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Frontotemporal dementia: a bridge between dementia and neuromuscular disease

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Abstract

The concept that frontotemporal dementia (FTD) is a purely "cortical" dementia has largely been refuted by the recognition of its close association with motor neuron disease, and the identification of transactive response DNA-binding protein 43 (TDP-43) as a major pathological substrate underlying both diseases. Genetic findings have transformed this field and revealed connections between disorders that were previous thought clinically unrelated. The discovery of the C9ORF72 locus as responsible for majority of hereditary FTD, ALS and FTD-ALS cases and the understanding that repeat-containing RNA plays a crucial role in pathogenesis of both disorders has paved the way for development of potential biomarkers and therapeutic targets for these devastating diseases. In this review, we summarize the historical aspects leading up to our current understanding of the genetic, clinical and neuropathological overlap between FTD and ALS, and include brief discussions on chronic traumatic encephalopathy (CTE) given its association with TDP-43 pathology, increased dementia risk and reports of ALS in CTE patients. Additionally we describe other genetic associations between dementia and neuromuscular disease, such as inclusion body myositis with Paget's disease and frontotemporal dementia (IBMPFD).

Keywords

frontotemporal dementia; amyotrophic lateral sclerosis; motor neuron disease; neuromuscular disease; C9ORF72

Introduction

Frontotemporal dementia (FTD) is a progressive neurodegenerative condition characterised by selective involvement of the frontal and temporal lobes, that is associated with changes in behaviour, personality, frontal executive deficits and language dysfunction. Previously classified as a "cortical dementia", it is now clear that FTD often occurs in association with motor neuron disease (FTD-MND) and amyotrophic lateral sclerosis (ALS).[1] As will be described, the recent discovery of a gene that can cause both FTD and ALS, *C9ORF72*, has

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transformed the way that these two conditions are being considered, from both a mechanistic and therapeutic perspective. Similarly, mutations in the valosin containing protein gene (*VCP*) cause, FTD, ALS, inclusion body myopathy and Paget's disease of bone (IBMPFD).[2,3] In this review we describe the clinical, genetic and pathological features of FTD subtypes linked to neuromuscular disease and discuss the implications of these findings for future therapeutic efforts for these conditions.

The first description of FTD came from Arnold Pick in 1892, who reported upon a patient with progressive aphasia and anterior temporal lobar atrophy.[4] Neuropathological findings of argyrophilic neuronal inclusions (also known as 'Pick bodies') in a patient with this syndrome were later reported by Alois Alzheimer in 1911.[5] Once considered rare, FTD is now recognized as the second most common early-onset dementia under 65 years of age,[6] and there is clinical and neuropathological evidence that FTD also occurs in the very old.[7] The term FTD is used to describe patients with three distinct clinical syndromes in whom non-Alzheimer's disease pathology is expected. These FTD subtypes include behavioral variant FTD (bvFTD), a disorder with prominent behavioral abnormalities and two language variants - semantic variant primary progressive aphasia (svPPA) and non-fluent variant PPA (nfvPPA). The most common FTD subtype, bvFTD, manifests with disinhibition, compulsive or perseverative behaviour, overeating, apathy and emotional blunting. Cortical atrophy is most severe in the frontal and anterior temporal lobes, often worse on the right than on the left side. The svPPA patients exhibit loss of conceptual knowledge for words (left-sided degeneration) or faces and people (right-sided degeneration) due to selective involvement of the anterior temporal lobes. nfvPPA is characterized by agrammatic, non-fluent language output and apraxia of speech.[8]

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease that targets motor neurones in the brain and spinal cord, leading to paralysis and ultimately death within 3 years from onset.[9] It is now understood to be a complex multisystem neurodegenerative disease[10] due to the fact that areas other than the motor cortices of the brain undergo degeneration. While various genes involved in familial forms of ALS have been identified, roughly 90% of cases of ALS are sporadic. The early literature on ALS beginning in the 1880s, recognized that dementia often accompanied ALS,[11] although this association was largely neglected until recent years. More than 100 years after the findings of Marie and Reynolds, AJ Hudson rekindled awareness of the links between ALS and dementia writing about ALS and dementia on Guam, and ALS and dementia in specific families.[12] This dementia-ALS- parkinsonian syndrome found on Guam has almost completely disappeared,[13] leaving questions about its etiology unanswered, although genetic and environmental etiologies have been suggested. In 1993 mutations in superoxide dismutase 1 gene (*SOD1*) became the first known genetic cause of familial ALS.[14] These mutations account for approximately 10% of all familial ALS cases. While this mutation causes ALS, an association with FTD is uncommon[15] and therefore not the focus of this review.

The modern age in FTD-MND began in 1990 when Mitsuyama[16] reported 71 patients with a presenile dementia and motor neuron disease. The strong association between dementia and MND and the large number of cases reported by Mitsuyama,[16] marked a paradigm shift for the field. Around the same time, Neary and colleagues described four patients with rapidly

progressive dementia in association with clinical features of MND. The pattern of dementia indicated frontal lobe dysfunction, and was confirmed with evidence of reduced tracer uptake in the frontal lobes on SPECT imaging. Autopsy of 2 patients revealed frontal lobe atrophy and spinal cord changes consistent with MND, with clinical and pathological changes distinctive from those seen in AD.[17] This work helped clarify that ALS was associated with a specific type of dementia associated with frontal lobe dysfunction.

The realization that FTD-MND had distinctive neuropathology began in the 1980s with the first reports of ubiquitin-positive immunoreactive inclusions in the cytoplasm of motor neurons (including familial ALS cases).[18,19] Additionally, evidence of ubiquitin-positive inclusions in the extra-motor cortex was shown in both pure ALS patients[20] and ALS patients with dementia.[21] These ubiquitin-positive inclusions became the pathological hallmark of the combined FTD-MND syndrome. Despite this plethora of reports, there was controversy surrounding the concept of a link between both diseases, particularly with the neuromuscular community, due to the conventional view of MND as a disease confined to the motor system. With the report of Lomen-Hoerth and colleagues[22] that 15% of patients of FTD suffered from ALS, it became apparent that these two conditions were strongly linked. Especially important in the determining the link between FTD and MND was the identification of the transactive response DNA-binding protein 43 (TDP-43) in 2006 as the major inclusion protein associated with ubiquitinated inclusions in the vast majority of ALS patients, and in the most common pathological subtype of FTD, now referred to as frontotemporal lobar degeneration with TDP-43 pathology (FTLD-TDP).[23,24] The significance of this finding was initially challenged by traditional members of the ALS community, entrenched in *SOD1* mouse models of ALS where TDP-43 was not present. Yet, the strong association between FTD, ALS and TDP-43 is now widely accepted.

Epidemiology

The high rate of FTD misdiagnosis has made it challenging to determine its exact prevalence and incidence, and only a few studies have attempted to do so. European studies estimated the prevalence of FTD at 15–22 per 100,000 inhabitants aged 45–64 years, similar to the prevalence of early-onset AD in this age group.[6,25,26] A Dutch study found a lower prevalence of FTD relative to AD at 9.4 per 100,000 in an older age group ranging from 60–69 years, consistent with some pathological series.[27] Two studies reported incidence of FTD at 3.5–4.1 cases per 100,000 person-years in the age group 45–64 years,[28,29] with no obvious gender differences.[27,29–31] The mean age of onset of FTD is typically in the fifth to seventh decades of life[32] with approximately 10% having an onset over 70 years.[33]. Onset may begin as early as the third decade and as late as after the ninth decade; with the prevalence in older age groups likely to be underestimated.[34] Median survival in FTD has been estimated at 6–11 years from symptom onset and 3–4 years from diagnosis.[35–37] In our centre, bvFTD has been found to be associated with the shortest survival (median 8.7 years from onset), svPPA with the longest survival (11.9 years) and nfvPPA with intermediate survival (9.4 years),[36] contrasting with that of Hodges et al. who reported the longest survival in nfvPPA (mean 10.6 years from onset) followed by bvFTD (8.2 years) and SD (6.9 years).[35] The wide range of disease duration (2–20 years) is likely to reflect the wide differences in underlying pathology.[33,35] Survival appears to be shorter and decline more

rapid compared to Alzheimer's disease,[36] and across centres, the presence of MND is associated with early mortality (2.4–4.9 years from onset and 1.2–1.4 years from diagnosis).[35,36]

The frequency of FTD in ALS patients varies in the literature, with symptoms of FTD seen in 5–50% of ALS patients.[1,22,38] Similarly, approximately 15% of FTD patients develop clinical symptoms of motor neuron dysfunction.[1] Other studies have reported the incidence of FTD in patients with bulbar-onset ALS as high as 48%.[39] While the exact phenotype and natural history of impaired cognition in ALS remain unclear due to heterogeneity in patient ascertainment and methods used to assess cognition, current estimates suggest that more than half of patients with ALS have cognitive impairment. In two large epidemiologic studies, the occurrence of mild cognitive impairment has been reported in up to 36% and 51% of patients with sporadic ALS, respectively.[40,41] Thus, reports of the frequency, severity, and type of cognitive impairment in ALS patients vary substantially, and large population-based clinical studies of the prevalence and natural history of cognitive decline in ALS need to be performed.

In addition to familial associations between ALS and FTD, sporadic cases of FTD in association with ALS also seem to be common,[42] although the prevalence and etiology for this co-association remains understudied. In some instances, FTD precedes ALS by many years; in others, ALS precedes FTD.[43] It has been noted that a percentage of ALS patients with no previous diagnosis of FTD have early behavioural changes preceding the onset of the symptoms of ALS. Although the behavioural changes may not justify a diagnosis of FTD, the changes can be noticeable, disturbing to the family, and undiagnosed.[44] Several suggested risk factors for dementia in ALS include older age, male sex, low education, family history of dementia, low forced vital capacity, pseudobulbar palsy, and bulbar site of onset,[22,39,40,45] but these associations have not been reported consistently.

Pathological substrates underlying the link between frontotemporal dementias and neuromuscular disease

Frontotemporal lobar degeneration (FTLD)

Frontotemporal lobar degeneration, or FTLD, is the common underlying pathology of clinical FTD subtypes, as well as syndromes including ALS, progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD). FTLD can be divided into two major subtypes: FTLD with tau-positive inclusions (FTLD-tau); and FTLD with ubiquitin-positive and TDP-43-positive but tau-negative inclusions (FTLD-TDP).[46] Roughly 90% of FTD syndromes show either TDP-43 proteinopathy (50%) or tauopathy (40%).[47] Consensus opinion currently recognises five major pathological subtypes of FTLD (FTLD-tau, FTLD-TDP, FTLD-FUS, FTLD-UPS and FTLD-no inclusions or FTLD-no inclusions).[46] FTLD-TDP appears to be the primary pathology underlying the overlap between FTD and motor neuron disease, and as such, will be the focus of this pathological discussion.

FTLD-TDP - History and classification

In 2006, two papers by Sampathu et al and Mackenzie et al were published, each describing pathological heterogeneity in cases of FTLD with ubiquitin-positive, tau-negative inclusions (FTLD-U).[48,49] Shortly thereafter, further work by Neumann et al. led to the identification of the transactive response DNA-binding protein with MW 43 kD (TDP-43) as the ubiquitinated pathological protein in most cases of FTLD-U as well as the majority of sporadic ALS and some familial ALS cases.[23] TDP-43 pathology is present in 90% of ubiquitin-positive FTLD cases and non-SOD1 ALS cases with FUS-positive inclusions accounting for the majority of remaining ubiquitin-positive TDP-43 negative inclusions.[23,50,51] A fourth FTLD-U subtype with TDP-43 pathology was described, associated with the familial syndrome of inclusion body myopathy with Paget's disease of bone and FTD caused by mutations in the *VCP* gene, as described earlier.[52] As a result, cases of FTLD with TDP-43 pathology are now designated as FTLD-TDP and the term FTLD-U is no longer recommended.[24] The two different classification systems for FTLD-U/FTLD-TDP, however, continued to be a source of confusion and to resolve this issue, the principal authors of the original two papers proposed a new classification for FTLD-TDP pathology to provide a single harmonized system. At autopsy, most FTD-ALS cases have neuronal cytoplasmic inclusions immunoreactive for both ubiquitin and TDP, previously classified as FTLD-TDP type 3 according to the Mackenzie classification[24,53] or type 2 according to the Sampathu classification,[48] but now known as FTLD-TDP type B in the new harmonized classification.[54]

FTLD-FUS, FTLD-UPS and FTLD-ni

Approximately 6–20% of FTLD disorders are not associated with TDP-43 or tau pathology, but are characterized by ubiquitin-positive, TDP-43/tau negative inclusions. Many such cases have shown immunoreactivity with the fused-in-sarcoma (FUS) antibody,[50,55] but none of the FTLD-FUS cases had *FUS* gene mutations.[56] The FUS protein is involved in DNA repair and regulation of RNA splicing,[57] and vermiform or C-shaped morphology of the intranuclear inclusions appear to be pathognomic of this subtype.[55] FTLD-FUS cases are characterized by a young age at onset, behavioural variant of FTD, negative family history and caudate atrophy on MRI.[55,58] FUS-positive inclusions are also found in patients with neuronal filament inclusion disease (NIFID), who mainly present with a behavioural variant of FTD, rapid clinical course, negative family history and pyramidal and/or extrapyramidal symptoms.[59] Altogether, these studies represent a continuum in which FUS pathology has been consistently reported in rare subgroups of FTLD in the absence of TDP-43 and tau-positive inclusions. Finally, cases of ubiquitin-positive, TDP-43 and FUS-negative inclusions have been termed FTLD-UPS cases. Most of these cases carry a *CHMP2B* mutation,[60] but a few do not.[56]

Genetics underlying the link between frontotemporal dementias and neuromuscular disease

Recent advances in genetics have furthered our insight into the clinical and pathological link between the frontotemporal dementias and neuromuscular disease. Out of all the relevant genes and genetic mutations identified in the last few years, the most important discovery

remains that of the *C9ORF72* locus on chromosome 9p, responsible for a majority of the hereditary cases of FTD, ALS and FTD-ALS. Before the identification of *C9ORF72*, only 20–30% of familial ALS cases were explained by mutations in the superoxide dismutase-1 gene (*SOD1*), and the genes encoding TDP-43 (*TARDBP*) and fused in sarcoma (*FUS*). Mutations in *TARDBP* are responsible for 4–6% of cases of non-*SOD1* familial ALS and 1% of apparently sporadic ALS.[61] On rare occasions mutations in *TARDBP* cause FTD or corticobasal syndrome.[62] Mutations in *FUS* are causative of approximately 1 and 4% of apparent sALS and fALS respectively.

About 40% of patients with bvFTD have a positive family history, but a family history of dementia is much lower in patients with svPPA and nfPPA.[33,63–66] In 10% of all FTD patients, family history is consistent with an autosomal dominant inheritance.[33,64,66] The majority of families with autosomal dominant FTD have a mutation in one of three genes; the microtubule-associated-protein-tau gene (*MAPT*), the progranulin gene (*GRN*) and the *C9ORF72* gene. The co-occurrence of ALS and MND were very low in *GRN* carriers.[67] In another study of 97 gene carriers, although information was sparse on some patients with MND, the authors concluded that MND is a bona fide feature of some cases of *PGRN*+ FTLDTDP.[68] In other families with tau mutation MND is reported in a subset of patients.[69] Because *MAPT* and *GRN* are so rarely associated with MND they are not discussed further in this review.

C9ORF72 or "C9FTLD/ALS", Chr9p21.2

Historical aspects of the C9ORF72 discovery—A locus on chromosome 9 in the 9p21.2-p13.3 region, first described in two independent reports by Vance et al. and Morita et al. in 2006,[70,71] was found to contain a gene likely responsible for a substantial proportion of autosomal dominant FTD-ALS cases. Subsequently, linkage to the same chromosome 9p region was found in additional independent FTD-ALS kindreds.[72–74] defining a shared candidate region of 7.7 Mb containing 52 candidate genes.[75] In 2011, Boxer et al described a new FTD-ALS family definitively linked to chromosome 9p with novel clinical, neuroimaging and neuropathological findings. A consistent and unique aspect of the neuropathology was the presence of some NCI and neurites that labelled for ubiquitin and p62 but not TDP-43, suggesting that some protein in addition to TDP-43 was contributing to this clinico-pathological entity.[76] Soon afterwards, two groups independently identified the cause of the chromosome 9 linked FTD and ALS to be an expansion of a GGGGCC hexanucleotide repeat in the chromosome 9 open reading frame 72 gene (*C9ORF72*) (now commonly known as C9FTLD/ALS), publishing their findings in Neuron.[77,78] The GGGGCC hexanucleotide repeat is located between two five prime non-coding exons of *C9ORF72* (a gene involved in RNA metabolism). This important discovery raised new hope with clinicians and researchers by providing novel avenues for studying the pathogenesis of ALS and FTD.

Epidemiology of C9ORF72 repeat expansions—While a repeat length of greater than 30 has arbitrarily been defined as pathogenic in some studies; it remains unknown how many repeats are truly needed to cause disease. In most healthy individuals, repeat lengths with a maximum of 20 repeats are found; whereas in FTD and ALS patients disease-

associated expansions of a few hundred to several thousand repeats have been identified using southern blotting techniques. Most research laboratories now use PCR-based methods combining amplicon-length analysis and repeat-primed PCR to determine the presence of pathogenic repeat expansions as recommended by a blinded international study.[79] Using these methods, many cohorts of FTD patients have now been screened, and it has been established that the *C9ORF72* expansion is the most frequent mutation associated with familial cases of FTD and ALS-FTD, accounting for roughly 25% of familial FTD,[80] about 40% of familial ALS,[78] and 6% of sporadic FTD cases. Frequency varies widely across different populations, with the highest frequencies in geographically isolated populations such as Finland (29%)[78] probably due to a founder effect, and the lowest frequency found in the Netherlands (2.2%).[80] The mutation is most frequently found in Caucasian populations, although the expansion has recently been shown in a few Chinese cases, one with sporadic FTD and two kindreds with familial ALS–FTD.[81,82]

In ALS, *C9ORF72* repeat expansions are even more common. In a Northern England population, *C9ORF72* expansions were found to be present in 43% of ALS cases with an identifiable family history and in 7% of apparently sporadic cases.[83] The frequency varies globally: *C9ORF72* expansions were found in 61% of familial ALS and 19% of sporadic ALS patients in Finland, 22% of familial ALS cases in Germany and only 3.4% in Japan.[80,84] Prevalence has been found to be as high as 83% and 73% in Belgian and Swedish cohorts, respectively.[77,78,80,85–88] The apparent correlation of expansion frequency with distance from Scandinavia is consistent with a suggested common founder carrying the pathogenic mutation approximately 100 (or even more than 250) generations ago in Northern Europe, with this expansion then spreading across the globe.[80,88]

Estimates suggest that *C9ORF72* expansions are rarely penetrant at <35 years, 50% penetrant by 58 years, and usually >95% penetrant at 80 years,[80,89] although the penetrance may not actually reach 100% at 80 years, as carriers of the expansion without the clinical phenotype have been reported over the age of 80 years.[90] The high frequency of sporadic FTD and ALS patients carrying *C9ORF72* repeat expansions provides further support for the idea of reduced penetrance, even at old age, and suggests that other genetic and environmental factors may contribute to the disease penetrance and presentation. Finally, two Italian studies investigated the possibility of anticipation in *C9ORF72* carriers, and found that *C9ORF72*-related FTD families showed possible evidence of anticipation with a mean difference in age of onset between the parent and offspring of 9.8 years; with age of onset 7 years earlier in the subsequent generation in Italian ALS cases.[89,91] Chio et al[91] stress that care is required in interpreting these data because of the small cohort studied and because the individual kindreds were not sufficiently detailed to detect an effect beyond two generations. Southern blot analysis to confirm repeat expansion size was not performed in their cohort at the time due to lack of sufficient quantities of DNA required.

Clinical phenotypes of C9FTLD/ALS—The age at onset and disease duration appear to be highly variable in *C9ORF72* repeat expansion carriers, even within a single family. The age at onset ranges from 27 to 83 years, with disease duration varying between 3 and 264 months.[80,92,93] *C9ORF72*-related ALS cases tended to have an earlier age of onset and shorter disease duration compared with ALS patients who do not carry the expansion,

although this was not found in all cohorts.[83,94] With regards to prognosis, data suggests *C9ORF72*-related ALS has a shorter survival than non-*C9ORF72* ALS.[83,94,95] Gender may also play a role as male *C9ORF72*-related ALS cases have been reported to have a younger age of onset than non-*C9ORF72* ALS cases.[96]

C9ORF72-related FTD most commonly presents with the behavioural variant syndrome, but memory complaints are reported at presentation by one-half of the patients in one study.[97] *C9ORF72* mutation patients also appeared to have a higher prevalence of psychosis, hallucinations (both visual and auditory) and delusions, compared with sporadic FTD patients.[98] A British study found that one-third of the *C9ORF72*-related FTD cases presented with psychosis, compared to only 4% in the non-*C9ORF72* cases.[99] Similarly, a very high psychosis rate was found in a San Francisco cohort.[100] Therefore, the presence of psychiatric symptoms in the context of FTD-ALS should prompt consideration of a *C9ORF72* repeat expansion.[101] nfvPPA is the second most common FTD variant associated with *C9ORF72* expansions, while svPPA has rarely been associated with *C9ORF72* expansions.[97,99]

The clinical phenotype of *C9ORF72*-related FTD appears to be somewhat similar to FTD caused by mutations in *GRN* and *MAPT*, but there are subtle differences across these genes. One study showed that the *C9ORF72*- related FTD cases showed an earlier age of onset than *GRN* mutation carriers, whilst survival was similar..[102] In our experience, *C90RF72* tends to cause less frontotemporal atrophy than do the other genes, but often show subtle parieto-occipital, thalamic and cerebellar atrophy. All ALS regional phenotypes may be associated with *C9ORF72* repeat expansions, but the most frequent phenotype (over 40%) appears to be bulbar-onset ALS,[83] higher than the expected frequency of 19–30%.[103] Millecamps et al. compared phenotypic differences between *C9ORF72*-related ALS and other ALS-causing genes, and found that *C9ORF72*-related cases had a significantly higher incidence of bulbar onset compared to ALS cases with mutations in *SOD1, TARDBP, FUS* and other familial ALS cases.[104] Other phenotypes such as progressive muscular atrophy (PMA) and primary lateral sclerosis (PLS) form part of the MND spectrum of disease; however, screening for the *C9ORF72* expansion found the expanded repeats at relatively low frequencies in PMA (1.6%) and PLS (0.9%) patients.[105] ALS cases with the repeat expansion show a higher incidence of dementia or a family history of dementia than do cases without an expansion.[83,86,95] Disease duration of *C9ORF72*-related ALS is significantly shorter than in patients with mutations in *SOD1, TARDBP* or other familial ALS cases, but does not differ from *FUS* mutation cases. There is an older age of onset in *C9ORF72*-related ALS compared to *SOD1* and *FUS*-related ALS, but not when compared with *TARDBP* and other familial ALS cases.[104]

Finally, many *C9ORF72* gene carriers have a long prodrome of psychiatric disease with symptoms that range from childishness, borderline personality, antisocial personality disorder and bipolar illness.[106] How the frontal, ventral striatal, thalamic and cerebellar changes in gene carriers contribute to the psychiatric symptomatology remains unknown. Also, C9FTLD/ALS phenotypes show higher association with other neurological motor and phenotypes. Motor associations include parkinsonism that is distinctive from idiopathic Parkinson's disease (PD).[78,83,107,108] Despite a slight over-representation of parkinsonism in

C9ORF72-related ALS cases, studies have failed to detect *C9ORF72* repeat expansions in patients with a pure Parkinson's disease clinical phenotype,[109,110] suggesting a pathogenesis distinct from classical idiopathic Parkinson's disease characterized by alpha-synucleinopathy. Interestingly, neurodegeneration has been seen in the substantia nigra of *C9ORF72*-related ALS cases, providing a clue to this motor association.[107]

Neuropathology of C9ORF72-related diseases—Neuropathological studies in *C9ORF72* repeat expansions are characterized by TDP-43 pathology in various neuroanatomical regions. Pathological TDP-43 proteins are ubiquinated, hyperphosphorylated and N-terminal truncated[23,111], and TDP-43 pathology in *C9ORF72* expansion cases have been shown to consist of compact and granular neuronal cytoplasmic inclusions (NCI), dystrophic neurites (DN), glial cytoplasmic inclusions (GCI) and variable presence of neuronal intranuclear inclusions (NII). TDP-43 pathology is found consistently in the frontal and temporal cortices (in carriers with clinical FTLD and FTD/ALS syndromes), pyramidal motor system (carriers with clinical ALS), and frequently in other limbic (hippocampus and amygdala), brainstem (midbrain/substantia nigra) and subcortical structures (striatum and thalamus)[112,113]. In many cases (FTD/ALS or clinical ALS more than clinical FTD), some TDP-43 immunoreactive neuronal and glial inclusions were present in the ventral grey matter of the spinal cord and/or brainstem motor nuclei, with the morphology of NCIs in lower motor neurons consisting of bundles of filaments, compact round bodies and diffuse cytoplasmic granules[113].

C9ORF72 expansion cases with clinical ALS show pathology indistinguishable from typical sporadic ALS, with predominant degeneration and TDP- 43-positive NCI and pre-inclusions of variable morphology in upper motor neurons and lower brainstem and spinal cord motor neurons, with the extramotor cortex, hippocampus and subcortical regions usually mildly or not affected at all[93]. Clinical phenotype appears to correlate strongly with the degree of TDP-43 pathology and degenerative changes in the respective CNS regions[114]. The pattern of neocortical TDP-43 accumulation in the majority of *C9ORF72* cases is consistent with FTLD-TDP type B pathology[115](according to the 2011 Mackenzie classification)[54] with compact NCI in all cortical layers and relatively few DN and NII[113,114]. Concomitant Type A TDP-43 pathology (usually associated with clinical bvFTD or nfvPPA) has also been found more frequently than expected in C9 expansion cases[99,112–114], with the suggestion that as type A TDP-43 pathology is also seen in other neurodegenerative diseases such as AD, additional type A pathology in *C9ORF72* cases may develop in genetically susceptible patients with advancing age[113].

Apart from the consistent presence of TDP-43, another highly characteristic pathological feature of patients with *C9ORF72* expansions is the significant presence of NCI in the cerebellar granule cell layer, hippocampal pyramidal neurons and neocortex that stain positive for proteins of the ubiquitin proteasome system (UPS) including ubiquitin, ubiquilins and p62, but are negative for TDP-43[93,112,113,116]. The presence of ubiquitin immunoreactive lesions is interesting, as similar pathology was originally described in patients with *UBQLN2* mutations that result in X-linked ALS and ALS/FTD[117]. This UPS-positive, TDP-43-negative pathology is the result of unconventional, repeat-associated non-ATG initiated (RAN) translation of sense and antisense transcripts[118,119] with the

abnormally expanded repeat in *C9ORF72*. Translation of the transcripts with the expanded repeat in the six alternate reading frames is predicted to generate five different polypeptides, each composed of dipeptide repeats (DPR): glycine-alanine (GA), glycine-proline (GP), glycine-arginine (GR), alanine- proline (AP) and arginine-proline (RP), that have been shown to be a major component of p62 inclusions in *C9ORF72*-related FTLD[120]. The potential pathomechanism of DPRs in *C9ORF72*-related disease is discussed further below.

Neuropathology of ALS and FTD-ALS—Delineation of motor neuron pathology is critical for those patients in whom there is no ante-mortem evidence of ALS, but features of FTLD are found concurrently with one or more aspects of the neuropathology of ALS. Neuropathological hallmarks of ALS include intracellular inclusions like bunina bodies (small eosinophilic neuronal inclusion arranged in beaded chains), ubiquitinated inclusions, and hyaline conglomerates.[121,122] Cases of ALS with FTLD show signs of spongiform degeneration in frontal and precentral gyrus (cortical layers II and III) and diffuse subcortical gliosis.[122,123] Neuronal loss in the anterior cingulate gyrus as well as in the substantia nigra and amygdala are also observed.[122] Pathologically, sporadic ALS, FTD-ALS and familial ALS (with or without *SOD-1* mutation) have been characterized by ubiquitin-positive inclusions; with all groups also showing TDP-43 positive inclusions, with the exception of familial ALS with *SOD-1* mutations.[124] These data suggest a pathological overlap between 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 with *SOD-1* mutations are ubiquitin-positive but TDP-43 negative,[124] implying that neurodegeneration in *SOD-1* mutations may exclude TDP-43 accumulation. Additionally, larger numbers of sALS and fALS need to be assessed for *FUS* pathology, as *FUS*-positive immunoreactivity has been reported in LMNs in familial ALS,[57] while the majority of sporadic ALS cases seem to be related to TDP-43 pathology.[125]

Potential pathogenic mechanisms of C9ORF72-related disease—The rapid development over the last three years in research into the pathogenicity of C9-related disease has been accelerated by knowledge derived through the study of other repeat expansion disorders. Likely mechanisms for toxicity include large repeat-containing RNAs, which form nuclear RNA foci. Sense and antisense transcripts of the expanded repeat aberrantly interact with various RNA-binding proteins, inhibiting them from binding to their actual targets, resulting in the formation of discrete RNA foci. These foci have the capacity to sequester select RNA-binding proteins, thereby impairing their function and probably leading to widespread changes in protein expression. Another potential mechanism is the loss of *C9ORF72* function due to decreased *C9ORF72* mRNA expression as a result of abnormal DNA and histone methylation. While the functions of *C9ORF72* are unknown, there is increasing evidence that it binds to lysosomal membranes.

A third potential mechanism includes repeat-associated non-ATG (RAN) translation of the bidirectional expanded repeat GGGGCC and CCCCGG transcripts as described above. The abnormal production of dipeptide repeat proteins (DPRs) collectively referred to as C9RAN proteins, form neuronal inclusions throughout the central nervous system of C9FTLD/ALS patients, initially thought to be contributing to neurodegeneration. Of note, all C9RAN

proteins, but especially poly(GA), poly(GP) and poly(GR), are among the proteins making up many TDP-43 negative, p62-positive inclusions described earlier that are found characteristically in the cerebellum and hippocampus in *C9ORF72* expansion carriers.[120] Even with the highly consistent pattern of DPR pathology in *C9ORF72* cases regardless of the clinical phenotype, the apparent lack of association of DPR pathology with degenerative changes suggest that DPR proteins may not play a direct role in neurodegeneration in *C9ORF72* cases, and its pathomechanistic role currently remains unclear[114]. It has been suggested that DPR proteins may be a potentially protective response that has also been seen in other neurodegenerative diseases such as Huntington's disease[114].

Molecular genetic disease modifiers in C9ORF72-related disease—Given the large clinical variability associated with *C9ORF72* repeat expansions it is interesting that there appears to be a higher than expected coincidence of repeat expansions found in individuals carrying other genetic variants of ALS, i.e. oligogenic inheritance,[126] suggesting that another 'hit' increases disease susceptibility or lowers age at onset. Oligogenic inheritance has also been reported in FTD, with the *C9ORF72* expansion being identified in patients carrying *GRN* and *MAPT* mutations.[127,128] Overall more than twenty patients have been described that harbour mutations in *C9ORF72* in combination with changes (rare variants or mutations) in other ALS- and/or FTD-associated genes.[129] While some of these may merely represent benign polymorphisms, it is anticipated that at least some of these mutations act as disease modifiers, thereby contributing to the pleiotropy encountered in patients with *C9ORF72* mutations.

In fact, *TMEM106B* genotypes were identified as the first genetic factor modifying disease presentation in *C9ORF72* expansion carriers.[130] *TMEM106B* was first identified in 2010 as a risk factor for FTD-TDP in a genome-wide association study of patients with autopsy-proven FTD-TDP, as well as *GRN* mutation carriers.[131] This association appeared to be stronger in the *GRN* mutation carriers than in the autopsied patients, with the major risk allele rs1990622 associated with an earlier age at onset. It was hypothesized that *TMEM106B* affects risk for FTD-TDP by modulating *GRN* levels.[131,132]

Two major international multi-site studies published earlier this year (Gallagher et al. and van Blitterswijk et al.) looked for similar associations in *C9ORF72* carriers, namely with regards to disease risk, age at onset and age at death. [130,133] Both studies had seemingly conflicting results that can be explained by methodologic differences - Gallagher et al calculated the odds ratio (OR) for disease risk for the major allele (T) and found an increased disease risk (OR>1) for carriers of the major allele, with a surprising association with later age at onset and age at death. In contrast, they reported that the *TMEM106B* genotype did not affect age at onset or death in their FTLD-TDP cases who were negative for *GRN* mutations or *C9ORF72* expansions. [133] On the other hand, van Blitterswijk et al calculated the OR for the minor allele (G), which appeared to protect *C9ORF72* carriers from developing FTD (OR<1), but not MND (there was no apparent difference in *TMEM106B* genotype frequencies in ALS C9 carriers compared to controls).[130] An allelic model was used by Gallagher et al for analysis of disease risk, but van Blitterswijk et al used a recessive model respective to the minor allele as it proved the best fit. Nonetheless, both

found that *TMEM106B* single nucleotide polymorphisms were strongly associated with disease risk.

Using a dominant genotypic model in the survival analysis, Gallagher et al. found that the minor allele homozygotes present with a significantly lower age at onset and age at death which the authors suggest may be due to a complex interplay between the *TMEM106B* genotype, *C9ORF72* expansion, and manifestation as either ALS or FTD. Van Blitterswijk et al. grouped all *C9ORF72* expansion carriers including ALS cases for their age at onset analysis and had similar findings which did not reach statistical significance. Essentially, the combined results of about 400 *C9ORF72* carriers from both groups indicate that *TMEM106B* is a major disease modifier for FTD, independently of whether the disease is caused by pathogenic mutations in *GRN* or *C9ORF72*. Whether it affects disease risk in the *C9ORF72* expansion carriers by affecting *C9ORF72* levels or by other mechanisms remains to be determined.

The role of the repeat length in determining disease onset and presentation has also been studied. Van Blitterswijk and colleagues determined the size of the hexanucleotide expansion in different parts of the CNS in frozen autopsy specimens from patients with MND, FTD or both.[134] Importantly, they noted that the expansion was polyclonal within the CNS, with variable expansion sizes in different regions. Independent of the clinical phenotypes, the repeat lengths were larger in the frontal lobes and spinal cord than in the cerebellum. They identified a positive correlation between age at onset and repeat length in the frontal cortex in FTD patients. Assessment of cerebellum samples from the overall cohort found that longer repeat size appeared to present a survival disadvantage, whereas expansion size in other parts of the CNS or blood leukocytes did not appear to correlate with prognosis.[134] Importantly, the repeat length did not influence the clinical disease presentation.

Other genes associated with ALS

***TARDBP* mutations, Chr1p36.22—**Since the discovery of mutations in the TAR DNA binding protein 43 (*TARDBP* or TDP-43) gene on chromosome 1 in 2008, over 3,000 ALS patients have been screened for mutations in this gene. *TARDBP* mutations have a prevalence of 4–6% in familial ALS and 1% in sporadic ALS, with differences in prevalence evident geographically.[61] Screening of family members of sporadic ALS patients reveals healthy *TARDBP* mutation carriers, implying that the penetrance is incomplete, with some carriers remaining neurologically intact at an advanced age.[126,135–137] Cognitive deficits are rarely found in ALS patients with *TARDBP* mutations. To date, mutations have been found in two French fALS patients with dementia,[138] one Norwegian fALS patient with FTD,[139] one patient with FTD, PSP, and chorea[140] and only one patient with isolated FTD.[62] These cases demonstrate that *TARDBP* mutations can cause sporadic and familial ALS, but rarely FTD-ALS or isolated FTD.

***FUS* mutations, Chr16p11.2—**So far, 58 mutations of the *FUS* gene have been identified, with a mutation frequency of approximately 4% in fALS and <1% in sALS patients. Most of the mutations are missense, but splicing, in-frame insertions and deletions

as well as two nonsense mutations have been identified in ALS patients. *FUS* mutations have been associated with a juvenile onset of the disease. Cognitive impairment is rarely seen with ALS caused by *FUS* mutations: only three cases had FTD features[141] and two other Parkinsonism and dementia.[141,142] Van Langenhove et al performed mutational analysis in 122 patients with FTD and 15 patients with FTD-ALS, and identified one novel missense mutation in one FTD patient; but the biologic relevance of this mutation remains uncertain.[143]

Other genes associated with FTD

VCP mutations, Chr9p13.3—Valosin-containing protein (*VCP*), is a member of the AAA-ATPase gene super family (ATPase associated with diverse cellular activities), with multiple cellular functions, including acting as a molecular chaperone in endoplasmic reticulum-associated protein degradation. *VCP* also participates in the stress response, in programmed cell death, and it interacts with the ubiquitin-proteasome system. *VCP* is located on chromosome 9p13.3, and mutations result in an autosomal dominant disorder associated with FTD called inclusion body myopathy with Paget's disease of bone and FTD (IBMPFD) Pathologically, mutations in this gene are associated with FTLD-U (ubiquitin positive, tau-negative) and are characterized by numerous neuronal intranuclear inclusions and relatively few neuronal cytoplasmic inclusions;[52] the ubiquinated inclusions are not composed of the mutated *VCP* protein, but rather TDP-43. The neuropathology is now classified as TDP-43 type D.[144] *VCP*-linked ALS is characterized by P62-, ubiquitin-, and TDP-43-positive inclusions.[145] Pathologically, affected muscles display hallmarks of IBM - atrophic, angulated muscle fibres with frequent rimmed vacuoles, and TDP-43- and/or *VCP*-immunoreactive sarcoplasmic inclusions in the absence of inflammation. Paget's disease of bone typically shows characteristic radiologic findings or an elevation in serum alkaline phosphatase level and is confirmed by typical findings in bone biopsy.[144,146] Diagnosis of IBMPFD should be considered if an individual has two or more of the following features: progressive myopathy, Paget's disease of bone, and FTD. Heterogeneity in clinical phenotypes may manifest as IBM in about 90% of patients, Paget's in 50%, and FTD in about one-third of cases.[147]

Rarely, *VCP* mutations are associated with sporadic amyotrophic lateral sclerosis (ALS), familial ALS, or familial FTD-ALS.[148] A possible link between *VCP* and motor neuron disease was first reported by Johnson and colleagues in 2010 when they identified a p.R191Q amino acid change in *VCP* in an Italian family with autosomal dominant ALS. Subsequently, they screened a cohort of 210 fALS and 78 autopsy-proven ALS cases for *VCP*, and identified 4 additional mutations; suggesting that *VCP* mutations may account for 1–2% of fALS cases, and providing evidence directly implicating defects in the ubiquination/protein degradation pathway in motor neuron disease.[149] Further screening of ALS and ALS-FTD cases by Koppers and colleagues confirmed that *VCP* mutations are a rare cause of fALS, with their role in sALS, if present, appearing to be very limited.[145] Similar conclusions were reached when analyses in British, Australian and Chinese fALS and sALS cohorts did not detect any known *VCP* mutations.[150–152]

CHMP2B mutations/FTD-3, Chr3p11.2—Mutations in the charged multivesicular body protein 2B (*CHMP2B*) gene, a rare cause of ALS, have only been described to cause FTD in individuals from Danish and Belgian ancestry. A large Danish family with autosomal dominant FTD caused by mutation in *CHMP2B* on chromosome 3 has been followed closely by a multinational and multidisciplinary research group for more than two decades. Signs and symptoms typical of bvFTD are the most common feature associated with this mutation. Late in the disease course, a motor syndrome typically develops, with features of parkinsonism, dystonia, myoclonus and pyramidal signs, leading to a bedridden state. None of the patients up to that point, however, had clinical signs of motor neuron impairment, but none had EMG testing. While clinically demented family members have shown severe and generalized cognitive impairment except for preserved episodic memory, perhaps in keeping with known sparing of the hippocampus in the disease, the study of preclinical symptoms indicate predominantly frontal lobe involvement in subjects with the mutation, years before overt dementia symptoms manifest.[153] Neuropathologically, ubiquitin- and p62-positive neuronal cytoplasmic inclusions (NCIs) are observed in the dentate granule cell layer of the hippocampus and to a lesser extent in the frontal cortex. These inclusions are negative for both TDP-43 and FUS, leading to the classification of FTD-3 as FTLD-UPS.[60]

Five *CHMP2B* missense mutations in eight individuals have been identified in a range of FTD-MND spectrum disorders.[154] Cox et al. screened 433 MND patients (of which 40 were of the primary muscular atrophy (PMA) subtype in the North of England for *CHMP2B* mutations and identified three distinct *CHMP2B* missense mutations in four patients. Interestingly, all four patients suffered from PMA.[155] In essence, the early clinical picture of FTD caused by *CHMP2B* mutations is similar to bvFTD, while neuroimaging and neuropathological findings are somewhat distinct. Mutations in the *CHMP2B* gene are also known to be associated with MND, primarily the PMA subtype. More work, however, is required to fully assess the role and importance of *CHMP2B* missense mutations in FTD and MND.

Other genes in the ALS-FTD spectrum

SQSTM1 mutations, Chr5q35—The sequestosome 1 (*SQSTM1*) gene is located on 5q35 and encodes p62, a multifunctional protein that interacts with misfolded and ubiquitinated proteins and acts as a cargo receptor for the degradation of ubiquitinated proteins through autophagic or proteasomal pathways. Mutations in *SQSTM1* result in Paget disease of bone.[156] There is evidence of p62 involvement in neurodegeneration, with *SQSTM1* knockout mice developing memory impairment associated with the accumulation of hyperphosphorylated tau and neurofibrillary tangles.[157] Increased p62 immunoreactivity has also been found in several neurodegenerative disorders, such as AD, dementia with Lewy bodies, FTLD, Parkinson disease (PD), and Huntington disease (HD).[158] Similarly, C9-related FTD or ALS cases have been shown to contain abundant neuronal p62-positive inclusions.[112] *SQSTM1* mutations have been identified in patients with familial (<2%) and sporadic ALS (4%).[159] This was further confirmed by Rubino et al. in an Italian cohort that found this mutation in patients with either FTD or ALS but not in healthy controls.[160] A French cohort identified 4 heterozygous missense mutations in 4 unrelated families with FTD, with 1 family showing clinical symptoms of FTD-ALS.[161] Although the frequency of

the mutations in their series of familial cases was low (3.8%), it was close to the frequency found by Rubino and colleagues (1.8%). Both studies support a pathogenic role for the p62 protein in FTD disorders.

UBQLN2 mutations, ChrXp11.21—Mutations *UBQLN2* which encodes ubiquilin-2, a member of the ubiquitin protein family, have been shown to cause dominant X-linked ALS and ALS-dementia,[117] and also rarely sporadic ALS.[162] Ubiquilins mediate proteasome-dependent protein degradation, and ubiquilin-2 mutations may disrupt proper clearance of misfolded or damaged proteins, leading to impaired cellular functioning, especially in motor neurons that are vulnerable to protein accumulation. *UQBLN2* mutations affect proline residues in a unique 12-unit PXX tandem-repeat domain within the *UBQLN2* protein, although mutations outside of this region occur and are associated with more FTD-predominant phenotypes.[163,164] *UBQLN2*-positive inclusions have also been observed in non-*UBQLN2*-linked ALS, accumulating in P62-positive aggregates with variable TDP-43 co-localization[117] and also in the setting of *FUS* mutations.[165] Staining for *UBQLN2* in *C9ORF72*-linked disease reveals dystrophic neuritis with focal swellings, dot-like stipples, and irregular aggregates in the molecular layer and CA1-CA4 region of the hippocampus; neuronal inclusions in the granular layer of the cerebellum; and dystrophic neurites and aggregates in the neocortex; which is absent in cases without the expansion.[166] These findings hint at common downstream pathways, possibly involving the ubiquitin proteasome system, in *UBQLN2*- and *C9ORF72*-linked ALS.

Age at disease onset varies widely, from the late teens to the seventh decade, possibly earlier in males than females, with average disease duration of less than 4 years. Symptoms of FTD may precede motor manifestations. Data on the frequency of *UBQLN2* in different populations and disease phenotypes is still very limited,[162] with almost no reports of the mutation causing pure dementia. Based on a screening of 206 ALS and FTD patients, however, Synofzik and colleagues reported 3 novel *UBQLN2* mutations, accounting for 1.2% (2/161) of ALS and 2.2% (1/45) of FTD patients, including a patient with pure FTD. All mutations were located in highly conserved domains outside the PXX repeat region and not observed in 1450 ethnically matched control X chromosomes. Of note, all affected patients presented with apparently sporadic disease.[164] Essentially, *UBQLN2* mutations are rare in Central European ALS and FTD patients, but may contribute significantly to patients with seemingly sporadic disease.

FTD-ALS linked to Chromosome 16p12.1–12.2

While *C9ORF72* mutations account for a substantial proportion of familial FTD-ALS cases, several *C9ORF72*-negative families remain. Dobson-Stone et al[167] identified a large European-Australian family with autosomal dominant inheritance of dementia and/or ALS, with affected members developing either ALS or dementia; some of those with dementia also had ALS and/or extrapyramidal features. Neuropathology was most consistent with FTD with type B TDP pathology, but with additional phosphorylated tau pathology consistent with corticobasal degeneration. DNA samples were negative for mutations in all known dementia and ALS genes, including *C9ORF72* and *FUS*. Genome-wide linkage analysis provided highly suggestive evidence of a locus on chromosome 16p12.1–16q12.2,

responsible for an unusual cluster of neurodegenerative phenotypes. This region overlaps with a separate locus on 16q12.1–q12.2 reported in an independent ALS family, indicating that this region may harbour a second major locus for FTD-ALS.[167]

Shared cellular pathways between ALS and FTDs—The ALS- and FTD-linked genes discussed earlier can be separated into 2 functional groups: those associated with RNA processing, and those involved in protein degradation pathways. There is strong evidence for the involvement of TDP-43 and FUS proteins in RNA-related pathways: both are RNA processing proteins with roles in multiple steps of RNA regulation including RNA transcription, splicing, transport, translation and microRNA production.[168] In the neurons of FTD/ALS patients with either TDP-43 or FUS pathology, the defining protein relocates from the nucleus to the cytoplasm and forms aggregates,[169,170] which may cause cytotoxicity via 3 possible mechanisms: loss of normal nuclear function leading to dysregulation of nuclear RNA processing; gain of extraneous cytoplasmic RNA binding activity; or aggregation-dependent toxicity.[171] The major difference between the two proteins appears to be that of loss of nuclear relocalization as a primary feature of *FUS* mutations, in contrast to increased aggregation propensity that may be the major feature of *TARDBP* mutations.

The cell has two major pathways for protein recycling: the ubiquitin proteasome system, where proteins are targeted for destruction within the proteasome by the addition of poly-ubiquitin residues, and macro-autophagy, where proteins and organelles are sequestered within autophagosomes which fuse with lysosomes leading to the degradation of vesicle cargo. The possible involvement of the ubiquitin proteasome system in neurodegeneration is highlighted by the ubiquitination of aggregates in multiple disorders, and through the presence of mutations in *UBQLN2* and *VCP* in ALS and FTD. Four genes (*UBQLN2, SQSTM1, OPTN* and *VCP*) linked to ALS and/or FTD have strong links to protein degradation pathways, and TDP-43 aggregations appear to be degraded through both autophagy and the ubiquitin proteasome system, meaning both pathways could be of relevance to ALS/FTD pathogenesis.[172]

It is also possible that both pathways converge in the pathogenesis of FTD-ALS. One possibility is that impairment of protein degradation pathways lead to protein aggregation, which may result in abnormal RNA-binding protein (TDP-43 or FUS) function. Of note, the pathology in patients carrying *VCP, OPTN* and *UBQLN2* mutations is dominated by abnormal cytoplasmic levels and aggregations of TDP-43;[117,144,173] this hypothesis, however, has not been shown in cases with *FUS*. It has been demonstrated that *VCP* and TDP-43 interact genetically and that *VCP* mutations lead to redistribution of TDP-43 to the cytoplasm in vitro and in vivo, replicating the major pathology observed in IBMPFD and other TDP-43 proteinopathies. Once cytoplasmically localized, TDP-43 and *VCP* appear to interact and enhance neurotoxicity and aggregation.[174] Similarly, both TDP-43 and *FUS* have been shown to be intrinsically aggregation prone, with an initial seeding reaction important for wild-type and mutant TDP-43 aggregation.[175,176] A further mechanism in which defects in protein degradation could lead to accumulation of TDP-43/*FUS* is through stress granules, through either the ubiquitin proteasome system or through autophagy inhibition, leading to the sequestration of RNA binding proteins and perhaps formation of

TDP-43/*FUS* ubiquitinated aggregates.[177,178] Alternatively, it is possible that a primary alteration in RNA processing leads to a secondary impairment in protein degradation, with depletion of TDP-43 being shown to lead to an inhibition of autophagy.[179] As such, loss of TDP-43 function can be linked to the ubiquitin-specific autophagy pathways that have been evident in *SQSTM1 VCP, OPTN* and *UBQLN2* mutations. Impaired function of mutant TDP-43 and *FUS* could impair either ubiquitin-specific or general protein clearance pathways in the cell through dysregulation of RNA processing.[179]

Chronic traumatic encephalopathy (CTE), tau, TDP-43 and motor neuron involvement

For many decades an association between trauma and dementia was noted in boxers. A very slowly progressive dementing condition, with behavioral changes, amnesia and Parkinsonian features, named “dementia-pugilistica”, was eloquently described by Martland in the 1920s.[180] More recently, progressive cognitive decline, depression, anxiety, suicidality, disinhibition and memory disturbance was described in a subgroup of retired National Football League players. Labelled “chronic traumatic encephalopathy”, this disorder is characterized by the massive aggregation of tau in the amygdala, orbital-frontal and dorsal-lateral frontal cortex, with the presence of these aggregates across all six cortical layers.[181] Additionally, many patients exhibit the aggregation of other misfolded proteins, particularly TDP-43. Other individuals show features of Parkinson’s disease with alpha-synuclein aggregates, and still others show Alzheimer’s disease changes with plaques and tangles.[182] One possible confounder is that head trauma may be a risk factor for multiple degenerative disorders including FTD, AD, CTE and PD.[182] It has also been suggested that the increased prevalence of late-life cognitive impairment in retired NFL players may reflect diminished cerebral reserve.[183] While the risk factors, clinical features, and neuropathological substrates of CTE are still unknown, this entity is an important and not rare risk associated with repeated head trauma. It has been shown that a significant number of retired NFL players fulfil criteria for mild cognitive impairment,[183] but larger, controlled studies are needed to confirm exact prevalence. Finally, there is a link between FTD-like syndromes and ALS in the NFL players. The precise clinical features and risk factors for CTE-related ALS are unknown. McKee noted that the NFL players with ALS disseminated TDP-43 from cortex to brainstem and spinal cortex.[184] Given the overwhelming clinic-pathological links involving tau and TDP-43, CTE offers a unique opportunity to explore the relationship between FTD, ALS and traumatic brain injury.

Further potential links between dementia and neuromuscular disease

ATXN2 (SCA2), Chr12q24.12

Spinocerebellar ataxia 2 (SCA2) is an autosomal dominant cerebellar ataxia with often prominent extra-cerebellar features such as opthalmoplegia, pyramidal and extrapyramidal signs, neuropathy and cognitive impairment in some patients.[185] It is a polyglutamine disease caused by CAG repeat expansions in *ATXN2* exon 1.[186,187] A few long-standing SCA cases have been described to develop features of MND and a subsequent rapidly progressive course.[188] The identification of the SCA2 gene product ataxin-2 as a modifier of

TDP-43 toxicity in yeast and Drosophila[189] has led to genetic studies investigating the role of *ATXN2* mutations in ALS, with several studies showing intermediate-range CAG repeat expansions (27–33 repeats) to be more frequent in ALS patients than in controls.[189–192] The repeat expansions associated with ALS are interrupted CAA-CAG sequences as opposed to the pure CAG repeat expansions typically associated with SCA2.[193] No expanded repeats have been identified to date in patients with FTLD.[194] Cases that have been described include a single family carrying the mutation with both typical ALS and typical SCA2,[195] and another family with fully pathological *ATXN2* CAG repeat expansion and two different phenotypes of classical SCA2 and FTLD-ALS without ataxia.[196] Neuropathology of the FTD-ALS case in the second family revealed prominent polyglutamine and p62-positive intranuclear neuronal inclusions in the pontine nuclei with pronounced neocortical and spinal TDP-43 pathology.

Most recently, Lattante and colleagues screened a large French cohort of ALS, FTD, FTD-ALS and PSP patients for *ATXN2* CAG repeat lengths, including over 300 patients with *C9ORF72* expansion carriers, and found a significant association with intermediate repeat size (>29 repeats) in patients with fALS, sALS and familial FTD-ALS.[197] Interestingly, 23% of their intermediate-repeat *ATXN2* carriers had co-occurrence of pathogenic *C9ORF72* expansions, all in the FTD-ALS and fALS subgroups, suggesting that *ATXN2* polyQ expansions may act as a strong modifier of the FTD phenotype in the presence of a *C9ORF72* expansion, leading to an FTD-ALS clinical phenotype. In the cohort of *C9ORF72* carriers, 3% also carried an intermediate *ATXN2* repeat length, whereas PSP and FTD patients had *ATXN2* repeat lengths similar to those of controls. Similarly, a multicentre study on *C9ORF72* carriers led by van Blitterswijk suggested that intermediate *ATXN2* expansions possibly act as disease modifiers in *C9ORF72* expansion carriers, the effect being most profound in probands with MND or FTD/MND (2.1% vs 0% in controls, p=0.013). *ATXN2* expansion frequency was similar in probands with FTD and controls.[198]

In conclusion, *ATXN2* repeat expansions can cause either SCA or ALS, but also a neuropathological overlap syndrome of SCA2 and FTLD/MND presenting clinically as pure FTLD-ALS without ataxia. *ATXN2* intermediate repeat length has been shown to be a strong risk factor for ALS and FTD-ALS,[197] as well as being a disease modifier in *C9ORF72* repeat expansions with intermediate repeat length rendering *C9ORF72* carriers more susceptible to development of MND.[198] More studies, however, are needed to validate this growing body of evidence.

Polyglucosan body disease (Adult-onset), *GBE1* Chr3p12.3

Adult polyglucosan body disease (APBD) is a rare neurogenetic disorder that is characterized by onset >40 years with neuromuscular signs of polyneuropathy, myelopathy, with more than half displaying cognitive involvement that may be cortical or subcortical in nature. MRI reveals cortical atrophy, and white matter changes that are bilateral, periventricular and symmetric. Diffuse atrophy is also seen universally in the medulla and spinal cord. EMG shows evidence of motor and sensory axonal loss,[199,200] with symptoms progressing over one to two decades leading to functional and cognitive decline. Neuropathologically there is intracellular accumulation of polyglucosan bodies in the central

and peripheral nervous systems and in other tissues, leading to demyelination and gliosis.[201–203] Most patients with APBD have an allelic form of glycogen storage disease type IV (GSD-IV) caused by glycogen branching enzyme (GBE) deficiency.[204] Diagnosis is confirmed by a significant reduction of GBE enzymatic activity in peripheral blood leukocytes or cultured skin fibroblasts. The majority of patients are of Ashkenazi Jewish descent,[205] and the disease is likely to be underdiagnosed or misdiagnosed.[206,207] Farmer et al. reported an individual with clinical bvFTD and no clinical evidence of neuromuscular disease, in who autopsy revealed two distinct neuropathologic diagnoses of APBD and FTLD-TDP. This was the first reported case of both diseases coexisting within a single individual.[208] Bit-Ivan and colleagues are also in the process of reporting a case of APBD with GBE1 haploinsufficiency and concomitant FTLD.[209] It remains unclear if these findings are coincidental in these patients, or if pathogenic pathways intersect to promote these coexisting pathologies.

Hexosaminidase A GM2 gangliosidosis (late-onset Tay-Sachs disease) Chr15q23

Late-onset Tay-Sachs (LOTS) disease is an autosomal recessive, progressive lysosomal storage disorder caused by a partial deficiency of beta-hexosaminidase A (HEXA) activity. Deficient levels of HEXA result in the intracellular accumulation of GM2-ganglioside, resulting in toxicity to nerve cells. Clinical manifestations primarily involve the CNS and lower motor neurons, and include ataxia, weakness, spasticity, bulbar symptoms, dystonia, seizures, and cognitive decline.[210] It is prevalent among Ashkenazi Jews, but rare cases have been reported among non-Jewish people, often in association with private or unique alleles.[211] In contrast to the classic infantile form of TSD, which usually leads to death between 3 and 5 years of life, patients with LOTS have a more protracted clinical course. The adult-onset form manifests in late childhood or teens (and in other cases much later), with signs of cerebellar and anterior horn cell involvement that may be evident early on. Of note, some patients have prominent neuropsychiatric problems such as bipolar disorder and depression.[212] Psychosis has been reported in 30% to 50% of LOTS and many are misdiagnosed with schizophrenia. Mood disorders are present in more than 25% and cognitive impairment in more than 20%.[213] Neuropsychological assessment has found evidence of impairment in executive function and memory without clinical evidence of dementia.[214] While pathology is separate entirely from the ALS-FTD spectrum, a clinical presentation of motor neuron involvement with prominent psychosis and cognitive impairment should prompt a consideration of LOTS, particularly in patients of Ashkenazi Jewish descent.

Conclusion and future directions

Both FTD and ALS are etiologically complex diseases with genetic and presumably environmental factors contributing to their onset. Both share clinical, genetic, neuropathological features and neurodegenerative pathways, suggesting that they may be part of a common disease spectrum. The recent, rapid advances made in our understanding of *C9ORF72*-related disease, especially with the theory that repeat-containing RNA is crucial to disease pathogenesis, allows the development of biomarkers to aid in identification of presymptomatic persons at-risk, aid in accurate diagnosis and disease

monitoring especially in the context of clinical trials; as well as the development of potential therapeutic strategies for an otherwise devastating familial disease. Additionally, the increasingly recognized entity of CTE has added to the growing body of evidence that environmental factors are at play as much as inherited ones in the pathogenesis of FTD-ALS syndromes. It is also of particular interest that TDP-43 and p-62 pathology have been discovered in other inherited conditions such as SCA2, with FTD-ALS spectrum diseases reported in conjunction with inherited metabolic conditions such as adult polyglucosan disease and late-onset Tay-Sachs disease. Whether these associations are merely coincidences remain to be determined. From a larger perspective, the frontotemporal dementias have proven themselves to not be a bridge exclusively to ALS, but rather to a widening spectrum and variety of neuromuscular diseases, most of which we have attempted to summarise in this review.

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Table 1

Genes associated with frontotemporal dementia (FTD).

FTD-related genes/ Chromosomal location	Major pathological substrate	fFTD (%)	sFTD (%)	FTD-ALS syndromes (%)	Age at onset (years)	Disease duration	Cognitive impairment/ Psychiatric features	Motor neuron features	Clinical presentation	MRI findings
C9ORF72 9p21.2	TDP-43 Type A & B; p62 inclusions	25	6	30	27–83; mean 55.3 to 58.3; possibility of anticipation	3 months to 22 years	Up to half; psychosis in up to 1/3	Any phenotype but bulbar ALS >40%, rarely in PMA and PLS	Typically bvFTD (>80%); rest nfvPPA, very rarely svPPA; may have parkinsonism	Less frontotemporal atrophy; Global atrophy, may involve parieto-occipital region, thalamus, cerebellum
GRN 17q21.32	TDP-43 Type A	5–11**	5	Rare	Median 58.0 (IQR 5.03–65.0)	3 – 18 years; median 7 yrs (IQR 4.5–8.0)	Psychosis common; delusions & hallucinations in up to 25%	Rare (may be up to 5% in some cohorts*	Usually bvFTD (>50%); rest mostly nfvPPA; more parkinsonism	Asymmetrical fronto-temporal-parietal atrophy
MAPT 17q21.32	FTLD-tau	2–11**	-	Rare	Mean 48, range 38–58	Mean 9 years, range 3.5–14.5 years	Typically bvFTD	Rare	Usually bvFTD; may be associated with other tauopathies (PSP, CBD, AGD)	Relatively symmetrical orbitofrontal, medial temporal atrophy
VCP 9p13.3 (IBMPFD)	TDP-43 Type D	<1	-	Rare	Onset of weakness mean 42, range 24–61; Mean age of FTD diagnosis 57, range 48.9 to 60.2	Death from respiratory failure/cardio myopathy in 40s to 60s	FTD symptoms in 30% of cases; aphasia/language deficits common	Rare; 1–2% of fALS cases; <1% of sALS cases (without dementia)	Progressive myopathy/IBM (90%) Paget's disease of bone (50%), FTD (30%)	Limited information; pathologically frontotemporal neuronal loss
CHMP2B 3p11.2	FTLD-UPS	<1	-	Rare	Mean 58, range 46–65	Mean duration of 10 years	Early bvFTD features, progressive dynamic aphasia	Rare; 1%; notably PMA subtype of ALS	FTD only in Danish/Belgian ancestry; early bvFTD, motor syndrome later on(parkinsonism, dystonia, myoclonus, pyramidal signs)	Generalised cortical atrophy at diagnosis, most marked in frontal, parietal-occipital lobes
SQSTM1 5q35	P62	<2–4.4%+	-	<2–2.7+	Mean 60, range 48–73+	Mean 10.2, range 2–29+	Behavioural disorder at presentation in more than 2/3of an FTD cohort+	Limb or bulbar ALS; one study showed limb >	Paget's disease of bone in >1/3; bvFTD at presentation in > 2/3 in	Frontotemporal atrophy; may be asymmetric

FTD-related genes/ Chromosomal location	Major pathological substrate	fFTD (%)	sFTD (%)	FTD-ALS syndromes (%)	Age at onset (years)	Disease duration	Cognitive impairment/ Psychiatric features	Motor neuron features	Clinical presentation	MRI findings
								bulbar presentation in FTD cohort screened for the mutation[+] bulbar presentation[++]		
UBQLN2 Xp11.21	Ubiquilin-2; TDP-43	-	1 case of pure FTD	Rare; X-linked dominant juvenile ALS & adult ALS-dementia	Teens to 7th decade	< 4 years	May have features of frontal-type dementia	1–2% of apparent sporadic ALS and FTD	bvFTD syndrome precedes motor symptoms	-

fFTD = familial FTD; sFTD = sporadic FTD; FTD-ALS = frontotemporal dementia-amyotrophic lateral sclerosis; TDP-43 = transactive response DNA binding protein 43 kDa; PMA = primary muscular atrophy; PLS = primary lateral sclerosis; bvFTD = behavioural variant FTD; nfvPPA = non-fluent variant primary progressive aphasia; svPPA = semantic variant primary progressive aphasia; IQR = interquartile range; FTLD = frontotemporal lobar degeneration; PSP = progressive supranuclear palsy; CBD = corticobasal degeneration; AGD = argyrophilic grain disease; fALS = familial ALS; sALS = sporadic ALS; IBM = inclusion body myositis; FTLD-UPS = frontotemporal lobar degeneration-ubiquitin protease system

[*] Chen-Plotkin et al. Arch Neurol. 2011 Apr;68(4):488-97

[+] Le Ber I et al. JAMA Neurol. 2013 Nov;70(11):1403-10

[++] Fecto F et al. Arch Neurol. 2011 Nov;68(11):1440-6

[**] Rohrer JD et al. The heritability and genetics of frontotemporal lobar degeneration. Neurology 2009; 73:1451–1456; Seelaar H et al. Distinct genetic forms of frontotemporal dementia. Neurology 2008; 71:1220–1226; Cruts M et al. Null mutations in progranulin cause ubiquitin-positive frontotemporal dementia linked to chromosome 17q21. Nature 2006; 442:920–924; Gass J et al. Mutations in progranulin are a major cause of ubiquitin-positive frontotemporal lobar degeneration. Hum Mol Genet 2006; 15:2988–3001; Le Ber I et al. Progranulin null mutations in both sporadic and familial frontotemporal dementia. Hum Mutat 2007; 28:846–855; Pickering-Brown SM et al. Frequency and clinical characteristics of progranulin mutation carriers in the Manchester frontotemporal lobar degeneration cohort: comparison with patients with MAPT and no known mutations. Brain 2008; 131:721–731.

Table 2

Genes associated with amyotrophic lateral sclerosis (ALS).

ALS-related genes/ Chromosomal location	Major pathological substrate	fALS (%)	sALS (%)	FTD-ALS syndromes (%)	Age at onset (years)	Disease duration	Cognitive impairment	Motor neuron phenotype	Clinical presentation	MRI findings
C9ORF72 9p21.2	TDP-43 type A & B; p62 inclusions	~40	3–19	30	27–83; mean 55.3 to 58.3; possibility of anticipation	3 months to 22 years	Up to half; psychosis in up to 1/3	Any phenotype but bulbar ALS >40%, rarely in PMA and PLS	Typically bvFTD	Global atrophy, may involve parieto-occipital region, thalamus, cerebellum
SOD1 21q22.11	P62- & ubiquilin positive, TDP-43 negative	12–23	0–7	Rare	Varies according to mutation	< 1 year –up to 20 years depending on mutation	Rarely associated with FTD	"Classical ALS"; but genotype-phenotype correlation varies, defined for only a few mutations	-	-
TARDBP 1p36.22	TDP-43	4–6	1	Rare; Single case report	Mean 55, range 30–77	Mean 3.3 years (SD 2.3 years)	Rarely seen	25% bulbar-onset (similar to sporadic ALS)	FTD, corticobasal syndrome	-
FUS 16p11.2	Fused-in sarcoma immune-reactive inclusions (FUS-ir), TDP-43 negative	4	1	Rare	Mean 46, range 13–80	Mean 3.4 years (SD 5.7 years)	Rarely seen	Both juvenile- and adult-onset ALS; predominantly LMN involvement, rarely reported cognitive impairment*	Handful of cases with FTD, parkinsonism with dementia; no mutations found in FTLD-FUS cases so far	-
SQSTM1 5q35	p62	2	4	<2–2.7+ }	Mean 54, (SD 10.9)++	Mean 6.3 years (SD 5.3)++	Behavioural disorder at presentation in more than 2/3of an FTD cohort+	Limb or bulbar ALS; one study showed limb > bulbar presentation ++	Behavioural disorder at presentation (in cohorts of FTD screened for the mutation)+	Frontotemporal atrophy; may be asymmetric (in FTD cohort)
UBQLN2 Xp11.21	Ubiquilin-2; TDP-43	Rare; X-linked dominant juvenile ALS & adult ALS-dementia	1–2% of apparent sporadic ALS & FTD	Rare; X-linked dominant juvenile ALS & adult ALS-dementia	Teens to 7th decade	<4 years	May have features of frontal-type dementia	1–2% of apparent sporadic ALS and FTD	bvFTD syndrome precedes motor symptoms	-

fALS = familial ALS; sALS = sporadic ALS; FTD-ALS = frontotemporal dementia-amyotrophic lateral sclerosis; TDP-43 = transactive response DNA binding protein 43 kDa; PMA = primary muscular atrophy; PLS = primary lateral sclerosis; bvFTD = behavioural variant FTD; LMN = lower motor neuron

[*] Mackenzie IR et al. Acta Neuropathol. 2011 Jul;122(1):87–98

[+] Le Ber I et al. JAMA Neurol. 2013 Nov;70(11):1403-10

[++] Fecto F et al. Arch Neurol. 2011 Nov;68(11):1440-6