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Frontotemporal Lobar Degeneration

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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 neuroimaiging 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 FTLD. 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 FTLD in the early stage of the disease, differences to other variants of FTLD itself but also to Alzheimer's disease may even out at later time points. The various forms of FTLD 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

FTLD 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 FTLD* (bvFTLD) 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 FTLD

BvFTLD is the most common subtype of FTLD. Patients with bvFTLD 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 bvFTLD.

BvFTLD 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 bvFTLD. In many FTLD 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 form 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 FTLD 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 FTLD 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 FTLD, *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 FTLD 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 FTLD (Procter, Qurne et al. 1999). Treatment of FTLD 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 FTLD (Procter, Qurne et al. 1999; Yang and Schmitt 2001; Franceschi, Anchisi et al. 2005). Selective

Differential diagnosis	Diagnostic work up
Dementia • Alzheimer's disease • Primary progressive aphasia-logopenic • Vascular dementia • Normal pressure hydropcephalus	 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
Affective disorders • Depression • Mania	 Past history, response to antidepressive medication Past history, response to mood stabilizers
Schizophrenia	Past history, response to antipsychotics
Morbus Wilson	CT/MRI, coeruloplasmin
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 efficious 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 antipsychoctics 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 FTLD 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 FTLD 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 bvFTLD 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 FTLD 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 FTLD 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 basalganglia 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 FTLD. 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, Gijselinck 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 FTLD (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 FTLD and 23 % in cases of familial FTLD (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 FTLD groups and 4-10 % in groups of cases of familial FTLD (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, Gijselinck et al. 2006; Gijselinck, 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 FTLD 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 bafiomycin 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 FTLD 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 FTLD (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 bvFTLD (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 FTLD-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 FTLD 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 FTLD-UPS (ubiquitin – proteasomal system). It is noteworthy, that FTLD-UPS also includes cases without *CHMP2B* mutation, suggesting that the full complement of FTLD 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 FTLD-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; Gijselinck, Engelborghs et al. 2010; Shatunov, Mok et al. 2010). Genome – wide linkage studies verified an association familial bvFTLD, FTLD-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 FTLD 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 FTLD-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
MAPT	17q21.1	Microtubule associated protein tau	bvFTLD, FTDP	134	44
PGRN	17q21.31	Progranulin	bvFTLD, PNFA, CBD	231	69
VCP	9p13.3	Valosin-containing protein	IBMPFD	41	17
CHM2B	3p11.2	Charged multivesicular Body Protein 2B	bvFTLD with movement deficits	5	4
TARDBP	1p36.2	TAR DNA-binding protein of 43 kDa (TDP-43)	bvFTLD, FTLD-ALS	92	34
Not determined (C9ORF72)	Linkage to chromosome 9p13.2-21.3	Not determined (*C9ORF72:* uncharacterized)	bvFTLD, FTLD-ALS		

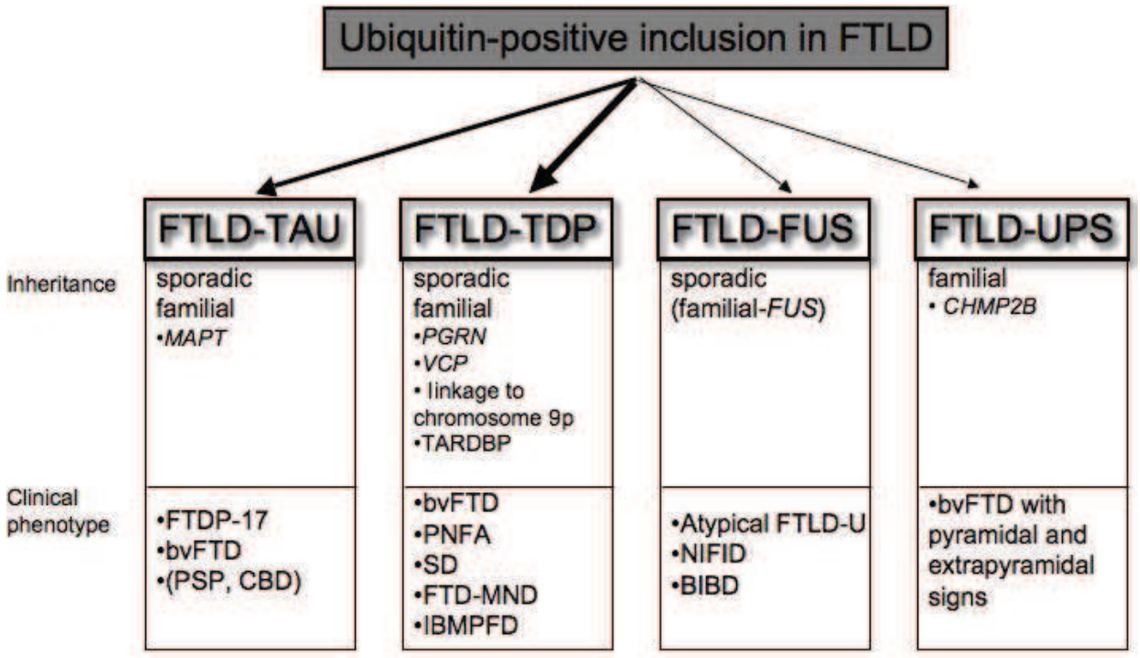
Table 2.

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 FTLD, 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 FTLD, 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 FTLD-TDP pathology is used (Mackenzie, Neumann et al. 2011).

Type A presents mainly cases with bvFTLD 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 bvFTLD and FTLD-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., bvFTLD, 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- ubiqutin 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 intermedate 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 FTLD-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.

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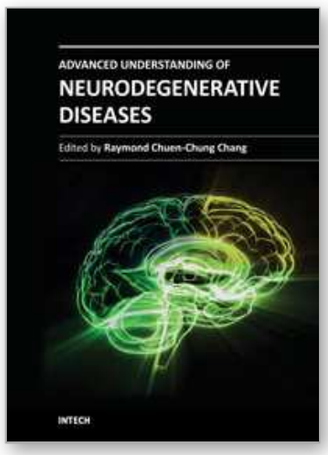

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Advanced Understanding of Neurodegenerative Diseases focuses on different types of diseases, including Alzheimer's disease, frontotemporal dementia, different tauopathies, Parkinson's disease, prion disease, motor neuron diseases such as multiple sclerosis 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.

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