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Clinical, genetic, and pathological heterogeneity of frontotemporal dementia: a review

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Abbreviations

FTD, frontotemporal dementia; FTLD, frontotemporal lobar degeneration; *MAPT*, *microtubule associated protein tau*; *GRN*, *progranulin*; *FUS*, *fused in sarcoma*; FTLD-tau, FTLD with tau-positive inclusions; FTLD-TDP, FTLD with TDP-43-positive inclusions; FTLD-FUS, FTLD with FUS positive inclusions.

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Abstract

Frontotemporal dementia (FTD) is the second most common young-onset dementia, and is clinically characterized by progressive behavioural change, executive dysfunction and language difficulties. Three clinical syndromes, behavioural variant FTD, semantic dementia and progressive non-fluent aphasia, form part of a clinicopathological spectrum named frontotemporal lobar degeneration (FTLD).

The classical neuropsychological phenotype of FTD has been enriched by tests exploring Theory of Mind, social cognition and emotional processing. Imaging studies have detailed the patterns of atrophy associated with different clinical and pathological subtypes. These patterns offer some diagnostic utility while measures of progression of atrophy may be of use in future trials.

Between 30–50 percent of FTD is familial and mutations in two genes, *MAPT* and *Progranulin* (*GRN*), account for about half of these cases. Rare defects in *VCP*, *CHMP2B*, *TARDP* and *FUS* genes have been found in a small number of families. Linkage to chromosome 9p13.2-21.3 has been established in familial FTD with motor neuron disease, although the causative gene is yet to be identified.

Recent developments in the immunohistochemistry of FTLD, and also in amyotrophic lateral sclerosis (ALS), have led to a new pathological nomenclature. The two major groups are those with tau-positive inclusions (FTLD-tau) and those with ubiquitin-positive and TDP-43 positive inclusions (FTLD-TDP). Recently a new protein involved in familial ALS, fused in sarcoma (*FUS*), has been found in FTLD patients with ubiquitin-positive and TDP-43-negative inclusions.

In this review we discuss recent clinical, neuropsychological, imaging, genetic and pathological developments that have changed our understanding of FTD, its classification and criteria. The potential to establish an early diagnosis, predict underlying pathology during life

and quantify disease progression will all be required for disease-specific therapeutic trials in the future.

Introduction

Frontotemporal dementia (FTD) is the second most common early-onset dementia and is characterized clinically by progressive behavioural changes and frontal executive deficits and/or selective language difficulties. Although recognised over a century ago the last few years have seen rapid advances in our understanding of FTD, its genetic causes and pathological substrates.(1-5) In 1892 Arnold Pick described a patient with progressive aphasia and lobar atrophy,(6) and in 1911 the presence of argyrophilic neuronal inclusions at neuropathological examination, later known as ‘Pick bodies’, was reported by Alois Alzheimer.(7)

The selective involvement of the frontal and/or temporal cortices with relative preservation of more posterior cerebral regions determines the presentation, and gives rise to the terms FTD as a clinical syndrome with distinct subtypes, and the term frontotemporal lobar degeneration (FTLD) to describe the pathological syndrome. The disease progresses from an insidious onset of behavioural change or language impairment and cognitive decline to a severe and more generalised dementia, accompanied by progressive cerebral hypometabolism and atrophy of frontal and temporal lobes preferentially.

The clinical spectrum of FTD encompasses distinct canonical syndromes: the behavioural variant of FTD (bvFTD) and the language variants, semantic dementia (SD) and progressive non-fluent aphasia (PNFA). There is also overlap of FTD with motor neuron disease (FTD-MND or FTD-ALS), as well as the parkinsonian syndromes, progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS).(8) Recent advances in FTD have identified novel genetic defects and a chromosomal locus in hereditary forms of FTLD,(9-14) as well as novel neuropathological associations, e.g. the proteins TAR DNA binding protein of 43 kDa (TDP-

43) and fused in sarcoma (FUS) are now recognized in the pathological classification of FTLD.(15-19)

In this review we will discuss the different clinical variants, neuropsychological aspects, neuroimaging, hereditary forms, pathological subtypes and the clinicopathological associations of FTD with the focus on recent developments.

Epidemiology

The exact prevalence of FTD remains uncertain, as there have been only a few studies and these have produced a wide range of estimates. The highest prevalences have been reported from two independent studies in the UK and one Italian study with an estimated prevalence of FTD of 15 – 22 per 100,000 inhabitants aged 45 – 64 years,(4-5, 20) which was almost half the prevalence of AD in this age group.(5) However, a study from the Netherlands estimated the prevalence of FTD to be significantly lower (9.4 per 100,000 in the age group of 60 – 69 years).(21) The lower prevalence relative to AD in that series is consistent with some pathological series.(22-23) The estimated prevalence in a Swedish population-based sample of 85-year-olds was 3.1 per 100 inhabitants.(24)

Two reported incidence studies of FTD were remarkably consistent; 3.5 and 4.1 cases per 100,000 person-years in the age-group of 45 – 64 years.(25-26) There do not appear to be clear gender differences in susceptibility.(21, 23, 26-27)

The average age at onset is around 50 – 60 years, although approximately 10 percent have an age at onset over 70 years (up to 89 years).(9) There is a wide range in durations of illness (2 – 20 years) partly reflecting different underlying pathologies. Patients with FTD-MND have the shortest survival with a mean of three years.(9, 28)

Clinical presentation

BvFTD, SD and PNFA all share an insidious onset and inexorably progressive but variable decline. Each clinical syndrome is associated with topographically distinct cerebral involvement: with bvFTD associated with symmetrical (or right-sided) frontal and anterior temporal dysfunction, PNFA left frontotemporal dysfunction and SD anterior temporal (typically left more than right) deficits. BvFTD is the most common of these subtypes and accounts for about half of all cases (9, 29) without any clear differences in presentation between sporadic and familial bvFTD, or between late and early onset bvFTD.(30) While all of the subtypes can occur in conjunction with motor neuron disease (FTD-MND), it is most commonly seen with bvFTD, occasionally with PNFA and only very rarely with SD.

Emotional blunting, loss of empathy, apathy, selfishness and neglect of personal hygiene are typical of bvFTD, but may be seen in all subtypes.(31) Other frequently reported symptoms are disinhibition, irritability, gluttony, altered preference for foods (particularly for sweets), wandering, pacing, motor and verbal stereotypies, and hoarding.(31) It has been suggested that bvFTD can be subdivided into apathetic and disinhibited variants depending on initial presentation,(32) however these symptoms frequently co-occur and the usefulness of this distinction is questionable.(30) A stereotyped-compulsive syndrome has been recognized as a third variant.(33)

A significant correlation with specific topographic patterns of atrophy, hypoperfusion or hypometabolism has been found for several of these symptoms. Apathy is associated with atrophy and dysfunction of the right anterior cingulate cortex and superior frontal gyrus,(34) disinhibition with the right subgenual cingulate cortex and orbitofrontal cortex,(34-36)

overeating with an orbitofrontal-striatal circuit,(37) and executive dysfunction with the dorsolateral and prefrontal cortex.(38)

The core features of current clinical criteria for bvFTD encompass an insidious onset and gradually progressive course, early disruption of social and personal conduct, early emotional blunting and lack of insight.(2-3) Stereotypic behaviour, alterations in eating behaviour, and loss of social awareness particularly support a diagnosis of FTD, while more posterior symptoms such as difficulty with spatial orientation and locating objects suggest Alzheimer's disease (AD).(31, 39-40) Apathy, mood changes, and dysexecutive symptoms occur in both and have not been found to be effective discriminators of FTD from AD.(39, 41-42)

The clinical criteria focus on behavioural changes rather than cognitive disturbances, and therefore might equally apply to a number of psychiatric syndromes, including (late-onset) depression and schizophrenia. However, virtually no studies have focussed on the differentiation of bvFTD from psychiatric disorders. With this in mind, an interesting group of patients is the “non-progressive”, “benign” or “slow” bvFTD, who do not (or only slowly) progress over time, and do not show definite structural atrophy or hypometabolism many years from symptom onset.(43-45) Behavioural symptoms may appear to progress according to carer description but without measurable cognitive change.(45) As these patients with a non-progressive bvFTD appear to have a normal life expectancy and seldom come to autopsy, the underlying pathology is still unknown.(44-45) Possible diagnoses that have been suggested include decompensated Asperger syndrome or personality disorder, mild bipolar syndrome, or an otherwise previously undescribed neuropsychiatric syndrome with functional disruption of the same orbitofrontal-amygdala-polar network.(44)

Autopsy-proven studies have shown that the current clinical criteria correctly classify approximately 80-90 percent of bvFTD cases, whereas 3 to 17 percent are pathologically-proven AD.(46-49) However, the criteria lack sensitivity (37 percent) in the early phase of bvFTD.(50) Therefore, revised criteria for bvFTD have been proposed in light of recent advances.(51) The most important revisions are the incorporation of neuroimaging and genetic findings within the criteria and expansion of the role of supportive behavioural features for the diagnosis of bvFTD.(51)

The nosology of the language variants of FTD remains controversial. PNFA and SD are the canonical subtypes of what is collectively often termed primary progressive aphasia (PPA). Fluent speech, progressive impairment of single-word comprehension, preserved articulatory abilities, and a multimodal breakdown of semantic memory are the characteristic features of SD.(52) Patients with SD may show behavioural changes in the course of the disease similar to bvFTD.(53) In particular they may become egocentric and develop fixed daily routines.(53) PNFA patients present with apraxia of speech and/or expressive agrammatism: single-word comprehension and object knowledge are relatively preserved and behavioural symptoms are less common. However, there are patients with progressive language impairment who do not fit into the SD and PNFA: a third, more recently defined, subtype of PPA is the logopenic or phonological variant (LPA) which is characterized by a slow rate of speech output, word-finding difficulties, deficits in sentence repetition, and occasional phonemic errors in spontaneous speech and naming, whereas motor speech, expressive grammar and single-word comprehension are relatively spared.(52, 54) It remains unclear whether there are further subtypes of PPA although there is some evidence that patients with *GRN* mutations have a non-fluent PPA syndrome distinct to either PNFA or LPA.(55)

PPA subtypes have an association with different types of underlying pathology. SD is associated most commonly with FTLD-TDP type 1 (17) pathology and only rarely with FTLD-tau or AD pathology.(49, 56-57) PNFA is commonly associated with FTLD-tau,(56, 58-59), although AD and to a lesser extent FTLD-TDP pathology have also been described.(49, 57-58) Finally, LPA is predominantly associated with AD pathology.(58-59) Although these are relatively strong associations, they are not absolute, and it is currently not possible to predict with certainty the underlying pathology of specific PPA syndromes.(57) However, using multimodal predictors including qualitative clinical features, neuropsychological test scores, and atrophy on MRI improve the noninvasive prediction of the underlying pathology in non-fluent PPA.(60)

*** *INSERT TABLE 1 HERE (52, 55, 61-64) , SEE PAGE 41* ***

Motor neuron disease (MND) may occur early or late in the disease course in a subset of FTD patients.(65-66) Muscle atrophy, weakness, and fasciculations are often most prominent in the upper extremities and the tongue. The disease has a rapidly progressive course with a mean survival of three years. It is now accepted that FTD and MND are part of the same clinicopathological spectrum. A third of all FTD-MND cases have a positive family history for dementia, FTD, MND, or FTD-MND. The causative gene defect in FTD-MND has yet to be discovered.

Some patients with predominantly right temporal lobe atrophy (RTLA) present with prominent behavioural changes, episodic memory disturbances, topographical disorientation and prosopagnosia.(67-68) Patients with RTLA are usually diagnosed clinically with either

bvFTD or SD.(68) It has been suggested that patients with bvFTD and RTLA have FTLD-tau pathology, whereas patients with SD and RTLA have FTLD-TDP pathology.(68)

Neuropsychology and social cognition

Impairment of executive function including planning, organisation, judgement, problem solving and mental flexibility, is characteristic of FTD,(69) whereas memory, visual perception, and spatial skills are usually relatively well-preserved.(50, 70-74). However, executive dysfunction may be absent or overshadowed by pronounced behavioural changes in early disease, and may also be seen in AD.(75) Verbal fluency (letter and categorical) is usually impaired in bvFTD and PNFA, but to a lesser degree also in AD.(76-78) In SD patients, semantic fluency is more impaired than letter fluency.(76, 78)

Early episodic memory impairment, a characteristic feature of AD, has also been reported in pathologically-proven bvFTD cases, and in patients with *GRN* gene mutations.(79-80) Though orientation in time and place, delayed free recall and delayed recognition are more often impaired in AD than in FTD at initial assessment, it still remains difficult to differentiate FTD from AD in the early phase using standard neuropsychological tests.(81)

As standard neuropsychological tests cannot reliably differentiate bvFTD from AD,(82-84) several investigators have explored the utility of emotional processing and social recognition tasks in the clinical diagnosis of FTD over recent years. Social dysfunction and emotional blunting commonly occur in FTD.(44, 75, 85-91) Theory of Mind (ToM) tests require the interpretation of social situations and ascribing mental state to oneself and others, and may reveal subtle deficits not detected with standard neuropsychological testing.(75) Recent reports suggest that the neural basis for ToM tasks, social cognition and empathy lies within the medio- and/or orbitofrontal cortex, which is affected early in bvFTD.(92) Patients with bvFTD have impaired scores on these tests of social judgments and cognitive flexibility, and

express concrete, literal interpretations.(75, 93) Performances in ToM tests do not correlate with executive functioning on standard neuropsychological testing in the early phase.(85, 94-95) However, in a more advanced stage, when atrophy spreads to dorsolateral frontal structures, the ToM ability and executive functioning become strongly related.(75, 93-94) Empathy as rated by caregivers is clearly impaired in bvFTD and SD patients and correlates with ToM tasks.(85, 96)

In line with these observations, recognition of facial emotions is impaired in patients with bvFTD, in particular for negative emotions (anger, fear, sadness and disgust).(85, 87-91, 97) The same applies for the recognition of vocal emotions, in particular for anger and sad voices.(89) Interpretation of sarcastic statements is impaired in FTD, and is correlated with the ability to recognize negative emotions.(44) Self-conscious emotions, such as embarrassment and amusement, are another important aspect of emotion functioning which may be disrupted in FTD.(98-99) Social cognition tests also seem to help to differentiate bvFTD patients with imaging abnormalities from the non-progressive bvFTD with normal neuroimaging.(85, 96)

It will be interesting to investigate further whether impaired social cognition is a very early feature of familial FTD as has already been described in a single case study of a presymptomatic mutation carrier; studying presymptomatic mutation carriers may allow identification of sensitive (even preclinical) cognitive predictors of decline and its neural substrate.(100)

Neuroimaging

Patients with FTD classically have frontal and temporal atrophy and hypometabolism which is often asymmetric. In the clinical setting this is often best seen using volumetric structural MRI scans (with coronal T1 images being particularly useful for assessing asymmetry) or

with functional imaging using either FDG-PET or, less commonly, HMPAO-SPECT. More recently, however, neuroimaging studies have aimed to refine these initial findings, mostly in clinical cohorts, but also in pathologically and genetically-confirmed FTD.

Studies of mild bvFTD in clinically-defined cohorts show involvement particularly of frontal and paralimbic areas,(101) namely the anterior cingulate cortex and frontal insula as well as medial frontal and orbitofrontal cortices, hippocampus, striatum and thalamus, more in the right than left hemisphere. With increasing disease severity, more diffuse atrophy in similar areas is seen with involvement of more lateral frontal areas and subsequently more posterior temporal and anterior parietal atrophy.(102) It remains unclear whether this pattern of atrophy is a feature of bvFTD independent of the underlying pathology (which is heterogeneous) or whether different pathologies have distinct patterns of atrophy. Unfortunately, there are currently no studies which directly compare all of the pathological subtypes. Patients with FUS pathology seem to have a similar pattern of frontal paralimbic atrophy to that described above but in addition have severe caudate involvement compared to FTLT-tau or FTLT-TDP.(103-105) Studies comparing genetically-defined FTD patients with either *GRN* or *MAPT* mutations (106-107) have described different patterns between the two groups: *GRN* mutations are associated with asymmetrical frontal, temporal and inferior parietal lobe atrophy whereas *MAPT* mutations are associated with relatively symmetrical anteromedial temporal lobe and orbitofrontal grey matter atrophy.(106-107) The presence of early parietal lobe atrophy in *GRN* mutations, a feature which may distinguish such cases from other FTD patients, has been shown in studies of presymptomatic mutation carriers.(100, 108) Whether patients with different mutations in the same gene have distinct patterns of atrophy is unclear although one small study suggests there may be a difference between patients with *MAPT* mutations that affect splicing of exon 10 (more medial temporal lobe atrophy) compared with

mutations that do not affect splicing of exon 10 (more lateral temporal lobe atrophy).(109) Bringing these findings together, one study that used a cluster analysis to investigate bvFTD suggested there may be four types of bvFTD anatomically: a temporal-dominant subtype associated with *MAPT* mutations; a temporofrontoparietal subtype that can be associated with *GRN* mutations but also with other pathologies such as corticobasal degeneration (CBD); as well as frontal-dominant and frontotemporal subtypes.(110) Larger studies of pathologically-proven patients are needed to confirm these findings.

Early voxel-based morphometry (VBM) studies of SD showed asymmetrical atrophy of the anterior and inferior temporal lobes,(111-112) usually affecting the left more than the right hemisphere. These findings were supported by subsequent region of interest (ROI) studies of the temporal lobe, which identified involvement particularly of the temporal pole and anterior parts of the entorhinal cortex, fusiform gyrus, inferior temporal gyrus, amygdala and hippocampus with relative sparing of the superior temporal gyrus.(113-114) Most studies have used clinically-defined cohorts but one study looking at measurement of cortical thickness in patients with left greater than right temporal lobe atrophy showed a similar pattern of involvement in a pathologically-confirmed cohort of patients, all with FTLTDP.(115). This study also showed that areas within the left hemisphere outside the temporal lobe are involved with increasing disease severity, namely orbitofrontal, inferior frontal, insular, and anterior cingulate cortices.(115) Increasing involvement of the temporal lobe in the right hemisphere is seen with disease progression.(115-116) A mirror-image pattern of initial atrophy and disease progression seems to occur in those with right greater than left temporal lobe involvement (RTLA).(117) Although SD is characteristically FTLTDP pathologically, in a small number of cases, Pick's disease (FTLD-tau) and occasionally AD pathology can be seen. One small study showed similar patterns of atrophy in the FTLTDP

and FTLT-tau but with a qualitatively different pattern in those with AD who had mostly hippocampal involvement, lack of the knife-edge anterior temporal atrophy seen in the other groups and without the sparing of the superior temporal gyrus.(118)

Studies of PNFA are fewer and more heterogeneous, which reflects the clinical heterogeneity of this group. As with SD, there is asymmetrical involvement with more atrophy in the left hemisphere and most significant involvement of the inferior frontal lobe and anterior insula.(52, 116, 119-120) With increasing severity there is involvement of left superior temporal, middle and superior frontal and anterior parietal lobes.(116) ROI studies have also shown involvement of the caudate in PNFA.(121) There are few pathologically-confirmed studies of PNFA and these are usually in mixed pathological groups but they show similar findings to the clinical cohort studies.(116, 122) Some small studies suggest there may be different patterns of atrophy in PNFA patients with PSP clinically (and therefore likely pathologically) compared to those without PSP,(123) and also in those with *GRN* mutations (FTLD-TDP pathologically) compared to those without.(63) More detailed studies of PNFA subgroups will be needed to confirm these findings.

*** *INSERT FIGURE 1 HERE****

Being able to distinguish FTD from AD is important clinically and recent studies have suggested that atrophy or cortical thinning of precuneus, posterior cingulate, posterior temporal and parietal areas is characteristic of AD pathology independent of clinical diagnosis and is therefore helpful in distinguishing those with atypical AD presentations (which may include bvFTD or a progressive aphasia) from those with FTLT pathology.(124-126) Clinically, however, VBM or cortical thickness studies are unlikely to be available and

simpler techniques such as visual rating scales have been developed which can help to differentiate FTD from AD.(127) More sophisticated methods using techniques such as support vector machines are being developed which allow automatic classification of patients into FTD or AD groups with little user input necessary, although currently these are computationally demanding.(128) Another possibility is to use support vector machine-based MRI analyses that integrate gray matter and diffuse tensor imaging (DTI), which has shown accurate pathological or CSF-defined categorization of FTLD and AD.(129)

A different neuroimaging tool that accurately differentiates FTLD from AD is arterial spin labeling (ASL) perfusion MRI, which reveals noninvasive quantification of cerebral blood flow, without the use of ionizing radiation as in SPECT or PET.(130) Patients with AD pathologically can also be defined using amyloid molecular imaging (e.g. PIB-PET) (131) but the availability of such scans is currently limited to a few large research centres.

One of the more novel concepts to emerge from recent neuroimaging studies of FTD using the technique of resting-state fMRI is the idea that FTD is caused by degeneration within specific intrinsic functional connectivity networks that are selectively vulnerable to FTLD pathologies.(132) Consistent with earlier VBM findings in structural MRI studies of bvFTD, resting-state fMRI studies show attenuated connectivity within an anterior ‘salience’ network of dorsal anterior cingulate and frontoinsula cortices which has connectivity to subcortical and limbic structures.(133) In contrast there appears to be enhanced connectivity in the more posterior ‘default’ network which has been shown to be affected in AD.(133) These findings have been linked to specific neuropathological findings (early involvement of von Economo neurons in FTD),(134) and further work will be needed to look at whether specific pathological subtypes can be linked to specific and distinct neural network degeneration.

Cerebrospinal fluid and plasma biomarkers

Currently cerebrospinal fluid (CSF) biomarkers have limited ability to identify FTD reliably. This might be explained by both the pathological heterogeneity and the large variation in neurodegenerative severity. Levels of CSF tau in FTD are normal, increased or even decreased.(135) Levels of CSF phosphorylated tau are essentially normal in FTD, in contrast with AD. Levels of CSF amyloid beta(1-42) have been found to be either decreased or in the normal range. An indication of lower amyloid beta(1-40) levels in FTD compared with AD and control subjects, might particularly be useful to distinguish FTD patients from subjects without a neurodegenerative disorder.(135)

Decreased levels of progranulin protein are found in plasma, serum and cerebrospinal fluid (CSF) by enzyme-linked immunosorbent assay (ELISA), and may reliably differentiate *GRN* mutations carriers from non-carriers.(136-140)

It remains to be investigated if measurement of plasma or CSF levels of TDP-43 is useful diagnostically, as plasma phosphorylated TDP-43 levels have been found to be correlated with the extent of TDP-43 pathology in FTLT.(141-142)

Recent biomarker studies on CSF are using multi-analyte profiling to derive novel biomarkers for neurodegenerative disorders and have delivered some promising neuropeptides (agouti-related peptide (AgRP), adrenocorticotrophic hormone (ACTH), IL-17 and IL-23 and Fas) which are useful in distinguishing FTLT-TDP from FTLT-tau patients.(143-144)

Genetics

A positive family history has been found in 30 – 50 percent of patients with bvFTD, whereas patients with SD or PNFA have a much lower frequency.(9-11, 21, 145-146) The heritability in FTD-MND differs between studies from 10 – 60 percent.(9, 11, 146) An autosomal

dominant mode of inheritance is found in 10 – 27 percent of all FTD patients.(9-11, 21, 145-146).

Genetic heterogeneity of FTLD is reflected by the identification of mutations in the *microtubule associated protein tau (MAPT)* and *progranulin (GRN)* genes in approximately 50 percent of the familial cases, whereas mutations in the *valosin containing protein (VCP)*, charged *multivesicular body protein 2B (CHMP2B)*, *TAR-DNA binding protein (TARDP)*, and *fused in sarcoma (FUS)* genes are found in less than five percent. Familial FTD-MND has been linked to chromosome 9, but the causative gene defect has yet to be discovered.

MAPT

More than 40 mutations in the *MAPT* gene have been identified in families with FTD and parkinsonism linked to chromosome 17q (FTDP-17) with accumulation of hyperphosphorylated tau protein in neurons and/or glial cells (<http://www.molgen.ua.ac.be/FTDmutations>).(12) Alternative splicing of exons 2, 3 and 10 of the *MAPT* gene gives rise to six isoforms: three isoforms containing three amino-acid repeats (3R), and three isoforms with four repeats (4R).(147) Mutations can be distinguished into missense mutations in exon 9 -13 affecting the normal function of the tau protein to stabilize microtubules, and intronic and some coding mutations affecting the splicing of exon 10 at the mRNA level, resulting in a change of the ratio of 3R to 4R tau isoforms.(148)

The mean age at onset is 55 years and usually shows a small intrafamilial variation between 45 and 65 years, although the disease may present before the age of 40 years or after 70 years in a few mutations.(149) The mean duration of illness is approximately nine years, but varies between five and twenty years. There exists a dementia-dominant phenotype with prominent behavioural changes including disinhibition and obsessive-compulsive behaviour,(149) and a

parkinsonism-dominant phenotype with CBS or PSP-like syndromes.(80) Patients may develop language problems e.g. mild semantic impairment during the illness.(150)

Progranulin

More than 60 mutations in the *GRN* gene on chromosome 17 (1.7 Mb centromeric to the *MAPT* gene) have been identified to date, and account for approximately 5 – 10 percent of all FTD patients, and up to 22 percent in familial FTD.(9, 13-14, 151-153) Its frequency is similar to that of *MAPT* gene mutations in hereditary FTD.(9, 146) *GRN* gene mutations are occasionally reported in sporadic cases.(9, 151-153) Whether this is due to a low penetrance of the *GRN* mutation in one of the parents or to a spontaneous mutation in the patient is unknown.

GRN encodes the progranulin protein, which is a growth factor implicated in wound healing and tumour growth inflammation, and is abundantly expressed in specific neuronal subsets.(154) The neuropathology of patients with *GRN* mutations is characterized by tau-negative, and ubiquitin- and TDP-43-positive inclusions.(155)

The mean age at onset is around 60 years ranging from 35 to 89 years, with a penetrance of 90 percent by the age of 70 years.(80, 151) Within families, the onset age shows considerable variation with a difference of up to 20 years between consecutive generations.(9, 80) The mean duration is eight years (range 3 – 22 years).

Apathy and social withdrawal are the most common behavioural changes. Twenty-five percent of patients presents with early isolated language dysfunction, suggestive of an anomic non-fluent type (without motor speech impairment) and with relatively early single word

comprehension impairment.(156) Hallucinations and delusions are frequently reported.(157-159) Episodic memory deficits occur in 10 – 30 percent, and may lead to the clinical diagnosis of amnesic variant of MCI or together with parietal deficits, like dyscalculia, visuospatial dysfunction, and limb apraxia to AD.(157-158, 160-162)

Extrapyramidal features are frequently seen, and include CBS with limb apraxia, asymmetric parkinsonism, and dystonia.(157-158, 163-165) ALS is only a very rare part of the clinical spectrum within *GRN* families,(9, 151, 161, 163, 166) e.g. it has been reported in a single patient of a large Canadian family.(13, 167)

Other hereditary forms

The genetic heterogeneity of FTD is further emphasized by the rare occurrence of mutations in the *VCP*, *CHMP2B*, *TARDBP* and *FUS* genes.(168-171) *VCP* gene mutations are associated with inclusion body myopathy (90%), Paget's disease of the bone (45%) and FTD (38%) (IBMPFD), presenting between the age of 40 and 60 years.(168, 172)

The clinical presentation of *CHMP2B* gene mutations consists of a frontal lobe syndrome and a more global cognitive impairment, with parkinsonism, dystonia, pyramidal signs, and myoclonus later in the course of the disease.(173) ALS has been reported in only two patients.(174)

TARDBP gene mutations on chromosome 1 are found in five percent of familial ALS,(170, 175-182) and occasionally in FTD or FTD-MND cases.(170-171) Also *FUS* gene mutations are found in five percent of the familial ALS cases,(183-186) and in one clinical bvFTD patient, but not in FTD-MND.(187) However, for the majority of the FTD-MND families, the genetic defect has yet to be identified. A number of these families have been linked to a locus on chromosome 9p13.2-21.3, but at time of writing an exhaustive sequencing of all genes in this region has not revealed any coding or splice-donor site mutations.(188-193)

There still remains a subgroup of FTD patients with a positive family history without known gene mutations. These patients usually have bvFTD and memory problems with or without MND, TDP-43 pathology and neuronal loss and gliosis of the cornu ammonis 1 and subiculum of the hippocampus (hippocampal sclerosis) at neuropathological examination.(9)

Genetic risk factors

Several investigators have tried to identify genetic risk factors for FTD. Homozygosity for the T allele of the SNP rs5848 was found to have a 3.2 fold increased risk for developing FTLD-TDP,(194) but this observation could not be replicated in other studies.(195-196) The same is true for three other SNPs of the *GRN* gene, which were initially found to be associated with younger onset age or shorter survival in FTLD or ALS.(9, 194) Also, an association of the *Cystatin C* gene (*CST3*) haplotype B, the $\epsilon 4$ allele of the apolipoprotein E gene (*APOE*), and heterozygosity of the codon 129 polymorphism of the *prion protein* gene (*PNRP*) could not be confirmed in further studies.(197-201) Finally, SNPs in the *Ubiquitin associated protein 1* (*UBAPI*) gene have been associated with FTD,(202) which was supported by a reduced mRNA expression from the disease-associated haplotype in a quantitative analysis.(202)

Recently, an international genome wide association study (GWAS) with pathologically proven FTLD-TDP patients has demonstrated a significant association with three SNPs within the *TMEM106B* gene on chromosome 7p21.(203) *TMEM106B* variants also contribute to genetic risk for FTLD-TDP in individuals with *GRN* gene mutations.(203) *TMEM106B* encodes an uncharacterized transmembrane protein of 274 amino acids.(203) Expression data showed increased *TMEM106B* expression in the frontal cortex of FTLD-TDP than in controls, suggesting that increased *TMEM106B* expression in the brain might be linked to mechanisms of disease in FTLD-TDP and that risk alleles at *TMEM106B* confer genetic susceptibility by increasing gene expression.(203)

Genetic screening in clinical practice

The benefit of genetic screening in FTD depends on the strength of the family history and the clinical subtype. Genetic defects, either *MAPT* or *GRN*, are most often found in patients with an autosomal dominant form of bvFTD.(9, 146) Genetic screening in SD is unlikely to be useful, although patients who develop semantic impairment later in the illness may have a *MAPT* gene mutation,(9, 146) whereas a *GRN* mutation can be found in a familial form of PNFA.(9, 146, 156) Current gene defects are very rare in FTD-MND, and genetic screening is therefore likely not to be useful at present.(9, 146) Screening in sporadic patients will be of little value as a very few mutations have been found in sporadic patients, except for those with a concealed or incomplete family history. In this latter group, careful consideration is necessary before embarking on and genetic screening.(146)

Pathology

FTLD is the common underlying pathology of clinical FTD subtypes, and also includes ALS, PSP, and CBD. The major pathological hallmark of FTLD is selective atrophy of the frontal and temporal cortex, with neuronal loss, gliosis and spongiosis of the superficial layers, especially of layer II. The nomenclature has been changed several times since it was first described by Arnold Pick over a hundred years ago.(6) The term Pick's disease is now reserved for cases of FTLD with intraneuronal argyrophilic inclusions, the so-called Pick bodies, which consist of abnormal three-repeat tau protein (FTLD-tau).

FTLD is a neuropathologically heterogeneous disorder, which can be divided into two major subtypes; FTLD with tau-positive inclusions (FTLD-tau), and FTLD with ubiquitin-positive

and TDP-43-positive, but tau-negative inclusions (FTLD-TDP).(18) FTLD-tau includes patients with *MAPT* mutations, Pick's disease, PSP, CBD, argyrophilic grain disease (AGD), and multiple system tauopathy with dementia (MSTD).(18) *MAPT* mutations are associated with different types of tau inclusions (Pick bodies, neurofibrillary tangles and pretangles) in the frontal and temporal cortex, hippocampus and subcortical nuclei, and sometimes in midbrain, brainstem, cerebellum and spinal cord.(149) Glial tangles and coiled bodies in white matter are found in a few *MAPT* mutations and consist predominantly of four-repeat tau isoforms.(149)

FTLD-TDP is the second major subtype of FTLD, with ubiquitin-positive inclusions, which have the TDP-43 protein as major constituent.(204) The further classification into four different FTLD-TDP subtypes according to the morphology and distribution of the inclusions (15-16) can be predicted to some extent by the clinical picture: SD is strongly associated with abundant dystrophic neurites (type 1), FTD-MND with numerous neuronal cytoplasmatic inclusions in both superficial and deep cortical laminae (type 2), *GRN* mutations are characterized by numerous cytoplasmatic inclusions, dystrophic neurites and neuronal intranuclear inclusions (type 3), and *VCP* mutations are characterized by numerous intranuclear and infrequent number of neuronal cytoplasmatic inclusions and dystrophic neurites (type 4).(15, 17) It remains unclear what differences in underlying pathophysiology determine the distinction between these TDP-43 subtypes.

A small number of FTLD cases with ubiquitin-positive, TDP-43 negative pathology,(205-208) have recently shown immunoreactivity with the FUS antibody.(19, 103) None of these FTLD-FUS cases had *FUS* gene mutations.(208) FTLD-FUS cases are characterized by a young age at onset, bvFTD, a negative family history, and caudate atrophy on MRI.(103-104)

FUS-positive inclusions are also found in patients with neuronal filament inclusion disease (NIFID).(209) NIFID patients mostly present with bvFTD symptoms, a negative family history, and pyramidal and/or extrapyramidal movement disorder.(209)

The FUS protein contains 526 amino-acids and is as nuclear protein involved in DNA repair and the regulation of RNA splicing.(183-184) Mutations in the *FUS* gene on chromosome 16 have emphasized its pathogenetic role in the clinicopathological spectrum of FTD and ALS.(187)

Finally, the pathological heterogeneity of FTLN has been further emphasized by cases with ubiquitin-positive, TDP-43 and FUS-negative inclusions, termed FTLN-UPS. Most of the FTLN-UPS cases carry a *CHMP2B* mutation,(210) but there remains a few without *CHMP2B* mutations.(208). Further research on FTLN-UPS is necessary to elucidate the full complement of FTLN pathologies.(208)

Future clinicopathological studies, including neuroimaging and genetics are necessary to improve the prediction of the underlying pathology. Especially the prediction of the underlying pathology in (sporadic) bvFTD will be important, as tau-, TDP-43-, or FUS-pathology could be the disease-modifying protein in these patients.

*** *INSERT FIGURE 2 HERE* ***

Future directions

Important advances in the field research on FTD over the last decade have led to an impressive change in the clinical recognition of this disease. Future scientific efforts should focus on three major lines of research: 1. to improve the early detection of the disease 2. to develop reliable markers in predicting the underlying pathology, and 3. to unravel its

pathophysiology in order to develop therapeutic strategies preventing or delaying the disease process.

Concerning the clinical diagnosis, an international study has been initiated to revise the clinical criteria based on a large sample of pathologically-proven cases. The aim is that neuroimaging and genetic data, and the most salient clinical features should be incorporated in a revised set of simplified criteria of bvFTD. A second clinical issue will be to monitor the progression of the disease in individual patients, which has now become available by the recent introduction of FTD rating scale (FRS)(211) characterizing the features of different severity stages. Finally, the use of social cognition tasks will help in the early detection of bvFTD and discrimination from non-progressive bvFTD. Their use offers us the opportunity to investigate the relative contributions of individual brain regions to social cognition in FTD.

Although relatively specific atrophy patterns have been found in clinical FTD subtypes, neuroimaging features as biomarkers for underlying pathology in bvFTD have yet to be determined. Support vector machines and arterial spin labeling are new neuroimaging tools to accurately differentiate FTD from AD. Another novel and promising neuroimaging technique is resting-state fMRI, which has shown changes in the salience network in FTD. An interesting question will be whether the early (or even presymptomatic) *MAPT* or *GRN* mutation carriers can be detected using this technique.

The differentiation of PPA into SD, PNFA, and LPA has proven to be an important step in predicting underlying pathology in these groups: TDP-43 pathology is most commonly found in SD, tau-pathology in PNFA, and AD-pathology in LPA. Multimodal predictors, including clinical parameters, neuropsychological test scores, and atrophy patterns, will improve the

prediction of the underlying pathology in clinical PPA syndromes. However, radioactive compounds to detect tau or TDP-43 pathology in the brain with PET scanning would be of great help to differentiate bvFTD into its two major pathological subtypes during life. The recent recognition of the FUS protein as a pathological component of neuronal inclusions in a specific subtype of FTLD emphasizes the existence of different pathways, and will also contribute to further understanding of the underlying pathophysiology. Another strategy would be the development of new CSF biomarkers, which could be derived by large-scale proteomics analysis.

Several common (*MAPT*, *GRN*) and rare (*VCP*, *CHMP2B*, *TARDBP*, *FUS*), genetic factors have been found in hereditary FTD over recent years. However, we still have to identify one or more gene defects in familial FTD with and without MND. Whole exome sequencing as innovative genetic technique might reveal new genetic defects in small families with FTD and for pathologically well-characterized FTLD subtypes (like FTLD-FUS). Identification of novel genetic defect(s) will help to understand the pathophysiology of TDP-43 in hereditary and probably also of the sporadic FTLD-TDP. A large genome-wide association study of more than 3000 DNA samples is currently underway and may hopefully reveal additional genetic factors with a small effect on the disease process.

All these small steps in unravelling the pathophysiology should finally lead to the development of therapeutic interventions for FTD.

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References

1. Clinical and neuropathological criteria for frontotemporal dementia. The Lund and Manchester Groups. *Journal of neurology, neurosurgery, and psychiatry*. 1994 Apr;57(4):416-8.
2. Neary D, Snowden JS, Gustafson L, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology*. 1998 Dec;51(6):1546-54.
3. 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 Nov;58(11):1803-9.
4. Ratnavalli E, Brayne C, Dawson K, et al. The prevalence of frontotemporal dementia. *Neurology*. 2002 Jun 11;58(11):1615-21.
5. Harvey RJ, Skelton-Robinson M, Rossor MN. The prevalence and causes of dementia in people under the age of 65 years. *Journal of neurology, neurosurgery, and psychiatry*. 2003 Sep;74(9):1206-9.
6. Pick A. Über die Beziehungen der senilen Hirnatropie zur Aphasie. *Praeger Medizinischen Wochenschrift*. 1892;17:165-7.
7. Alzheimer A. Über eigenartige Krankheitsfälle des späteren Alters. *Zbl Ges Neurol Psych*. 1911;4:356-85.
8. Kertesz A, McMonagle P, Blair M, et al. The evolution and pathology of frontotemporal dementia. *Brain*. 2005 Sep;128(Pt 9):1996-2005.
9. Seelaar H, Kamphorst W, Rosso SM, et al. Distinct genetic forms of frontotemporal dementia. *Neurology*. 2008 Oct 14;71(16):1220-6.
10. Chow TW, Miller BL, Hayashi VN, et al. Inheritance of frontotemporal dementia. *Arch Neurol*. 1999 Jul;56(7):817-22.
11. Goldman JS, Farmer JM, Wood EM, et al. Comparison of family histories in FTLTD subtypes and related tauopathies. *Neurology*. 2005 Dec 13;65(11):1817-9.
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 6/18/1998;393(6686):702-5.
13. Baker M, Mackenzie IR, Pickering-Brown SM, et al. Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. *Nature*. 2006 Aug 24;442(7105):916-9.
14. Cruts M, Gijselinck I, van der Zee J, et al. Null mutations in progranulin cause ubiquitin-positive frontotemporal dementia linked to chromosome 17q21. *Nature*. 2006 Aug 24;442(7105):920-4.
15. Sampathu DM, Neumann M, Kwong LK, et al. Pathological heterogeneity of frontotemporal lobar degeneration with ubiquitin-positive inclusions delineated by ubiquitin immunohistochemistry and novel monoclonal antibodies. *Am J Pathol*. 2006 Oct;169(4):1343-52.
16. Mackenzie IR, Baborie A, Pickering-Brown S, et al. Heterogeneity of ubiquitin pathology in frontotemporal lobar degeneration: classification and relation to clinical phenotype. *Acta Neuropathol (Berl)*. 2006 Nov;112(5):539-49.
17. Cairns NJ, Bigio EH, Mackenzie IR, et al. Neuropathologic diagnostic and nosologic criteria for frontotemporal lobar degeneration: consensus of the Consortium for Frontotemporal Lobar Degeneration. *Acta Neuropathol (Berl)*. 2007 Jul;114(1):5-22.

18. Mackenzie IR, Neumann M, Bigio EH, et al. Nomenclature and nosology for neuropathologic subtypes of frontotemporal lobar degeneration: an update. *Acta Neuropathol.* 2009 Nov 19.
19. Neumann M, Rademakers R, Roeber S, et al. Frontotemporal lobar degeneration with FUS pathology. *Brain.* 2009 Aug 11.
20. Borroni B, Alberici A, Grassi M, et al. Is Frontotemporal Lobar Degeneration a Rare Disorder? Evidence from a Preliminary Study in Brescia County, Italy. *J Alzheimers Dis.* 2009 Sep 11.
21. Rosso SM, Donker Kaat L, Baks T, et al. Frontotemporal dementia in The Netherlands: patient characteristics and prevalence estimates from a population-based study. *Brain.* 2003;126(Pt 9):2016-22. Epub 03 Jul 22.
22. Brun A. Frontal lobe degeneration of non-Alzheimer type. I. Neuropathology. *Archives of gerontology and geriatrics.* 1987 Sep;6(3):193-208.
23. Ikeda M, Ishikawa T, Tanabe H. Epidemiology of frontotemporal lobar degeneration. *Dementia and geriatric cognitive disorders.* 2004;17(4):265-8.
24. Gislason TB, Sjogren M, Larsson L, et al. The prevalence of frontal variant frontotemporal dementia and the frontal lobe syndrome in a population based sample of 85 year olds. *Journal of neurology, neurosurgery, and psychiatry.* 2003 Jul;74(7):867-71.
25. Knopman DS, Petersen RC, Edland SD, et al. The incidence of frontotemporal lobar degeneration in Rochester, Minnesota, 1990 through 1994. *Neurology.* 2004 Feb 10;62(3):506-8.
26. Mercy L, Hodges JR, Dawson K, et al. Incidence of early-onset dementias in Cambridgeshire, United Kingdom. *Neurology.* 2008 Nov 4;71(19):1496-9.
27. Hou CE, Yaffe K, Perez-Stable EJ, et al. Frequency of dementia etiologies in four ethnic groups. *Dementia and geriatric cognitive disorders.* 2006;22(1):42-7.
28. Hodges JR, Davies R, Xuereb J, et al. Survival in frontotemporal dementia. *Neurology.* 2003 Aug 12;61(3):349-54.
29. Johnson JK, Diehl J, Mendez MF, et al. Frontotemporal lobar degeneration: demographic characteristics of 353 patients. *Arch Neurol.* 2005 Jun;62(6):925-30.
30. Le Ber I, Guedj E, Gabelle A, et al. Demographic, neurological and behavioural characteristics and brain perfusion SPECT in frontal variant of frontotemporal dementia. *Brain.* 2006 Nov;129(Pt 11):3051-65.
31. Bathgate D, Snowden JS, Varma A, et al. Behaviour in frontotemporal dementia, Alzheimer's disease and vascular dementia. *Acta neurologica Scandinavica.* 2001 Jun;103(6):367-78.
32. Snowden JS, Bathgate D, Varma A, et al. Distinct behavioural profiles in frontotemporal dementia and semantic dementia. *Journal of neurology, neurosurgery, and psychiatry.* 2001 Mar;70(3):323-32.
33. Snowden JS, Neary D, Mann DMA. *Fronto-temporal lobar degeneration: fronto-temporal dementia, progressive aphasia, semantic dementia.* Churchill-Livingstone, London. 1996.
34. Zamboni G, Huey ED, Krueger F, et al. Apathy and disinhibition in frontotemporal dementia: Insights into their neural correlates. *Neurology.* 2008 Sep 2;71(10):736-42.
35. McMurtry AM, Chen AK, Shapira JS, et al. Variations in regional SPECT hypoperfusion and clinical features in frontotemporal dementia. *Neurology.* 2006 Feb 28;66(4):517-22.
36. Peters F, Perani D, Herholz K, et al. Orbitofrontal dysfunction related to both apathy and disinhibition in frontotemporal dementia. *Dementia and geriatric cognitive disorders.* 2006;21(5-6):373-9.

37. Woolley JD, Gorno-Tempini ML, Seeley WW, et al. Binge eating is associated with right orbitofrontal-insular-striatal atrophy in frontotemporal dementia. *Neurology*. 2007 Oct 2;69(14):1424-33.
38. Huey ED, Goveia EN, Paviol S, et al. Executive dysfunction in frontotemporal dementia and corticobasal syndrome. *Neurology*. 2009 Feb 3;72(5):453-9.
39. Bozeat S, Gregory CA, Ralph MA, et al. Which neuropsychiatric and behavioural features distinguish frontal and temporal variants of frontotemporal dementia from Alzheimer's disease? *Journal of neurology, neurosurgery, and psychiatry*. 2000 Aug;69(2):178-86.
40. Miller BL, Ikonte C, Ponton M, et al. A study of the Lund-Manchester research criteria for frontotemporal dementia: clinical and single-photon emission CT correlations. *Neurology*. 1997 Apr;48(4):937-42.
41. Marra C, Quaranta D, Zinno M, et al. Clusters of cognitive and behavioral disorders clearly distinguish primary progressive aphasia from frontal lobe dementia, and Alzheimer's disease. *Dementia and geriatric cognitive disorders*. 2007;24(5):317-26.
42. Chow TW, Binns MA, Cummings JL, et al. Apathy symptom profile and behavioral associations in frontotemporal dementia vs dementia of Alzheimer type. *Arch Neurol*. 2009 Jul;66(7):888-93.
43. Davies RR, Kipps CM, Mitchell J, et al. Progression in frontotemporal dementia: identifying a benign behavioral variant by magnetic resonance imaging. *Arch Neurol*. 2006 Nov;63(11):1627-31.
44. Kipps CM, Nestor PJ, Acosta-Cabronero J, et al. Understanding social dysfunction in the behavioural variant of frontotemporal dementia: the role of emotion and sarcasm processing. *Brain*. 2009 Mar;132(Pt 3):592-603.
45. Kipps CM, Nestor PJ, Fryer TD, et al. Behavioural variant frontotemporal dementia: not all it seems? *Neurocase*. 2007 Aug;13(4):237-47.
46. Rosen HJ, Hartikainen KM, Jagust W, et al. Utility of clinical criteria in differentiating frontotemporal lobar degeneration (FTLD) from AD. *Neurology*. 2002 Jun 11;58(11):1608-15.
47. Knopman DS, Boeve BF, Parisi JE, et al. Antemortem diagnosis of frontotemporal lobar degeneration. *Ann Neurol*. 2005 Apr;57(4):480-8.
48. Forman MS, Farmer J, Johnson JK, et al. Frontotemporal dementia: clinicopathological correlations. *Ann Neurol*. 2006 Jun;59(6):952-62.
49. Alladi S, Xuereb J, Bak T, et al. Focal cortical presentations of Alzheimer's disease. *Brain*. 2007 Oct;130(Pt 10):2636-45.
50. Mendez MF, Shapira JS, McMurtry A, et al. Accuracy of the clinical evaluation for frontotemporal dementia. *Arch Neurol*. 2007 Jun;64(6):830-5.
51. Rascofsky K, Hodges JR, Kipps CM, et al. Diagnostic criteria for the behavioral variant of frontotemporal dementia (bvFTD): current limitations and future directions. *Alzheimer Dis Assoc Disord*. 2007 Oct-Dec;21(4):S14-8.
52. Gorno-Tempini ML, Dronkers NF, Rankin KP, et al. Cognition and anatomy in three variants of primary progressive aphasia. *Ann Neurol*. 2004 Mar;55(3):335-46.
53. Rosen HJ, Allison SC, Ogar JM, et al. Behavioral features in semantic dementia vs other forms of progressive aphasia. *Neurology*. 2006 Nov 28;67(10):1752-6.
54. Gorno-Tempini ML, Brambati SM, Ginex V, et al. The logopenic/phonological variant of primary progressive aphasia. *Neurology*. 2008 Oct 14;71(16):1227-34.
55. Rohrer JD, Crutch SJ, Warrington EK, et al. Progranulin-associated primary progressive aphasia: a distinct phenotype? *Neuropsychologia*. 2010 Jan;48(1):288-97.
56. Davies RR, Hodges JR, Kril JJ, et al. The pathological basis of semantic dementia. *Brain*. 2005 Sep;128(Pt 9):1984-95.

57. Grossman M. Primary progressive aphasia: clinicopathological correlations. *Nat Rev Neurol*. 2010 Feb;6(2):88-97.
58. Mesulam M, Wicklund A, Johnson N, et al. Alzheimer and frontotemporal pathology in subsets of primary progressive aphasia. *Ann Neurol*. 2008 Jun;63(6):709-19.
59. Deramecourt V, Lebert F, Debachy B, et al. Prediction of pathology in primary progressive language and speech disorders. *Neurology*. 2010 Jan 5;74(1):42-9.
60. Hu WT, McMillan C, Libon D, et al. Multimodal predictors for Alzheimer disease in nonfluent primary progressive aphasia. *Neurology*. 2010 Aug 17;75(7):595-602.
61. Amici S, Gorno-Tempini ML, Ogar JM, et al. An overview on Primary Progressive Aphasia and its variants. *Behav Neurol*. 2006;17(2):77-87.
62. Brambati SM, Ogar J, Neuhaus J, et al. Reading disorders in primary progressive aphasia: a behavioral and neuroimaging study. *Neuropsychologia*. 2009 Jul;47(8-9):1893-900.
63. Rohrer JD, Ridgway GR, Crutch SJ, et al. Progressive logopenic/phonological aphasia: Erosion of the language network. *NeuroImage*. 2009 Aug 11.
64. Wilson SM, Henry ML, Besbris M, et al. Connected speech production in three variants of primary progressive aphasia. *Brain*. 2010 Jul;133(Pt 7):2069-88.
65. Seelaar H, Schelhaas HJ, Azmani A, et al. TDP-43 pathology in familial frontotemporal dementia and motor neuron disease without Progranulin mutations. *Brain*. 2007 May;130(Pt 5):1375-85.
66. Lomen-Hoerth C, Anderson T, Miller B. The overlap of amyotrophic lateral sclerosis and frontotemporal dementia. *Neurology*. 2002 Oct 8;59(7):1077-9.
67. Chan D, Anderson V, Pijnenburg Y, et al. The clinical profile of right temporal lobe atrophy. *Brain*. 2009 May;132(Pt 5):1287-98.
68. Josephs KA, Whitwell JL, Knopman DS, et al. Two distinct subtypes of right temporal variant frontotemporal dementia. *Neurology*. 2009 Nov 3;73(18):1443-50.
69. Gregory CA, Hodges JR. Clinical features of frontal lobe dementia in comparison to Alzheimer's disease. *Journal of neural transmission*. 1996;47:103-23.
70. Diehl-Schmid J, Pohl C, Perneczky R, et al. Behavioral disturbances in the course of frontotemporal dementia. *Dementia and geriatric cognitive disorders*. 2006;22(4):352-7.
71. Hodges JR, Patterson K, Ward R, et al. The differentiation of semantic dementia and frontal lobe dementia (temporal and frontal variants of frontotemporal dementia) from early Alzheimer's disease: a comparative neuropsychological study. *Neuropsychology*. 1999 1/1999;13(1):31-40.
72. Kramer JH, Jurik J, Sha SJ, et al. Distinctive neuropsychological patterns in frontotemporal dementia, semantic dementia, and Alzheimer disease. *Cogn Behav Neurol*. 2003 Dec;16(4):211-8.
73. Libon DJ, Xie SX, Wang X, et al. Neuropsychological decline in frontotemporal lobar degeneration: a longitudinal analysis. *Neuropsychology*. 2009 May;23(3):337-46.
74. Wittenberg D, Possin KL, Rascovsky K, et al. The early neuropsychological and behavioral characteristics of frontotemporal dementia. *Neuropsychology review*. 2008 Mar;18(1):91-102.
75. Snowden JS, Gibbons ZC, Blackshaw A, et al. Social cognition in frontotemporal dementia and Huntington's disease. *Neuropsychologia*. 2003;41(6):688-701.
76. Rogers TT, Ivanoiu A, Patterson K, et al. Semantic memory in Alzheimer's disease and the frontotemporal dementias: a longitudinal study of 236 patients. *Neuropsychology*. 2006 May;20(3):319-35.
77. Rascovsky K, Salmon DP, Hansen LA, et al. Disparate letter and semantic category fluency deficits in autopsy-confirmed frontotemporal dementia and Alzheimer's disease. *Neuropsychology*. 2007 Jan;21(1):20-30.

78. Libon DJ, McMillan C, Gunawardena D, et al. Neurocognitive contributions to verbal fluency deficits in frontotemporal lobar degeneration. *Neurology*. 2009 Aug 18;73(7):535-42.
79. Hodges JR, Davies RR, Xuereb JH, et al. Clinicopathological correlates in frontotemporal dementia. *Ann Neurol*. 2004 Sep;56(3):399-406.
80. van Swieten JC, Heutink P. Mutations in progranulin (GRN) within the spectrum of clinical and pathological phenotypes of frontotemporal dementia. *Lancet neurology*. 2008 Oct;7(10):965-74.
81. Hornberger M, Piguet O, Graham AJ, et al. How preserved is episodic memory in behavioral variant frontotemporal dementia? *Neurology*. 2010 Feb 9;74(6):472-9.
82. Nedjam Z, Devouche E, Dalla Barba G. Confabulation, but not executive dysfunction discriminate AD from frontotemporal dementia. *Eur J Neurol*. 2004 Nov;11(11):728-33.
83. Hutchinson AD, Mathias JL. Neuropsychological deficits in frontotemporal dementia and Alzheimer's disease: A meta-analytic review. *Journal of neurology, neurosurgery, and psychiatry*. 2007 Mar 19.
84. Collette F, Amieva H, Adam S, et al. Comparison of inhibitory functioning in mild Alzheimer's disease and frontotemporal dementia. *Cortex; a journal devoted to the study of the nervous system and behavior*. 2007 Oct;43(7):866-74.
85. Lough S, Kipps CM, Treise C, et al. Social reasoning, emotion and empathy in frontotemporal dementia. *Neuropsychologia*. 2006;44(6):950-8.
86. Rosen HJ, Wilson MR, Schauer GF, et al. Neuroanatomical correlates of impaired recognition of emotion in dementia. *Neuropsychologia*. 2006;44(3):365-73.
87. Lavenu I, Pasquier F. Perception of emotion on faces in frontotemporal dementia and Alzheimer's disease: a longitudinal study. *Dementia and geriatric cognitive disorders*. 2005;19(1):37-41.
88. Fernandez-Duque D, Black SE. Impaired recognition of negative facial emotions in patients with frontotemporal dementia. *Neuropsychologia*. 2005;43(11):1673-87.
89. Keane J, Calder AJ, Hodges JR, et al. Face and emotion processing in frontal variant frontotemporal dementia. *Neuropsychologia*. 2002;40(6):655-65.
90. Kipps CM, Mioshi E, Hodges JR. Emotion, social functioning and activities of daily living in frontotemporal dementia. *Neurocase*. 2009 Jun;15(3):182-9.
91. Mendez MF, McMurtry A, Licht E, et al. The scale for emotional blunting in patients with frontotemporal dementia. *Neurocase*. 2006 Aug;12(4):242-6.
92. Broe M, Hodges JR, Schofield E, et al. Staging disease severity in pathologically confirmed cases of frontotemporal dementia. *Neurology*. 2003 Mar 25;60(6):1005-11.
93. Eslinger PJ, Moore P, Troiani V, et al. Oops! Resolving social dilemmas in frontotemporal dementia. *Journal of neurology, neurosurgery, and psychiatry*. 2007 May;78(5):457-60.
94. Adenzato M, Cavallo M, Enrici I. Theory of mind ability in the behavioural variant of frontotemporal dementia: an analysis of the neural, cognitive, and social levels. *Neuropsychologia*. 2010 Jan;48(1):2-12.
95. Gregory C, Lough S, Stone V, et al. Theory of mind in patients with frontal variant frontotemporal dementia and Alzheimer's disease: theoretical and practical implications. *Brain*. 2002 Apr;125(Pt 4):752-64.
96. Rankin KP, Kramer JH, Miller BL. Patterns of cognitive and emotional empathy in frontotemporal lobar degeneration. *Cogn Behav Neurol*. 2005 Mar;18(1):28-36.
97. Lavenu I, Pasquier F, Lebert F, et al. Perception of emotion in frontotemporal dementia and Alzheimer disease. *Alzheimer Dis Assoc Disord*. 1999 Apr-Jun;13(2):96-101.
98. Sturm VE, Rosen HJ, Allison S, et al. Self-conscious emotion deficits in frontotemporal lobar degeneration. *Brain*. 2006 Sep;129(Pt 9):2508-16.

99. Sturm VE, Ascher EA, Miller BL, et al. Diminished self-conscious emotional responding in frontotemporal lobar degeneration patients. *Emotion*. 2008 Dec;8(6):861-9.
100. Rohrer JD, Warren JD, Barnes J, et al. Mapping the progression of progranulin-associated frontotemporal lobar degeneration. *Nat Clin Pract Neurol*. 2008 Aug;4(8):455-60.
101. Seeley WW, Crawford R, Rascofsky K, et al. Frontal paralimbic network atrophy in very mild behavioral variant frontotemporal dementia. *Arch Neurol*. 2008 Feb;65(2):249-55.
102. Schroeter ML, Raczka K, Neumann J, et al. Neural networks in frontotemporal dementia--a meta-analysis. *Neurobiology of aging*. 2008 Mar;29(3):418-26.
103. Seelaar H, Klijnsma KY, de Koning I, et al. Frequency of ubiquitin and FUS-positive, TDP-43-negative frontotemporal lobar degeneration. *Journal of neurology*. 2009 Nov 28.
104. Josephs KA, Whitwell JL, Parisi JE, et al. Caudate atrophy on MRI is a characteristic feature of FTL-D-FUS. *Eur J Neurol*. 2010 Mar 3.
105. Rohrer JD, Ridgway GR, Modat M, et al. The clinical and neuroanatomical phenotype of FUS-associated frontotemporal lobar degeneration. *Journal of neurology, neurosurgery, and psychiatry*. 2010;In Press.
106. Rohrer JD, Ridgway GR, Modat M, et al. Distinct profiles of brain atrophy in frontotemporal lobar degeneration caused by progranulin and tau mutations. *NeuroImage*. 2010 Jan 4.
107. Whitwell JL, Jack CR, Jr., Boeve BF, et al. Voxel-based morphometry patterns of atrophy in FTL-D with mutations in MAPT or PGRN. *Neurology*. 2009 Mar 3;72(9):813-20.
108. Cruchaga C, Fernandez-Seara MA, Seijo-Martinez M, et al. Cortical atrophy and language network reorganization associated with a novel progranulin mutation. *Cereb Cortex*. 2009 Aug;19(8):1751-60.
109. Whitwell JL, Jack CR, Jr., Boeve BF, et al. Atrophy patterns in IVS10+16, IVS10+3, N279K, S305N, P301L, and V337M MAPT mutations. *Neurology*. 2009 Sep 29;73(13):1058-65.
110. Whitwell JL, Przybelski SA, Weigand SD, et al. Distinct anatomical subtypes of the behavioural variant of frontotemporal dementia: a cluster analysis study. *Brain*. 2009 Nov;132(Pt 11):2932-46.
111. Mummery CJ, Patterson K, Wise RJ, et al. Disrupted temporal lobe connections in semantic dementia. *Brain*. 1999 Jan;122 (Pt 1):61-73.
112. 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 Jan;47(1):36-45.
113. Chan D, Fox NC, Scahill RI, et al. Patterns of temporal lobe atrophy in semantic dementia and Alzheimer's disease. *Ann Neurol*. 2001 Apr;49(4):433-42.
114. Galton CJ, Patterson K, Graham K, et al. Differing patterns of temporal atrophy in Alzheimer's disease and semantic dementia. *Neurology*. 2001 Jul 24;57(2):216-25.
115. Rohrer JD, Warren JD, Modat M, et al. Patterns of cortical thinning in the language variants of frontotemporal lobar degeneration. *Neurology*. 2009 May 5;72(18):1562-9.
116. Rohrer JD, McNaught E, Foster J, et al. Tracking progression in frontotemporal lobar degeneration: serial MRI in semantic dementia. *Neurology*. 2008 Oct 28;71(18):1445-51.
117. Brambati SM, Rankin KP, Narvid J, et al. Atrophy progression in semantic dementia with asymmetric temporal involvement: a tensor-based morphometry study. *Neurobiology of aging*. 2009 Jan;30(1):103-11.
118. Pereira JM, Williams GB, Acosta-Cabronero J, et al. Atrophy patterns in histologic vs clinical groupings of frontotemporal lobar degeneration. *Neurology*. 2009 May 12;72(19):1653-60.

119. Ogar JM, Dronkers NF, Brambati SM, et al. Progressive nonfluent aphasia and its characteristic motor speech deficits. *Alzheimer Dis Assoc Disord*. 2007 Oct-Dec;21(4):S23-30.
120. Nestor PJ, Graham NL, Fryer TD, et al. Progressive non-fluent aphasia is associated with hypometabolism centred on the left anterior insula. *Brain*. 2003 Nov;126(Pt 11):2406-18.
121. Looi JC, Lindberg O, Zandbelt BB, et al. Caudate nucleus volumes in frontotemporal lobar degeneration: differential atrophy in subtypes. *Ajnr*. 2008 Sep;29(8):1537-43.
122. Josephs KA, Duffy JR, Strand EA, et al. Clinicopathological and imaging correlates of progressive aphasia and apraxia of speech. *Brain*. 2006 Jun;129(Pt 6):1385-98.
123. Rohrer JD, Paviour D, Bronstein AM, et al. Progressive supranuclear palsy syndrome presenting as progressive nonfluent aphasia: a neuropsychological and neuroimaging analysis. *Mov Disord*. 2010 Jan 30;25(2):179-88.
124. Lehmann M, Rohrer JD, Clarkson MJ, et al. Reduced cortical thickness in the posterior cingulate gyrus is characteristic of both typical and atypical Alzheimer's disease. *J Alzheimers Dis*. 2010;20(2):587-98.
125. Whitwell JL, Jack CR, Jr., Przybelski SA, et al. Temporoparietal atrophy: A marker of AD pathology independent of clinical diagnosis. *Neurobiology of aging*. 2009 Nov 13.
126. Migliaccio R, Agosta F, Rascovsky K, et al. Clinical syndromes associated with posterior atrophy: early age at onset AD spectrum. *Neurology*. 2009 Nov 10;73(19):1571-8.
127. Davies RR, Scallan VL, Graham A, et al. Development of an MRI rating scale for multiple brain regions: comparison with volumetrics and with voxel-based morphometry. *Neuroradiology*. 2009 Aug;51(8):491-503.
128. Kloppel S, Stonnington CM, Chu C, et al. Automatic classification of MR scans in Alzheimer's disease. *Brain*. 2008 Mar;131(Pt 3):681-9.
129. Avants BB, Cook PA, Ungar L, et al. Dementia induces correlated reductions in white matter integrity and cortical thickness: a multivariate neuroimaging study with sparse canonical correlation analysis. *NeuroImage*. 2010 Apr 15;50(3):1004-16.
130. Hu WT, Wang Z, Lee VM-Y, et al. Distinct cerebral perfusion patterns in FTL and AD. *Neurology*. 2010;In press.
131. Rabinovici GD, Furst AJ, O'Neil JP, et al. 11C-PIB PET imaging in Alzheimer disease and frontotemporal lobar degeneration. *Neurology*. 2007 Apr 10;68(15):1205-12.
132. Seeley WW, Crawford RK, Zhou J, et al. Neurodegenerative diseases target large-scale human brain networks. *Neuron*. 2009 Apr 16;62(1):42-52.
133. Zhou J, Greicius MD, Gennatas ED, et al. Divergent network connectivity changes in behavioural variant frontotemporal dementia and Alzheimer's disease. *Brain*. 2010 May;133(Pt 5):1352-67.
134. Seeley WW, Carlin DA, Allman JM, et al. Early frontotemporal dementia targets neurons unique to apes and humans. *Ann Neurol*. 2006 Dec;60(6):660-7.
135. Verwey NA, Kester MI, van der Flier WM, et al. Additional Value of CSF Amyloid-beta ₄₀ Levels in the Differentiation between FTL and Control Subjects. *J Alzheimers Dis*. 2010 Feb 17.
136. Coppola G, Karydas A, Rademakers R, et al. Gene expression study on peripheral blood identifies progranulin mutations. *Ann Neurol*. 2008 Jul;64(1):92-6.
137. Finch N, Baker M, Crook R, et al. Plasma progranulin levels predict progranulin mutation status in frontotemporal dementia patients and asymptomatic family members. *Brain*. 2009 Mar;132(Pt 3):583-91.
138. Ghidoni R, Benussi L, Glionna M, et al. Low plasma progranulin levels predict progranulin mutations in frontotemporal lobar degeneration. *Neurology*. 2008 Oct 14;71(16):1235-9.

139. Sleegers K, Brouwers N, Van Damme P, et al. Serum biomarker for progranulin-associated frontotemporal lobar degeneration. *Ann Neurol*. 2009 May;65(5):603-9.
140. Carecchio M, Fenoglio C, De Riz M, et al. Progranulin plasma levels as potential biomarker for the identification of GRN deletion carriers. A case with atypical onset as clinical amnesic Mild Cognitive Impairment converted to Alzheimer's disease. *Journal of the neurological sciences*. 2009 Aug 13.
141. Steinacker P, Hendrich C, Sperfeld AD, et al. TDP-43 in cerebrospinal fluid of patients with frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Arch Neurol*. 2008 Nov;65(11):1481-7.
142. Foulds PG, Davidson Y, Mishra M, et al. Plasma phosphorylated-TDP-43 protein levels correlate with brain pathology in frontotemporal lobar degeneration. *Acta Neuropathol*. 2009 Nov;118(5):647-58.
143. Hu WT, Chen-Plotkin A, Arnold SE, et al. Biomarker discovery for Alzheimer's disease, frontotemporal lobar degeneration, and Parkinson's disease. *Acta Neuropathol*. 2010 Sep;120(3):385-99.
144. Hu WT, Chen-Plotkin A, Grossman M, et al. Novel CSF biomarkers for frontotemporal lobar degeneration. *Neurology*. 2010;In press.
145. Stevens M, van Duijn CM, Kamphorst W, et al. Familial aggregation in frontotemporal dementia. *Neurology*. 1998 Jun;50(6):1541-5.
146. Rohrer JD, Guerreiro R, Vandrovcsa J, et al. The heritability and genetics of frontotemporal lobar degeneration. *Neurology*. 2009 Nov 3;73(18):1451-6.
147. Goedert M, Spillantini MG, Jakes R, et al. Multiple isoforms of human microtubule-associated protein tau: sequences and localization in neurofibrillary tangles of Alzheimer's disease. *Neuron*. 1989 Oct;3(4):519-26.
148. Goedert M, Spillantini MG, Potier MC, et al. Cloning and sequencing of the cDNA encoding an isoform of microtubule-associated protein tau containing four tandem repeats: differential expression of tau protein mRNAs in human brain. *The EMBO journal*. 1989 Feb;8(2):393-9.
149. van Swieten J, Spillantini MG. Hereditary frontotemporal dementia caused by Tau gene mutations. *Brain pathology (Zurich, Switzerland)*. 2007 Jan;17(1):63-73.
150. Boeve BF, Hutton M. Refining frontotemporal dementia with parkinsonism linked to chromosome 17: introducing FTDP-17 (MAPT) and FTDP-17 (PGRN). *Arch Neurol*. 2008 Apr;65(4):460-4.
151. Gass J, Cannon A, Mackenzie IR, et al. Mutations in progranulin are a major cause of ubiquitin-positive frontotemporal lobar degeneration. *Human molecular genetics*. 2006 Oct 15;15(20):2988-3001.
152. Le Ber I, van der Zee J, Hannequin D, et al. Progranulin null mutations in both sporadic and familial frontotemporal dementia. *Human mutation*. 2007 Apr 13.
153. Pickering-Brown SM, Baker M, Gass J, et al. Mutations in progranulin explain atypical phenotypes with variants in MAPT. *Brain*. 2006 Nov;129(Pt 11):3124-6.
154. Ahmed Z, Mackenzie IR, Hutton ML, et al. Progranulin in frontotemporal lobar degeneration and neuroinflammation. *J Neuroinflammation*. 2007;4:7.
155. Mackenzie IR, Baker M, Pickering-Brown S, et al. The neuropathology of frontotemporal lobar degeneration caused by mutations in the progranulin gene. *Brain*. 2006 Nov;129(Pt 11):3081-90.
156. Mesulam M, Johnson N, Krefft TA, et al. Progranulin mutations in primary progressive aphasia: the PPA1 and PPA3 families. *Arch Neurol*. 2007 Jan;64(1):43-7.
157. Le Ber I, Camuzat A, Hannequin D, et al. Phenotype variability in progranulin mutation carriers: a clinical, neuropsychological, imaging and genetic study. *Brain*. 2008 Mar;131(Pt 3):732-46.

158. Benussi L, Binetti G, Sina E, et al. A novel deletion in progranulin gene is associated with FTDP-17 and CBS. *Neurobiology of aging*. 2008 Mar;29(3):427-35.
159. Boeve BF, Baker M, Dickson DW, et al. Frontotemporal dementia and parkinsonism associated with the IVS1+1G->A mutation in progranulin: a clinicopathologic study. *Brain*. 2006 Nov;129(Pt 11):3103-14.
160. Josephs KA, Ahmed Z, Katsuse O, et al. Neuropathologic features of frontotemporal lobar degeneration with ubiquitin-positive inclusions with progranulin gene (PGRN) mutations. *Journal of neuropathology and experimental neurology*. 2007 Feb;66(2):142-51.
161. Kelley BJ, Haidar W, Boeve BF, et al. Prominent phenotypic variability associated with mutations in Progranulin. *Neurobiology of aging*. 2009 May;30(5):739-51.
162. Rademakers R, Baker M, Gass J, et al. Phenotypic variability associated with progranulin haploinsufficiency in patients with the common 1477C->T (Arg493X) mutation: an international initiative. *Lancet neurology*. 2007 Oct;6(10):857-68.
163. Beck J, Rohrer JD, Campbell T, et al. A distinct clinical, neuropsychological and radiological phenotype is associated with progranulin gene mutations in a large UK series. *Brain*. 2008 Mar;131(Pt 3):706-20.
164. Masellis M, Momeni P, Meschino W, et al. Novel splicing mutation in the progranulin gene causing familial corticobasal syndrome. *Brain*. 2006 Nov;129(Pt 11):3115-23.
165. Rohrer JD, Warren JD, Omar R, et al. Parietal lobe deficits in frontotemporal lobar degeneration caused by a mutation in the progranulin gene. *Arch Neurol*. 2008 Apr;65(4):506-13.
166. Pickering-Brown SM, Rollinson S, Du Plessis D, et al. Frequency and clinical characteristics of progranulin mutation carriers in the Manchester frontotemporal lobar degeneration cohort: comparison with patients with MAPT and no known mutations. *Brain*. 2008 Mar;131(Pt 3):721-31.
167. Mackenzie IR, Baker M, West G, et al. A family with tau-negative frontotemporal dementia and neuronal intranuclear inclusions linked to chromosome 17. *Brain*. 2006 Apr;129(Pt 4):853-67.
168. Watts GD, Wymer J, Kovach MJ, et al. Inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia is caused by mutant valosin-containing protein. *Nature genetics*. 2004 Apr;36(4):377-81.
169. Skibinski G, Parkinson NJ, Brown JM, et al. Mutations in the endosomal ESCRTIII-complex subunit CHMP2B in frontotemporal dementia. *Nature genetics*. 2005 Aug;37(8):806-8.
170. Benajiba L, Le Ber I, Camuzat A, et al. TARDBP mutations in motoneuron disease with frontotemporal lobar degeneration. *Ann Neurol*. 2009 Apr;65(4):470-3.
171. Borroni B, Bonvicini C, Alberici A, et al. Mutation within TARDBP leads to Frontotemporal Dementia without motor neuron disease. *Human mutation*. 2009 Aug 4.
172. Kimonis VE, Fulchiero E, Vesa J, et al. VCP disease associated with myopathy, Paget disease of bone and frontotemporal dementia: review of a unique disorder. *Biochimica et biophysica acta*. 2008 Dec;1782(12):744-8.
173. Gydesen S, Brown JM, Brun A, et al. Chromosome 3 linked frontotemporal dementia (FTD-3). *Neurology*. 2002 Nov 26;59(10):1585-94.
174. Parkinson N, Ince PG, Smith MO, et al. ALS phenotypes with mutations in CHMP2B (charged multivesicular body protein 2B). *Neurology*. 2006 Jul 6.
175. Yokoseki A, Shiga A, Tan CF, et al. TDP-43 mutation in familial amyotrophic lateral sclerosis. *Ann Neurol*. 2008 Apr;63(4):538-42.
176. Gitcho MA, Baloh RH, Chakraborty S, et al. TDP-43 A315T mutation in familial motor neuron disease. *Ann Neurol*. 2008 Apr;63(4):535-8.

177. Sreedharan J, Blair IP, Tripathi VB, et al. TDP-43 mutations in familial and sporadic amyotrophic lateral sclerosis. *Science* (New York, NY. 2008 Mar 21;319(5870):1668-72.
178. Daoud H, Valdmanis PN, Kabashi E, et al. Contribution of TARDBP mutations to sporadic amyotrophic lateral sclerosis. *Journal of medical genetics*. 2009 Feb;46(2):112-4.
179. Kabashi E, Valdmanis PN, Dion P, et al. TARDBP mutations in individuals with sporadic and familial amyotrophic lateral sclerosis. *Nature genetics*. 2008 May;40(5):572-4.
180. Kuhnlein P, Sperfeld AD, Vanmassenhove B, et al. Two German kindreds with familial amyotrophic lateral sclerosis due to TARDBP mutations. *Arch Neurol*. 2008 Sep;65(9):1185-9.
181. Rutherford NJ, Zhang YJ, Baker M, et al. Novel mutations in TARDBP (TDP-43) in patients with familial amyotrophic lateral sclerosis. *PLoS genetics*. 2008;4(9):e1000193.
182. Van Deerlin VM, Leverenz JB, Bekris LM, et al. TARDBP mutations in amyotrophic lateral sclerosis with TDP-43 neuropathology: a genetic and histopathological analysis. *Lancet neurology*. 2008 May;7(5):409-16.
183. Vance C, Rogelj B, Hortobagyi T, et al. Mutations in FUS, an RNA processing protein, cause familial amyotrophic lateral sclerosis type 6. *Science* (New York, NY. 2009 Feb 27;323(5918):1208-11.
184. Kwiatkowski TJ, Jr., Bosco DA, Leclerc AL, et al. Mutations in the FUS/TLS gene on chromosome 16 cause familial amyotrophic lateral sclerosis. *Science* (New York, NY. 2009 Feb 27;323(5918):1205-8.
185. Chio A, Restagno G, Brunetti M, et al. Two Italian kindreds with familial amyotrophic lateral sclerosis due to FUS mutation. *Neurobiology of aging*. 2009 Aug;30(8):1272-5.
186. Groen EJ, van Es MA, van Vught PW, et al. FUS mutations in familial amyotrophic lateral sclerosis in the Netherlands. *Arch Neurol*. 2010 Feb;67(2):224-30.
187. Van Langenhove T, van der Zee J, Sleegers K, et al. Genetic contribution of FUS to frontotemporal lobar degeneration. *Neurology*. 2010 Feb 2;74(5):366-71.
188. Le Ber I, Camuzat A, Berger E, et al. Chromosome 9p-linked families with frontotemporal dementia associated with motor neuron disease. *Neurology*. 2009 May 12;72(19):1669-76.
189. 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 Apr;129(Pt 4):868-76.
190. Morita M, Al-Chalabi A, Andersen PM, et al. A locus on chromosome 9p confers susceptibility to ALS and frontotemporal dementia. *Neurology*. 2006 Mar 28;66(6):839-44.
191. Momeni P, Schymick J, Jain S, et al. Analysis of IFT74 as a candidate gene for chromosome 9p-linked ALS-FTD. *BMC neurology*. 2006;6:44.
192. Valdmanis PN, Dupre N, Bouchard JP, et al. Three families with amyotrophic lateral sclerosis and frontotemporal dementia with evidence of linkage to chromosome 9p. *Arch Neurol*. 2007 Feb;64(2):240-5.
193. Luty AA, Kwok JB, Thompson EM, et al. Pedigree with frontotemporal lobar degeneration--motor neuron disease and Tar DNA binding protein-43 positive neuropathology: genetic linkage to chromosome 9. *BMC neurology*. 2008;8:32.
194. Rademakers R, Eriksen JL, Baker M, et al. Common variation in the miR-659 binding-site of GRN is a major risk factor for TDP43-positive frontotemporal dementia. *Human molecular genetics*. 2008 Dec 1;17(23):3631-42.
195. Simon-Sanchez J, Seelaar H, Bochtanovits Z, et al. Variation at GRN 3'-UTR rs5848 Is Not Associated with a Risk of Frontotemporal Lobar Degeneration in Dutch Population. *PloS one*. 2009;4(10):e7494.
196. Rollinson S, Rohrer JD, van der Zee J, et al. No association of PGRN 3'UTR rs5848 in frontotemporal lobar degeneration. *Neurobiology of aging*. 2009 May 13.

197. Verpillat P, Camuzat A, Hannequin D, et al. Apolipoprotein E gene in frontotemporal dementia: an association study and meta-analysis. *Eur J Hum Genet.* 2002 Jul;10(7):399-405.
198. Srinivasan R, Davidson Y, Gibbons L, et al. The apolipoprotein E epsilon4 allele selectively increases the risk of frontotemporal lobar degeneration in males. *Journal of neurology, neurosurgery, and psychiatry.* 2006 Feb;77(2):154-8.
199. Rohrer JD, Mead S, Omar R, et al. Prion protein (PRNP) genotypes in frontotemporal lobar degeneration syndromes. *Ann Neurol.* 2006 Nov;60(5):616; author reply 7.
200. Li X, Rowland LP, Mitumoto H, et al. Prion protein codon 129 genotype prevalence is altered in primary progressive aphasia. *Ann Neurol.* 2005 Dec;58(6):858-64.
201. Benussi L, Ghidoni R, Galimberti D, et al. The CST3 B haplotype is associated with frontotemporal lobar degeneration. *Eur J Neurol.* 2009 Aug 5.
202. Rollinson S, Rizzu P, Sikkink S, et al. Ubiquitin associated protein 1 is a risk factor for frontotemporal lobar degeneration. *Neurobiology of aging.* 2009 Apr;30(4):656-65.
203. Van Deerlin VM, Sleiman PMA, Martinez-Lage M, et al. Common genetic variants at 7p21 show strong association with frontotemporal lobar degeneration with TDP-43 inclusions. *Nature genetics.* 2010;Accepted.
204. Neumann M, Sampathu DM, Kwong LK, et al. Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Science (New York, NY).* 2006 Oct 6;314(5796):130-3.
205. Josephs KA, Lin WL, Ahmed Z, et al. Frontotemporal lobar degeneration with ubiquitin-positive, but TDP-43-negative inclusions. *Acta Neuropathol.* 2008 Aug;116(2):159-67.
206. Mackenzie IR, Foti D, Woulfe J, et al. Atypical frontotemporal lobar degeneration with ubiquitin-positive, TDP-43-negative neuronal inclusions. *Brain.* 2008 May;131(Pt 5):1282-93.
207. Roeber S, Mackenzie IR, Kretschmar HA, et al. TDP-43-negative FTLD-U is a significant new clinico-pathological subtype of FTLD. *Acta Neuropathol.* 2008 Aug;116(2):147-57.
208. Urwin H, Josephs KA, Rohrer JD, et al. FUS pathology defines the majority of tau- and TDP-43-negative frontotemporal lobar degeneration. *Acta Neuropathol.* 2010 May 20.
209. Neumann M, Roeber S, Kretschmar HA, et al. Abundant FUS-immunoreactive pathology in neuronal intermediate filament inclusion disease. *Acta Neuropathol.* 2009 Aug 9.
210. Holm IE, Isaacs AM, Mackenzie IR. Absence of FUS-immunoreactive pathology in frontotemporal dementia linked to chromosome 3 (FTD-3) caused by mutation in the CHMP2B gene. *Acta Neuropathol.* 2009 Oct 21.
211. Mioshi E, Hsieh S, Savage S, et al. Clinical staging and disease progression in frontotemporal dementia. *Neurology.* 2010 May 18;74(20):1591-7.

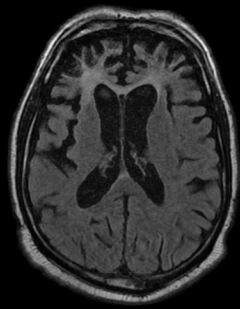
Figure 1: Clinical, genetic and pathological spectrum of FTL D

Figure 2: Imaging of FTD subtypes

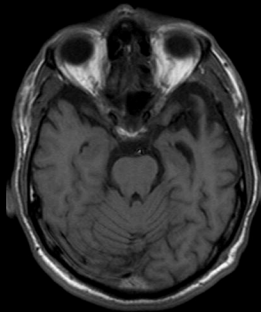
(A) Frontal atrophy on axial fluid attenuated inversion recovery (FLAIR) MRI of a patient with bvFTD. (B) Axial T1-weighted image with left temporal lobe atrophy in a patient with SD. (C) Coronal T1-weighted MR image of a patient with PNFA and left inferior frontal and superior temporal atrophy. (D) Axial T1-weighted MR image in a patient with predominant right temporal lobe atrophy.

Table 1: Language characteristics in PPA variants (52, 55, 61-64)

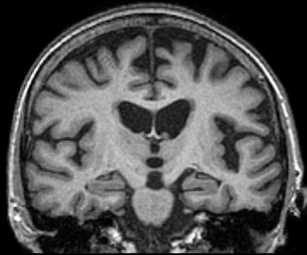
	Spontaneous Speech	Motor speech	Single word comprehension	Grammar / Sentence comprehension	Sentence Repetition	Naming/ word retrieval	Fluency	Reading
SD	Fluent Grammatically correct Empty and circumlocutory Semantic errors	Spared	Impaired	Initially spared, becomes impaired as single word comprehension deteriorates	Spared	Anomia (nouns > verbs)	Impaired (categorical > letter)	Surface dyslexia
PNFA	Decreased fluency Articulatory errors Apraxia of speech and/or Agrammatism	Impaired	Initially spared, becomes affected in late disease	Impaired for complex sentences	Can be impaired	Spared initially but anomic as disease progresses (verbs > nouns)	Impaired (letter > categorical)	Phonological dyslexia
LPA	Slow output with word-finding pauses Phonemic paraphasias	Spared	Relatively spared	Impaired for simple and complex sentences	Impaired	Impaired	Impaired (letter ≈ categorical)	Phonological dyslexia



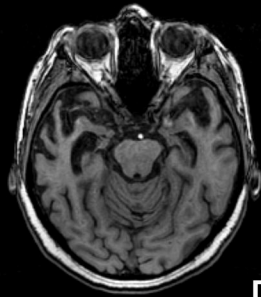
A



B



C



D

