We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Frontotemporal Lobar Degeneration

Johannes Schlachetzki

*Molecular Neurology, University Hospital of Erlangen
Germany*

1. Introduction

Frontotemporal lobar degeneration (FTLD) comprises diseases with a very diverging spectrum in regards to clinical presentation, genetics, and neuropathology. In 1892 Arnold Pick published the case of 71-year old male with progressive symptoms of aphasia, apathy, and dementia (Pick 1892). The pathological examination revealed cortical atrophy with emphasis on the left temporal lobe (Pick 1892). Pick described another case of a 60-year old male with progressive signs of negligence, apathy, apraxia, and dementia (Pick 1906). This patient had bilateral frontal cortical atrophy on pathological examination (Pick 1906). Both cases demonstrate the main clinical and pathological spectrums while at the same time pointing at the clinical and pathological heterogeneity. Leading clinical symptoms were language deficits and behavioral changes. Both cases showed selective cortical atrophy of the left temporal lobe and both frontal lobes while relatively sparing the parietal and occipital lobes.

The frontal lobes harbor the prefrontal cortex with its three distinct parts that differ in phylogeny, assembly, connectivity and function:

1. dorsolateral convexity
2. medial part: anterior gyrus cinguli
3. limbic orbito-frontal cortex

The dorsolateral convexity is important for the *executive functions*, i.e., anticipatory, analytical and imaginative thinking, as well as cognitive flexibility. The medial part is involved in attention, motivation, empathy, and emotion. The orbito-frontal cortex plays an important role in controlling impulses, emotions, and social behavior. The prefrontal cortex is closely connected with the sensory association cortices, the limbic system, and the basal ganglia.

In the first part of this chapter, focus will be on clinical symptoms, diagnostics including neuropsychological and neuroimaging findings, and therapy, while the second and third part will highlight recent findings in neurogenetics and neuropathology, respectively.

2. Clinical presentation

FTLD is the second most common cause for dementia before 65 years of age. Mean age of onset is around 45 to 60 years. However, FTLD may also contribute to a high degree in older patients (Seelaar, Kamphorst et al. 2008; Hodges, Mitchell et al. 2010). Up to 50% have a positive family history of FTLD (Stevens, van Duijn et al. 1998; Neary, Snowden et al. 2005).

In the early stage of the disease, changes in behavior and/or deficits in language may indicate FTLN. The onset of the disease is usually subtle and slowly progressive. Typically, no signs of impairment in memory or visiospatial function may be evident. The pronounced changes in behavior and/or language may lead to the diagnosis of FTLN in the early stage of the disease, differences to other variants of FTLN itself but also to Alzheimer's disease may even out at later time points. The various forms of FTLN merge into a later stage characterized by apathy, severely impaired intellectual function, echolalia, and mutism. The duration of the illness and the decline is variable and ranges between 2 and 20 years (Hodges, Davies et al. 2003).

2.1 Clinical variants

FTLN is clinically defined according to the consensus criteria by Neary and colleagues (Neary, Snowden et al. 1998). The site of focal cerebral atrophy, i.e., frontal and/or temporal, left and/or right determines the clinical presentation. *Behavioral variant FTLN* (bvFTLN) is associated with usually a symmetrical frontal dysfunction. The language variants *progressive non-fluent aphasia* (PNFA) and *semantic dementia* (SD) are subsumed under the clinical syndrome of primary progressive aphasia (Mesulam 2001) and show involvement of the left anterior temporal lobe.

2.1.1 Behavioral variant FTLN

BvFTLN is the most common subtype of FTLN. Patients with bvFTLN show progressive personality and behavioral changes. Deficits in executive function, social interpersonal conduct, loss of insight (anosognosia), emotional blunting, stereotyped verbal output, hyperorality, dietary changes with weight gain, mood changes including irritability, depression, fatuous euphoria, tactlessness, loss of concern for feeling for others, lack of empathy, reduced emotional engagement, utilisation behavior, obsessive behavior, and neglect of personal hygiene all encompass the wide spectrum of clinical symptoms in bvFTLN.

BvFTLN can be subdivided into an (1) dorsolateral/medial type with an apathetic profile, and (2) basal type with pronounced behavioral changes (Snowden, Bathgate et al. 2001).

Parkinsonian features like rigidity and bradykinesia can be associated with bvFTLN. In many FTLN patients with Parkinsonism, a genetic linkage to chromosome 17 (*tau*, *PGRN*) was found, and these cases were termed FTDP-17.

Incontinence, orthostatic dysregulation, and the presence of frontal signs (saccadic eye movements, disturbed upward gaze, paratonia, inexhaustible blink reflex, abnormal Luria sequence) on neurological examination may be present.

CT or MRI may be normal early in the course, but symmetrical atrophy frontal atrophy and involvement and atrophy of the prefrontal cortex, the paralimbic areas anterior cingulum and frontal insula, and thalamus (Grimmer, Diehl et al. 2004). At later stages, atrophy may be observed of the temporal and parietal cortex (Diehl-Schmid, Grimmer et al. 2007). [F18]-FDG-PET and HMPAO-SPECT are useful to establish the clinical diagnosis and show the typical involvement of the frontal and temporal lobes (Mendez, Shapira et al. 2007; Mosconi, Tsui et al. 2008).

2.1.2 Progressive non-fluent aphasia

PNFA patients show apraxia of speech and agrammatism. Sentence repetition may be impaired. Later in the disease, PNFA may present with mutism, alexia, and agraphia. Word

comprehension and object knowledge are initially spared. Behavioral changes and anosognosia are uncommon in the disease, but may develop later in the course. On CT or MRI scan, left-sided atrophy of the inferior frontal lobe and anterior insula is often appreciated.

2.1.3 Semantic dementia

Typical signs of patients with SD are *anomia* and *loss of word meaning*. Albeit still having fluent speech, the content of speech is empty and semantic paraphasias can be detected. Semantic memory progressively becomes impaired. Patients with SD may not recognize faces or objects. Writing may be spared and figures may be copied. In contrast to PNFA, SD are more prone to develop behavioural changes and anosognosia early in the disease.

Neuroimaging studies with CT or MRI of SD show bilateral atrophy of the anterior and inferior temporal lobes. The left temporal lobe is usually more affected than the right. Progression of lobar atrophy can be automatically observed over a short period of time (Frings, Mader et al. 2011).

2.2 Associated diseases with FTLD

2.2.1 FTLD-ALS

FTLD may be associated with amyotrophic lateral sclerosis (ALS), termed FTLD-ALS. Signs of motor neuron disease can be found in a small subset of patients with FTLD (Hodges, Davies et al. 2003; Mitsuyama and Inoue 2009). Affection of upper motoneurons is characterized by fasciculations, hyperreflexia, and positive Babinski signs whereas affection of lower motoneurons by muscle atrophy and weakness. Dementia, typically behavioral changes and/or PNFA, is usually rapid and patients have a very short disease duration with only about three years (Hodges, Davies et al. 2003). It has been reported that 5-15% of patients diagnosed with ALS also show signs of deficits in executive function, suggesting that these patients may belong to the FTLD-ALS subtype (Ringholz, Appel et al. 2005). FTLD-ALS is pathologically characterized by TDP-43 positive neuronal cytoplasmic inclusions (Mackenzie, Baborie et al. 2006; Sampathu, Neumann et al. 2006). A genetic linkage to chromosome 9p has been established for some cases of FTLD-ALS.

2.2.2 CBD and PSP

Corticobasal degeneration (CBD) and *progressive supranuclear palsy* (PSP) belong into the same clinical, genetic, and pathological spectrum of FTLD (Kertesz and Munoz 2004; Josephs, Petersen et al. 2006).

Patients with CBD present as atypical Parkinson's disease with strong asymmetry of rigidity and unilateral apraxia (sometimes "alien limb" phenomenon). Sometimes dystonia, myoklonus, sensory deficits, and early speech disturbance like dysphasia can be observed. Behavioral and personality changes are subtler than in FTLD patients early in the course of the disease. Later, apathy, disinhibition, irritability, and subcortical dementia can be present. On neuropathological examination, focal, asymmetrical cortical atrophy and degeneration with loss of pigment of the substantia nigra can be noticed. Because CBD is characterized by the accumulation of tau protein in neurons and glia, it is classified as a tauopathy.

PSP also belongs to the group of tauopathies. Clinically, impaired upward and especially downward gaze and frequent falls indicate a diagnosis of PSP. Decreased verbal fluency

with loss of speech later in the course, apathy, behavioural changes and pseudobulbar palsy may contribute. Macroscopic examination reveals focal atrophy of the midbrain and pontine tegmentum. Microscopically, neuronal and glial accumulation of tau protein can be appreciated.

2.2.3 Rare forms associated with FTLD

Neuronal intermediate filament inclusions disease (NIFID), *basophilic inclusion body disease* (BIBD), and *inclusion body myopathy with Paget's disease and frontal dementia* (IBMPFD) are very rare diseases. They share clinical and pathological similarities with FTLD (Kertesz and Munoz 2004; Josephs, Petersen et al. 2006).

NIFID is characterized as early-onset sporadic bvFTLD with affection of the pyramidal and extrapyramidal motor systems. Neuronal inclusions observed on microscopic examination show immunoreactivity for class IV intermediate filaments and accumulation of the FUS protein (Josephs, Holton et al. 2003; Cairns, Grossman et al. 2004; Neumann, Roeber et al. 2009). BIBD is characterized pathologically by basophilic inclusions on haematoxylin and eosin staining. These inclusions are immunoreactive for FUS (Munoz, Neumann et al. 2009). Clinically, symptoms vary and can present as bvFTLD, ALS or combination of both.

IBMPFD is caused by mutations in the *VCP* gene. Accumulation of TDP-43 can be appreciated on microscopic examination (van der Zee, Pirici et al. 2009). Adult-onset proximal/distal muscle weakness, spine or hip pain and deformity and enlargement of long bones, as well as signs of FTLD characterize IBMPFD.

2.3 Neuropsychological assessment

Standard neuropsychological tests do not provide high sensitivity and specificity for the diagnosis of FTLD, in particular to differentiate from Alzheimer's disease (Walker, Meares et al. 2005; Hutchinson and Mathias 2007). But maybe the most important aspect of neuropsychological assessment is not the test battery itself but the accurate observation of the patient during testing. *General appearance, motor activity, speech, and linguistic content* may already be suggestive for FTLD. Patients with bvFTLD often grasp at objects during testing, although they were not asked to do so. This phenomenon can be frequently observed and is called *utilisation*. Patient also *imitate* persons verbally and/or gestural. E.g., they repeat words or sentences (echolalia). *High distractibility, low flexibility, indifference, rule breaking behavior, stereotype behavior, impaired drive and motivation, and missing cooperation* during testing are indicative of frontal lobe dysfunction. Disturbed social behavior and anosognosia may be seen as well.

Patients often perform normal on the *Mini mental status examination* (MMSE). Recall of learned verbal and figural information are often without pronounced deficits. Sometimes many false positive answers are given on the recognition part of verbal memory. Copying of figures can be impaired, and bvFTLD patients often draw bizarre pictures.

Tests assessing impairment of executive function including planning, organisation, judgement, problem solving, mental flexibility in FTLD patients may support the diagnosis of FTLD. Usually, memory, visual perception, and spatial skills are relatively well preserved (Hodges, Patterson et al. 1999; Mendez, Shapira et al. 2007; Wittenberg, Possin et al. 2008).

Because of impaired executive function and motivation, FTLD patients can score strikingly low in the verbal fluency test. Patients are asked to name as many words (e.g., animals, words that begin with the letter "S") as he can within 60 seconds. The five-point test may

also help to identify patients with executive dysfunction and tests figural fluency. 5 points are given (4 in the rectangle and 1 in the middle), and participants are required to draw as many patterns by connecting at least 2 points within three minutes. Visual attention and task switching may be also checked by performing Trail Making A and B.

More time consuming is the Wisconsin card sorting test (WCST) tests the cognitive flexibility of the patient. Here, the participant has to match cards either to color, design, or quantity. During the course of the test, the matching rules are changed. Another test for cognitive flexibility and selective attention is the stroop color word test. Here, the participant has to suppress a habitual in favour of a novel response. In this experiment the participant is required to say the color of the word, not what the word says.

A test that requires advanced planning and strategical thinking are the tower of London and tower of Hanoi tests. The participant has to arrange different discs and stacks onto other racks in order to come from one starting position to a certain defined end.

Deficits in speech and language are characteristic for primary progressive aphasia. Spontaneous speech, fluency, comprehension, sentence repetition, naming, and reading need to be evaluated.

2.4 Differential diagnosis

Patients with FTLT can be distinguished from Alzheimer's disease (AD) early in the course of the disease because of remarkable changes in their behavior, personality changes, poor motivation, and/or severe language impairment. AD manifests with early deficits in short-term memory, visuo-spatial deficits. In AD, mediobasal temporal atrophy with enlargement of the temporal horns of the ventricle can be observed on CT and MRI scan. SPECT and PET studies can reveal hypoperfusion and hypometabolism temporo-parietal in AD patients. In FTLT patients, memory is usually not impaired, and normal test values can be found in the MMSE or CERAD. CSF markers (abeta, p-tau) are very sensitive for AD.

Patients with *progressive supranuclear palsy* also demonstrate executive dysfunction, which may precede the typical motor symptoms of PSP, characterized by vertical eye movement paralysis and frequent falls. Another movement disorder may mimic cardinal features of FTLT, *corticobasal degeneration* with unilateral rigidity, bradykinesia, apraxia, dystonia (Lang, Bergeron et al. 1994; Jendroska, Rossor et al. 1995).

Other differential diagnoses are listed in the table 1.

2.5 Pharmacotherapy

Therapeutic options for FTLT are limited and primarily aim at the treatment of somatic and psychiatric symptoms. A disease modifying therapy is not available yet.

A *cholinergic* deficit has not been observed in FTLT (Procter, Qurne et al. 1999). Treatment of FTLT patients with *acetylcholinesterase-inhibitors* such as galantamine and donepezil did not improve cognition (Mendez, Shapira et al. 2007; Kertesz, Morlog et al. 2008). However, rivastigmine was able to attenuate behavioral symptoms in an open label study (Moretti, Torre et al. 2004).

NMDA-receptor antagonist memantine may be promising in the treatment of behavioral disturbances (Swanberg 2007; Diehl-Schmid, Forstl et al. 2008; Vossel and Miller 2008; Kavirajan 2009; Chow, Graff-Guerrero et al. 2011).

The *serotonergic* and *dopaminergic* neurotransmitter systems seems to be affected in FTLT (Procter, Qurne et al. 1999; Yang and Schmitt 2001; Franceschi, Anchisi et al. 2005). Selective

Differential diagnosis	Diagnostic work up
<i>Dementia</i> <ul style="list-style-type: none">Alzheimer’s diseasePrimary progressive aphasia-logopenicVascular dementiaNormal pressure hydrocephalus	Lumbar puncture (Abeta, tau), SPECT/PET (parietal and temporal lobes bilaterally) Language and memory deficits early in the disease CT/MRI CT/MRI, spinal tab
<i>Affective disorders</i> <ul style="list-style-type: none">DepressionMania	Past history, response to antidepressive medication Past history, response to mood stabilizers
Schizophrenia	Past history, response to antipsychotics
Morbus Wilson	CT/MRI, caeruloplasmin
Huntington’s disease	Genetic testing
Lues	Syphilis serology
Brain tumors	CT/MRI
Alcohol and drug abuse	Past History, blood work (MCV, liver enzymes)

Table 1.

serotonin-reuptake inhibitors (SSRI) such as paroxetin, fluvoxamine, and trazodone have been shown to be efficacious in the treatment of obsessive behaviour, agitation, irritability, and depression (Swartz, Miller et al. 1997; Litvan 2001; Perry and Miller 2001; Moretti, Torre et al. 2003; Lebert, Stekke et al. 2004; Huey, Putnam et al. 2006). E.g., paroxetin improved anxiety, and perseveration (Chow and Mendez 2002), however, conflicting results have been reported (Deakin, Rahman et al. 2004). The *monoamine-oxidase B* inhibitor selegiline improved cognition (Moretti, Torre et al. 2002).

The usage of antipsychotics should be contained especially when parkinsonian symptoms such as bradykinesia are present (Pijnenburg, Sampson et al. 2003).

2.6 Summary

FTLD should be suspected in younger patients, who present with progressive behavioral/personality changes or language/naming impairment. A positive family history may support the diagnosis. Relatives or caregivers should accompany the patient to the hospital in order to give a detailed history. Physical examination may reveal signs of frontal/executive deficits and parkinsonism. A neuropsychological assessment should be done. Here, MMSE, verbal fluency, verbal and figural memory should be tested and special attention is needed to observe behavior during testing. Imaging studies such as CT or MRI can reveal focal frontal and/or temporal atrophy. However, atrophy may be absent early in the course of the disease. If FTLD is suspected, SPECT/PET should be performed. No specific lab or CSF marker are available yet, but should be performed to exclude differential diagnosis.

A disease-modifying therapy has not been discovered. Main focus lies on the treatment of psychiatric symptoms.

3. Genetics

The overall frequency of positive family history for dementia in a German FTL D patient cohort was 24 % (Schlachetzki, Schmidtke et al. 2009). This proportion is below reported frequencies in several earlier series with a positive family history of up to 40-50% of FTL D cases (Neary, Snowden et al. 2005) (Stevens, van Duijn et al. 1998). The possibility remains that the true proportion of dominantly inherited cases is obscured by instances of early death of mutation carriers in the parental generation, siblings that carry mutations but are yet undiagnosed, or illegitimate descent.

30-50 % of patients with bvFTL D have a positive family history. Patients presenting clinically with SD or PNFA show a lower frequency (Seelaar, Kamphorst et al. 2008; Chow, Miller et al. 1999; (Stevens, van Duijn et al. 1998; Rohrer, Guerreiro et al. 2009).

Mutations in *microtubule associated protein tau* (MAP) and *progranulin* (PGRN) can be found in the majority of cases, whereas mutations in *valosin containing protein* (VCP), *charged multivesicular body protein 2B* (CHMP2B), *TDP-43* are rare. In about 30 % of FTL D patients with a positive family history, no mutations have been found so far.

The number of mutations and families of each gene can be found at <http://www.molgen.ua.ac.be/admutations/default.cfm?MT=1&ML=0&Page=ADMDB>.

3.1 MAPT

MAPT gene is located on chromosome 17q21.1 and encodes for the protein tau. It contains 11 exons. Exons 2,3, and 10 are alternatively spliced, allowing for 6 isoforms. In 1998 mutations in the *MAPT* gene were identified in patients presenting clinically with FTL D with Parkinsonism linked to chromosome 17 (FTDP-17) (Hutton, Lendon et al. 1998; Poorkaj, Bird et al. 1998; Spillantini, Crowther et al. 1998). This hereditary tauopathy is a rare clinical syndrome, described in around 120 families worldwide and shows a great intra- and interfamilial clinical heterogeneity. More than 40 different *MAPT* mutations have been described and could be classified into two groups: (i) mutations that change the biochemical properties of tau, and (ii) that alter the alternative splicing of tau mRNA. FTDP-17 cases usually present clinically with behavioral changes associated with motor deficits later in the course of the disease, mainly PSP or CBD like symptoms. FTDP-17 is autosomal dominantly inherited. On pathological examination FTDP-17 cases with *MAPT* mutations have (i) a predominant symmetric atrophy of the frontal and temporal lobes, accounting for the observed behavioral changes, and (ii) of the basal ganglia and brainstem nuclei, that explain the parkinsonism observed in these cases (Ghetti, Spina et al. 2008). The microscopic examination reveals cytoplasmic neuronal and/or glial inclusions with immunoreactivity against hyperphosphorylated tau. Depending on the type of *MAPT* mutation, distribution and amount of neurofibrillary tangles, neuropil threads, and glial inclusions composed of insoluble tau vary.

Pathological changes in *MAPT* include missense mutations in exons 9 to 13 (e.g., G272V, P301L and R406W) and mutations in the 5' splice site of exon 10. Missense mutations in exon 9 to 13 impair the function of tau to promote microtubule assembly, organization, and stabilization. The splice site mutation of exon 10 increases the proportion of 4R tau (four microtubule-binding repeats) in neurons and glia by the increased transcription into tau mRNA that includes exon 10 (Hutton, Lendon et al. 1998).

The rate of whole brain atrophy seems to be bigger in patients with *MAPT* mutations (Whitwell, Weigand et al. 2011).

3.2 *PGRN*

PGRN gene is located on chromosome 17 in close vicinity to *MAPT* locus. At present, *PGRN* mutations exceed the number of *MAPT* mutations in patients with FTLT. Pathogenic mutations include missense and nonsense mutations, or small insertions or deletions in the exons or introns of the gene (Gass, Cannon et al. 2006). Most of the mutations lead to frameshift and premature stop codons. E.g., point mutations were identified in two cases of a German cohort of 79 patients (Schlachetzki, Schmidtke et al. 2009). Pathogenic mutations in *PGRN* invariably lead to mutant mRNA transcripts, which undergo nonsense-mediated decay, thereby resulting in haploinsufficiency (Baker, Mackenzie et al. 2006; Cruts, Gijssels et al. 2006).

Overall, the frequency of *PGRN* mutations is similar to that of mutations in *MAPT* (Rosso, Donker Kaat et al. 2003). Prevalence of mutations in *PGRN* is suggested to account for 1-15 % of all cases with FTLT (Bruni, Momeni et al. 2007; Gass, Cannon et al. 2006; Le Ber, van der Zee et al. 2007; Schlachetzki, Schmidtke et al. 2009), but up to 26 % of familial cases (Pickering-Brown, Baker et al. 2006; Cruts, Kumar-Singh et al. 2006; Bronner, Rizzu et al. 2007). In a large series from the USA, mutations were found in 10 % of all patients with FTLT and 23 % in cases of familial FTLT (Gass, Cannon et al. 2006). Several other studies from France, Italy, the Netherlands, the UK, Belgium, Finland, and the USA have reported lower frequencies of on average 5 % in unselected FTLT groups and 4-10 % in groups of cases of familial FTLT (Le Ber, Camuzat et al. 2008; Le Ber, van der Zee et al. 2007; Bruni, Momeni et al. 2007; Borroni, Archetti et al. 2008; Bronner, Rizzu et al. 2007; Pickering-Brown, Rollinson et al. 2008; Cruts, Gijssels et al. 2006; Gijssels, van der Zee et al. 2008; Gass, Cannon et al. 2006; Huey, Grafman et al. 2006). The differences in the reported frequencies may be due to differences in the mode of ascertainment of patients, in ethnic variations as well as to founder effects.

Mean age at onset of FTLT patients with *PGRN* mutations is around 60 years. The majority of patients with *PGRN* mutations show the behavioural-variant phenotype with apathy and social withdrawal as prominent characteristics (van Swieten, Stevens et al. 1999). *PGRN* mutations have also been found in patients who present with language impairment early in the course of the disease, diagnosed as primary non-fluent progressive aphasia (PPA) (Gass, Cannon et al. 2006; Huey, Grafman et al. 2006; Josephs, Ahmed et al. 2007; Snowden, Neary et al. 2007; Mesulam, Johnson et al. 2007). Patients from different families with the same mutation do not necessarily show the same clinical phenotype or age at onset (Huey, Grafman et al. 2006).

On microscopic examination, all cases with *PGRN* mutations share a common subtype, characterized by NCIs and irregular dystrophic neurites in the neocortex and subcortical nuclei (Josephs, Ahmed et al. 2007; Gass, Cannon et al. 2006; Behrens, Mukherjee et al. 2007; Lopez de Munain, Alzualde et al. 2008; Mackenzie, Baker et al. 2006; Snowden, Pickering-Brown et al. 2006; Spina, Murrell et al. 2007). This subtype is referred to as type A (Mackenzie, Neumann et al.). Former classifications used different numbers: type I by Mackenzie et al. and type 3 by Sampathu and co-workers (Mackenzie, Baker et al. 2006; Sampathu, Neumann et al. 2006).

Mutations in *PGRN* may also present clinically also with symptoms of parkinsonism (FTDP-17) (Benussi, Binetti et al. 2008; Boeve and Hutton 2008; Ghetti, Spina et al. 2008; Gabryelewicz, Masellis et al. 2010; Di Fabio, Tessa et al. 2010). First findings may lead to new therapeutic approaches. Inhibitors of vacuolar ATPase like bafilomycin A1 and alkalizing molecules like amiodarone have been shown to significantly increase the

concentration of progranulin intra- and extracellularly in an animal model (Capell, Liebscher et al. 2011). This may prevent progranulin-mediated neurodegeneration and may be a feasible therapeutic option. These agents could increase PGRN levels in the serum, plasma or CSF. Concentrations of progranulin in plasma, serum, and CSF are predictive in mutation carriers with and without symptoms (Sleegers, Brouwers et al. 2009; Ghidoni, Benussi et al. 2008; Finch, Baker et al. 2009). Thus, genetic screening could then be performed in patients with altered PGRN levels in plasma or serum.

3.3 VCP

VCP is located on chromosome 3 and contains 5 exons. *VCP* encodes for the VCP (VCP/p97) protein, which is a member of the ATPase associated with a variety of activities protein family. VCP is a ubiquitously expressed and is involved in numerous cellular processes including proteasomal ubiquitin-dependent protein degradation. VCP regulates autophagosome maturation under basal conditions and in cells challenged by proteasome inhibition, but not in cells challenged by starvation, suggesting that VCP might be selectively required for autophagic degradation of ubiquitinated substrates.

VCP mutations are a rare cause for FTLN with a variable penetrance and are mainly autosomal-dominant inherited. The first mutation in the *VCP* gene was described in 2004 (Watts, Wymer et al. 2004), since then more mutations have been identified in familial cases (Haubenberger, Bittner et al. 2005; Gidaro, Modoni et al. 2008; Djamshidian, Schaefer et al. 2009; Bersano, Del Bo et al. 2009). A mutation has also been described in a sporadic case (Bersano, Del Bo et al. 2009). There is no evidence, that common variants in *VCP* confer a strong risk to the development of sporadic FTLN (Schumacher, Friedrich et al. 2009). Only missense mutations have been described so far. The mutations are located mainly within the ubiquitin-binding domain, suggesting that the pathological accumulation of TDP-43 may be due to problems within the protein degradation system.

VCP mutations can be found in patients with IBMPFD. About 1/3 of these patients actually present with bvFTLN (Kimonis, Fulchiero et al. 2008). A high degree of clinical heterogeneity has been described within families but also among unrelated families bearing the same *VCP* mutation.

On neuropathological examination, mutant *VCP* cases are characterized by neuronal nuclear inclusions containing ubiquitin (Schroder, Watts et al. 2005) and TDP-43 (Neumann, Mackenzie et al. 2007). Phosphorylated TDP-43 was detected only in insoluble brain extracts from affected brain regions. Identification of TDP-43, but not VCP protein, within ubiquitin-positive inclusions supports the hypothesis that *VCP* gene mutations lead to a dominant negative loss or alteration of VCP function culminating in impaired degradation of TDP-43 (Neumann, Mackenzie et al. 2007). TDP-43 positive Intranuclear inclusions and dystrophic neurites are characteristic (van der Zee, Pirici et al. 2009; Watts, Thomasova et al. 2007) and are referred to as FTLN-TDP pathology type D (Mackenzie, Neumann et al. 2011). Inclusions are also present in muscle and heart and are immunoreactive for TDP-43 and beta-amyloid (Watts, Thomasova et al. 2007; Kimonis, Fulchiero et al. 2008). Presently, the link between TDP-43 and VCP is unsolved. Transgenic mice with *VCP* mutations have been described which mimic the three cardinal symptoms of the disease. E.g., it has been shown that mutant VCP may result in enhanced activation of the NF-kappaB signaling cascade (Custer, Neumann et al. 2010). In addition, impaired autophagy has been shown (Ju, Fuentealba et al. 2009; Badadani, Nalbandian et al. 2010). It was shown in cell culture models, that mutations in the *VCP* gene relocate TDP-43 from the nucleus into the cytosol, decreases proteasome

activity, induces endoplasmic reticulum stress and thereby impairs cell viability (Gitcho, Strider et al. 2009). In a drosophila model, mutant *VCP* leads to a redistribution of TDP-43 to the cytoplasm and thereby induces cytotoxicity, thus implying a toxic gain of function of TDP-43 (Ritson, Custer et al. 2010).

3.4 CHMP2B

CHMP2B is located on chromosome 3, and contains 6 exons. It encodes for the protein charged multivesicular protein 2B. CHMP2B protein is a member of ESCRT-III (endosomal sorting complex required for transport III) and is involved in vesicular fusion events within the endosome - lysosome compartments plays an important role in the process of degradation via autophagy. Mutations in this gene are very rare (Cannon, Baker et al. 2006; van der Zee, Urwin et al. 2008) and have been first described in a Danish family (Skibinski, Parkinson et al. 2005). Pathogenic mutations described so far lead to a partial truncation of the C-terminal region. Patients present clinically with bvFTLD and show pyramidal and extrapyramidal signs later in the course of the disease (Gydesen, Brown et al. 2002) and have an autosomal - dominant family history. Missense mutations in the *CHMP2B* gene causative for FTLN have not been identified so far and seem to be unlikely (Ferrari, Kapogiannis et al. 2011).

On neuropathological examination, inclusions are ubiquitin-positive but negative for tau, TDP-43, and FUS. Thus, the protein within the inclusion bodies still needs to be determined. *CHMP2B* cases are classified as FTLN-UPS (ubiquitin - proteasomal system). It is noteworthy, that FTLN-UPS also includes cases without *CHMP2B* mutation, suggesting that the full complement of FTLN pathologies is yet to be elucidated.

CHMP2B is involved in the protein degradation system, and mutations *CHMP2B* could cause inclusion bodies and disruption of endosome-lysosome fusion by a defective protein degradation system (Urwin, Authier et al. 2010).

In addition, *CHMP2B* mutant animal showed disrupted integrity of dendritic spines and synapses (Belly, Bodon et al. 2010).

3.5 Linkage to chromosome 9p13.2-21.3

A linkage to chromosome 9p13.2-21.3 has been suggested in many autosomal-dominant families with bvFTLD or FTLN-ALS (Morita, Al-Chalabi et al. 2006; Vance, Al-Chalabi et al. 2006; Valdmanis, Dupre et al. 2007; Luty, Kwok et al. 2008; Le Ber, Camuzat et al. 2009; Gijssels, Engelborghs et al. 2010; Shatunov, Mok et al. 2010). Genome - wide linkage studies verified an association familial bvFTLD, FTLN-ALS, and ALS cases with the chromosomal locus 9p13.2-21.3 (van Es, Veldink et al. 2009; Laaksovirta, Peuralinna et al. 2010; Shatunov, Mok et al. 2010). However, the responsible gene could not be identified so far. These data confirm that FTLN and amyotrophic lateral sclerosis (ALS) share a common genetic risk factor on chromosome 9p (Rollinson, Mead et al. 2011).

On pathological examination, cases with linkage to chromosome 9p13.2-21.3 show a TDP-43 proteinopathy, classified to type B with moderate neuronal cytoplasmic inclusions and few dystrophic neurites in all layers (Mackenzie, Neumann et al. 2011; Cairns, Neumann et al. 2007). Recently, a hexanucleotide GGGGCC repeat in intron 1 of *C9ORF72* has been identified to be the cause of chromosome 9p13.2-21.3-linked FTLN-ALS (DeJesus-Hernandez, Mackenzie et al. 2011; Renton, Majounie et al. 2011). The function of the *C9ORF72* encoding protein has not been characterized yet. It has been suggested that the repeat expansion may imply loss-of-function and gain-of-function mechanisms by affecting

transcription and causing the formation of nuclear RNA foci (Dejesus-Hernandez, Mackenzie et al. 2011).

3.6 TARDBP

TARDBP encodes the protein TDP-43. It includes 7 exons. In 2008 mutations in the *TARDBP* gene on chromosome 1 encoding TDP-43 were first described in ALS patients with a positive family history but also in cases of sporadic ALS (Gitcho and Baloh 2008; Kabashi 2008; Sreedharan 2008). A mutation in *TARDBP* is found in about 4% and 1.5% of patients with sporadic and familial ALS, respectively. After these findings, an extensive search begun to identify mutations in *TARDBP* gene of patients with FTLD. In contrast to ALS, *TARDBP* mutations may be only a rare cause of FTLD. Mainly missense mutations have been described in patients with bvFTLD (Borroni, Bonvicini et al. 2009), FTLD-MND (Benajiba, Le Ber et al. 2009; Borghero, Floris et al. 2011), and FTLD with supranuclear palsy and choreatic movements (Kovacs, Murrell et al. 2009). Most missense changes involve exon 6, which encodes a Gly-rich region and the C-terminus. This may lead to a toxic gain-of function as well as loss of function of TDP-43 by interfering with protein-protein-interactions due to increased propensity to aggregate and by alteration of the phosphorylation site (Kabashi, Lin et al. 2010). In one family with FTLD-ALS a variant in the 3'-untranslated region (3'-UTR) of the *TARDBP* gene has been described and showed FTLD-TDP pathology on neuropathological examination (Gitcho, Bigio et al. 2009).

3.7 FUS

Mutations in the *FUS* gene on chromosome 16 were first identified to be responsible in a few cases with familial ALS (Kwiatkowski, Bosco et al. 2009; Vance, Rogelj et al. 2009). Altogether, *FUS* mutations account only for a minority of familial ALS patients (4%) and roughly 1% in sporadic cases. One missense mutation in a patient with bvFTLD and negative family history was described (Van Langenhove, van der Zee et al. 2010). No autopsy data is available for this proposed case of FTLD-FUS, so it remains uncertain whether *FUS* mutations truly cause FTLD.

3.8 Summary

30 to 50% of patients with bvFTLD have a positive family history. The frequency for familial PNFA and SD as well as FTLD-ALS is very low. Taken together, general genetic screening for patients presenting with symptoms suggesting FTLD cannot be recommended at this point. So far, testing for mutations in *PGRN* and *MAPT* may be plausible for FTLD patients with a positive family history. Most importantly, it is essential to obtain a thorough family history by asking the relatives or caregivers during several visits for family members that showed signs of personality changes or language impairment, as well as signs of movement disorders. The clinical subtype may also hint at a candidate gene. So far, patients with familial bvFTLD may contain mutations in the *MAPT* or *PGRN* genes, patients with PNFA in the *PGRN* gene. For SD and FTLD-MND, genetic screening cannot be recommended. In sporadic cases, *PGRN* mutations may be found, but here again, genetic screening will not be of great value.

Despite a great effort to find genetic risk factors for FTLD, none has been surely identified so far. At the moment, not all gene mutations have been identified in patients with familial FTLD.

Gene	Location	Protein	Clinical Phenotype	Families	Mutations
<i>MAPT</i>	17q21.1	Microtubule associated protein tau	bvFTLD, FTDP	134	44
<i>PGRN</i>	17q21.31	Progranulin	bvFTLD, PNFA, CBD	231	69
<i>VCP</i>	9p13.3	Valosin-containing protein	IBMPFD	41	17
<i>CHM2B</i>	3p11.2	Charged multivesicular Body Protein 2B	bvFTLD with movement deficits	5	4
<i>TARDBP</i>	1p36.2	TAR DNA-binding protein of 43 kDa (TDP-43)	bvFTLD, FTLD-ALS	92	34
<i>Not determined (C9ORF72)</i>	Linkage to chromosome 9p13.2-21.3	Not determined (C9ORF72: uncharacterized)	bvFTLD, FTLD-ALS		

Table 2.

4. Neuropathology

The pathological hallmark of FTLD is the presence of intracellular protein aggregates. These inclusions are immunoreactive for ubiquitin. In the last couple of years it has become clear that FTLD encompasses a vast spectrum of neuropathological features. The protein tau was the first protein identified as the main component of intraneuronal inclusions in around 40 % of cases with FTLD. For over a decade other associated disease proteins in cases positive for ubiquitin but negative for tau could not be identified. Subsequently, these cases were termed FTLD-U. Then in 2006 and 2009, TDP-43 and FUS were identified to be the main components in many ubiquitin-positive, tau-negative inclusions, and the terms FTLD-TDP and FTLD-FUS were introduced, respectively. Up to date, the associated protein in most cases has been identified, with the exemption of cases with *CHMP2B* mutations. In other pathological cases with FTLD, no clear pathology could be identified and was termed „dementia lacking distinctive histology“ (DLDH). DLDH may be very rare, and it has been suggested that lack of sensitivity for ubiquitin immunostaining may account for the failure to find specific pathology (Mackenzie, Shi et al. 2006). In the following section, an overview over the three key disease associated proteins, namely tau, TDP-43, and FUS, will be given.

4.1 Tau

Tau is physiological localized to the axon in order to stabilize microtubules, filaments of the cytoskeleton apparatus (Goedert, Wischik et al. 1988). Tau is a phosphoprotein with high numbers of serine and threonine residues; thereby tau serves as a substrate by many kinases. Tau is crucial for the neuronal metabolism including signal transduction and

intracellular transport as well as neuronal plasticity. Six isoforms of tau are known and are generated by alternative mRNA splicing. The isoforms differ in the number of amino acids in the protein chain, the presence of three (3R tau type) or four (4R tau type) domains responsible for binding to microtubules, and one or two inserts containing from 29 to 58 amino acids. The isoforms are modified posttranslational by hyperphosphorylation, glycation, or oxidation, which can change the protein's properties and disturb its normal function.

Under pathological conditions, tau becomes posttranslational modified through enhanced phosphorylation at its serine and threonine residues as well as at additional sites. Hyperphosphorylated tau then dissociates from microtubules, causing them to depolymerize. Tau then is deposited in aggregates and can now also be found in dendrites. Hyperphosphorylated inclusions can be found in the soma and neurites of neurons (neurofibrillar tangles), as well as in astroglia ("astrocytic plaque"), and oligodendrocytes ("coiled bodies"). In glia, tau can be found predominantly in its 4R isoform. One common hypothesis is that soluble rather than insoluble tau is neurotoxic.

Tau inclusions can be found within frontal and temporal cortex, as well as hippocampus and subcortical neurons, but also sometimes in midbrain, brainstem, cerebellum, and spinal cord.

Mutations have been identified in the *MAPT* gene, leading mainly to a clinical phenotype of FTLD with parkinsonism.

PSP and CBD are considered a tauopathy as well and are thought to be within the clinical, genetical, and pathological spectrum of FTLD. Here also, tau aggregates can be found within glial cells.

4.2 TDP-43

TDP-43 is highly conserved, abundantly expressed protein in neurons and glia, and predominantly localized to the nucleus (Buratti, Dork et al. 2001; Wang, Wang et al. 2004).

TDP-43 is involved in transcription and splicing regulation (Buratti and Baralle 2008; Lagier-Tourenne, Polymenidou et al. 2010). In addition, TDP-43 may have an effect on microRNA biogenesis, apoptosis, stabilisation of mRNA, and cell division (Strong, Volkening et al. 2007; Buratti and Baralle 2008). The protein TDP-43 is encoded by the gene *TARDBP* located on chromosome 1p36.2. *TARDBP* contains 5 coding and one non-coding exon. TDP-43 is composed of 414 amino acids and has a molecular weight of 43 kDa. TDP-43 consists of two RNA-recognition motif domains, and a Gly-rich C-terminal site for binding to single-stranded DNA, RNA, and protein. In addition it possesses a nuclear localization signal and a nuclear export signal, so TDP-43 shuttles between the nucleus and cytoplasm (Buratti, Dork et al. 2001; Wang, Wang et al. 2004; Buratti, Brindisi et al. 2005; Ayala, Misteli et al. 2008; Winton, Igaz et al. 2008). Transient redistribution from the nucleus to the cytoplasm following neuronal injury indicates that TDP-43 is involved in repair mechanisms (Sato, Takeuchi et al. 2009). TDP-43 may regulate neuronal plasticity and maintenance of dendritic integrity (Wang, Wu et al. 2008; Lu, Ferris et al. 2009).

In FTL, TDP-43 undergoes post-translational modifications, i.e., hyperphosphorylation, ubiquitination, and N-terminal truncation (Neumann, Sampathu et al. 2006; Hasegawa, Arai et al. 2008; Igaz, Kwong et al. 2008). In FTL, staining against TDP-43 localized to the cytoplasm and neurites in the frontotemporal cortex and the dentate granule cells of the hippocampus. TDP-43 positive inclusion bodies are not restricted to neurons, but were identified in glia as well (Mackenzie, Baborie et al. 2006; Sampathu, Neumann et al. 2006).

Nevertheless, TDP-43 can be distinguished according to their subcellular location and proportion into four patterns (Mackenzie, Baborie et al. 2006; Sampathu, Neumann et al. 2006; Mackenzie, Neumann et al. 2011). Here, the harmonized classification system for FTL-TDP pathology is used (Mackenzie, Neumann et al. 2011).

Type A presents mainly cases with bvFTL and PNFA; TDP-43 is highly expressed in neuronal cytoplasmic inclusions and dystrophic neurites in cortical layer 2. Type A represents all cases with *PGRN* mutations. Type B is associated with bvFTL and FTL-ALS, and TDP-43 is mainly located in cytoplasmic inclusions. Type C presents with SD and with TDP-43 in dystrophic neurites. Type D is found only in patients with *VCP* mutations with high neuronal intranuclear TDP-43 inclusions.

The pathogenesis of TDP-43 proteinopathy is unclear. The subcellular redistribution of TDP-43 from the nucleus into the cytoplasm in neurons with inclusion bodies suggests a loss-of function mechanism. This is supported by *in vitro* studies in human cell lines, in which knock-down of TDP-43 induced impaired neurite outgrowth and increased cell death (Ayala, Misteli et al. 2008; Iguchi, Katsuno et al. 2009).

It is noteworthy that TDP-43 can present with each clinical subtype, i.e., bvFTL, SD, and PNFA. TDP-43 proteinopathies can be found associated with genetic mutations in *GRN*, *linkage to chromosome 9p*, and *VCP*.

Other disorders with TDP-43 pathology were reported in Perry Syndrome (Wider, Dickson et al. 2009), Guamanian ALS-parkinsonism-dementia complex (Hasegawa, Arai et al. 2007), but also in some cases of Alzheimer's disease and dementia with Lewy bodies (Arai, Mackenzie et al. 200; Higashi, Iseki et al. 2007). TDP-43 has not been described in inclusion bodies in Parkinson's disease so far.

4.3 FUS

In 2009, FUS (fused in sarcoma) protein was identified in cases of ubiquitin-positive, tau-negative and TDP-43 negative cases (Neumann, Rademakers et al. 2009). Up to 10% of

FTLD- ubiquitin positive, tau and TDP-43 negative cases are immunoreactive for FUS (Mackenzie, Neumann et al. 2011).

Neuropathological subtypes of FTLD-TDP (Mackenzie, Neumann et al. 2011)		
Classification	Pathology	Disease association
Type A	Abundant NCI and DN Variable NII	bvFTLD, PNFA PGRN mutations
Type B	Few NCI and DN	bvFTLD, FTLD-ALS with linkage to chromosome 9p
Type C	Abundant DN, few NCI	SD, bvFTLD
Type D	Abundant NII Abundant DN, few NCI	IBMPFD with VCP mutations
NCI – neuronalcytoplasmic inclusions DN – dystrophic neurites NII – neuronal intranuclear inclusions		

Table 3.

FUS protein is comprised of 526 amino acids, ubiquitously expressed, and is located to the nucleus and cytoplasm (Andersson, Stahlberg et al. 2008). Its precise function is scarcely deciphered but it may be involved in cell proliferation, transcription regulation such as regulation of RNA splicing, and RNA and microRNA processing (Lagier-Tourenne, Polymenidou et al. 2010). FUS was originally discovered as a part of the fusion oncogenes in human cancers (Law, Cann et al. 2006). It contains an RNA recognition motif, a zinc finger motif and possesses a non-classical nuclear localization signal at its C-terminus (Law, Cann et al. 2006; Zakaryan and Gehring 2006).

Pathologically, FUS positive inclusions are found in neuronal and glial cells. Albeit to a lesser degree, like TDP-43 there is redistribution from the nucleus to the cytoplasm. No disease-associated modifications of this protein like truncation, phosphorylation have yet been identified.

Cases with FTLD-FUS on neuropathological examination show a more or less characteristic clinical phenotype. Patients had an early-onset bvFTLD, and showed motor symptoms including mild rigidity and/or intermittent hyperkinesias. FUS pathology is abundant in the frontal and temporal lobe, as well as hippocampus and maybe in the striatum and brainstem (Neumann, Rademakers et al. 2009; Neumann, Roeber et al. 2009). Most cases show inclusions in the lower motor neuron, despite missing clinical features of motor neuron disease. FUS show intranuclear inclusions with vermiform filaments that can be found in dentate granule cells (Neumann, Rademakers et al. 2009; Neumann, Roeber et al. 2009).

On neuroimaging studies, caudate atrophy may be indicator of FTLD-FUS, since the volume is smaller than in patients with FTLD-tau and FTLD-TDP (Josephs, Whitwell et al.).

Neuronal intermediate filament inclusion disease (NIFID) is characterized microscopically by neuronal inclusions for all class IV intermediate filaments like α -internexin and FUS (Neumann, Roeber et al. 2009). FUS pathology is also seen in cases with BIBD (Munoz, Neumann et al. 2009).

4.4 Summary

FTLD is characterized by focal atrophy of the frontal and/or temporal lobes with relative sparing of the parietal and occipital. Neuronal loss is mainly observed within layer 2.

Abnormal protein aggregates are located mainly in the cytoplasm. These inclusions stain positive ubiquitin. Tau, TDP-43, or FUS were identified as the ubiquitinated pathological protein in most cases. However, some ubiquitin-positive, tau-negative, TDP-43-negative and FUS-negative cases are still open and are termed FTL-D-UPS. Some of these cases carry a CHMP2B mutation, but the pathological protein is not yet identified.

Tau, TDP-43, and FUS all undergo post-translational modification, but the exact toxic species has not been identified.

5. References

- Andersson, M. K., A. Stahlberg, et al. (2008). "The multifunctional FUS, EWS and TAF15 proto-oncoproteins show cell type-specific expression patterns and involvement in cell spreading and stress response." *BMC Cell Biol* 9: 37.
- Arai, T., I. R. Mackenzie, et al. (2009). "Phosphorylated TDP-43 in Alzheimer's disease and dementia with Lewy bodies." *Acta Neuropathol* 117(2): 125-36.
- Ayala, Y. M., T. Misteli, et al. (2008). "TDP-43 regulates retinoblastoma protein phosphorylation through the repression of cyclin-dependent kinase 6 expression." *Proc Natl Acad Sci U S A* 105(10): 3785-9.
- Badadani, M., A. Nalbandian, et al. (2010). "VCP associated inclusion body myopathy and paget disease of bone knock-in mouse model exhibits tissue pathology typical of human disease." *PLoS One* 5(10).
- Baker, M., I. R. Mackenzie, et al. (2006). "Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17." *Nature* 442(7105): 916-9.
- Behrens, M. I., O. Mukherjee, et al. (2007). "Neuropathologic heterogeneity in HDDD1: a familial frontotemporal lobar degeneration with ubiquitin-positive inclusions and progranulin mutation." *Alzheimer Dis Assoc Disord* 21(1): 1-7.
- Belly, A., G. Bodon, et al. (2010). "CHMP2B mutants linked to frontotemporal dementia impair maturation of dendritic spines." *J Cell Sci* 123(Pt 17): 2943-54.
- Benajiba, L., I. Le Ber, et al. (2009). "TARDBP mutations in motoneuron disease with frontotemporal lobar degeneration." *Ann Neurol* 65(4): 470-3.
- Benussi, L., G. Binetti, et al. (2008). "A novel deletion in progranulin gene is associated with FTDP-17 and CBS." *Neurobiol Aging* 29(3): 427-35.
- Bersano, A., R. Del Bo, et al. (2009). "Inclusion body myopathy and frontotemporal dementia caused by a novel VCP mutation." *Neurobiol Aging* 30(5): 752-8.
- Boeve, B. F. and M. Hutton (2008). "Refining frontotemporal dementia with parkinsonism linked to chromosome 17: introducing FTDP-17 (MAPT) and FTDP-17 (PGRN)." *Arch Neurol* 65(4): 460-4.
- Borghero, G., G. Floris, et al. (2011). "A patient carrying a homozygous p.A382T TARDBP missense mutation shows a syndrome including ALS, extrapyramidal symptoms, and FTD." *Neurobiol Aging*. DOI:10.1016/j.neurobiolaging.2011.06.009
- Borrioni, B., S. Archetti, et al. (2008). "Progranulin genetic variations in frontotemporal lobar degeneration: evidence for low mutation frequency in an Italian clinical series." *Neurogenetics* 9(3): 197-205.
- Borrioni, B., C. Bonvicini, et al. (2009). "Mutation within TARDBP leads to frontotemporal dementia without motor neuron disease." *Hum Mutat* 30(11): E974-83.
- Bronner, I. F., P. Rizzu, et al. (2007). "Progranulin mutations in Dutch familial frontotemporal lobar degeneration." *Eur J Hum Genet* 15(3): 369-74.

- Bruni, A. C., P. Momeni, et al. (2007). "Heterogeneity within a large kindred with frontotemporal dementia: a novel progranulin mutation." *Neurology* 69(2): 140-7.
- Buratti, E. and F. E. Baralle (2008). "Multiple roles of TDP-43 in gene expression, splicing regulation, and human disease." *Front Biosci* 13: 867-78.
- Buratti, E., A. Brindisi, et al. (2005). "TDP-43 binds heterogeneous nuclear ribonucleoprotein A/B through its C-terminal tail: an important region for the inhibition of cystic fibrosis transmembrane conductance regulator exon 9 splicing." *J Biol Chem* 280(45): 37572-84.
- Buratti, E., T. Dork, et al. (2001). "Nuclear factor TDP-43 and SR proteins promote in vitro and in vivo CFTR exon 9 skipping." *Embo J* 20(7): 1774-84.
- Cairns, N. J., M. Grossman, et al. (2004). "Clinical and neuropathologic variation in neuronal intermediate filament inclusion disease." *Neurology* 63(8): 1376-84.
- Cairns, N. J., M. Neumann, et al. (2007). "TDP-43 in familial and sporadic frontotemporal lobar degeneration with ubiquitin inclusions." *Am J Pathol* 171(1): 227-40.
- Cannon, A., M. Baker, et al. (2006). "CHMP2B mutations are not a common cause of frontotemporal lobar degeneration." *Neurosci Lett* 398(1-2): 83-4.
- Capell, A., S. Liebscher, et al. (2011). "Rescue of progranulin deficiency associated with frontotemporal lobar degeneration by alkalizing reagents and inhibition of vacuolar ATPase." *J Neurosci* 31(5): 1885-94.
- Chow, T. W., A. Graff-Guerrero, et al. (2011). "Open-label study of the short-term effects of memantine on FDG-PET in frontotemporal dementia." *Neuropsychiatr Dis Treat* 7: 415-24.
- Chow, T. W. and M. F. Mendez (2002). "Goals in symptomatic pharmacologic management of frontotemporal lobar degeneration." *Am J Alzheimers Dis Other Dement* 17(5): 267-72.
- Chow, T. W., B. L. Miller, et al. (1999). "Inheritance of frontotemporal dementia." *Arch Neurol* 56(7): 817-22.
- Cruts, M., I. Gijssels, et al. (2006). "Null mutations in progranulin cause ubiquitin-positive frontotemporal dementia linked to chromosome 17q21." *Nature* 442(7105): 920-4.
- Cruts, M., S. Kumar-Singh, et al. (2006). "Progranulin mutations in ubiquitin-positive frontotemporal dementia linked to chromosome 17q21." *Curr Alzheimer Res* 3(5): 485-91.
- Custer, S. K., M. Neumann, et al. (2010). "Transgenic mice expressing mutant forms VCP/p97 recapitulate the full spectrum of IBMPFD including degeneration in muscle, brain and bone." *Hum Mol Genet* 19(9): 1741-55.
- Deakin, J. B., S. Rahman, et al. (2004). "Paroxetine does not improve symptoms and impairs cognition in frontotemporal dementia: a double-blind randomized controlled trial." *Psychopharmacology (Berl)* 172(4): 400-8.
- DeJesus-Hernandez, M., I. R. Mackenzie, et al. (2011). "Expanded GGGGCC Hexanucleotide Repeat in Noncoding Region of C9ORF72 Causes Chromosome 9p-Linked FTD and ALS." *Neuron*.
- Di Fabio, R., A. Tessa, et al. (2010). "Familial frontotemporal dementia with parkinsonism associated with the progranulin c.C1021T (p.Q341X) mutation." *Parkinsonism Relat Disord* 16(7): 484-5.
- Diehl-Schmid, J., H. Forstl, et al. (2008). "A 6-month, open-label study of memantine in patients with frontotemporal dementia." *Int J Geriatr Psychiatry* 23(7): 754-9.
- Diehl-Schmid, J., T. Grimmer, et al. (2007). "Decline of cerebral glucose metabolism in frontotemporal dementia: a longitudinal 18F-FDG-PET-study." *Neurobiol Aging* 28(1): 42-50.

- Djamshidian, A., J. Schaefer, et al. (2009). "A novel mutation in the VCP gene (G157R) in a German family with inclusion-body myopathy with Paget disease of bone and frontotemporal dementia." *Muscle Nerve* 39(3): 389-91.
- Ferrari, R., D. Kapogiannis, et al. (2010). "Novel Missense Mutation in Charged Multivesicular Body Protein 2B in a Patient With Frontotemporal Dementia." *Alzheimer Dis Assoc Disord*. DOI: 10.1097/WAD.0b013e3181df20c7
- Finch, N., M. Baker, et al. (2009). "Plasma progranulin levels predict progranulin mutation status in frontotemporal dementia patients and asymptomatic family members." *Brain* 132(Pt 3): 583-91.
- Franceschi, M., D. Anchisi, et al. (2005). "Glucose metabolism and serotonin receptors in the frontotemporal lobe degeneration." *Ann Neurol* 57(2): 216-25.
- Frings, L., I. Mader, et al. (2011). "Quantifying change in individual subjects affected by frontotemporal lobar degeneration using automated longitudinal MRI volumetry." *Hum Brain Mapp*. DOI: 10.1002/hbm.21304
- Gabryelewicz, T., M. Masellis, et al. (2010). "Intra-familial clinical heterogeneity due to FTL-DU with TDP-43 proteinopathy caused by a novel deletion in progranulin gene (PGRN)." *J Alzheimers Dis* 22(4): 1123-33.
- Gass, J., A. Cannon, et al. (2006). "Mutations in progranulin are a major cause of ubiquitin-positive frontotemporal lobar degeneration." *Hum Mol Genet* 15(20): 2988-3001.
- Ghetti, B., S. Spina, et al. (2008). "In vivo and postmortem clinicoanatomical correlations in frontotemporal dementia and parkinsonism linked to chromosome 17." *Neurodegener Dis* 5(3-4): 215-7.
- Ghidoni, R., L. Benussi, et al. (2008). "Low plasma progranulin levels predict progranulin mutations in frontotemporal lobar degeneration." *Neurology* 71(16): 1235-9.
- Gidaro, T., A. Modoni, et al. (2008). "An Italian family with inclusion-body myopathy and frontotemporal dementia due to mutation in the VCP gene." *Muscle Nerve* 37(1): 111-4.
- Gijssels, I., S. Engelborghs, et al. (2010). "Identification of 2 Loci at chromosomes 9 and 14 in a multiplex family with frontotemporal lobar degeneration and amyotrophic lateral sclerosis." *Arch Neurol* 67(5): 606-16.
- Gijssels, I., J. van der Zee, et al. (2008). "Progranulin locus deletion in frontotemporal dementia." *Hum Mutat* 29(1): 53-8.
- Gitcho, M. and R. H. Baloh (2008). "TDP-43 A315T mutation in familial motor neuron disease." *Ann Neurol*.
- Gitcho, M. A., E. H. Bigio, et al. (2009). "TARDBP 3'-UTR variant in autopsy-confirmed frontotemporal lobar degeneration with TDP-43 proteinopathy." *Acta Neuropathol* 118(5): 633-45.
- Gitcho, M. A., J. Strider, et al. (2009). "VCP mutations causing frontotemporal lobar degeneration disrupt localization of TDP-43 and induce cell death." *J Biol Chem* 284(18): 12384-98.
- Goedert, M., C. M. Wischik, et al. (1988). "Cloning and sequencing of the cDNA encoding a core protein of the paired helical filament of Alzheimer disease: identification as the microtubule-associated protein tau." *Proc Natl Acad Sci U S A* 85(11): 4051-5.
- Goldman, J. S., J. M. Farmer, et al. (2005). "Comparison of family histories in FTL-D subtypes and related tauopathies." *Neurology* 65(11): 1817-9.
- Grimmer, T., J. Diehl, et al. (2004). "Region-specific decline of cerebral glucose metabolism in patients with frontotemporal dementia: a prospective 18F-FDG-PET study." *Dement Geriatr Cogn Disord* 18(1): 32-6.

- Gydesen, S., J. M. Brown, et al. (2002). "Chromosome 3 linked frontotemporal dementia (FTD-3)." *Neurology* 59(10): 1585-94.
- Hasegawa, M., T. Arai, et al. (2007). "TDP-43 is deposited in the Guam parkinsonism-dementia complex brains." *Brain* 130(Pt 5): 1386-94.
- Hasegawa, M., T. Arai, et al. (2008). "Phosphorylated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis." *Ann Neurol* 64(1): 60-70.
- Haubenberger, D., R. E. Bittner, et al. (2005). "Inclusion body myopathy and Paget disease is linked to a novel mutation in the VCP gene." *Neurology* 65(8): 1304-5.
- Higashi, S., E. Iseki, et al. (2007). "Concurrence of TDP-43, tau and alpha-synuclein pathology in brains of Alzheimer's disease and dementia with Lewy bodies." *Brain Res* 1184: 284-94.
- Hodges, J. R., R. Davies, et al. (2003). "Survival in frontotemporal dementia." *Neurology* 61(3): 349-54.
- Hodges, J. R., J. Mitchell, et al. (2010). "Semantic dementia: demography, familial factors and survival in a consecutive series of 100 cases." *Brain* 133(Pt 1): 300-6.
- Hodges, J. R., K. Patterson, et al. (1999). "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* 13(1): 31-40.
- Huey, E. D., J. Grafman, et al. (2006). "Characteristics of frontotemporal dementia patients with a Progranulin mutation." *Ann Neurol* 60(3): 374-80.
- Huey, E. D., K. T. Putnam, et al. (2006). "A systematic review of neurotransmitter deficits and treatments in frontotemporal dementia." *Neurology* 66(1): 17-22.
- Hutchinson, A. D. and J. L. Mathias (2007). "Neuropsychological deficits in frontotemporal dementia and Alzheimer's disease: a meta-analytic review." *J Neurol Neurosurg Psychiatry* 78(9): 917-28.
- Hutton, M., C. L. Lendon, et al. (1998). "Association of missense and 5'-splice-site mutations in tau with the inherited dementia FTDP-17." *Nature* 393(6686): 702-5.
- Igaz, L. M., L. K. Kwong, et al. (2008). "Enrichment of C-terminal fragments in TAR DNA-binding protein-43 cytoplasmic inclusions in brain but not in spinal cord of frontotemporal lobar degeneration and amyotrophic lateral sclerosis." *Am J Pathol* 173(1): 182-94.
- Iguchi, Y., M. Katsuno, et al. (2009). "TDP-43 depletion induces neuronal cell damage through dysregulation of Rho family GTPases." *J Biol Chem* 284(33): 22059-66.
- Jendroska, K., M. N. Rossor, et al. (1995). "Morphological overlap between corticobasal degeneration and Pick's disease: a clinicopathological report." *Mov Disord* 10(1): 111-4.
- Josephs, K. A., Z. Ahmed, et al. (2007). "Neuropathologic features of frontotemporal lobar degeneration with ubiquitin-positive inclusions with progranulin gene (PGRN) mutations." *J Neuropathol Exp Neurol* 66(2): 142-51.
- Josephs, K. A., J. L. Holton, et al. (2003). "Neurofilament inclusion body disease: a new proteinopathy?" *Brain* 126(Pt 10): 2291-303.
- Josephs, K. A., R. C. Petersen, et al. (2006). "Clinicopathologic analysis of frontotemporal and corticobasal degenerations and PSP." *Neurology* 66(1): 41-8.
- Josephs, K. A., J. L. Whitwell, et al. (2010). "Caudate atrophy on MRI is a characteristic feature of FTLD-FUS." *Eur J Neurol* 17(7): 969-75.
- Ju, J. S., R. A. Fuentelba, et al. (2009). "Valosin-containing protein (VCP) is required for autophagy and is disrupted in VCP disease." *J Cell Biol* 187(6): 875-88.

- Kabashi, E. (2008). "TARDBP mutations in individuals with sporadic and familial amyotrophic lateral sclerosis." *Nat Genet*.
- Kabashi, E., L. Lin, et al. (2010). "Gain and loss of function of ALS-related mutations of TARDBP (TDP-43) cause motor deficits in vivo." *Hum Mol Genet* 19(4): 671-83.
- Kavirajan, H. (2009). "Memantine: a comprehensive review of safety and efficacy." *Expert Opin Drug Saf* 8(1): 89-109.
- Kertesz, A., D. Morlog, et al. (2008). "Galantamine in frontotemporal dementia and primary progressive aphasia." *Dement Geriatr Cogn Disord* 25(2): 178-85.
- Kertesz, A. and D. Munoz (2004). "Relationship between frontotemporal dementia and corticobasal degeneration/progressive supranuclear palsy." *Dement Geriatr Cogn Disord* 17(4): 282-6.
- Kimonis, V. E., E. Fulchiero, et al. (2008). "VCP disease associated with myopathy, Paget disease of bone and frontotemporal dementia: review of a unique disorder." *Biochim Biophys Acta* 1782(12): 744-8.
- Kovacs, G. G., J. R. Murrell, et al. (2009). "TARDBP variation associated with frontotemporal dementia, supranuclear gaze palsy, and chorea." *Mov Disord* 24(12): 1843-7.
- Kwiatkowski, T. J., Jr., D. A. Bosco, et al. (2009). "Mutations in the FUS/TLS gene on chromosome 16 cause familial amyotrophic lateral sclerosis." *Science* 323(5918): 1205-8.
- Laaksovirta, H., T. Peuralinna, et al. (2010). "Chromosome 9p21 in amyotrophic lateral sclerosis in Finland: a genome-wide association study." *Lancet Neurol* 9(10): 978-85.
- Lagier-Tourenne, C., M. Polymenidou, et al. (2010). "TDP-43 and FUS/TLS: emerging roles in RNA processing and neurodegeneration." *Hum Mol Genet* 19(R1): R46-64.
- Lang, A. E., C. Bergeron, et al. (1994). "Parietal Pick's disease mimicking cortical-basal ganglionic degeneration." *Neurology* 44(8): 1436-40.
- Law, W. J., K. L. Cann, et al. (2006). "TLS, EWS and TAF15: a model for transcriptional integration of gene expression." *Brief Funct Genomic Proteomic* 5(1): 8-14.
- Le Ber, I., A. Camuzat, et al. (2009). "Chromosome 9p-linked families with frontotemporal dementia associated with motor neuron disease." *Neurology* 72(19): 1669-76.
- Le Ber, I., A. Camuzat, et al. (2008). "Phenotype variability in progranulin mutation carriers: a clinical, neuropsychological, imaging and genetic study." *Brain* 131(Pt 3): 732-46.
- Le Ber, I., J. van der Zee, et al. (2007). "Progranulin null mutations in both sporadic and familial frontotemporal dementia." *Hum Mutat* 28(9): 846-55.
- Lebert, F., W. Stekke, et al. (2004). "Frontotemporal dementia: a randomised, controlled trial with trazodone." *Dement Geriatr Cogn Disord* 17(4): 355-9.
- Litvan, I. (2001). "Therapy and management of frontal lobe dementia patients." *Neurology* 56(11 Suppl 4): S41-5.
- Lopez de Munain, A., A. Alzualde, et al. (2008). "Mutations in progranulin gene: clinical, pathological, and ribonucleic acid expression findings." *Biol Psychiatry* 63(10): 946-52.
- Lu, Y., J. Ferris, et al. (2009). "Frontotemporal dementia and amyotrophic lateral sclerosis-associated disease protein TDP-43 promotes dendritic branching." *Mol Brain* 2: 30.
- Luty, A. A., J. B. Kwok, et al. (2008). "Pedigree with frontotemporal lobar degeneration--motor neuron disease and Tar DNA binding protein-43 positive neuropathology: genetic linkage to chromosome 9." *BMC Neurol* 8: 32.
- Mackenzie, I. R., A. Baborie, et al. (2006). "Heterogeneity of ubiquitin pathology in frontotemporal lobar degeneration: classification and relation to clinical phenotype." *Acta Neuropathol* 112(5): 539-49.

- Mackenzie, I. R., M. Baker, et al. (2006). "The neuropathology of frontotemporal lobar degeneration caused by mutations in the progranulin gene." *Brain* 129(Pt 11): 3081-90.
- Mackenzie, I. R., M. Neumann, et al. (2011). "A harmonized classification system for FTLD-TDP pathology." *Acta Neuropathol* 122(1): 111-3.
- Mackenzie, I. R., M. Neumann, et al. (2011). "Nomenclature and nosology for neuropathologic subtypes of frontotemporal lobar degeneration: an update." *Acta Neuropathol* 119(1): 1-4.
- Mackenzie, I. R., J. Shi, et al. (2006). "Dementia lacking distinctive histology (DLDH) revisited." *Acta Neuropathol* 112(5): 551-9.
- Mendez, M. F., J. S. Shapira, et al. (2007). "Preliminary findings: behavioral worsening on donepezil in patients with frontotemporal dementia." *Am J Geriatr Psychiatry* 15(1): 84-7.
- Mendez, M. F., J. S. Shapira, et al. (2007). "Accuracy of the clinical evaluation for frontotemporal dementia." *Arch Neurol* 64(6): 830-5.
- Mesulam, M., N. Johnson, et al. (2007). "Progranulin mutations in primary progressive aphasia: the PPA1 and PPA3 families." *Arch Neurol* 64(1): 43-7.
- Mesulam, M. M. (2001). "Primary progressive aphasia." *Ann Neurol* 49(4): 425-32.
- Mitsuyama, Y. and T. Inoue (2009). "Clinical entity of frontotemporal dementia with motor neuron disease." *Neuropathology* 29(6): 649-54.
- Moretti, R., P. Torre, et al. (2004). "Rivastigmine in frontotemporal dementia: an open-label study." *Drugs Aging* 21(14): 931-7.
- Moretti, R., P. Torre, et al. (2002). "Effects of selegiline on fronto-temporal dementia: a neuropsychological evaluation." *Int J Geriatr Psychiatry* 17(4): 391-2.
- Moretti, R., P. Torre, et al. (2003). "Frontotemporal dementia: paroxetine as a possible treatment of behavior symptoms. A randomized, controlled, open 14-month study." *Eur Neurol* 49(1): 13-9.
- Morita, M., A. Al-Chalabi, et al. (2006). "A locus on chromosome 9p confers susceptibility to ALS and frontotemporal dementia." *Neurology* 66(6): 839-44.
- Mosconi, L., W. H. Tsui, et al. (2008). "Multicenter standardized 18F-FDG PET diagnosis of mild cognitive impairment, Alzheimer's disease, and other dementias." *J Nucl Med* 49(3): 390-8.
- Munoz, D. G., M. Neumann, et al. (2009). "FUS pathology in basophilic inclusion body disease." *Acta Neuropathol* 118(5): 617-27.
- Neary, D., J. Snowden, et al. (2005). "Frontotemporal dementia." *Lancet Neurol* 4(11): 771-80.
- Neary, D., J. S. Snowden, et al. (1998). "Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria." *Neurology* 51(6): 1546-54.
- Neumann, M., I. R. Mackenzie, et al. (2007). "TDP-43 in the ubiquitin pathology of frontotemporal dementia with VCP gene mutations." *J Neuropathol Exp Neurol* 66(2): 152-7.
- Neumann, M., R. Rademakers, et al. (2009). "A new subtype of frontotemporal lobar degeneration with FUS pathology." *Brain* 132(Pt 11): 2922-31.
- Neumann, M., S. Roeber, et al. (2009). "Abundant FUS-immunoreactive pathology in neuronal intermediate filament inclusion disease." *Acta Neuropathol* 118(5): 605-16.
- Neumann, M., D. M. Sampathu, et al. (2006). "Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis." *Science* 314(5796): 130-3.
- Perry, R. J. and B. L. Miller (2001). "Behavior and treatment in frontotemporal dementia." *Neurology* 56(11 Suppl 4): S46-51.

- Pick, A. (1892). "Ueber die Beziehungen der senilen Hirnatrophie zur Aphasie." *Prager Medizinische Wochenschrift* 17: 165-167.
- Pick, A. (1906). "Über einen weiteren Symptomenkomplex im Rahmen der Dementia senilis, bedingt durch umschriebene stärkere Hirnatrophie (gemischte Apraxie)." *Monatsschr. Neurol. Psychiat.* 19: 97-108.
- Pickering-Brown, S. M., M. Baker, et al. (2006). "Mutations in progranulin explain atypical phenotypes with variants in MAPT." *Brain* 129(Pt 11): 3124-6.
- Pickering-Brown, S. M., S. Rollinson, et al. (2008). "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* 131(Pt 3): 721-31.
- Pijnenburg, Y. A., E. L. Sampson, et al. (2003). "Vulnerability to neuroleptic side effects in frontotemporal lobar degeneration." *Int J Geriatr Psychiatry* 18(1): 67-72.
- Poorkaj, P., T. D. Bird, et al. (1998). "Tau is a candidate gene for chromosome 17 frontotemporal dementia." *Ann Neurol* 43(6): 815-25.
- Procter, A. W., M. Qurne, et al. (1999). "Neurochemical features of frontotemporal dementia." *Dement Geriatr Cogn Disord* 10 Suppl 1: 80-4.
- Renton, A. E., E. Majounie, et al. (2011). "A Hexanucleotide Repeat Expansion in C9ORF72 Is the Cause of Chromosome 9p21-Linked ALS-FTD." *Neuron*.
- Ringholz, G. M., S. H. Appel, et al. (2005). "Prevalence and patterns of cognitive impairment in sporadic ALS." *Neurology* 65(4): 586-90.
- Ritson, G. P., S. K. Custer, et al. (2010). "TDP-43 mediates degeneration in a novel *Drosophila* model of disease caused by mutations in VCP/p97." *J Neurosci* 30(22): 7729-39.
- Rohrer, J. D., R. Guerreiro, et al. (2009). "The heritability and genetics of frontotemporal lobar degeneration." *Neurology* 73(18): 1451-6.
- Rollinson, S., S. Mead, et al. (2011). "Frontotemporal lobar degeneration genome wide association study replication confirms a risk locus shared with amyotrophic lateral sclerosis." *Neurobiol Aging* 32(4): 758 e1-7.
- Rosso, S. M., L. Donker Kaat, et al. (2003). "Frontotemporal dementia in The Netherlands: patient characteristics and prevalence estimates from a population-based study." *Brain* 126(Pt 9): 2016-22.
- Sampathu, D. M., M. Neumann, et al. (2006). "Pathological heterogeneity of frontotemporal lobar degeneration with ubiquitin-positive inclusions delineated by ubiquitin immunohistochemistry and novel monoclonal antibodies." *Am J Pathol* 169(4): 1343-52.
- Sato, T., S. Takeuchi, et al. (2009). "Axonal ligation induces transient redistribution of TDP-43 in brainstem motor neurons." *Neuroscience* 164(4): 1565-78.
- Schlachetzki, J. C., K. Schmidtke, et al. (2009). "Frequency of progranulin mutations in a German cohort of 79 frontotemporal dementia patients." *J Neurol* 256(12): 2043-51.
- Schroder, R., G. D. Watts, et al. (2005). "Mutant valosin-containing protein causes a novel type of frontotemporal dementia." *Ann Neurol* 57(3): 457-61.
- Schumacher, A., P. Friedrich, et al. (2009). "No association of common VCP variants with sporadic frontotemporal dementia." *Neurobiol Aging* 30(2): 333-5.
- Seelaar, H., W. Kamphorst, et al. (2008). "Distinct genetic forms of frontotemporal dementia." *Neurology* 71(16): 1220-6.

- Shatunov, A., K. Mok, et al. (2010). "Chromosome 9p21 in sporadic amyotrophic lateral sclerosis in the UK and seven other countries: a genome-wide association study." *Lancet Neurol* 9(10): 986-94.
- Skibinski, G., N. J. Parkinson, et al. (2005). "Mutations in the endosomal ESCRTIII-complex subunit CHMP2B in frontotemporal dementia." *Nat Genet* 37(8): 806-8.
- Sleegers, K., N. Brouwers, et al. (2009). "Serum biomarker for progranulin-associated frontotemporal lobar degeneration." *Ann Neurol* 65(5): 603-9.
- Snowden, J., D. Neary, et al. (2007). "Frontotemporal lobar degeneration: clinical and pathological relationships." *Acta Neuropathol* 114(1): 31-8.
- Snowden, J. S., D. Bathgate, et al. (2001). "Distinct behavioural profiles in frontotemporal dementia and semantic dementia." *J Neurol Neurosurg Psychiatry* 70(3): 323-32.
- Snowden, J. S., S. M. Pickering-Brown, et al. (2006). "Progranulin gene mutations associated with frontotemporal dementia and progressive non-fluent aphasia." *Brain* 129(Pt 11): 3091-102.
- Spillantini, M. G., R. A. Crowther, et al. (1998). "Tau pathology in two Dutch families with mutations in the microtubule-binding region of tau." *Am J Pathol* 153(5): 1359-63.
- Spina, S., J. R. Murrell, et al. (2007). "Corticobasal syndrome associated with the A9D Progranulin mutation." *J Neuropathol Exp Neurol* 66(10): 892-900.
- Sreedharan, J. (2008). "TDP-43 mutations in familial and sporadic amyotrophic lateral sclerosis." *Science*.
- Stevens, M., C. M. van Duijn, et al. (1998). "Familial aggregation in frontotemporal dementia." *Neurology* 50(6): 1541-5.
- Strong, M. J., K. Volkening, et al. (2007). "TDP43 is a human low molecular weight neurofilament (hNFL) mRNA-binding protein." *Mol Cell Neurosci* 35(2): 320-7.
- Swanberg, M. M. (2007). "Memantine for behavioral disturbances in frontotemporal dementia: a case series." *Alzheimer Dis Assoc Disord* 21(2): 164-6.
- Swartz, J. R., B. L. Miller, et al. (1997). "Frontotemporal dementia: treatment response to serotonin selective reuptake inhibitors." *J Clin Psychiatry* 58(5): 212-6.
- Urwin, H., A. Authier, et al. (2010). "Disruption of endocytic trafficking in frontotemporal dementia with CHMP2B mutations." *Hum Mol Genet* 19(11): 2228-38.
- Valdmanis, P. N., N. Dupre, et al. (2007). "Three families with amyotrophic lateral sclerosis and frontotemporal dementia with evidence of linkage to chromosome 9p." *Arch Neurol* 64(2): 240-5.
- van der Zee, J., D. Pirici, et al. (2009). "Clinical heterogeneity in 3 unrelated families linked to VCP p.Arg159His." *Neurology* 73(8): 626-32.
- van der Zee, J., H. Urwin, et al. (2008). "CHMP2B C-truncating mutations in frontotemporal lobar degeneration are associated with an aberrant endosomal phenotype in vitro." *Hum Mol Genet* 17(2): 313-22.
- van Es, M. A., J. H. Veldink, et al. (2009). "Genome-wide association study identifies 19p13.3 (UNC13A) and 9p21.2 as susceptibility loci for sporadic amyotrophic lateral sclerosis." *Nat Genet* 41(10): 1083-7.
- Van Langenhove, T., J. van der Zee, et al. (2010). "Genetic contribution of FUS to frontotemporal lobar degeneration." *Neurology* 74(5): 366-71.
- van Swieten, J. C., M. Stevens, et al. (1999). "Phenotypic variation in hereditary frontotemporal dementia with tau mutations." *Ann Neurol* 46(4): 617-26.
- Vance, C., A. Al-Chalabi, et al. (2006). "Familial amyotrophic lateral sclerosis with frontotemporal dementia is linked to a locus on chromosome 9p13.2-21.3." *Brain* 129(Pt 4): 868-76.

- Vance, C., B. Rogelj, et al. (2009). "Mutations in FUS, an RNA processing protein, cause familial amyotrophic lateral sclerosis type 6." *Science* 323(5918): 1208-11.
- Vossel, K. A. and B. L. Miller (2008). "New approaches to the treatment of frontotemporal lobar degeneration." *Curr Opin Neurol* 21(6): 708-16.
- Walker, A. J., S. Meares, et al. (2005). "The differentiation of mild frontotemporal dementia from Alzheimer's disease and healthy aging by neuropsychological tests." *Int Psychogeriatr* 17(1): 57-68.
- Wang, H. Y., I. F. Wang, et al. (2004). "Structural diversity and functional implications of the eukaryotic TDP gene family." *Genomics* 83(1): 130-9.
- Wang, I. F., L. S. Wu, et al. (2008). "TDP-43, the signature protein of FTLD-U, is a neuronal activity-responsive factor." *J Neurochem* 105(3): 797-806.
- Watts, G. D., D. Thomasova, et al. (2007). "Novel VCP mutations in inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia." *Clin Genet* 72(5): 420-6.
- Watts, G. D., J. Wymer, et al. (2004). "Inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia is caused by mutant valosin-containing protein." *Nat Genet* 36(4): 377-81.
- Whitwell, J. L., S. D. Weigand, et al. (2011). "Trajectories of brain and hippocampal atrophy in FTD with mutations in MAPT or GRN." *Neurology* 77(4): 393-8.
- Wider, C., D. W. Dickson, et al. (2009). "Pallidonigral TDP-43 pathology in Perry syndrome." *Parkinsonism Relat Disord* 15(4): 281-6.
- Winton, M. J., L. M. Igaz, et al. (2008). "Disturbance of nuclear and cytoplasmic TAR DNA-binding protein (TDP-43) induces disease-like redistribution, sequestration, and aggregate formation." *J Biol Chem* 283(19): 13302-9.
- Wittenberg, D., K. L. Possin, et al. (2008). "The early neuropsychological and behavioral characteristics of frontotemporal dementia." *Neuropsychol Rev* 18(1): 91-102.
- Yang, Y. and H. P. Schmitt (2001). "Frontotemporal dementia: evidence for impairment of ascending serotonergic but not noradrenergic innervation. Immunocytochemical and quantitative study using a graph method." *Acta Neuropathol* 101(3): 256-70.
- Zakaryan, R. P. and H. Gehring (2006). "Identification and characterization of the nuclear localization/retention signal in the EWS proto-oncoprotein." *J Mol Biol* 363(1): 27-38.

Advanced Understanding of Neurodegenerative Diseases

Edited by Dr Raymond Chuen-Chung Chang

ISBN 978-953-307-529-7

Hard cover, 442 pages

Publisher InTech

Published online 16, December, 2011

Published in print edition December, 2011

Advanced Understanding of Neurodegenerative Diseases focuses on different types of diseases, including Alzheimer's disease, frontotemporal dementia, different tauopathies, Parkinson's disease, prion disease, motor neuron diseases such as multiple sclerosis and spinal muscular atrophy. This book provides a clear explanation of different neurodegenerative diseases with new concepts of understand the etiology, pathological mechanisms, drug screening methodology and new therapeutic interventions. Other chapters discuss how hormones and health food supplements affect disease progression of neurodegenerative diseases. From a more technical point of view, some chapters deal with the aggregation of prion proteins in prion diseases. An additional chapter to discuss application of stem cells. This book is suitable for different readers: college students can use it as a textbook; researchers in academic institutions and pharmaceutical companies can take it as updated research information; health care professionals can take it as a reference book, even patients' families, relatives and friends can take it as a good basis to understand neurodegenerative diseases.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Johannes Schlachetzki (2011). Frontotemporal Lobar Degeneration, Advanced Understanding of Neurodegenerative Diseases, Dr Raymond Chuen-Chung Chang (Ed.), ISBN: 978-953-307-529-7, InTech, Available from: <http://www.intechopen.com/books/advanced-understanding-of-neurodegenerative-diseases/frontotemporal-lobar-degeneration>

INTech
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2011 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](https://creativecommons.org/licenses/by/3.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen