the course of the illness, or it may only be present for a number of months. Given the enormous variability in symptom profiles of different patients, a comprehensive list of possibilities is provided below with the aim of informing – not overwhelming – the reader.

- **Activity** changes: may become underactive, inert, passive, OR overactive with pacing, wandering, increased talking, laughing, singing, and/or sexual behaviours
- Flattened **affect**: reduced range of emotions, bland, shallow
- **Aggression**: aggressive and/or violent behaviours
- **Agitation**: may manifest as anxiety or restlessness
- **Agrammatism**: the use of short, simple phrases devoid of grammatical function words such as “a” or “the”
- **Alexia** and/or **agraphia**: problems with reading and writing
- **Apathy**: absence or reduction in enthusiasm and/or emotion; may manifest as lack of interest in previous activities, social isolation; may be misdiagnosed as depression
- **Apraxia**: difficulties performing purposeful, coordinated movements
- **Attentional** deficits: may manifest as trouble concentrating, distractibility, inability to finish tasks
- **Comprehension** impairments: difficulty understanding complex sentences, OR difficulty understanding the meaning of single words, objects, smells, tastes, sounds, etc.; less familiar and less common concepts may be lost first
- **Concrete** thinking: thinking literally and/or difficulty considering abstract concepts
- Impaired **coordination**: difficulty manipulating small objects such as buttons



- Impaired **decision making** ability: inability to adequately reason or plan in order to make appropriate decisions
- **Disinhibition:** making sexually inappropriate or insulting comments in uncharacteristic fashion; laughing or singing at inappropriate times; loss of behavioural and/or speech “filter”; criminal acts; sexualised behaviours outside of socially acceptable norms
- **Dysarthria:** impaired speech ability due to neuromuscular changes
- **Eating or drinking** changes: may eat or drink excessively and indiscriminately, develop a preference for sweet food, or eat in ritualised manners
- **Egocentricity:** must have his/her own way; unable to see another’s point of view; self-centeredness and lack of interest in others
- **Emotional blunting** or dysregulation: emotional shallowness, apathy, reduced primary and social emotional reactions and/or overreactions, rapid and/or large fluctuations between emotions
- **Emotion recognition** disturbance: trouble interpreting emotional facial expressions, difficulty understanding how he/she ought to feel according to circumstances, difficulty drawing inferences from social situations
- Reduced **empathy:** indifference toward others
- **Eye movement** limitations: in individuals with PSPS, downward gaze may be difficult and may contribute to falls
- Impaired **face recognition** (or *prosopagnosia*): difficulty recognising familiar faces
- **Fatuousness:** making silly jokes, acting in a childish fashion
- **Hoarding:** collecting and storing objects without a purpose
- **Hyperorality:** overeating, bingeing; excessive eating or cigarette smoking; placing objects into mouth; see Eating or drinking changes
- **Impulsivity:** may contribute to behaviours such as overspending, gambling
- **Incontinence:** voiding bladder or bowels without concern, often not because the individual is physically unable to remain continent





- Reduced **initiative**: may spend all day doing very little
- Reduced **insight**: reduced awareness or understanding of the disease and symptoms in self, and/or unconcern regarding symptoms
- **Irritability**: may be oversensitive to stimuli
- Impaired **judgement**: unable to foresee future consequences of actions; behaviour may be driven by stimuli rather than by planning and forethought
- **Language** impairment (or *aphasia*): may have difficulty formulating sentences, finding words, and/or understanding the meaning of words or grammatically complex sentences (see Comprehension and Word finding difficulties)
- Reduced **motivation**: may require external prompting for completing daily activities; see Reduced initiative
- **Movement** or motor symptoms: tremor, stiffness or abnormal posturing of limbs, physical slowing, weakness, clumsiness, balance or gait difficulties, stooped posture, muscular twitching or jerking, reduced facial expressions
- **Mutism**: some language and motor symptoms may progress to a total absence of speech production
- Impaired **organisational** ability: behaviours and thoughts may appear disorganised
- **Perseveration**: repetitive behaviours or speech
- Decline in **personal hygiene**: failure to wash, groom, and/or dress appropriately
- **Personality** change or exaggeration of personality traits
- Impaired **planning**: difficulty thinking ahead strategically
- Impaired **problem solving**: due to Impaired reasoning skills
- Primitive **reflexes**: abnormal presence of early-life reflexes
- Impaired **reasoning** skills: may lead to problems such as difficulty managing finances
- **Restlessness**: may manifest as overactivity, pacing, wandering



- **Rigid** or inflexible thinking: difficulty with change and switching attention; may seem impossible to reason with; must follow routine; inability to adapt to novel circumstances
- **Ritualistic** or stereotyped behaviours or speech: repetitive movements or actions; repeating phrases; e.g., hand rubbing, clapping, wandering fixed route, rituals regarding daily activities; may be elicited by particular situation
- Altered **sensory reactions**: abnormal responses to stimuli such as indifference to scalding water or an excessive response to a tap on the shoulder
- Altered **sexual** behaviour: loss of libido or inappropriate sexual behaviour/advances
- **Social** inappropriateness or impaired social cognition: may demonstrate social faux-pas, decline in manners, lack of warmth and rapport, inconsiderate behaviour, tactlessness, lack of shame or embarrassment, immodesty; inability to see things from another's perspective or recognise mental states of others; difficulty understanding sarcasm, humour, or figures of speech
- **Speech** difficulties: slow and effortful speech production and/or articulation, slurred speech, repetition of parts of a word, incorrect or disordered production of word sounds, stuttering, changes in inflection
- **Swallowing** difficulties: difficulty with control or coordination of the muscles responsible for swallowing, posing risk of food/drink aspiration and related complications
- **Utilisation** behaviour: stimulus-bound behaviour, or the tendency to use objects within reach even when context is inappropriate (e.g., drinking from an empty cup)
- **Word finding** difficulties: may substitute generic words such as "thing" when unable to access desired words



## **Prognosis**

The duration of illness in FTD varies a great deal and depends on a number of factors. One important factor is the nature of the clinical subtype. Shorter courses are often seen in patients with FTD-MND [13], and patients with bvFTD tend to progress more rapidly than patients with PNFA and SD [29]. The nature of the neuropathology also appears to be relevant, with tau-positive cases progressing more slowly than others [13]. Variability in course can also depend on the presence of physical symptoms. Those who remain physically well may have a prolonged course, while those who develop neurological signs (regardless of onset type) may decline more quickly [1]. Furthermore, the rate of future progression can often be gauged by the history of progression. If an individual experienced a slow and insidious onset with very gradual progression, the rate of progression is likely to continue in this fashion. Similarly, rapid symptom onset and progression may herald a similarly rapid decline and shorter course of illness.

The median lifespan from onset of symptoms is reported to be 6-8 years, with a range of 2-20 years [15]. Patients with FTD-MND, however, tend to decline over a 3-year period [13, 22]. Many individuals with FTD may require residential care within one year after diagnosis, though this may occur years after symptom onset [13, 30, 31]. A cure for FTD is not currently available, but symptoms can be managed in a number of ways (see Module 3 – Managing frontotemporal dementia). Encouragingly, a great deal of ongoing research is occurring worldwide with the aim of improving the diagnosis and treatment of this condition.

When a diagnosis of FTD is made, it is important for the patient and carer(s) to prepare for change. Change occurs not only in the way the affected individual behaves and thinks, but also in the nature of the symptoms he or she will experience throughout the course of the illness. Living with FTD is a difficult journey and is ideally approached with flexibility, patience, and understanding.

## **Genetics**

Up to 40% of patients with FTD have a positive family history of dementia [4, 32, 33], but many of these positive family histories include other unrelated forms of dementia. Only about 10% of people with FTD appear to have affected first degree relatives [33]. Heritability also varies according to clinical presentation (*phenotype*), with evidence to suggest that bvFTD may be the most heritable [33].

A handful of genetic mutations are known to cause FTD, though these don't account for all cases of familial FTD [2]. They include three commonly involved genes, C9ORF72, microtubule associated protein tau (*MAPT*) and progranulin (*GRN*).



Three more rarely involved genes, valosin containing protein (*VCP*), chromatin modifying protein 2B (also known as charged multivesicular body protein 2B; *CHMP2B*), and the gene encoding transactive response DNA binding protein of 43 kD (TDP-43), known as *TARDBP*. Another gene, fused in sarcoma (*FUS*), is associated with motor neuron disease (MND) and is involved in the pathogenesis of some cases of FTD. More causative genes are being described each month in medical journals, but are often specific to particular families or communities.

### ***Pathology***

Each genetic mutation is associated with a specific type of brain pathology. Increasingly, specific brain pathologies are being linked with the way a person presents; that is, a patient's clinical presentation or *phenotype* [10]. For example, an individual presenting with apathy, withdrawal, and muscle weakness may be found to have FTD-MND, which is associated with TDP-43 deposits in the brain. Another might present with unusual, disinhibited behaviours along with a family history of younger onset dementia, and may be found to have tau pathology in the brain associated with the *MAPT* genetic mutation. Such clinico-pathological correlations are only now being clarified.

The symptoms of FTD are caused by protein depositions (or *inclusions*) in brain cells, usually in neurons, the important brain cells in the cortex (grey matter) of our brains. These neuronal inclusions affect the frontal and anterior temporal lobes of the brain, which result in atrophy (loss of brain volume/shrinkage) and dysfunction in these regions. FTD was historically referred to as *Pick's disease* after Pick described atrophy and neuronal inclusions in the brains of six people who had presented with dementia. It is now known that only a small proportion of FTD patients have Pick-type histological changes, or classical Pick's disease.

A number of different protein depositions are associated with FTLD. The two main pathologic types of FTLD are associated with inclusions comprised of the protein tau in about 50% and inclusions comprised of the protein TDP-43 in most of the remainder of genetic cases [10] (see Figure 3). The protein *FUS* is also involved in some rare cases. Multiple histological subtypes have also been identified within each pathologic category, some of which closely correlate with phenotypic presentations [10, 34].

### **Tauopathies**

*MAPT* mutations and the disease processes underlying a number of Parkinson's disease-like conditions (also known as *Parkinson's plus* conditions) are all associated with tau-positive neuronal inclusions (known as FTLD-T or FTLD-tau). These conditions include corticobasal degeneration (CBD, once called corticobasal ganglionic degeneration, or CBGD), progressive supranuclear palsy (PSP), most cases of progressive subcortical

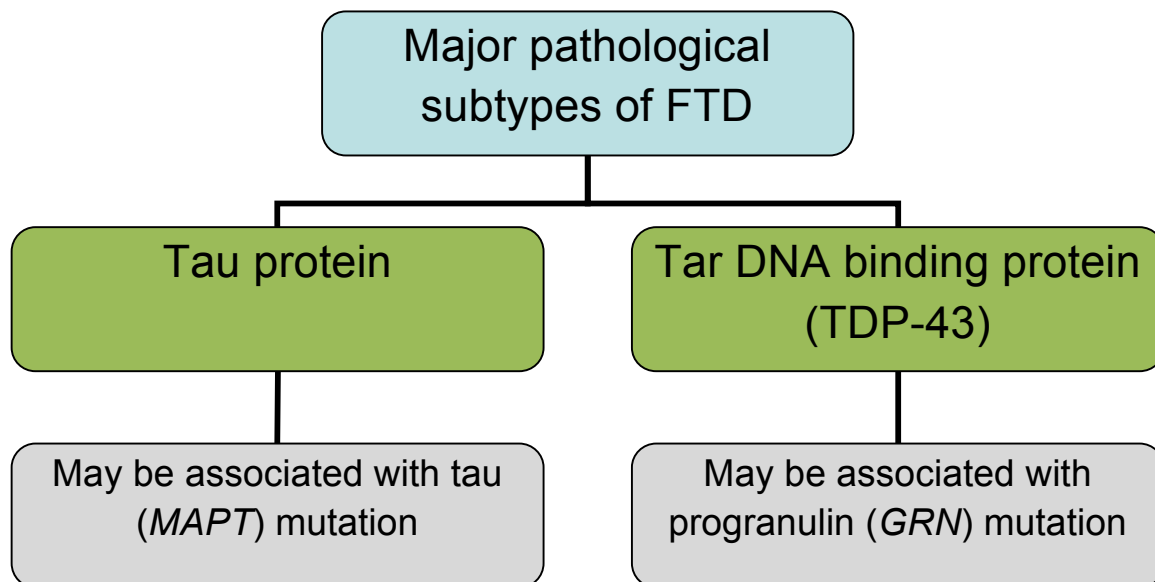


gliosis (PSG) and Pick’s disease. MAPT mutations are associated with different types of tau inclusions in different parts of the brain.

### TDP-43 proteinopathies

TDP-43 inclusions are immunoreactive to a common brain protein called ubiquitin; thus, inclusions comprised of TDP-43 used to be described as “ubiquitin-positive” before the underlying protein was described in the mid-2000’s. *C9ORF72*, *GRN*, *VCP*, and *TARDBP* mutations are associated with ubiquitin-positive inclusions comprised of TDP-43 (known as TDP-43 positive FTLD-U, or FTLD-TDP). TDP-43 is also the main component of inclusions found in FTD-MND [35] which are most commonly related to *C9ORF72* mutations.

The *C9ORF72* mutation was described in late 2011 by two research groups, and now is thought to be the commonest mutation causing genetic cases of bvFTD or FTD-MND (and MND). It may be also more common in specific clinical phenotypes of FTD (such as psychosis, or excessive sweet food preference). It may also be found in cases without a family history. The mutation is a novel one with excess repetition of some of the constituent nucleotides of DNA (the building blocks) [36].



**Figure 6.** Diagram of two of the major pathological subtypes of FTD and the associated common genetic mutation. These mutations only occur in a percentage of people with FTD. There are several other pathological proteins described (see below).



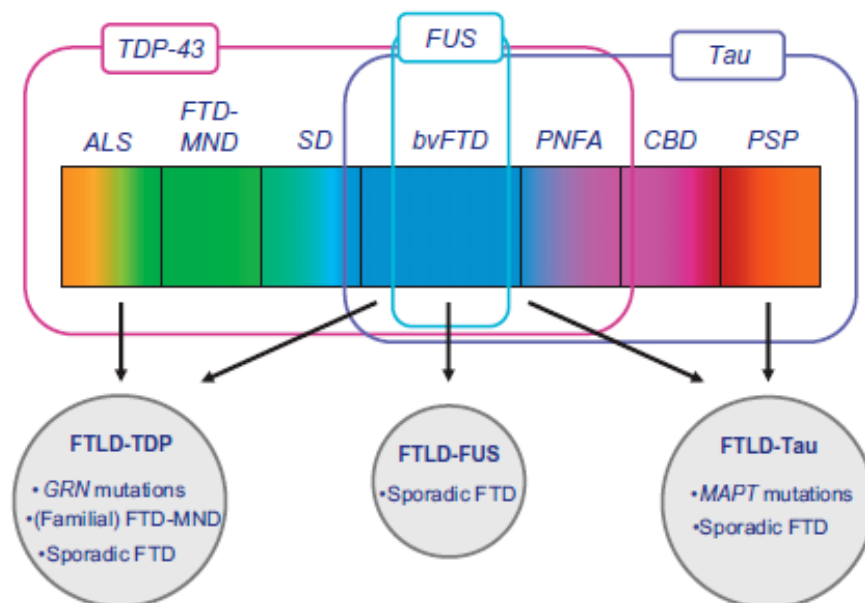
## FUS depositions

A small number of families with FTD have been found to have ubiquitin-positive, TDP-43 negative pathology. They have recently been shown to have inclusions that react with an antibody to the protein FUS. None of these FTLD-FUS cases had FUS gene mutations [2]. FTLD-FUS cases are characterised by a young age at onset, bvFTD clinical diagnosis, and a negative family history. FUS-positive inclusions are also found in people with particular types of brain pathology known as neuronal intermediate filament inclusion disease (NIFID) and basophilic inclusion body disease (BIBD) [10].

## FTD-UPS

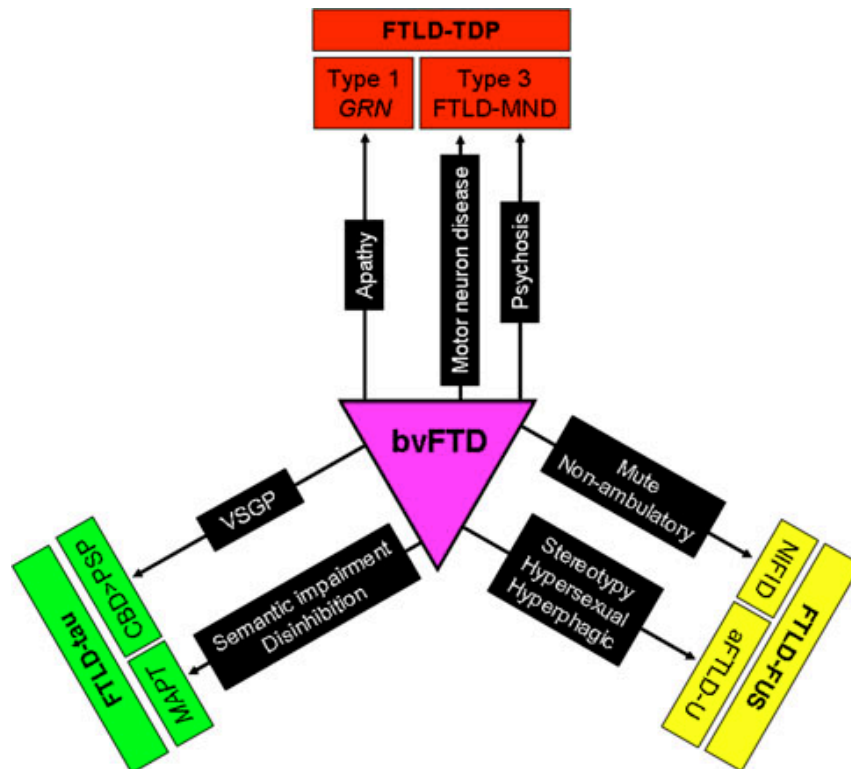
The pathological heterogeneity of FTLD is further demonstrated by cases with ubiquitin-positive, TDP-43, tau- and FUS-negative inclusions, now termed FTD-UPS [10]. Many individuals with FTD-UPS carry a CHMP2B mutation but a few cases without CHMP2B mutations have been reported in which the ubiquitinated proteins have not yet been identified [10, 33, 35].

Pathologic phenotypes tend to show some relationship with clinical phenotypes, but these associations are not reliably predictive (see Figures 4 and 5). In these diagrams, FTD-MND is now known to be most often associated with C9ORF72 mutations.





**Figure 7.** Seelaar and colleagues' illustration of the clinical, genetic, and pathological spectrum of frontotemporal lobar degeneration [2].



**Figure 8.** Josephs and colleagues' [10] illustration of the clinical features that help to predict the underlying molecular pathology in patients presenting with bvFTD. VSGP: vertical supranuclear gaze palsy; aFTLD-U: atypical FTLN with ubiquitin-only immunoreactive changes. FTLN-TDP types are based on the classification of Mackenzie and colleagues [37].

### Summary

Frontotemporal dementia (FTD) is a relatively unfamiliar but common form of younger onset dementia that typically occurs between 45 and 65 years of age. Many thousands of Australians are thought to be suffering from this condition. FTD is associated with atrophy and dysfunction in the frontal and anterior temporal regions of the brain, in contrast to the medial temporal regions affected in Alzheimer's Disease (AD). Thus, the symptoms of FTD are very different from the symptoms of AD. There are a number of clinical subtypes of FTD, and symptoms can vary a great deal even amongst individuals with similar subtypes. Our understanding of the nature of the brain pathology and genetic mutations associated with FTD is increasing, though the cause of most cases is still unknown. There is no cure for FTD at this time, but many symptoms can be managed effectively.





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