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FTD and ALS: a tale of two diseases

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Abstract

The first reports of disorders that in terms of cognitive and behavioral symptoms resemble frontotemporal dementia (FTD) and in terms of motor symptoms resemble amyotrophic lateral sclerosis (ALS) bring us back to the second half of the 1800s. Over the last 150 years, and especially in the last two decades, there has been growing evidence that FTD signs can be seen in patients primarily diagnosed with ALS, implying clinical overlap among these two disorders. In the last decade pathological investigations and genetic screening have contributed tremendously in elucidating the pathology and genetic variability associated with FTD and ALS. To the most important recent discoveries belong TAR DNA binding protein [TARDBP or TDP-43] and the fused in sarcoma gene [FUS] and their implication in these disorders. FTD and ALS are the focus of this review which aims to 1. summarize clinical features by describing the diagnostic criteria and specific symptomatology, 2. describe the morphological aspects and related pathology, 3. describe the genetic factors associated with the diseases and 4. summarize the current status of clinical trials and treatment options.

A better understanding of the clinical, pathological and genetic features characterizing FTD and ALS will shed light into overlaps among these two disorders and the underpinning mechanisms that contribute to the onset and development. Nevertheless, advancements in the knowledge of the biology of these two disorders will help developing novel and, hopefully, more effective diagnostic and treatment options.

Keywords

ALS; FTD; FUS; motor disease; proteinopathies; TAU; TDP-43; ubiquitin inclusions

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Conflict of interest

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Introduction

Frontotemporal lobar degeneration (FTLD) is second only to Alzheimer's disease (AD) as a cause of dementia in patients less than 65 years of age [1, 2, 3, 4]. Frontotemporal dementia (FTD) (otherwise known as behavioral variant FTD or bv-FTD) represents a vast subgroup within the broad spectrum of neurological disorders that constitute FTLD. Amyotrophic lateral sclerosis (ALS) has mainly been described as a neurological disorder that affects the motor system, but is now recognized as a multisystem neurodegenerative disease due to the fact that other than motor areas of the brain undergo degeneration. Both FTD and ALS are heterogeneous at the clinical, neuropathological and genetic levels and, even though they come across as distinct progressive disorders, there is increasing evidence of the fact that they share some clinical, neuropathological and genetic features. This implies that these two disorders **1.** share neurodegenerative pathways and **2.** may be part of a common spectrum.

The aim of this review is to describe the two disorders from a clinical, pathological and genetic point of view, to highlight commonalities and overlapping features between them and to give an overview of the recent advancements in clinical trials and treatment procedures.

The first reports of neurodegenerative disorders showing bv-FTD like characteristics and ALS like features bring us back to the second half of the 1800s.

In 1892 the neuropsychiatrist Arnold Pick (1851-1924) described a 71 year-old man (the first reported patient with bv-FTD-like clinical features in medical history) showing progressive cognitive impairment together with bouts of aggressiveness [5]. This patient also had aphasia and, after autopsy, brain atrophy in the left hemisphere (temporal lobe) was evident [6, 5]. In 1904 Pick presented the case of a 41 year-old woman showing stereotyped behavior [7]. Pick, later, also described the case of a 75 year-old woman with semantic dementia like symptoms [8]. Considering these historical case reports one can identify Arnold Pick as the father not only of what was going to be called Pick's Disease (PiD), but also of the whole spectrum of FTLD. While Arnold Pick described in detail the clinical features of his patients, Pick bodies, the histopathological hallmark of PiD, were first identified by Alois Alzheimer in 1911 [9]. Pick bodies are distinct spherical argyrophilic inclusions (seen with silver staining) that accumulate in neurons of the frontal lobes; the microtubule associated protein TAU (MAPT) was later shown to be the main component of these inclusions [10], even though also ubiquitin immunoreactive inclusions have been described [2]. The typical Pick type histology is identified by astrocytic gliosis together with intraneuronal inclusions and inflated neurons in all or most cortical layers [2]. In the 80s non-Alzheimer dementia designated as dementia of frontal lobe type (DFT) [11] or frontal lobe non-Alzheimer degeneration with dementia (FLD) [12] was suggested to represent forms of PiD by sharing characteristics of white matter alterations such as gliosis and loss of myelin with PiD. During the 90s, the term Pick's disease was dropped in favor of FTD with or without Pick bodies, while then, in the early 2000s, the term of "Pick's complex" was coined to identify non rare neurodegenerative disorders with overlapping clinical, pathological (tauopathies) and genetic features [8, 13, 14, 15]. PiD is currently considered as a subgroup of FTD [16]; pathological evaluations have shown the presence of Pick bodies in 10-30% of sporadic FTD cases [17].

In 1869, about 20 years earlier than Arnold Pick, a French neurologist, Jean-Martin Charcot (1825-1893), first described amyotrophic lateral sclerosis [18, 19, 20]. Amyotrophic lateral sclerosis is also called as *Maladie de Charcot* (Charcot's disease) or *Lou Gehrig's disease* after the case of the American baseball player who was diagnosed with ALS in 1939 and

died in 1941. The term “amyotrophic” refers to the loss of muscle mass while the term “lateral” refers to the tract where nerves run down both sides of the spinal cord which is one of the sites where neurons undergo degeneration. Finally the term “sclerosis” refers to the scar tissue-like appearance of the spinal cord after degeneration of the descending cerebrospinal tracks. Charcot linked the symptoms of ALS to the motor neurons of the brain and the spinal cord; but he also did mention that non motor areas of the brain might be involved in onset and/or progression of the disorder [18]. In 1981, it was reported that patients with ALS may show FTD signs: 26 sporadic ALS (sALS) cases were associated with dementia and 10 familial ALS (fALS) cases were associated with dementia or parkinsonism [21]. Neuropathologic examination of these cases revealed a mix of typical ALS neuropathology together with **1.** frontal and frontotemporal degeneration and **2.** degeneration of the substantia nigra and globus pallidus [20]. In 1987 a subgroup of FTLD involving frontotemporal grey matter without Alzheimer histological features, frontal lobe degeneration of non-Alzheimer’s type (FLD) was reported to share some similar morphological aspects with the ALS-dementia complex [22]. At the end of the 1980s, the first reports of pathology associated with ubiquitin immunoreactive inclusions in motoneurons were published: a study showed that ubiquitin positive inclusions were found in 31 ALS cases, 4 of which were familial (fALS) [23, 24]. In 1991 and later in 1992, evidence of ubiquitin positive inclusions in the extramotor cortex was shown in both pure ALS patients [25] and ALS patients with dementia [26]. There was increasing evidence of the fact that patients diagnosed with ALS also showed subclinical signs of frontotemporal syndromes such as behavioral, cognitive or language dysfunctions with a frequency varying from 5% up to 40% [20]. Frequency of FTD clinical features in ALS varies in the literature but, currently, it is accepted that some symptoms of FTD can be detected in up to 50% of ALS patients [20, 27, 28, 29, 30]. The clinical overlap between FTD and ALS is also reflected in neuropathology. Ubiquitin inclusions were recognized as the pathological hallmark of FTD combined with ALS during the 90s. It took almost 10 more years to refine these observations and identify, in 2006, the main component of the ubiquitin inclusions in both FTLD-U and ALS patients: the TAR DNA binding protein 43 (TARDBP or TDP-43) [31, 32]. As one can infer from the advances of the last two decades in the field of molecular biology, there has been growing evidence of the fact that FTD and ALS are not only sharing clinical features, but also that the underlying pathology is characterized by a common factor: ubiquitin-TDP-43 neuronal inclusions which show a variable topographic distribution in the brain.

Diagnostic criteria

Diagnostic criteria are fundamental for appropriate diagnostic classification and care of an individual patient. Moreover, based on diagnostic criteria, clinical research can be conducted to refine disease definitions and staging, to better understand the natural history of the disease, to develop more accurate prognosis guidelines and, lastly, to design and perform clinical trials aimed at improving treatment measures.

1. The most commonly used diagnostic criteria for FTD were discussed in 1996 and published in 1998. The Neary criteria [1] were the outcome of a consensus statement based on a conference among international investigators familiar with the disorder; **2.** the El Escorial clinical diagnostic criteria for ALS [33] were revisited and discussed at the 1998 World Federation of Neurology (WFN) ALS meeting at Airlie House in Warrenton, Virginia, USA and published in 2000; **3.** recently, to address the increasing evidence of clinical and pathological overlap of these two disorders, novel consensus criteria for the diagnosis of frontotemporal cognitive and behavioural syndromes in amyotrophic lateral sclerosis were discussed at the research workshop “The second international research workshop on FTD in ALS” in June 2007 and published in 2009 [34].

The diagnostic criteria for FTLT are described in detail by Neary *et al*, 1998 and one can refer for review to [1]. The main aim of these criteria is to identify and list **1.** the neurobehavioral profile necessary to fulfill the diagnostic criteria, **2.** the clinical features that must be present to fulfill the diagnostic criteria **3.** the clinical and physical features that can be supportive of but not necessary for diagnosis (lists 1-3). The focus of the criteria was on the main clinical features of the FTLTs, namely the behavioral variant FTD (bvFTD) and the predominantly receptive and expressive language disorders, semantic dementia (SD) and progressive non fluent aphasia (PNFA) respectively. Also a list of specific features and conditions are summarized in order to identify exclusion criteria (list 4) [1].

The diagnostic criteria for ALS based on the El Escorial revised criteria [33] refer to **1.** the use of clinical and electrophysiological or neuropathologic examination to assess the evidence of lower motor neurons (LMNs) degeneration, **2.** the use of clinical examination to assess evidence of upper motor neurons (UMNs) degeneration and **3.** the monitoring of changes in the disease phenotype based on the spreading of degeneration from one brain area (UMNs and/or LMNs) to other brain areas (cortical areas, frontotemporal lobes, hippocampi). Together with these diagnostic inclusion criteria also exclusion criteria that tend to rule out other disease processes that might be involved in UMN/LMNs are mentioned. Details can be reviewed in [33]. Further, in the case of individuals where clinical and/or electrophysiological criteria are not met or are unclear, genotype and correlation with cognitive dysfunctions can be evaluated (refer to Table III from [20]). Belsh JM criticized these criteria questioning whether they would effectively help and improve diagnosis. His main criticism was that those criteria would still not help in diagnosing the disorder at the early stages of the disease, when they would have been most useful [35].

The novel criteria developed by Strong *et al*, 2009, aim to address and define the syndromes of frontotemporal dysfunction in ALS [34]. These criteria are organized in a fourfold approach that identifies 4 “Axes”: the first defines the different types of motor neuron diseases, the second defines cognitive and behavioral dysfunctions associated with ALS, the third individuates possible non-motor disease manifestations and the fourth describes disease modifiers. Details of the criteria can be reviewed in [34]; as a summary, of relevant interest are: in Axis I the recommendation that first the type and pathology of motor neuron disease in patients should be defined together with specification whether the syndrome is either familial or sporadic and, in familial cases, genetic mutations should be documented. Axis II is where the disorders are defined as pure ALS, as ALS with cognitive impairment (ALSci), as ALS with behavioral impairment (ALSbi) or ALS with FTD signs as of the Neary criteria [1] which is ALS-FTD (table VI of [34] is thoroughly explanatory); Axis III focuses on non-motor disease manifestations, other than FTD-type cognitive and behavioral changes, for example extrapyramidal signs, cerebellar degeneration, autonomic dysfunction, sensory impairment or ocular movement abnormalities. Axis IV takes into account variables like age of onset, disease duration, site of disease onset (limbs or bulbar) and gender which all have different impact on onset and course of the disease (for example limbs onset is less aggressive than bulbar onset).

Moreover it is important, while diagnosing ALS-FTD, to keep into account possible pitfalls in diagnosis due to comorbid conditions like: **1.** other neurological conditions such as cerebrovascular disease or head injury [30, 16, 34], **2.** systemic conditions such as hypothyroidism or diabetes, **3.** pharmacological conditions such as substance/drugs abuse or **4.** psychiatric conditions such as depression, anxiety, psychosis [34]. Specifically, depression has been object of study in both FTD and ALS patients.

The diagnostic criteria for FTD and ALS are summarized in Table 1.

Depression in FTD

Patients with FTD can show a wide range of behavioral and affective symptoms [36]. Together with the previously described clinical features related to personality changes, psychiatric symptoms, such as blunted affect, apathy, lability, anxiety, irritability and euphoria can also be seen [37]. Symptoms of depression are reportedly seen in 40% of cases of FTD [38, 39] and some studies have shown that depressive symptoms in FTD patients can be short-lived but intense [40]. Early FTD could actually be confused with depression [41], so that some individuals are diagnosed and treated for major depression (MDD) before being diagnosed with FTD [41]. However, while patients with FTD frequently have some symptoms that overlap with those of MDD, especially lack of interest in usual activities and emotional withdrawal, they rarely have other symptoms of MDD such as depressed mood, guilt, or poor self-esteem. In fact, rather than poor self-esteem, FTD patients often have an inappropriately high opinion of their abilities [42]. From our experience, healthcare providers unfamiliar with FTD often mistake the apathy observed in FTD as a symptom of MDD. On the other hand, in different types of neurological disorders, symptoms of depression could be a consequence of cortical-subcortical circuit involvement [43, 44, 45, 46, 47] and depressive symptoms may represent a genuine manifestation of the FTD neuropathologic processes [41].

Depression in ALS

Depression in ALS is a complicated clinical and research topic. Having a disabling, fatal illness is a risk factor for depression [48]. Several neurologic disorders, such as Parkinson's disease (PD), Huntington's disease (HD), and multiple sclerosis (MS), appear to increase the incidence of depression through direct neurobiological effects above and beyond the effects of having a chronic disabling illness [49, 50, 51]. In addition, a subset of ALS patients will have symptoms of frontal lobe dysfunction, such as apathy, which can appear to be depressive symptoms. Finally, the symptoms of ALS can interfere with the accurate assessment of depressive symptoms and signs. For example, pseudobulbar affect can complicate the psychiatric assessment, and it can be difficult to detect psychomotor retardation in patients with paralysis. The prevalence of depressive disorders in ALS ranges from near 0% to 75% depending on the method used to assess depressive symptoms [52]. In the subset of patients who had the gold standard of diagnosis, a psychiatric diagnostic interview, the range is narrower and lower than for that of comparable medical disorders [52]. This has led some to hypothesize that ALS may have a 'protective' effect on depression, however others have suggested that this may instead reflect anosodiaphoria associated with frontal lobe dysfunction [53, 20]. In a recent study, we compared the prevalence of psychiatric disorders in patients with ALS and PLS, a related disorder that primarily affects upper motor neurons but which has a more indolent course than ALS [52]. One could hypothesize that if the psychosocial stress of motor neuron disease predisposes patients to depressive disorders, patients with ALS should have a higher prevalence of depressive disorders than patients with PLS. If, however, the prevalence of depressive disorders between the patients with ALS and PLS is similar, it suggests that they share a biological predisposition, whether it stems from upper motor neuron impairment or from extramotor frontal impairment. We found that the prevalence of current depressive disorders in ALS patients was higher than previously reported and similar to that observed in non-neurological medical disorders. By a non-significant trend, the PLS patients had a lower current prevalence of depressive disorders than the ALS patients. These data are consistent with the hypothesis that the psychosocial stress of MND is a risk factor for depression.

Clinical features of FTD and ALS

FTD

Frontotemporal dementia (FTD) is characterized by cognitive and behavioral dysfunction associated with changes in personal and social conduct, whereas language dysfunction is predominant in semantic dementia (SD) or progressive non fluent aphasia (PNFA) [30]. The three syndromes that comprise FTLD are frequently overlapping but, still, a specific feature usually predominates. In this picture, memory and visuospatial abnormalities remain initially intact differentiating FTLD from Alzheimer's disease (AD).

Behavioral variant FTD (bvFTD or simply FTD)—This syndrome is characterized by changes in personality and social conduct, presumably due to frontoinsula and right anterior temporal lobe and superior temporal sulcus (STS) involvement [54, 55]. Patients may also be affected by loss of volition and inertia, perhaps reflecting atrophy in the right dorsolateral prefrontal cortices (DLPFC), disinhibition and tendency to binge eating, possibly reflecting orbitofrontal cortex (OFC) involvement [56], emotional blunting and loss of insight. Deficits in executive functions, such as set sorting, planning, reasoning and problem solving, associated with dysfunction of the frontopolar and DLPFC [57] are also prominent. Patients affected by inertia have a tendency to minimal speech output that can develop into mutism [1]. The characteristics of behavioral variant, which may reflect a predominant site of frontal cortex involvement, can be summarized by three specific subtypes: **1.** disinhibition (the affected individual performs socially inappropriate behaviors, is overactive and distracted and often manifests binge eating), **2.** apathy (the affected individual shows apathy, inertia and loss of volition) and **3.** stereotypic behaviors (the affected individual performs stereotypic ritualistic behaviors) [58, 20].

Semantic dementia—Semantic dementia (SD) shows a severe naming and word comprehension impairment while speech output remains fluent and effortless; also, during speech output, there is a tendency for repetition. Moreover loss of facial recognition (prosopagnosia) can be noticed, presumably due to medial temporal lobe, fusiform gyrus, and anterior temporal pole involvement [59, 1]. Signs of behavioral changes can be seen in SD even if somehow distinctive from those observed in behavioral variant FTD [60]; based on the temporal lobe interested by atrophy, SD can be classified as right or left SD temporal variant [15]. In SD the major superior and inferior temporal white matter connections of the left hemisphere are also predominantly involved [61].

Progressive non fluent aphasia—Progressive non fluent aphasia (PNFA) is a disorder related to the expressive language characterized by effortful non fluent speech production, phonologic and grammatical errors and difficulties not only in word retrieval but also in reading and writing. These deficits are related with atrophy of the areas comprising the phonological loop, especially in the left frontal lobe [62]. Behavioral changes typical of FTD are less common in PNFA [63], but can emerge later [1] PNFA, as other FTLD variants, can develop extrapyramidal features leading to corticobasal syndrome (CBS) [64].

Worldwide FTLD is the second most common form of non-Alzheimer's dementia in the population under 65 years: it represents ~10-20% of all dementias [4] and appears with average onset age of mid to late 50s [65]. The disease can be distinguished in familial or sporadic and occurs equally distributed among men and women [66]. As a familial form of disorder it appears in ~40% of all FTLD cases [67]. Clinically, FTLD can appear alone or in combination with parkinsonism, progressive supranuclear palsy (PSP), corticobasal syndrome (CBS) and motor neuron disease (MND) [30, 68, 69, 15]. For example, in PSP behavioral changes are mild, but apathy can become prominent; in CBS behavioral changes

together with executive dysfunction or non fluent speech can occur. MND is rarely associated with SD, PNFA, PSP and CBS, but usually shows association with features of bvFTD [70, 15].

ALS

ALS is the most common form of adult onset motor neuron degeneration that affects the upper and the lower motor neurons (UMNs and LMNs) and the corticospinal tract [19]. The UMNs are located in the cerebral cortex, while the LMNs are found in the brainstem and the spinal cord [71]; the type of neurons found within the UMNs are the Giant cells of Betz while within the LMNs the alpha motor neurons are found [71]. A reason why the disease affects both types of neurons and these two specific areas of the brain could reside in the fact that the ontogenesis of UMNs and LMNs occurs respectively in the anterior and posterior portion of the neuronal tube, meaning that the progenitor cells are in line with each other and develop as an integrated network [71]. In ALS patients the involvement of the UMNs causes the phenotypes of hyperreflexia together with spasticity while, due to degeneration in the LMNs patients show progressive muscle weakness and muscle wasting [72].

In the US ~30,000 people are affected by ALS with a prevalence of men (60% of cases) [73]. ALS can develop in people while in their 40s until their 70s with an average onset age of ~55 years [73]. Survival for patients with ALS can vary from 2 to 5 years depending on severity and aggressiveness. Death occurs mainly because of respiratory insufficiency and, normally a shorter survival rate (~ 2 years) is observed in patients with ALS-FTD [72].

ALS is familial (fALS) in ~10% of cases therefore presents, mainly, as sporadic form (sALS) [72]. In ~60-70% of cases the disease starts in the limbs while in the remaining ~30-40% it shows bulbar onset. ALS patients who show overtly FTD signs have been reported [72]. Clinical overlap with FTD can be assessed by subclinical frontal dysfunctions or language impairment and now it is considered that up to 40-50% of ALS patients present FTD dysfunctions [74, 75]. In addition to that, occurrence of progressive aphasia phenotypes as well as the presence of frontotemporal atrophy has been noted in ALS patients [30]. Also, it has been reported that in about 5-10% of FTD cases patients develop ALS signs [76, 77, 78, 79], even though other reports claim that in ~50% of FTLN cases [74, 80] subclinical motor neuron degeneration can be found. Probably these discrepancies are due to different methods of assessment and disease definition.

The main clinical characteristics of FTD and ALS (specific and common) are summarized in Table 2.

Neuropathology of FTD and ALS

Symptoms of neurodegenerative diseases represent the phenotypic manifestation of underlying molecular events. There is a direct link between the type of pathology, its distribution in the different areas of the brain and the clinical symptoms. Advancements in the knowledge of the histopathology of neurological disorders will provide us not only with novel elements that will shed light on pathogenic mechanisms and disease phenotype, but will also help identifying common pathways that might explain overlapping clinical features like in the case of FTD and ALS.

Beside the clinical overlaps between FTD and ALS described in the previous sections, there is evidence of shared features also at the molecular level such as the ubiquitin-positive neuronal inclusions that had been described even before the discovery of TDP-43 (19). Different studies, after the first reports of TDP-43 aggregates associated to ubiquitin positive inclusions [31, 32], have supported the idea that there is substantial overlap at the clinical

and pathological level among neurological disorders that share the “TDP-43” proteinopathy [81, 19]. These observations reinforce the idea that ALS together with ALS-FTD/FTD-MND and FTL-D-U could be considered as progressive disorders that are part of a connected wide spectrum of multisystem degeneration [19]; in addition, Strong MJ, 2008 [20] and Strong *et al*, 2009 [3] highlight the fact that there is need for some caution when referring to ALS-D (ALS-dementia) which is a too general nomenclature and should be used only in cases where there are clear signs of FTD, as of the Neary criteria [1], in ALS patients [20].

FTD

FTD is pathologically associated with neurodegeneration that is manifested, grossly, with atrophy of the frontal and the temporal lobes [30, 82]. The morphologic aspects of the neurodegenerative processes can usually be assessed through neuroimaging during the diagnostic phase, while it's through post mortem brain investigation that the pathological evaluation ultimately confirms the diagnosis. Typically, in FTD patients, frontal and temporal areas show shrinkage and spongiform morphology due to extensive neuronal loss. Neuronal loss is progressive and increases during the course of the disease, even though the dynamics of this process may vary among different individuals.

There is a consistent body of literature supporting the fact that, within the three main syndromes of FTD there are somewhat distinct patterns of atrophy; for bvFTD atrophy affects bilateral frontal lobes, specifically the medial frontal lobes and the anterior temporal lobes [15]. SD shows asymmetric atrophy which is detected at the bilateral level in the middle, inferior and medial anterior temporal lobe while left perisylvian atrophy occurs in PNFA [62, 83, 15]. Macroscopic atrophy of basal ganglia and depigmentation of the substantia nigra can be seen in some cases [82]. Interestingly, posterior frontal lobe atrophy has been observed in FTD-MND [84] representing, possibly, a sign of overlapping neuropathological feature between FTD and ALS. In some cases of FTD, that fall under the group of the so called dementia lacking distinctive histopathology (DLDDH), also hippocampal sclerosis has been detected [85]; these observations imply to the heterogeneity and wide spread neuropathology in FTD cases. Further, cases of “DLDDH” have been reported with evidence of motor neuron degeneration and/or corticospinal tract degeneration [15]; but we have to distinguish the cases with hippocampal sclerosis and those with motor neuron and corticospinal tract degeneration because the first type of neuropathology seems more related to FTL-D-U than to FTD-MND [86]. The assessment of the morphology of the brain of a patient with FTD gives insight on the areas of the brain which are affected by degeneration and partly correlate with the clinical manifestation of the disease. Yet, it does not explain the selective vulnerability of particular brain regions to the disease process at the protein and genetic levels. Histological evaluation and immunohistochemistry (IHC) are relatively simple and straight forward techniques that help analyzing tissue structure and identifying proteins or proteins aggregates that are associated with neurological disorders. Ultimately, the pathological identification of the disease is defined by the group of cells being affected and the type of protein aggregates deposited in the brain. Nearly all neurodegenerative disorders are characterized by protein misfolding, protein cleavage, protein phosphorylation, changes in protein solubility and metabolism, and formation of protein aggregates [19, 16].

The abnormal accumulation of protein aggregates is represented, mainly, by cytoplasmic inclusions in neurons and/or glial cells. These lesions interfere with the normal function of these cells and cause cell death in a yet not entirely understood way [16]. Currently ~2/3 of frontotemporal dementias seem to be associated with ubiquitin pathology (FTL-D-U) and ~1/3 with TAU pathology [18].

Among FTD 90% of the different syndromes show either TDP-43 proteinopathy (50%) or tauopathy (40%) [87]. Noteworthy is also the fact that, after the discovery of mutations in *fALS* cases [88, 89] in the fused in sarcoma gene (*FUS*), which encodes for a multifunctional protein part of the heterogeneous nuclear ribonucleoprotein (hnRNP) [90], investigation of *FUS* genetic variability and *FUS* pathology in FTD became of extreme interest. To date different reports have described *FUS* immunoreactive inclusions in FTD subgroups that have been renamed as FTL-D-FUS [91, 92, 93].

In neurological disorders identified by TDP-43 proteinopathy two typical forms of neuronal and/or glial inclusions can be seen: the neuronal cytoplasmic inclusions (NCIs) and the neuronal intranuclear inclusions (NIIs). Further dysmorphic neurites (DNs) are observed [30, 19]. Specifically, based on the type and distribution of the inclusions, four pathological subtypes for FTL-D-U (also referred as FTL-D-TDP since TDP-43 is the pathological hallmark) have been identified [82]: **1.** with long dystrophic neurites, few NCIs and lacking NIIs, **2.** with numerous NCIs, few DNs and lacking NCIIIs (which is the subtype of FTL-D-U that corresponds to FTD-MND) [15] **3.** with numerous NCIs and DNs and occasional NIIs and **4.** with numerous NIIs and DNs and few NCIs.

The cases of FTD presenting TAU pathology are part of the group of tauopathies and present TAU hyperphosphorylated inclusions. TAU pathology is associated to mutations in the microtubule associate protein TAU gene (*MAPT*) but can also be observed in absence of *MAPT* abnormalities. Mutations in *MAPT* determine changes in the protein and cause protein dysfunction: TAU's binding to the microtubule becomes impaired causing the aggregation of TAU into neurofibrillary tangles made of hyperphosphorylated TAU protein [94]. TAU pathology can either be caused by toxic gain of function or harmful loss of function [16]. TAU hyperphosphorylation is mediated by the activity of glycogen synthase kinases (GSKs). Increased expression of GSKs is associated with hyperphosphorylation of TAU leading to disrupted microtubule functioning and consequently to tau pathology [16]. Among the ~10% of FTD disorders that are not associated with TDP-43 or TAU pathology, [15] noteworthy is a subgroup characterized by ubiquitin positive but TDP-43/TAU negative inclusions: "Dementia lacking distinctive histopathology" (DLHDH). This is a subgroup of FTD linked to chromosome 3, FTD3 [95] where neuronal inclusions (present in the cytoplasm of neurons located either in the dentate gyrus or sparse in the frontal or other cortical areas [96]) are characterized by ubiquitin and/or p62 positive inclusions. Based on the fact that these proteins are part of the ubiquitin proteasome system (UPS), a novel nomenclature was suggested for FTD3: FTL-D-UPS [97]. Among FTL-D-UPS a subgroup designated as atypical FTL-D (aFTL-D-U, a sporadic type of FTD with unique clinic-pathological features) showed NCIs immunoreactive for ubiquitin but TDP-43 negative [98]. Investigation of the pathology of 15 aFTL-D-U cases revealed the presence of the fused in sarcoma (*FUS*) protein positive immunoreactivity [91]. In these cases *FUS* immunoreaction was evident but no mutations or genetic abnormalities in *FUS* gene were detected [91]. Another study examining the *FUS* inclusions in FTD-UPS (FTD3 in this case) failed to identify *FUS* positive immunoreaction while ubiquitin positive NCIs were detectable in hippocampal dentate layer and in lesser extent in adjacent neocortex [99]. In another study *FUS* pathology was assessed in a small group of FTL-D with early onset (< 40 years old, severe behavioral changes, negative family history and with caudate atrophy) [93] with a frequency of 3% in FTD cohort, together with TDP-43 negative inclusions. Interestingly, in a report on the pathology of the uncommon neuronal intermediate filament inclusion disease (NIFID) TDP-43 negative and *FUS* positive inclusions were detected (but no mutations in *FUS* gene or abnormalities in *FUS* mRNA expression) [92]. These studies represent a continuum in which *FUS* pathology has been consistently reported in rare subgroups of FTL-D (aFTL-D, NIFID and a subgroup of FTL-D-U with early onset and caudate atrophy) [91, 92, 93] in absence of TDP-43 and TAU positive inclusions. Based on these

histopathological findings the novel subgroup FTL-D-FUS was coined. Noteworthy are the description of the type of pathology associated to FUS inclusions, namely vermiform or C-shaped morphology of the NIIs (which seem to be pathognomic) [93] and the fact that FUS pathology seems to appear early in the process of neurodegeneration: specifically, in NIFID, FUS inclusions were observed before IF inclusions suggesting that FUS loss of function may lead to IF accumulation [92]. Nevertheless, the association of *FUS* gene with FTL-D requires further investigation to shed light on the role of FUS protein in the pathogenesis of this disorder.

ALS

ALS is characterized by motor neurons pathology. Neuropathological hallmarks are: intracellular inclusions like bunina bodies (small eosinophilic neuronal inclusion arranged in beaded chains), ubiquitinated inclusions or skein-like structures, and hyaline conglomerates [100, 34]. The minimum criteria for the neuropathological diagnosis that defines ALS can be summarized as follows: loss of anterior horn cells (AHC), degeneration of the brainstem motor nuclei and of the descending tract of the corticospinal tract involved in motor function [34]. Generally degeneration in ALS takes place in UMNs and either brainstem or spinal LMNs. The cases of ALS with FTL-D cognitive impairment (ALSci) show signs of spongiform degeneration in frontal and precentral gyrus (cortical layers II and III) and diffuse subcortical gliosis [101, 102, 34]. Moreover, neuronal loss in the anterior cingulate gyrus as well as in the substantia nigra and amygdala are observed [34]. Prior to the discovery of TDP-43 associated with the ubiquitin positive inclusions found in ALS-FTD, the pathological features of this disorder included ubiquitin positive and TAU and -synuclein negative inclusions in superficial frontal and temporal cortical layers, entorhinal cortex and dentate granule cells [34]. Since the discovery of TDP-43 the neuropathology of ALS has undergone major revision. In fact, the pathology previously defined by ubiquitin positive inclusions is now identified as aggregates harboring hyperphosphorylated or C-terminally cleaved TDP-43 protein [103]. Pathological investigation of postmortem brain tissues of different small groups of sALS, ALS-FTD and fALS, with or without *SOD-1* mutations, revealed that all groups shared ubiquitin positive inclusions, while also all but the group of fALS with *SOD-1* mutations, showed TDP-43 positive inclusions [104]. These data suggest a pathological overlap among ALS and FTD, specifically ALS without *SOD-1* mutations, due to presence of both ubiquitin and TDP-43 positive inclusions in both types of disorders; familial ALS cases with *SOD-1* mutations, were only ubiquitin positive while TDP-43 negative [104]. This outcome could imply that *SOD-1* mutations may trigger a mechanism of neurodegeneration that excludes TDP-43 accumulation in favor of only ubiquitin aggregates. Even though a minority of cases (ALS with *SOD-1* mutations) seems not to develop TDP-43 pathology, abnormal TDP-43 immunoreactive inclusions are observed in the cytoplasm of neurons and glial cells in sALS, in FTL-D-U patients and in cases of ALS with dementia [31]. This characteristic provides evidence of a possible neuropathological link between the two neurological disorders. Moreover, FUS pathology needs to be assessed in larger number of patients with sALS and fALS to be explanatory of its involvement in pathogenesis: to date FUS positive immunoreactions was reported in LMNs in fALS cases as NCIs [89], while the majority of sALS cases seem to be related to TDP-43 pathology [105].

Genetics of FTD and ALS

A wide spectrum of genes encompassing diverse pathogenic variants has been found to be associated with FTD, ALS and FTD-ALS. Although there is a causal relationship between gene mutations and the pathogenesis of the diseases, there is, on the other hand, abundant evidence of cases with specific pathology (i.e. TAU pathology or TDP-43 pathology) lacking mutations in the genes encoding these proteins: this fact could imply that mutations

contribute partially to pathogenesis exerting their influence on pathogenic pathways that lead to the disease rather than being the direct cause of the disease. Genetics of the two disorders and overlaps are discussed in the following sections.

MAPT

MAPT gene is located on chromosome 17q21.1 and encodes for the 758 aminoacid long TAU protein. TAU protein undergoes complex post-transcriptional changes and can present in 6 different isoforms based on alternative splicing of exons 2, 3 and 10 [106]. TAU's primary function is to bind and stabilize the microtubules located in the axons of the neurons [107]. The microtubule binding domain (MT-binding domain) can be composed of three or four repeats depending on the alternative splicing of exon 10 [108]. Up to 68 variants have been reported in *MAPT* gene [109] causing missense, silent and splice site mutations [108]. These mutations determine abnormalities in the metabolism of the protein: the complex microtubule-TAU becomes disrupted and hyperphosphorylated TAU accumulates in the form of abnormal filaments within neurons and glial cells [110]. Abnormal TAU protein is associated with different neurological disorders which fall under the category of tauopathies due to common pathology defined by TAU aggregates. Tauopathies include Alzheimer's disease (AD) [111], a subgroup of FTD, progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) [110]. TAU plays an important role in the pathogenesis of these disorders [112]. The first mutations in *MAPT* gene were reported in 1998 in some FTLT familial cases [107, 113]. *MAPT* gene has been found mutated in circa 10-30% of familial FTD with concomitant TAU pathology [114, 108]; nevertheless it has been shown that 20-40% of familial FTD cases, even though linked to the same region on chromosome 17, did not reveal mutations in *MAPT* and did not have TAU pathology [115, 116, 117, 118]. Progranulin gene, *PGRN*, was reported to be mutated in these specific FTD cases [119]. Even though, up to date, there is no evidence of mutations in *MAPT* in ALS cases, there is a minority of cases where TAU deposits were detected suggesting that TAU metabolism is associated with a small subpopulation of ALS patients [20]. For example inclusions in neurons and astrocytes of immunoreactive TAU were reported in a case of ALSci within the anterior cingulate gyrus [120]. Moreover, ALS and FTD were shown to coexist within a family (different individuals of the same family were affected by either ALS or FTD) with evident widespread TAU neuropathology [121]. A study revealed that TAU can be hyperphosphorylated at threonine 175 and that, in these conditions, a kinase known to be involved in TAU phosphorylation, GSK-3 β , is overexpressed in ALSci [122]. Phosphorylation of threonine 175 was shown to be associated with the formation of TAU fibrils in cases of ALSci [123]. This finding confirms previous studies reporting correlation between TAU phosphorylation and ALS [124]. In conclusion TAU pathology can be detected in both FTD and ALS (specifically ALSci) cases, regardless of presence or absence of *MAPT* mutations. To date, no *MAPT* mutations have been identified in cases with ALS. Nevertheless the presence of TAU pathology in both neurological disorders strengthens the concept of pathological overlap.

PGRN

Progranulin gene (*PGRN*) is located on chromosome 17q21.32 and codes for a 593 aminoacid long precursor of granulin. Progranulin is a growth factor and is involved in different metabolic events such as wound healing, tumor growth and inflammation [125]. Further, Progranulin activates several kinase-dependant signaling cascades involved in controlling cell cycle and motility, stimulates the induction of vascular endothelial growth factor (VEGF) and seems to have a role in brain development [87]. Mutations in *PGRN*, as mentioned in the previous section, were associated with FTLT linked to chromosome 17 with ubiquitin-positive and TAU-negative inclusions. Currently up to 135 variants have been identified in *PGRN* ([109]; these variants lead to non-sense, frameshift or splice-site

mutations [87]. Also small insertions or deletions have been reported (either in intronic or exonic regions of the gene) [126]. *PGRN* non sense mutations result in aberrant mRNA transcript which undergoes non-sense mediated decay (NMD) [125]. It has been suggested that the reduced levels of expression of functional *PGRN*, haploinsufficiency, contribute to FTLN. Among the FTD patients collected in the USA ~10% of them carry mutations in *PGRN* and ~22% are familial cases [126]. In European cohorts, frequency of *PGRN* mutations seems to comprise 5% of all FTD of which 4-10% are familial cases [125]. The frequency of *PGRN* mutations increases up to 15-24% when considering the whole spectrum of FTLN-U. In fact mutations in *PGRN*, either exonic or intronic, have been associated with FTD, AD, PD, PSP (rarely) and CBS [127, 128, 129, 130, 131]. As of today, *PGRN* mutations related to ALS were reported in one ALS case with V5L missense mutation [132] and in a study involving Belgian and Dutch population where 11 missense mutations in *PGRN* were discovered and 5 of them were predicted to affect the protein function or expression levels [133]. These genetic abnormalities were considered relevant giving *PGRN* a role of disease modifier [133]. No other pathogenic mutations in *PGRN* have been detected in patients with ALS [125]. A recent work in an Italian cohort did not find any association for *PGRN* as major risk factor for ALS in Italian population [134]. Nevertheless, worthy of mentioning is the finding of the heterozygous change (p.S120Y) [134], previously observed in an independent sporadic ALS-FTD patient of European descent [135]. Haplotype analysis revealed a conserved *PGRN* region among these two subjects consistent with possible common ancestral allele [134]; although findings of Del Bo *et al.*, 2009 [134] speak mainly against a role for *PGRN* as a major risk factor in ALS, this specific variant (p.S120Y) might be associated with rare sALS. Moreover, an immunohistochemical study found increased *PGRN* protein presence in spinal cord, brainstem and partially in the motor cortex of ALS patients when compared with normal controls [136]. These data are certainly of interest but the meaning of this association would need to be further investigated. Worth of notice is another mechanism that leads to *PGRN* haploinsufficiency: it is the occurrence of deletion of larger fragments or entire gene, a phenomenon that has been reported by some studies [137, 138]. The investigation of such mechanism should become a routine in research as suggested in van Swieten JC and Heutink P, 2008 [1245]. In conclusion, it has been shown that mutations in *PGRN* are associated with AD and the FTLN spectrum (FTD, PD, PSP, CBS). Specifically, abnormalities in *PGRN* gene are related to FTLN-U (FTLN with ubiquitin inclusions). After the discovery of TDP-43 pathology, being TDP-43 the main protein associated to ubiquitin inclusions in FTLN-U as well as in ALS, one would expect *PGRN* being involved in etiology of ALS. There is no clear genetic association between *PGRN* and ALS since no mutations in *PGRN* have been reported in patients with ALS (beside the isolated cases reported in [132, 133]. Reports supporting pathological cleavage of TDP-43 by caspase 3 due to *PGRN* haploinsufficiency [139], or deletion of *PGRN* in a familial case of FTLN with TDP-43 aggregates raise the question of the role of *PGRN* abnormalities in TDP-43 pathology [137]. In contrast, another group reported that *PGRN* knockdown was associated with caspase mediated processing of TDP-43 as proposed by Zhang *et al.*, 2007 [140]. More recently, an extended study evaluated siRNA-mediated knockdown of *PGRN* in cell cultures and *PGRN* knockdown in a mouse model where no accumulation of TDP-43 C-terminus phosphorylated fragments was identified [141]. These reports suggest that *PGRN* haploinsufficiency might act on a pathway that leads to the accumulation of C-terminus truncated and phosphorylated TDP-43, other than the caspase mediated one. Further investigations and further functional studies will elucidate these pathways.

VCP

Valosin-containing protein gene (*VCP*) is located on chromosome 9p13.3 encoding an 806 amino acid long protein. *VCP* is a member of the AAA-ATPase (ATPases Associated with

various cellular Activities) superfamily involved in different cellular pathways like cell cycle, post-mitotic Golgi reassembly, suppression of apoptosis and DNA-damage response [142, 143, 144]. Further it was reported that VCP is involved in ubiquitin-dependent protein degradation [145]. To date, 14 variants have been reported for *VCP* [109]. The first link between mutations in *VCP* and FTD was described in 2004 when Watts *et al* [146] identified the pathogenic missense mutation R155C; the same mutation was found in other reports that followed [147, 148, 149]. Mutations in this gene were associated with FTL-D (ubiquitin-positive and TAU-negative); *VCP* is therefore considered as the susceptible locus for FTL-D linked to chromosome 9 [150]. There are reports showing linkage of familial cases of FTL-D, MND and FTL-D-MND to chromosome 9 [151, 152]. In fact, beside the reported mutations in *VCP*, also mutations in the intraflagellar transport 74 gene (*IFT74*), located on chromosome 9p21.2, a component of the vesicular transport system along neuronal axons and dendrites were identified [153]. Further, a locus of 8.1 cM between markers D9S157 and D9S1805 on chromosome 9 was reported to be linked to three families with ALS-FTD [154]. Recently, a genome wide association effort [155] identified two SNPs (rs2814707 and rs3849942) located on chromosome 9p21.2, in a linkage study for familial ALS with FTD. All this taken together suggests that the link to chromosome 9 is worth to be followed and investigated because that might explain or give more insights on the overlap among FTD and ALS.

CHMP2B

The charged multivesicular body protein 2B gene (*CHMP2B*) is located on chromosome 3p11.2. CHMP2B protein is composed of 213 amino acids and is a component of the heteromeric ESCRT-III (Endosomal Sorting Complex required for Transport III) complex. CHMP2B is involved in 1. the process of sorting and trafficking surface receptors or proteins into intraluminal vesicles (ILVs) for lysosomal degradation and 2. binding the Vps4 protein responsible for the dissociation of ESCRT components [96, 156]. The first mutation reported in *CHMP2B* was predicted to cause a C-terminus truncated protein: the mutation was described as autosomal-dominantly inherited in a Danish family with FTD, that had previously been reported as linked to chromosome 3, described as a “dementia lacking distinctive histopathology (DLHD)” [95, 157]. Screening of patients with FTD and other neurological disorders for *CHMP2B* variants resulted in the isolation of 10 variants [109]; almost all known mutations were found in FTD cases [158, 159, 160, 161, 162] and one in CBS [163]. Parkinson *et al*, 2006 [164] reported two missense mutations in *CHMP2B* in two ALS patients, while no concomitant mutations were found in *SOD1*, *ANG*, *VAPB* and *dynactin* (other genetic factors known to be involved in ALS, discussed later in this review). More recently another interesting report by Blair *et al* [165] investigated fALS and sALS cases diagnosed with ALS for *CHMP2B* mutations. No pathogenic variants were identified in *CHMP2B*, *SOD1* or *ANG* [165]. This report discourages from considering *CHMP2B* mutations as common cause for fALS or sALS. Further, authors commented on the mutations found by Parkinson *et al* suggesting that those mutations could be “specific” just for these two patients and their families and therefore rare non-pathogenic polymorphisms. Another recent report showed association between genetic variability in *CHMP2B* and ALS cases after the isolation of 4 missense mutations (one of them, p.T104N, novel) in a north English ALS cohort [166]. Despite of all these reports, the involvement of *CHMP2B* mutations in FTD and ALS remains controversial and in need of further investigation [167].

SOD1

Superoxide dismutase 1 gene (*SOD1*) is located on chromosome 21q22.11 and codes for a 154 amino acid long protein. SOD1 binds copper and zinc ions: it is a major cytoplasmic antioxidant enzyme that metabolizes superoxide radicals to molecular oxygen and hydrogen

peroxide, thus providing a defense against oxygen toxicity [168]. Mutations in *SOD1* represent the most common genetic abnormality in fALS [104]. Mutations in *SOD1* in ALS familial cases were first identified in 1993 [169]. More than 120 mutations have been reported, to date, in *SOD1* [170]. A study identified a small frequency of *SOD1* mutations also in sALS cases [171]. To date, pathogenic variants in *SOD1* have been linked to ~20% of fALS and ~1% of sALS cases [172]. Mutations in *SOD1* influence different toxic pathways; for instance, they trigger aberrant mitochondrial function, endoplasmic reticulum stress and excessive production of extracellular superoxide radicals [172]. It has been suggested that mutations in *SOD1* could cause protein misfolding which could reduce nuclear protection; this loss of function might be involved in ALS pathogenesis [173]. Moreover *SOD1* mutations could be involved in disruption of axonal transport: it was shown that fast axonal transport of mitochondria and transport of membrane-bound organelles was impaired in ante and retrograde direction and that mitochondria were damaged [174]. This may render UMNs and LMNs who possess the longest axons in the human body selectively vulnerable to the disease process.

OTHER GENES IN ALS

Apart from *SOD1*, other genes have been shown to be associated with ALS: frameshift mutations causing premature stop codons in *alsin*, a gene located on chromosome 2q33.1, were described in a familial case of ALS2, an autosomal recessive form of juvenile ALS [175, 176]. A missense mutation in *dynactin*, located on chromosome 2p13, was reported to be involved in impaired microtubule binding for the mutated protein [177, 178]; seven missense mutations were reported for *angiogenin* (*ANG*), located on chromosome 14q11.1-q11.2, in 11 sALS and 4 fALS cases [179], while *senataxin* (*SETX*), located on chromosome 9q34.13, was associated with another juvenile form of ALS, ALS4 [180]. A missense mutation in the vesicle-associated membrane protein/synaptobrevin-associated membrane protein B (*VAPB*) gene (*VAPB*), located on chromosome 20q13.33, was associated with severe ALS with rapid progression [181]. For more detailed review of these genes see [170, 182]. Noteworthy are some mutations in *angiogenin* (*ANG*) that have been reported in a small number of ALS cases [105]; first reported by Wu D *et al.*, 2007 [183] in pure ALS, interestingly, the missense mutation K171 was also reported in an Australian study as a non fully penetrant but segregating with disease mutation in a patient with ALS, FTD and parkinsonism [184]. The effect of this mutation was further investigated and revealed to be associated with TDP-43 pathology in an ALS patient [185]. Further, the K171 mutation was confirmed by another study [186] and an additional mutation within the same codon (causing K17E) was reported in 2 sALS cases (1 Irish and 1 Swedish proband) [179]. Moreover, an Italian sALS patient with frontal lobe dysfunction showed mutations in *ANG* [187]; it is yet unclear whether the mutations in *ANG* contribute to the ALS-FTD phenotype. Of further relevance is the fact that *SETX* (previously described) shows strong homology with DNA/RNA helicases, which suggests its involvement in DNA and RNA processing [180]. This is of interest considering that wild type *SETX*, TDP-43 and *FUS* have similar functions: these three proteins, when mutated, could potentially exert similar pathogenic effect. Another gene of interest is the vascular endothelial growth factor (*VEGF*), located on chromosome 6p12 that encodes a 232 amino acid long protein. *VEGF* acts as a growth factor; it is involved in angiogenesis, vasculogenesis and endothelial cell proliferation, it promotes cell migration, it inhibits apoptosis and induces permeabilization of blood vessels [188]. Genetic screening of *VEGF* has revealed genetic variability in its promoter in ALS cases [189]. Reports that followed did not reveal significant association between *VEGF* genetic variability and ALS [190]. Also, another study found no significant association between FTD and the previously reported at risk haplotype [190], other than the AGG haplotype [191]. Nevertheless, investigation of 4 known polymorphisms within the *VEGF* promoter in Italian FTD samples suggested that variability in *VEGF* was statistically

significant, conferring *VEGF* the role of possible susceptibility factor for sporadic FTLD as a modifier of FTLD [192].

All these putative pathogenic mechanisms need to be further investigated.

TDP-43

TAR DNA binding protein gene (*TARDBP* or *TDP-43*) is located on chromosome 1p36.22 and encodes for the 414 amino acid long protein TDP-43. TDP-43 presents with two RNA recognition motifs and a C-terminus glycine-rich region [193]. TDP-43 binds the transactive response (TAR) DNA sequence of the human immunodeficiency virus type 1 and is involved in exon skipping of the cystic fibrosis transmembrane conductance regulator gene and other genes; it has also been reported to be involved in the biogenesis of mRNA [193]. Normal TDP-43 is highly conserved and is ubiquitously expressed in many tissues, including the central nervous system (CNS); within the CNS, TDP-43 is located in the nucleus of neurons and glial cells [193]. To date, 38 variants have been found in TDP-43 [109], 32 of which (~85%) in the glycine-rich region (C-terminus of the protein). Although TDP-43 has been shown to be the main protein associated with the pathology of FTLD-U and ALS, genetic screening has been controversial leaving the question open whether mutations in *TDP-43* are really likely to be the cause of the evident neuropathology. Gijssels et al., 2009 [194] found no pathogenic variants or copy number variations in *TDP-43* within FTD and sALS cases from Belgium. These results showed lack of association between variants and disease, confirming negative results of two other previous studies in FTD cases [195, 196]; Rollinson et al., 2007 suggested that TDP-43 cytoplasmic accumulation is a consequence rather than a cause of FTLD [195]. Nevertheless, in a genetic study on fALS and sALS cohorts authors reported in one fALS case the missense mutation M337V which segregated within the family; interestingly a genome-wide scan performed within this family revealed linkage to chromosome 1p36, which contains *TDP-43* [197]. Two further missense mutations in *TDP-43* were reported in this study, Q331K and G294A, in sALS cases (British and Australian population), while no evidence of these mutations was found in controls [197]. Functional study for M337V and Q331K revealed possible toxic gain of function, therefore, suggesting these variants may have pathogenic effect in ALS [197]. In another study 8 missense mutations were identified within French and Canadian fALS and sALS cases; among these variations, one mutation, A315T, was present in mother and son, therefore segregating with the disease [198]. It is of interest that all of the 8 mutations were found in exon 6 affecting the C-terminus of TDP-43 and probably influencing TDP-43 function and transport [198]. In another study, two further missense mutations that segregated with the disease were reported in fALS cases: G290A and G298S, which were not found in controls [199]. Also in this case authors proposed that these mutations would contribute to both gains and losses of function [199]. In another report no variants were found in sALS cases and authors commented that variants in TDP-43 are unlikely common cause of sALS in north American population [200]. Mutations for *TDP-43* were investigated in German sALS and fALS cases: two missense mutations (G348C and N352S) were identified in two fALS cases while they were not found in controls. N352S specifically was predicted to increase TDP-43 phosphorylation. Authors suggested that mutations in *TDP-43* are rare cause of fALS by influencing directly neurodegeneration in ALS [201]. Three missense mutations (M337V, N345K, and I383V) were reported in further fALS cases [202]; in this study functional analysis revealed an increase of cleaved TDP-43 fragments of 25 kDa, that were considered contributing to neuronal apoptosis [202]. Investigation of French sALS cases revealed 6 missense mutations: 3 of them had already been reported while 3 were new (among these the truncating mutation Y374X) [203]. Investigations of Italian fALS and sALS cohorts identified 12 missense mutations (2/3 in sALS and 1/3 in fALS cases) in exon 6, 9 of which were novel: authors supported the idea

that missense mutations in *TDP-43* may have a causative role in ALS [204]. Another report revealed two novel missense mutations in sALS cases [205]. An interesting report showed the presence of *TDP-43* mutations in two patients with FTLN-MND contributing to the pathological overlap between FTLNs and MNDs [206]. A mutation found in Japanese population (one fALS Japanese case) was associated with increase of TDP-43 phosphorylation [207]. *TDP-43* mutations were then reported in a case other than ALS: K263E missense mutation was associated to a patient with FTD, PSP, and chorea with neuronal and glial TDP-43 immunoreactive deposits in subcortical nuclei and brainstem [208]. Worth of notice was also the report of an increase in mRNA levels of TDP-43 in two individuals from the same family with FTLN-TDP and ALS-FTLDbv, linked to a 3'UTR variant in *TDP-43* [209]. A previously reported mutation, N267S [204], was identified in an Italian patient with FTLDbv and without MND and authors considered that TDP-43 screening should also be extended to FTD cases only [210]. Moreover, screening of non-coding regions of *TDP-43* was performed: variants in the promoter region were found with higher frequency in sALS patient rather than in controls [211], suggesting that those variations might influence aberrant gene regulation in ALS patients. A novel *TDP-43* mutation, S393L, was described in an Italian fALS case, while this mutation was not observed within FTD patients screened in concomitance [212]. Four further mutations in *TDP-43* were associated with fALS and sALS cases [213]; furthermore, the analysis of Italian FTLN patients did not reveal pathogenic mutations in *TDP-43* [214]. Another report identified a novel missense mutation in a sALS patient [215]. A novel fALS related mutation, G294V, was identified in an Australian kindred; authors suggested that this variant might interfere with TDP-43 exon skipping activity [216]. Given the vast amount of data gathered in the last few years on TDP-43 mutations Kabashi E *et al.*, 2010 wanted to evaluate the effects of some of the reported missense mutations. A functional study elucidated the potential role of three of the most consistently reported mutations in *TDP-43*: A315T, G348C and A382T [217]. Differences between wild type TDP-43 and the three mutated forms were barely detectable 1. in transfected cell lines, while 2. perinuclear localization and aggregation of TDP-43 was shown in motor neurons from dissociated spinal cord cultures and 3. shorter motoneuronal axons and swimming deficits were observed in living zebrafish embryos. This approach gave substantial insight into phenotypes associated to 3 missense mutations in *TDP-43* strengthening the concept that *TDP-43* mutations are likely to be associated with toxic gains and losses of function. A recent approach intended to identify the frequency and genetic overlap among AD, PD and ALS based on *TDP-43* screening starting from the observation that TDP-43 aggregates had also been observed in AD and PD (other than FTLN-U and ALS). No variants were found in the cases of AD and PD while 7% of the investigated fALS and 0.5% of the investigated sALS did show mutations (including the two novel N352T and G384R) [218]. Recently *TDP-43* was also screened in a cohort of Chinese extraction showing association between *TDP-43* mutations and ALS; further screening is necessary to assess better the frequency and penetrance of *TDP-43* mutations in Chinese ALS patients [219]. For completeness, a summary on the known mutations in *TDP-43* and possible related pathogenic phenotypic effects are reviewed in [220]. TDP-43 pathology seems to be consistently associated with 50% of FTD cases [87] and with the majority of sALS and fALS cases (except those with *SOD-1* mutations) [104]. The association of *TDP-43* genetic variabilities with FTD and ALS however, remains unequivocal [194, 195, 196, 200, 214]. Most of the mutations in *TDP-43* have been identified in the C-terminus region of the protein (mainly in fALS and less frequently in sALS). Further, in one fALS case a missense mutation in the RNA binding domain has been reported [199]. Interestingly, also variants in the promoter region have been identified in sALS cases [211] and variations in the 3'-UTR have been described in a familial case where family members are affected by either FTD-TDP or ALS-FTLDbv [209]. Mutations in *TDP-43* have rarely been described in FTD cases [210] or FTD-MND or ALS-FTD. Most of *TDP-43* genetic variabilities seem to be related

with fALS cases. Further investigations are needed to shed light on the influence of *TDP-43* genetic variability in FTD, ALS, FTD-MND and ALD-FTD.

FUS

The fused in sarcoma gene (*FUS*) is located on chromosome 16p11.2 and encodes for the 526 amino acid long protein FUS. FUS is a multifunctional protein and is part of the heterogeneous nuclear ribonucleoprotein (hnRNP) complex which is involved in pre-mRNA splicing and in the export of fully processed mRNA to the cytoplasm. FUS has been implicated in cellular processes like regulation of gene expression, maintenance of genomic integrity and mRNA/microRNA processing (221). Mutations in *FUS* have been reported to cause fALS [88, 89]. In their extended study Kwiatkowski *et al.*, 2009 described 13 different variants of which 10 in exon 15, 2 in exon 5 and 1 in exon 6 of *FUS* [88]. The mutations co-segregated with the disease in fALS cases, while none of these variants was found in the sALS cases [88]; among the reported mutations, R521G missense mutation was investigated in a functional study showing aberrant retention of the mutated protein in the cytoplasm of the transfected cells [88]. Vance *et al.*, 2009 reported R521C, R521H in exon 15 and R514G in exon 14 in fALS cases and showed that, in the case of the 2 missense mutations in exon 15, transfected cells were characterized by increased cytoplasmic localization of FUS protein [89]. These studies represent the two first reports that identify *FUS* mutations as potential cause of fALS with a frequency of 4% which is second only to *SOD-1* mutations for fALS cases. After these two pioneering studies, many groups started and are currently screening their samples for *FUS* abnormalities. To date up to 24 variants have been reported for *FUS* gene [109]. Two novel missense mutations, R514S and P525L, were reported by an Italian group in fALS cases from different Italian regions [222]. Further, four *FUS* missense mutations (2 novel and 2 known) were reported in 4% of Italian fALS patients [223]. These variants were not found in normal controls, fact that confers probable pathogenicity to the mutations. Moreover 1-3bp deletion (exon 3) together with 2 missense mutations (both in exon 15) were found in both sALS and fALS in French-Canadian cohorts [224]. In another study exons 5, 6, 14 and 15 were screened in a big cohort of Italian patients (including fALS and sALS cases) [225]. They described 7 missense mutations (G191S, R216C, G225V, G230C, R234C, G507D, and R521C [all novel but the latter one]) in both sALS and fALS Italian patients giving evidence that as in [224] also non familial cases of ALS harboring mutations in *FUS*. Within a study where extended genetic screening in FTLD cases was performed, exon 15 for *FUS* was screened in a cohort of FTD patients: no mutations were found showing that FUS is probably not associated to FTLD or, in case, probably very rarely [226]. A small group of Belgian patients with familial history and *SOD1* negative mutations were evaluated for mutations in *FUS*; the study revealed one missense mutation, R521H, in exon 15 that segregated with the disease [227]. Further, screening of a German cohort of fALS and sALS cases resulted in the identification of the missense mutation R521C that was found in 1 fALS and 1 sALS cases; authors concluded that mutations in *FUS* have low frequency and are probably not a major cause of ALS in German population [228].

Based on the contribution of numerous studies, it seems that the genomic region in exon 15 coding for AA (amino acid) 521 is highly polymorphic. It has been suggested that variants in codons coding for AA 521 are associated, clinically, with early onset ALS and dropped head feature [105]. Blair IP *et al.*, 2009 reported a frequency of 3.2% of *FUS* mutations in fALS cases, while variants in sALS cases were not found [105]. Worth of notice is that, in this study, also one patient with FTD showed *FUS* mutations.

Groups of FTLD, ALS and FTLD-ALS patients were screened in another study: a novel missense mutation, M254V, was found in one FTLD patient, the known R521H mutation was reported for 1 patient with ALS, while no variants were detectable in FTLD-ALS cases.

The missense mutation found in the FTLD patient was not found in normal controls and in silico analysis predicted it being pathogenic [229]. Moreover, in this study, authors reported that they found the insertion/deletion (in/del) of two glycines [88], initially thought to be pathogenic, in asymptomatic individuals as well as in 4 control subjects conferring most probably non pathogenicity to this polymorphism [229].

In another report 6 *FUS* variants were found within sALS patients underlying a link between *FUS* mutations and sALS, even though the overall frequency of *FUS* mutation in sALS remains less than 1% [230]. Further, sporadic FTD patients were tested for association with the tagging single nucleotide polymorphisms (SNPs) rs741810 and rs1052352 for *FUS*: haplotype analysis failed to detect haplotypes associated with FTLD and the authors concluded that *FUS*/TLS is not a susceptibility factor for the development of sporadic FTLD [231]. Ultimately, 2 known (A521C and A521H) and 1 novel mutation (S462F) were reported in fALS cases (cohort from Netherlands) [232]. In addition, highly interestingly, a Q210H polymorphism was identified in 1 proband and 3 healthy control subjects [232].

In summary, questions raise on how mutations in *FUS* should be considered: in fact, we need to take into account that *FUS* might be a highly polymorphic gene and, possibly, in future studies other mutations that were thought to be pathogenic will be found in normal controls or asymptomatic individuals like in the case of Van Langenhove T *et al.*, 2010. More patients need to be screened to reach a better understanding of the involvement of *FUS* in FTD, ALS and ALS-FTD.

Clinical trials & Treatment options

Actual treatments focus mainly on the biochemical changes and abnormalities that accumulate after disease onset. Ideally, treatments for neurological disorders should aim at preventing or slowing down the process of neurodegeneration by targeting upstream events [16]. Since neurodegeneration is largely irreversible and adult neurogenesis is relatively limited, changes preceding neuronal loss need to be identified. Moreover, since clinical symptoms are usually late manifestations of the disease process, it is important to identify disease biomarkers which precede clinical manifestations. To address these requirements not only a close collaboration and exchange of knowledge and information between clinicians and basic researchers, but also major efforts in understanding the underlying pathways that cause neurodegenerative disorders are needed. We find ourselves in a time where acquired technologies allow us, on one side, to investigate the morphology and functionality of different areas of the brain and, on the other, to identify the pathology, the molecular genetics and protein biomarkers (from cerebrospinal fluids, CSF, blood serum/plasma, urine, biopsied tissues [when possible] or postmortem brain/spinal cord tissues) associated with neurological disorders. The proteins (TAU, PGRN, TDP-43) known to be most relevant to FTD and ALS, and their modifications in body fluids should be evaluated as biomarkers to detect disease status as suggested by Kovacs GG *et al.*, 2010 [233]. The collection and analysis of all these data will help in elucidating, one by one, the elements involved in the processes of neurodegeneration.

Taking all this together, we should be able to progressively increase our knowledge about the biology of neurological disorders and, therefore, be able to have a better picture of the micro/macro molecules and the pathologic pathways involved in neurodegeneration. Moving upstream and downstream these pathways through a multidisciplinary approach we should be able to improve diagnosis and treatment options to a highly personalized profile [233].

FTD: Current treatments and future promises

No treatments have been shown to slow the progression of FTLD. However, several medications such as memantine, antidepressants, antipsychotic medications, and cholinesterase inhibitors [222] have been used in FTLD. Most of these medications have been developed for use in other disorders such as psychiatric disorders or Alzheimer's disease. There is minimal evidence of efficacy for the use of these medications in FTD to reduce symptoms, see [234, 235] for reviews. However, new findings on the genetic, biochemical, and neuropathological underpinnings of FTD may suggest new, disease-modifying treatment options for FTD [234, 237]; these measures include treatments that could either inhibit TAU phosphorylation or stabilize microtubules. Hyperphosphorylation of TAU is associated with neurodegenerative processes: treatments targeting elements involved in TAU phosphorylation are being developed. Among them kinase inhibitors like synthase kinase-3 (GSK-3) and cyclin-dependent kinase-5 (cdk-5) that decrease the rate of TAU phosphorylation together with phosphatase enhancers aimed at dephosphorylating TAU are being explored [16]; moreover, investigations on the therapeutic effects of lithium highlighted that lithium can either influence inhibition of GSK-3 and reduce levels of phosphorylated TAU in cultured neurons and in *in vivo* mice models [238, 239]. Interestingly, as reported below in the treatments section for ALS, lithium has shown promise in ALS cases; the fact that the same type of agent may have therapeutic effects in both conditions suggests that it might act at a certain level or point of a not yet elucidated pathologic pathway and interfere, in both cases, with certain steps that lead to the neurodegeneration or pathology. Moreover, methylene blue has shown to inhibit self-aggregation of TAU [240]. Finally, it is from a different field, immunology, that promising methods may arise for the treatment of TAU pathology, specifically, immunization against TAU through vaccination with TAU. In two tangle mouse models, active immunization (targeting an AD phospho-TAU epitope) was shown to reduce TAU aggregates in the brain and to prevent and/or slow the progression of the tangle-related behavioral phenotype (including cognitive impairment) [241]. The mechanism by which these antibodies enter the brain and bind to pathological TAU within neurons is currently under investigation; nevertheless, although the therapeutic effect may in part be due to clearance of extracellular TAU, these findings are promising [241].

ALS: Current treatments and future promises

The only currently available disease modifying drug for ALS is riluzole, a benzodiazepine, which has several mechanisms of action: it has potent glutamate uptake activator activity [242, 243] and stabilizes the inactivated state of voltage-dependant sodium channels [244]. Two randomized double-blind placebo controlled trials and several meta-analyses in patients with ALS have demonstrated a modest benefit in survival [245]. Non-invasive ventilation (most commonly administered as BiPAP, rather than as continuous positive pressure) is also a disease modifying therapy [246, 247], and so is the optimization of nutritional status via percutaneous endoscopic gastrojejunostomy (PEG) [246] and, potentially, exercise [248].

Various drugs are currently being subjected to clinical trials; the list below highlights some of the most promising agents. Arimoclomol is a coinducer of heat shock gene expression; it has slowed the development of motor symptoms and prolonged survival in a transgenic mouse model of ALS [249] and has successfully completed a Phase IIa double-blinded placebo controlled clinical trial [250]. Ceftriaxone is an antibiotic, which increases the glutamate transporter expression that conveys antiapoptotic activity; it has been shown to prolong survival in fALS1 mice [251] and is currently under clinical trial. Edavarone is a free radical scavenger, which has completed a small Phase II trial with some evidence of benefit [252]. Lithium has been shown to up-regulate pro-survival and down-regulate pro-apoptotic pathways [253, 254]; based on these observations it was administered to a genetic

ALS animal model, the G93A mouse, showing potent neuroprotective action and a beneficial effect on survival [255]. Pioglitazone, an agonist of a peroxisome proliferator-activated receptor (PPAR- γ), protects motor neurons against p38-mediated neuronal death and NF- κ B-mediated glial inflammation [256] and has been shown to prolong survival in G93A mice [257, 258].

Vascular Endothelial Growth Factor (VEGF) has been administered intraventricularly in G93A rats and has prolonged survival [259]. G93A/VEGF^{+/+} double-transgenic mice showed delayed motor neuron loss, delayed motor impairment, and prolonged survival compared with G93A single transgenic mice, indicating that neuronal VEGF protects against motor neuron degeneration [260]. Moreover, injection of VEGF-expressing lentiviral vector into various muscles delayed onset and slowed progression of ALS in G93A mice, even when treatment was only initiated at the onset of paralysis [261]. This preclinical evidence lays the ground for VEGF gene therapy trials in ALS.

Passive immunization may also have a role in disease treatment. Based on observations on the toxicity of secreted chromogranins interacting with mutant forms of SOD1 linked to ALS [262], repeated injections of bacterially purified recombinant SOD1 mutant protein as an immunogen were effective in delaying disease onset and extending the life span of G37R SOD1 mice, but not of G93A mice [263].

Finally, big hopes lie in the prospect of stem cell therapy. In 2006, restoration of functional motor units in adult mice by embryonic stem cells injected in the spinal cord and reversal of paralysis was demonstrated [264]. Human mesenchymal stem cell transplantation was shown to extend survival, improve motor performance and decrease inflammation in G93A mice [265]. A subsequent Phase I study has demonstrated that mesenchymal stem cell transplantation into the spinal cord of ALS patients is safe, opening the way for future ALS stem cell based clinical trials [266].

Conclusion

Since the first historic reports of patients affected by FTD and ALS (second half of 1800s), over 150 years of research efforts resulted in the elucidation of many aspects that characterize these neurological disorders. To date, we find ourselves at a stage where we have to critically combine this enormous amount of knowledge and design novel and more effective research paths. Through the careful analysis of the clinical, pathological and genetic aspects related to these disorders we should be able to identify the elements that underlie and explain the symptomatology, which is the macroscopical phenotype and observable outcome of processes that involve molecular genetics and proteomic events (figure 1). Changes in genes and proteins affect complex intra- and extra-cellular *pathways* that, in turn, influence higher biological processes resulting in systemic degeneration. These facts raise important questions, such as: where and when does the disease process begin? Is this process reversible? What *pathways* underlie the symptomatology we observe in neurological disorders? Why certain genes or proteins seem to be more related with FTD and others with ALS? And why some seem to be related with both disorders? Unfolding the genetics of these disorders is the first fundamental step to take in the path of understanding the causes of disease onset and development. Yet, to date, genetics explains only a small percentage of these neurodegenerative disorders and studies that investigate the genetic variability are insufficient to clearly define the disease process, as in the case of TAU pathology in absence of *MAPT* mutations, for example. Therefore we most likely have to develop our research strategies around the *pathways* (figure 1) in order to draw a picture that clarifies and links more effectively the genetic variations to the pathology and to the observable phenotypes.

In literature there is evidence of *clinical* overlap among FTD and ALS like the presence of behavioral, cognitive and language dysfunctions in a portion of patients primarily diagnosed with ALS. Investigation of the *pathology* of these disorders has highlighted the fact that in some cases common areas of the brain undergo degeneration like posterior frontal lobe atrophy in FTD-MND cases, or motor neurons and corticospinal tract in “DLHD” cases, or the precentral gyrus, substantia nigra, amygdala together with subcortical gliosis and neuronal loss in anterior cingulate gyrus in ALS-FTD cases. The overlap becomes evident in *molecular pathology*, where pathologic inclusions are observed, mainly, in neurons and glial cells of patients affected by FTD, ALS or ALS-FTD. Typically, ubiquitin and TDP-43 positive inclusions can be seen in both FTD and ALS, while TAU pathology, which is mainly a hallmark of the FTLD spectrum, can be present, even though rarely, in ALS cases. ALS-FTD cases are mainly associated with ubiquitin positive, TAU and α -synuclein negative inclusions. TDP-43 positive inclusions are mainly associated with FTLD-U, sALS, ALS-FTD and rarely with fALS. Specifically, in ALS cases with *SOD-1* mutations, pathology has been shown to be ubiquitin positive and TDP-43, TAU and α -synuclein negative. FUS pathology, which is TDP-43 and TAU negative, has been shown in rare subgroups of FTLD (aFTLD, NIFND and FTD cases associated with early onset [< 40 years] and severe caudate nucleus atrophy) and in LMNs of mainly fALS cases. *Genetically*, *MAPT* mutations have been reported in FTLD cases but not in ALS cases. Abnormalities in *PGRN* have been associated with FTLD-U and very rarely with ALS having PRGN a possible role in TDP-43 cleavage. Moreover, the link to chromosome 9 seems to be relevant to both FTD and ALS; as suggested by the recent identification of two novel loci in a linkage study on a Belgian FTLD-ALS familial case [267]: one on chromosome 9p23-q21 and one on chromosome 14q31-q32. Although the disease haplotype co-segregated among the affected family members no genetic variants were identified in the genes within the haplotype suggesting that further investigations are needed to elucidate the implication of chromosome 9 (and 14) in these two disorders. Mutations in *SOD-1* explain up to 20% of fALS cases and are associated with ubiquitin positive yet TDP-43, TAU and α -synuclein negative inclusions. This fact raises the question whether abnormal *SOD-1* determines or induces different pathways (oxidative stress?) that encompass pathways resulting in tauopathy or TDP-43 proteinopathy. Also mutations in *ANG* seem to be relevant in ALS, rarely in ALS-FTD and seem to be associated with TDP-43 pathology. Finally, intriguing and yet open to speculations is the role of *TDP-43* and *FUS* genes. Reports on variations in these two genes have been contradictory: some studies showed association between *TDP-43* mutations and ALS (mainly sALS, rarely fALS), some showed association with FTD-MND, FTD/PSP and FTDbv (very rarely) and some did not show any association with neither FTD, nor ALS, nor ALS-FTD. A functional study that analyzed the effects of the three most recurrent missense mutations in *TDP-43* showed that these mutations cause motor dysfunction in living zebrafish embryos [217] suggesting a possible pathogenic role. These findings need to be confirmed in more complex animal models. *FUS* variations have been associated mainly with fALS (4%) and rarely with sALS. *FUS* mutations have been evaluated in functional studies revealing cytoplasmic accumulation of FUS protein in LMNs of fALS cases; mutations in *FUS* seem to be extremely rare (almost absent) in FTLD cases. There have been speculations about the fact that TDP-43 and FUS function as DNA/RNA processing factors and their genetic variability could be responsible for toxic gain of function triggering a disrupted RNA metabolism [268]. Most of the mutations in *TDP-43* and *FUS* appear in the C-terminus region of the protein; mutations in this region could explain the translocation and accumulation in the cytoplasm of the mutated protein. Still, the fact that not always mutations in *TDP-43* and *FUS* are found in FTD, ALS and ALS-FTD, together with the fact that there is increasing evidence of non pathogenic polymorphisms for *FUS* [229] raise the question whether TDP-43 and FUS pathology are primary events in pathogenesis or a byproduct of disease process.

More cases need to be screened and more functional studies need to be performed in order to elucidate the correlations between genetic variations and the clinical manifestation of FTD, ALS and ALS-FTD. More research is needed to understand the *pathways* which are affected by the pathogenic mutations. Elucidating these *pathways* will tremendously impact the development of more sensitive, accurate and effective treatment measures.

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Figure 1.

Table 1

FTD	Ref	ALS	Ref	FTD-ALS	Ref	Comorbid conditions	Ref
bvFTD							
<i>Insidious onset and gradual progression</i>	1	Lower motor neurons (LMNs) degeneration	33	Definition of pathology of motor neuron disease in patients	34	Cerebrovascular disease or head injury	16, 30, 34
<i>Early decline in social interpersonal conduct</i>	1	Upper motor neurons (UMNs) degeneration	33	Specification whether the syndrome is familial or sporadic	34	Hypothyroidism or diabetes	34
<i>Early impairment in regulation of personal conduct</i>	1	Changes in the disease phenotype based on the spreading of degeneration from one brain area (UMNs and/or LMNs) to other brain areas (cortical areas, frontotemporal lobes, hippocampi)	33	In familial cases; assessment of genetic mutations	34	Substance/drugs abuse	34
<i>Early emotional blunting</i>	1			Definition of: 1) pure ALS, 2) ALS with cognitive impairment (ALSci), 3) ALS with behavioral impairment (ALSbi) or ALS with FTD signs as of the Neary criteria	34	Depression, anxiety, psychosis	34
<i>Early loss of insight</i>	1			Exclusion of: 1) extrapyramidal signs, 2) cerebellar degeneration, 3) autonomic dysfunction, 4) sensory impairment, 5) ocular movement abnormalities	34		
SD							
<i>Insidious onset and gradual progression</i>	1			Consideration of variables like: 1) age of onset, 2) disease duration, 3) site of disease onset (limbs or bulbar), 4) gender	34		
<i>Progressive, fluent, empty spontaneous speech</i>	1						
<i>Loss of word meaning, manifest by impaired naming and comprehension</i>	1						
<i>Semantic paraphasias</i>	1						
<i>Impaired recognition of identity of familiar faces</i>	1						
<i>Impaired recognition of object identity</i>	1						
<i>Preserved perceptual matching and drawing reproduction</i>	1						
<i>Preserved single-word repetition</i>	1						

FTD	Ref	ALS	Ref	FTD-ALS	Ref	Comorbid conditions	Ref
Preserved ability to read aloud and write to dictation orthographically regular words	1						
PNFA		1					
Insidious onset and gradual progression	1						
Nonfluent spontaneous speech with at least one of the following: agrammatism, phonemic paraphasias, anomia	1						

Table 2

FTD		FTD-ALS		ALS	
Specific features	Reference	Common features	Reference	Specific features	Reference
Behavioral variant	1	Subclinical frontal dysfunction	74, 75	Hyperreflexia	72
changes in personality and social conduct	1				
loss of volition and inertia	1	Language impairment	74, 75	Spasticity	72
disinhibition and tendency to binge eating	1				
emotional blunting and loss of insight	1	Progressive aphasia phenotypes	30	Progressive muscle weakness	72
impaired planning, reasoning and problem solving	1				
addiction / aggressive behavior	1			Progressive muscle wasting	72
Language dysfunctions	1			Respiratory failure	72
Semantic dementia	1				
severe naming and word comprehension impairment	1				
loss of facial recognition (prosopagnosia)	1				
speech is fluent but with no content	1				
Progressive non fluent aphasia	1				
effortful non fluent speech output leading to mutism	1				
phonologic and grammatical errors	1				
difficulties in word retrieval, reading and writing	1				