Published in final edited form as:

Neurol Clin. 2007 August ; 25(3): 683–vi. doi:10.1016/j.ncl.2007.03.005.

Frontotemporal Lobar Degeneration

Keith A. Josephs, MST, MD

Department of Neurology, Divisions of Behavioral Neurology & Movement Disorders, Mayo Clinic and Mayo Foundation, Rochester, MN, U.S.A

Synopsis

Frontotemporal lobar degeneration (FTLD) is a syndromic diagnosis that encompasses at least three different variants. Imaging modalities are clinically useful in FTLD while pathology remains the gold standard for definitive diagnosis. To date three different genes have been identified that account for FTLD.

Keywords

Frontotemporal lobar degeneration; semantic dementia; progressive aphasia; progranulin; tau; ubiquitin

Historical Perspective

The clinical syndrome associated with FTLD was first described by Arnold Pick in 1892¹. However, it wasn't until almost 20 years later that the histopathology was described by Alois Alzheimer in 1911². He showed an absence of the senile plaques and neurofibrillary tangles that were characteristic of Alzheimer's disease (AD), as well as rounded inclusions today known as Pick bodies, and balloon cells today known as Pick cells. While the term Pick disease was first adopted to describe lobar atrophy it is now reserved for one specific type of pathology.

Interest in FTLD waned until the 1980's when the first diagnostic criteria were proposed by investigators in Lund and Manchester, and the term frontotemporal dementia was adopted to describe cases with behavioral and language impairment associated with frontal and temporal lobe atrophy³. These criteria were further refined by Neary and colleagues in 1998⁴ when the term FTLD was designated to encompass three clinical variants: frontotemporal dementia (FTD) characterized by prominent behavioral changes, semantic dementia (SD) characterized by a loss of word meaning, and progressive non-fluent aphasia (PNFA) characterized by agrammatic non-fluent speech. In addition, the term primary progressive aphasia (PPA) was coined in the United States by Mesulam in 1982⁵, to describe patients that presented with an isolated language impairment of word usage and comprehension. It is now recognized that there is overlap between PNFA and PPA, and between SD and PPA⁶. More recently there has been recognition as well that FTLD can overlap with other well recognized clinical syndromes including corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP)⁷⁻¹⁰. The

Correspondence to: Keith A. Josephs, MST, MD, Department of Neurology, Mayo Clinic & Mayo Foundation, 200 1st Street S.W., Rochester, MN 55905, Tele: (507)-538-1038, Fax: (507)-538-6012, email: E-mail: josephs.keith@mayo.edu.

Disclosure: The author has nothing to disclose

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

term Pick Complex was proposed by Kertesz as a term to encompass all variants of FTLN, CBS and PSP¹¹.

One of the most important developments in the field of FTLN has been the recognition that mutations in the tau gene and mutations in the progranulin gene, both located on chromosome 17, cause FTLN. Hutton and colleagues demonstrated that mutations in the microtubule associated protein tau (MAPT) causes FTLN with pathological findings of tau deposition in neurons and glia¹². Again, Hutton and colleagues demonstrated that mutations in the progranulin gene (PGRN) are a cause of FTLN without tau inclusions, but with ubiquitin-only immunoreactive inclusions (FTLN-U)¹³. Recently researchers from the University of Pennsylvania identified the major protein in tau-negative FTLN. This protein, TDP-43, was found in FTLN-U, as well as in cases with motor neuron disease (MND)¹⁴.

Syndromic Diagnosis

There are three main clinical variants of FTLN which are based on consensus statements from an international conference on FTLN⁴. These three syndromes are the behavioral variant of frontotemporal dementia (bvFTD), progressive non-fluent aphasia (PNFA), and semantic dementia (SD). In addition to these three syndromes FTLN has been linked with CBS, PSP, apraxia of speech (AOS), and MND.

Behavioral variant frontotemporal dementia

Of all the variants of FTLN the most common variant is bvFTD¹⁵, characterized by a significant change in the patients personality and social behavior, and impaired executive function. Patients with bvFTD usually present with behavioral alterations that are different from their usual personal and social behaviors. This includes becoming either more apathetic, or more disinhibited. The apathetic patients usually present in a somewhat depressed like state and lack motivation. These patients are also often hypersomnolent. The disinhibited patients usually present with excessive restlessness, wandering, and socially inappropriate behavior, for example making inappropriate conversations in an elevator or in a restaurant with a stranger. Other features of bvFTD include a lack of concern about ones appearance, as well as a lack of insight into ones illness. Increased jocularity, spontaneous giggling or laughter, unusual eating and oral behaviors, for example gluttony with cramming food into the mouth and eating non-edible food, hypersexuality, hyper-religiosity and perseverative and utilization behavior (the need to play with objects that are in ones visual sight or environment) can also occur. Repetitive behaviors and compulsions may develop later in the disease course although there are rare occurrences of compulsions being the presenting symptom of bvFTD¹⁶. For example, one patient with bvFTD would go to the bathroom to urinate every 5 minutes of each day. Stereotypic behaviors occur in bvFTD, and they take the form of repetitive behaviors, for example rubbing ones leg¹⁷. Paranoia, aggressiveness, selfishness, and lack of empathy can occur. Neuropsychological testing in patients with bvFTD may show abnormalities in tests of executive function¹⁸. However, many subjects with bvFTD may perform normally in neuropsychological testing reflecting the insensitivity of test batteries to detect deficits. Language impairment can occur early in the course of the illness in bvFTD but tends to be less prominent than the behavioral features⁴. Parkinsonism occurs in a subset of patient with bvFTD but tends to be a late feature¹⁹.

Progressive non-fluent aphasia

The second variant of FTLN is PNFA⁴. The characteristic features of PNFA are agrammatism with phonemic paraphasias and anomia, which should be present in isolation during the early stages of the disease. It is quite common however for behavioral abnormalities and executive dysfunction to develop later in the disease course. Patients with PNFA may have difficulty

with comprehension of sentences that are syntactically complex but should have preservation of single word comprehension. Aphasia can occur in isolation but quite frequently coexists with AOS (defined below). Agrammatism is defined as either making grammatical errors while speaking, such as the exclusion or incorrect use of articles, propositions, or verbs. Phonemic paraphasic errors refer to the transposition of phonemes and can be particularly prominent while the patient is reading, where there can be many phonemic paraphasias, for example, slissors for scissors. Another terminology that significantly overlaps with PNFA is that of primary progressive aphasia, or PPA, which refers to the presence of isolated language impairment, fluent or non-fluent, for the first two years of the disease course^{5, 20}. One study has also suggested that a subset of PPA cases have a different pattern of atrophy and may represent a separate syndrome known as 'logopenic' PPA²¹.

Semantic dementia

Semantic dementia (SD) is also referred to as the temporal variant of FTL^{4, 22}. In SD there is a progressive loss of word knowledge and meaning, that is, knowledge about objects, facts, and even people. Speech tends to be fluent but may not be meaningful. Comprehension is impaired at the single word level which differs from PNFA where comprehension is affected at the sentence level. Anomia is prominent; however the inability to name an object is matched by the patient's inability to give a detailed description of the object. In addition, patients with SD have a significant visual associative agnosia (impaired object recognition) and therefore may not be able to recognize objects that are presented visually²³. Therefore, word-picture matching tasks are performed poorly. Food preferences and preoccupation with cross-word puzzles are also common. There is evidence of a surface dyslexia while reading (incorrect pronunciation of orthographically irregular words, for example, yacht is pronounced ya-ch). The majority of cases with SD show temporal lobe atrophy, although on careful inspection the atrophy tends to be asymmetric, more frequently affecting left greater than right temporal lobe²². When the right temporal lobe is more severely affected than the left the presenting features tend to be different from those typically seen in left-sided patients. In the patients with more right sided atrophy, prosopagnosia (impaired facial recognition) and geographic disorientation are present, and the patients tend to have behavioral abnormalities including social awkwardness and rudeness.

Corticobasal syndrome

Corticobasal syndrome²⁴ has been linked with FTL⁴ since patients with CBS can evolve and develop behavioral features, personality changes, and executive dysfunction similar to those observed in bvFTD⁹. This syndrome is characterized by asymmetric cortical (apraxia, cortical sensory loss, myoclonic jerks), and basal ganglia (bradykinesia, rigidity, tremor, dystonia) features²⁴. Very rarely, patients may develop an alien limb phenomenon in which there is involuntary movements and personification of the limb. Symptoms do not respond to Levodopa treatment. The CBS may develop in patients who initially had features most characteristic of bvFTD, and is even more likely to develop in patients that initially present with PNFA⁹. There is also significant overlap between CBS and PSP. Initially CBS was felt to be specific to corticobasal degeneration pathology, however studies have demonstrated that CBS is non-specific and can occur as a result of any one of the pathologies that are discussed below²⁵.

Progressive supranuclear palsy (PSP)

Progressive supranuclear palsy, or Steele-Richardson Olszewski syndrome, is characterized by early falls, vertical, especially down gaze, supranuclear palsy, axial greater than appendicular rigidity, and levodopa resistance²⁶. Behavior and personality changes are less common and less severe than in CBS. Neuropsychological testing demonstrates some mild-to-moderate frontal lobe deficiencies. Patients may present with a non-fluent aphasia with

prominent AOS and only very late in the disease course show signs characteristic of PSP^{27, 28}. These patients tend to have PSP pathology. There have also been reports of an overlap syndrome between PSP and upper motor neuron disease²⁹.

Motor neuron disease

Motor neuron disease (MND) is defined as any evidence of pyramidal tract degeneration or anterior horn cell disease. Motor neuron disease can be isolated to the pyramidal tract (upper MND), anterior horn cells (lower MND), or mixed (amyotrophic lateral sclerosis). MND infrequently coexists with FTLN. This occurs most frequently with bvFTD, but has also been infrequently reported to coexist with PNFA and SD. Typically in these cases there are findings of lower MND or mixed upper and lower MND³⁰. Pathology in these cases almost always shows evidence of lobar degeneration as well as MND. However, not all pathologically confirmed cases show evidence of clinical MND³⁰. Clinical studies have identified a higher than expected frequency of MND in FTLN subjects, conversely a high frequency of frontal lobe dysfunction on neuropsychological tests has been observed in subjects with MND^{31, 32}.

Apraxia of Speech

Apraxia of speech (AOS) is also referred to as speech apraxia, aphemia, and phonetic disintegration. It is defined as a motor speech disorder with a slow speaking rate, abnormal prosody, and distorted sound substitutions, repetitions, and prolongations, at times accompanied by groping. It is common to lump AOS under the heading of PNFA in neurodegenerative diseases, however AOS can occur in the absence of aphasia and is considered a separate syndrome by some researchers²⁷. Imaging studies have identified specific anatomical correlates of AOS, distinct from those observed in PNFA²⁷. Clinicopathological studies have suggested that the presence of AOS is specific to tau biochemistry²⁷.

Ancillary Testing

Routine blood tests

Patients presenting with an FTLN syndrome should undergo routine blood tests. These include a complete blood count, electrolytes, thyroid function studies, liver function tests, and renal function tests, to rule out systemic illnesses causing a dementia. In very young patients, especially where there is diagnostic uncertainty, more elaborate testing may be required for diagnosis. Some of these tests may include screening for metabolic, genetic, and autoimmune disorders.

Cerebrospinal fluid

Cerebrospinal fluid (CSF) studies in FTLN are useful to exclude other causes of dementia. In the majority of cases of FTLN there can be elevated protein however the rest of the profile tends to be within normal limits. Oligoclonal bands are not present. Recent studies have investigated the diagnostic utility of tau, amyloid beta 42, and neurofilament. Phosphorylated tau protein have been reported to be elevated³³, but also have been reported to be normal³⁴. Total tau levels have been reported to be low³⁴ or normal³⁵. Some researchers have suggested that a combination of CSF tau and amyloid beta 42 may help differentiate FTLN from AD³⁶. Reports aiming to differentiate AD from FTLN by measuring neurofilament proteins have been conducted,^{35, 37} but need to be validated.

Electroencephalogram

An EEG is often performed as part of the clinical evaluation in FTLT. This is also important to rule out other causes of dementia, for example transient epileptic phenomena. There are however no specific EEG findings in FTLT and recently it was shown that there are no EEG abnormalities that are useful in differentiating FTLT from AD³⁸.

Neuroimaging

Patients show atrophy and hypometabolism of the frontal and temporal cortices, which matches the pathological findings. The occipital lobe is almost always spared, although the parietal lobe can be affected, especially in subjects that present with PNFA or CBS. The presence of frontal and anterior temporal lobe abnormalities on brain imaging is part of the diagnostic criteria for FTLT⁴. It should be noted however that there are cases of FTLT who even after more than ten years of illness duration may show very little atrophy³⁹. There are characteristic patterns of atrophy that have been suggested for each of the syndromic variants of FTLT and their related disorders. Subjects presenting with bvFTD usually show symmetric frontal lobe atrophy (Figure 1), although asymmetric right sided atrophy has been reported⁴⁰. Studies using automated image analysis techniques have allowed a more detailed assessment of patterns of atrophy, and have shown atrophy in a network of limbic areas that are likely to be involved in the fine tuning of behavior, including the ventromedial cortex, anterior cingulate and amygdala^{41, 42}. It seems to be becoming clearer however that subjects with frontal lobe features suggestive of bvFTD could also have right temporal lobe atrophy. Functional imaging studies have shown hypometabolism (Figure 2) or hypoperfusion in the same anatomical regions.

In contrast, patients with SD show atrophy and hypometabolism predominantly in the left anterior temporal lobe. However patients may present with more right temporal lobe atrophy (Figure 1). Practically all left temporal lobe regions can be involved, with particularly severe atrophy in inferior temporal regions, including the fusiform and inferior temporal gyrus, with relative sparing of the superior temporal gyrus^{43, 44}. Atrophy significantly affects the hippocampus and amygdala⁴³. There is also often involvement of the ventromedial and superior frontal lobes, which is consistent with the fact that patients with SD often develop behavioral abnormalities. There is also evidence that as the disease progresses the atrophy can extend from the left anterior temporal lobe to involve more posterior temporal regions, the inferior frontal lobe and the right anterior temporal lobe⁴⁵.

Unlike SD, patients with PNFA have consistently shown left frontal and perisylvian atrophy on magnetic resonance imaging (MRI) (Figure 1), with hypoperfusion and hypometabolism demonstrated in the same regions on functional imaging. In those that have become mute a pattern of atrophy affecting the left perisylvian region and extending into the left basal ganglia has been demonstrated⁴⁶.

Imaging studies have also been completed in other syndromic variants associated with FTLT. Posterior frontal and superior parietal atrophy is associated with CBS^{47, 48}, while those with PSP show areas of subcortical atrophy affecting the superior cerebellar peduncle and midbrain^{48, 49}. The anterior-posterior diameter of the midbrain is reduced⁵⁰ giving the so called “face of Mickey mouse” appearance. Patients with AOS show atrophy of the supplemental motor area and superior posterior frontal lobe²⁷. The logopenic variant of primary progressive aphasia was reported to be associated with left posterior temporal and inferior parietal lobule atrophy⁵¹. Subjects that present with prosopagnosia have shown predominantly right temporal lobe atrophy (Figure 1). This pattern of atrophy can also be seen in patients that present with predominant behavior features, as well as those with prominent geographic disorientation.

Recent studies have suggested that the pathological subtypes of FTLT may also have characteristic imaging findings. Patients with FTLT-U (defined below) have been shown to have predominant atrophy of the temporal lobes, particularly in posterior gyri, as well as some involvement of the frontal lobes, while patients with FTLT-MND show patterns of atrophy relatively restricted to just the frontal lobes⁵². Patients with PiD show severe involvement of the frontal lobes⁵³.

Pathology

The gross pathologic findings in FTLT are similar to MRI findings in FTLT. There is atrophy affecting the frontal and temporal lobes (Figure 3) and in some cases the parietal lobes. The occipital lobes are almost always spared. The frontal, temporal and parietal lobes can all be affected however it is most common to find varying degrees of atrophy in each region, at times correlating with the presenting syndromes. Histological diagnosis in FTLT however is heterogeneous⁵⁴. The presence or absence of tau-positive inclusions is used to simplify the classification and to determine if the case is reported as a tauopathy (tau-positive inclusions are the major findings) or a non-tauopathy (tau-positive inclusions are minor or absent). The major diagnostic tauopathies that underlie FTLT are corticobasal degeneration (CBD), progressive supranuclear palsy (PSP) and Pick disease (PiD). They all differ by the distribution of the pathology and the morphological features of the tau positive inclusions. Corticobasal degeneration was originally thought to be only associated with the CBS however has been found to underlie many other syndromes, especially PNFA⁵⁵. And while PSP was originally associated with the clinical syndrome of early falls, parkinsonism, and supranuclear gaze palsy, recent evidence have shown that PSP pathology can be found in subjects with PNFA especially when AOS is also present²⁷. Pick disease is less common than PSP and CBD in FTLT pathological studies⁷⁻¹⁰.

The two major non-tauopathies include those with ubiquitin-only immunoreactive changes (FTLT-U), and those with motor neuron disease (FTLT-MND). The former, FTLT-U, is the most common pathology that underlies FTLT^{56, 57}. In addition, FTLT-U is the most common pathology in the SD variant of FTLT^{8, 58}. There are many different terminologies that have been used to describe this pathology (Table 1) and the presence of intranuclear inclusions in FTLT-U is associated with familial FTLT and may suggest a mutation in the PGRN gene⁵⁹. Similar to the many terminologies that define FTLT-U, many terminologies also define FTLT-MND (Table 1). Unlike in FTLT-U where there is no evidence of motor neuron disease (MND), FTLT-MND is characterized by pathological findings of MND. When there is clinical evidence of MND pathological diagnosis of FTLT-MND has been shown to be 100% sensitive⁸. A recent discovery is the identification that a protein TDP-43 may be the major component of neuronal inclusions in FTLT-U and FTLT-MND however this remains to be validated¹⁴. Two other non-tauopathies worth mentioning are neurofilament inclusion body disease (NIBD)⁶⁰ and dementia lacking distinctive histology (DLDH) which is characterized by neuronal loss and gliosis affecting frontal and temporal cortex, but absence of any intraneuronal inclusions¹⁹.

Genetics

A positive family history of dementia occurs in approximately 40% of patients with FTLT. In the majority of these families, the pattern of inheritance has been autosomal dominant. Genetic studies have identified a loci on chromosome 9q, and genes on chromosome 3p and 17q. The first gene to be identified and linked to familial FTLT was the microtubule associated protein tau (*MAPT*) gene located on chromosome 17¹². Due to a consensus conference in 1996 cases linked to tau on chromosome 17q21 were termed frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17). To date approximately 35 different confirmed mutations

in *MAPT* have been identified in over 100 families. Pathologically, patients with FTL and *MAPT* mutations reveal tau-positive inclusions. The second gene to be linked with FTL is the *CHMP2B* gene (charged multivesicular body protein also known as chromatin-modifying protein 2B)⁶¹. This gene has been linked to a family from the Jutland region of Denmark which initially was thought to be associated with DLDH pathology. Recent reevaluation of some of the subjects from this family have, however, identified ubiquitin positive inclusions. Mutations in *CHMP2B* are however a rare cause of FTL, and were not identified in 141 familial probands from the USA and UK⁶². The most recent gene identified that causes FTL is progranulin (*PGRN*)^{13, 63}. Mutations in the *PGRN* gene are more common than the prior two mutations. Mutations in *PGRN* have been reported to account for approximately 10% of subjects with FTL, and 25% of those with a positive family history of dementia⁶⁴. Pathological diagnosis in subjects with a *PGRN* mutation has consistently been found to be FTL-U without any evidence of MND^{59, 65}. Clinical studies have suggested that patients with *PGRN* mutation have more frequent parkinsonism and language impairment than subjects without a mutation. Imaging and pathological studies have suggested that FTL-U subjects with a *PGRN* mutation have a more severe pattern of atrophy, particularly affecting the frontal and parietal lobes, than FTL-U subjects without *PGRN* mutations⁶⁶. Frontotemporal lobar degeneration with MND has been linked to chromosome 9p in two large families^{65, 67}.

Treatment

Pharmacological treatment for FTL is limited to addressing behavioral dyscontrol. These studies have focused mainly on drugs with serotonergic modulated properties. Treatment trials using serotonin reuptake inhibitors have had at best, modest effects^{68, 69}.

While there are no specific pharmacological treatments for aphasia many patients may benefit from speech therapy which aid in their ability to communicate with family and friends. Because speech therapy may be more beneficial for certain aspects of the language impairment proper syndromic diagnosis and recognition of important signs and symptoms, especially dysarthria that accompany the aphasia, is important.

Summary

Frontotemporal lobar degeneration is a syndromic diagnosis that includes at least three different syndromes: bvFTD, SD and PNFA. There is also significant overlap between FTL, PSP, CBS, AOS, and MND suggesting possible common etiopathogenesis. Imaging modalities are helpful in differentiate FTL from other causes of dementia and usually show a pattern of frontotemporal and parietal abnormalities depending on which syndrome is the most prominent. Pathology remains the gold standard for definitive diagnosis but is heterogeneous. The most common pathology has been identified as FTL-U. Recent studies have demonstrated that mutations in the *PGRN* gene are associated with FTL-U pathology. Two additional genes that are associated with FTL are the *MAPT* and *CHMP2B* genes. A genetic loci has been mapped to chromosome 9p is families in which FTL and MND overlap. Treatment in FTL is at best modest.

Acknowledgments

KAJ is supported by the NIH Roadmap Multidisciplinary Clinical Research Career Development Award Grant (K12/NICHD)-HD49078 (KAJ), and the Robert H. and Clarice Smith and Abigail Van Buren Alzheimer's Disease Research Program of the Mayo Foundation, U.S.A.

The author would like to acknowledge Dr. Jennifer L. Whitwell for critical review and aid with manuscript preparation, and Dr. Dennis W. Dickson for Figure 3.

References

1. Pick A. Über die Beziehungen der senilen Hirantropie zur aphasia. *Prager Medizinische Wochenschrift* 1892;17:165–167.
2. Alzheimer A. Über eigenartige Krankheitsfälle des späteren Alters. *Zeitschrift für die Gesamte Neurologie und Psychiatrie* 1911;4:356–385.
3. Brun A. Clinical and neuropathological criteria for frontotemporal dementia. The Lund and Manchester Groups. *J Neurol Neurosurg Psychiatry* 1994;57:416–418. [PubMed: 8163988]
4. Neary D, Snowden JS, Gustafson L, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology* 1998;51:1546–1554. [PubMed: 9855500]
5. Mesulam MM. Slowly progressive aphasia without generalized dementia. *Ann Neurol* 1982;11:592–598. [PubMed: 7114808]
6. Adlam AL, Patterson K, Rogers TT, et al. Semantic dementia and fluent primary progressive aphasia: two sides of the same coin? *Brain* 2006;129:3066–3080. [PubMed: 17071925]
7. Hodges JR, Davies RR, Xuereb JH, et al. Clinicopathological correlates in frontotemporal dementia. *Ann Neurol* 2004;56:399–406. [PubMed: 15349867]
8. Josephs KA, Petersen RC, Knopman DS, et al. Clinicopathologic analysis of frontotemporal and corticobasal degenerations and PSP. *Neurology* 2006;66:41–48. [PubMed: 16401843]
9. Kertesz A, McMonagle P, Blair M, et al. The evolution and pathology of frontotemporal dementia. *Brain* 2005;128:1996–2005. [PubMed: 16033782]
10. Forman MS, Farmer J, Johnson JK, et al. Frontotemporal dementia: clinicopathological correlations. *Ann Neurol* 2006;59:952–962. [PubMed: 16718704]
11. Kertesz A, Hudson L, Mackenzie IR, Munoz DG. The pathology and nosology of primary progressive aphasia. *Neurology* 1994;44:2065–2072. [PubMed: 7969961]
12. Hutton M, Lendon CL, Rizzu P, et al. Association of missense and 5'-splice-site mutations in tau with the inherited dementia FTDP-17. *Nature* 1998;393:702–705. [PubMed: 9641683]
13. Baker M, Mackenzie IR, Pickering-Brown SM, et al. Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. *Nature* 2006;442:916–919. [PubMed: 16862116]
14. Neumann M, Sampathu DM, Kwong LK, et al. Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Science* 2006;314:130–133. [PubMed: 17023659]
15. Johnson JK, Diehl J, Mendez MF, et al. Frontotemporal lobar degeneration: demographic characteristics of 353 patients. *Arch Neurol* 2005;62:925–930. [PubMed: 15956163]
16. Mendez MF, Perryman KM, Miller BL, et al. Compulsive behaviors as presenting symptoms of frontotemporal dementia. *J Geriatr Psychiatry Neurol* 1997;10:154–157. [PubMed: 9453681]
17. Mendez MF, Shapira JS, Miller BL. Stereotypical movements and frontotemporal dementia. *Mov Disord* 2005;20:742–745. [PubMed: 15786492]
18. Johanson A, Hagberg B. Psychometric characteristics in patients with frontal lobe degeneration of non-Alzheimer type. *Arch Gerontol Geriatr* 1989;8:129–137. [PubMed: 2735785]
19. Knopman DS, Mastri AR, Frey WH 2nd, et al. Dementia lacking distinctive histologic features: a common non-Alzheimer degenerative dementia. *Neurology* 1990;40:251–256. [PubMed: 2300243]
20. Mesulam MM. Primary progressive aphasia. *Ann Neurol* 2001;49:425–432. [PubMed: 11310619]
21. Gorno-Tempini ML, Dronkers NF, Rankin KP, et al. Cognition and anatomy in three variants of primary progressive aphasia. *Annals of Neurology* 2004;55:335–346. [PubMed: 14991811]
22. Thompson SA, Patterson K, Hodges JR. Left/right asymmetry of atrophy in semantic dementia: behavioral-cognitive implications. *Neurology* 2003;61:1196–1203. [PubMed: 14610120]
23. Snowden JS. Semantic dementia: a form of circumscribed cerebral atrophy. *Behavioural Neurology* 1989;2:167–182.
24. Boeve BF, Lang AE, Litvan I. Corticobasal degeneration and its relationship to progressive supranuclear palsy and frontotemporal dementia. *Ann Neurol* 2003;54:S15–19. [PubMed: 12833363]
25. Boeve BF, Maraganore DM, Parisi JE, et al. Pathologic heterogeneity in clinically diagnosed corticobasal degeneration. *Neurology* 1999;53:795–800. [PubMed: 10489043]

26. Litvan I, Agid Y, Calne D, et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. *Neurology* 1996;47:1–9. [PubMed: 8710059]
27. Josephs KA, Duffy JR, Strand EA, et al. Clinicopathological and imaging correlates of progressive aphasia and apraxia of speech. *Brain* 2006;129:1385–98. [PubMed: 16613895]
28. Josephs KA, Boeve BF, Duffy JR, et al. Atypical progressive supranuclear palsy underlying progressive apraxia of speech and nonfluent aphasia. *Neurocase* 2005;11:283–296. [PubMed: 16093229]
29. Josephs KA, Katsuse O, Beccano-Kelly DA, et al. Atypical progressive supranuclear palsy with corticospinal tract degeneration. *J Neuropathol Exp Neurol* 2006;65:396–405. [PubMed: 16691120]
30. Josephs KA, Parisi JE, Knopman DS, et al. Clinically undetected motor neuron disease in pathologically proven frontotemporal lobar degeneration with motor neuron disease. *Arch Neurol* 2006;63:506–512. [PubMed: 16606762]
31. Lomen-Hoerth C, Anderson T, Miller B. The overlap of amyotrophic lateral sclerosis and frontotemporal dementia. *Neurology* 2002;59:1077–1079. [PubMed: 12370467]
32. Lomen-Hoerth C, Murphy J, Langmore S, et al. Are amyotrophic lateral sclerosis patients cognitively normal? *Neurology* 2003;60:1094–1097. [PubMed: 12682312]
33. Arai H, Morikawa Y, Higuchi M, et al. Cerebrospinal fluid tau levels in neurodegenerative diseases with distinct tau-related pathology. *Biochem Biophys Res Commun* 1997;236:262–264. [PubMed: 9240421]
34. Grossman M, Farmer J, Leight S, et al. Cerebrospinal fluid profile in frontotemporal dementia and Alzheimer's disease. *Ann Neurol* 2005;57:721–729. [PubMed: 15852395]
35. Sjogren M, Minthon L, Davidsson P, et al. CSF levels of tau, beta-amyloid(1-42) and GAP-43 in frontotemporal dementia, other types of dementia and normal aging. *J Neural Transm* 2000;107:563–579. [PubMed: 11072752]
36. Riemenschneider M, Wagenpfeil S, Diehl J, et al. Tau and Abeta42 protein in CSF of patients with frontotemporal degeneration. *Neurology* 2002;58:1622–1628. [PubMed: 12058089]
37. Rosengren LE, Karlsson JE, Sjogren M, et al. Neurofilament protein levels in CSF are increased in dementia. *Neurology* 1999;52:1090–1093. [PubMed: 10102440]
38. Chan D, Walters RJ, Sampson EL, et al. EEG abnormalities in frontotemporal lobar degeneration. *Neurology* 2004;62:1628–1630. [PubMed: 15136699]
39. Josephs K, Whitwell JL, Jack CR Jr, Dickson DW. Frontotemporal lobar degeneration without lobar atrophy. *Arch Neurol*. 2006In press
40. Fukui T, Kertesz A. Volumetric study of lobar atrophy in Pick complex and Alzheimer's disease. *J Neurol Sci* 2000;174:111–121. [PubMed: 10727696]
41. Boccardi M, Sabatoli F, Laakso MP, et al. Frontotemporal dementia as a neural system disease. *Neurobiol Aging* 2005;26:37–44. [PubMed: 15585344]
42. Rosen HJ, Gorno-Tempini ML, Goldman WP, et al. Patterns of brain atrophy in frontotemporal dementia and semantic dementia. *Neurology* 2002;58:198–208. [PubMed: 11805245]
43. Chan D, Fox NC, Scahill RI, et al. Patterns of temporal lobe atrophy in semantic dementia and Alzheimer's disease. *Annals of Neurology* 2001;49:433–442. [PubMed: 11310620]see comment
44. Mummery CJ, Patterson K, Price CJ, et al. A voxel-based morphometry study of semantic dementia: relationship between temporal lobe atrophy and semantic memory. *Ann Neurol* 2000;47:36–45. [PubMed: 10632099]
45. Whitwell JL, Anderson VM, Scahill RI, et al. Longitudinal patterns of regional change on volumetric MRI in frontotemporal lobar degeneration. *Dementia & Geriatric Cognitive Disorders* 2004;17:307–310. [PubMed: 15178942]
46. Gorno-Tempini ML, Ogar JM, Brambati SM, et al. Anatomical correlates of early mutism in progressive nonfluent aphasia. *Neurology*. 2006
47. Boxer AL, Geschwind MD, Belfor N, et al. Patterns of brain atrophy that differentiate corticobasal degeneration syndrome from progressive supranuclear palsy. *Arch Neurol* 2006;63:81–86. [PubMed: 16401739]

48. Josephs K, Whitwell JL, Dickson D, et al. Voxel-based morphometry in autopsy proven PSP and CBD. *Neurobiol Aging*. 2006Epub
49. Paviour DC, Price SL, Stevens JM, et al. Quantitative MRI measurement of superior cerebellar peduncle in progressive supranuclear palsy. *Neurology* 2005;64:675–679. [PubMed: 15728291]
50. Righini A, Antonini A, De Notaris R, et al. MR imaging of the superior profile of the midbrain: differential diagnosis between progressive supranuclear palsy and Parkinson disease. *AJNR Am J Neuroradiol* 2004;25:927–932. [PubMed: 15205125]
51. Gorno-Tempini ML, Rankin KP, Woolley JD, et al. Cognitive and behavioral profile in a case of right anterior temporal lobe neurodegeneration. *Cortex* 2004;40:631–644. [PubMed: 15505973]
52. Whitwell JL, Jack CR Jr, Senjem ML, Josephs KA. Patterns of atrophy in pathologically confirmed FTLN with and without motor neuron degeneration. *Neurology* 2006;66:102–104. [PubMed: 16401855]
53. Whitwell JL, Josephs KA, Rossor MN, et al. Magnetic resonance imaging signatures of tissue pathology in frontotemporal dementia. *Arch Neurol* 2005;62:1402–1408. [PubMed: 16157747]
54. McKhann GM, Albert MS, Grossman M, et al. Clinical and pathological diagnosis of frontotemporal dementia: report of the Work Group on Frontotemporal Dementia and Pick's Disease. *Arch Neurol* 2001;58:1803–1809. [PubMed: 11708987]
55. McMonagle P, Blair M, Kertesz A. Corticobasal degeneration and progressive aphasia. *Neurology* 2006;67:1444–1451. [PubMed: 17060571]
56. Josephs KA, Holton JL, Rossor MN, et al. Frontotemporal lobar degeneration and ubiquitin immunohistochemistry. *Neuropathology & Applied Neurobiology* 2004;30:369–373. [PubMed: 15305982]
57. Lipton AM, White CL 3rd, Bigio EH. Frontotemporal lobar degeneration with motor neuron disease-type inclusions predominates in 76 cases of frontotemporal degeneration. *Acta Neuropathol (Berl)* 2004;108:379–385. [PubMed: 15351890]
58. Knibb JA, Xuereb JH, Patterson K, Hodges JR. Clinical and pathological characterization of progressive aphasia. *Ann Neurol* 2006;59:156–165. [PubMed: 16374817]
59. Josephs K, Ahmed Z, Katsuse O, et al. Neuropathological features of progranulin gene (PGRN) mutations. 2007Submitted
60. Josephs KA, Holton JL, Rossor MN, et al. Neurofilament inclusion body disease: a new proteinopathy? *Brain* 2003;126:2291–2303. [PubMed: 12876145]
61. Skibinski G, Parkinson NJ, Brown JM, et al. Mutations in the endosomal ESCRTIII-complex subunit CHMP2B in frontotemporal dementia. *Nat Genet* 2005;37:806–808. [PubMed: 16041373]
62. Cannon A, Baker M, Boeve B, et al. CHMP2B mutations are not a common cause of frontotemporal lobar degeneration. *Neurosci Lett* 2006;398:83–84. [PubMed: 16431024]
63. Cruts M, Gijsels I, van der Zee J, et al. Null mutations in progranulin cause ubiquitin-positive frontotemporal dementia linked to chromosome 17q21. *Nature* 2006;442:920–924. [PubMed: 16862115]
64. Gass J, Cannon A, Mackenzie IR, et al. Mutations in progranulin are a major cause of ubiquitin-positive frontotemporal lobar degeneration. *Hum Mol Genet* 2006;15:2988–3001. [PubMed: 16950801]
65. Morita M, Al-Chalabi A, Andersen PM, et al. A locus on chromosome 9p confers susceptibility to ALS and frontotemporal dementia. *Neurology* 2006;66:839–844. [PubMed: 16421333]
66. Whitwell JL, Jack CR Jr, Siung M, et al. Voxel based morphometry in progranulin gene (PGRN) mutations. *Arch Neurol*. 2007
67. Vance C, Al-Chalabi A, Ruddy D, et al. Familial amyotrophic lateral sclerosis with frontotemporal dementia is linked to a locus on chromosome 9p13.2-21.3. *Brain* 2006;129:868–876. [PubMed: 16495328]
68. Moretti R, Torre P, Antonello RM, et al. Frontotemporal dementia: paroxetine as a possible treatment of behavior symptoms. A randomized, controlled, open 14-month study. *Eur Neurol* 2003;49:13–19. [PubMed: 12464713]
69. Lebert F, Stekke W, Hasenbroekx C, Pasquier F. Frontotemporal dementia: a randomised, controlled trial with trazodone. *Dement Geriatr Cogn Disord* 2004;17:355–359. [PubMed: 15178953]

Figure 1.

Coronal T1-weighted MRI scans demonstrating frontal and caudate atrophy in a patient with behavioral changes and a diagnosis of bvFTD (A), left perisylvian atrophy in another patient with non-fluent speech and a diagnosis of PNFA (B) and right > left anterior temporal lobe atrophy in a patient with loss of facial recognition and word meaning and a diagnosis of right temporal variant of SD (C).

Figure 2.
F-18 fluorodeoxyglucose positive emission tomography (PET) scan demonstrating predominant frontal and some temporal lobe hypometabolism in a patient with personality changes and a diagnosis of bvFTD.

Figure 3.
On gross pathology there is severe frontal lobe atrophy with preserved primary motor and sensory cortex in a patient that had personality changes and executive dysfunction and a diagnosis of bvFTD.

Table 1
Other pathologic terminologies

FTLD-U

- Motor neuron disease inclusion dementia (MNDID)
- Dementia of motor neuron disease type
- Dementia with ubiquitin inclusion bodies
- Dementia with inclusions tau and synuclein-negative, ubiquitinated (ITSNU)
- Dementia with ubiquitinated inclusions
- Pick complex with ITSNU
- Dementia with ubiquitinated tau-negative non eosinophilic inclusions (UTNNEI)

FTLD-MND

- Pick's disease with ALS
 - Frontotemporal dementia with motor neuron disease (FTD-MND)
 - Motor neuron disease type dementia (MNDD)
 - Dementia with motor neuron disease
 - Dementia with ALS
 - ALS with dementia
 - Presenile dementia with motor neuron disease
 - Aphasic dementia and motor neuron disease
-