alzheimer's research&therapy

REVIEW

Cognitive and behavioral features of c9FTD/ALS

Bradley F Boeve*[1] and Neill R Graff-Radford[2]

Abstract

Numerous kindreds with familial frontotemporal dementia or amyotrophic lateral sclerosis or both have been linked to chromosome 9 (c9FTD/ALS), and an expansion of the GGGGCC hexanucleotide repeat in the non-coding region of chromosome 9 open reading frame 72 (*C9ORF72*) was identified in the summer of 2011 as the pathogenic mechanism. An avalanche of papers on this disorder is in progress, and a relatively distinctive phenotype is taking form. In this review, we present an illustrative case and summarize the demographic, inheritance, clinical, and behavioral aspects and presumed pathologic underpinnings of c9FTD/ALS on the basis of the available data on more than 250 patients with frontotemporal lobar degeneration syndromes, parkinsonism, or ALS or a combination of these disorders.

Introduction

Familial frontotemporal dementia (FTD) with or without parkinsonism has been associated with mutations in genes encoding microtubule-associated protein tau (*MAPT*), progranulin (*PGRN*), and less commonly valosin-containing protein (*VCP*), TAR DNA-binding protein (*TARDBP*), and fused in sarcoma (*FUS*), whereas familial amyotrophic lateral sclerosis (ALS) has been associated with mutations in genes encoding Cu/Zn superoxide dismutase-1 (*SOD1*), *TARDBP*, and *FUS* [1-9]. Although the phenotype of familial FTD or ALS linked to chromosome 9 or both has been appreciated for many years [10-17], the pathogenic genetic mutation remained elusive until two teams of investigators discovered the mechanism in the summer of 2011 and published their findings shortly thereafter [18,19]. The mutation is an expansion of the GGGGCC hexanucleotide repeat in the non-coding intronic region of the chromosome 9 open reading frame 72 (*C9ORF72*) gene [18,19], and the disease is known as frontotemporal dementia or amyotrophic lateral sclerosis (or both) linked to chromosome 9 (c9FTD/ALS) [18,20]. A number of papers on c9FTD/ALS have already been published, and a relatively distinctive phenotype is becoming clear. In this review, we present an illustrative case from our index kindred and then summarize the demographic, inheritance, clinical, and behavioral aspects of c9FTD/ALS on the basis of the available data.

Illustrative case from index kindred

The identification of the mutation in our index kindred known as the Vancouver-San Francisco-Mayo Clinic family 20 reflects collaborative work that was conducted by several groups of investigators over the course of almost two decades [16]. One case we have followed over the course of seven years illustrates many of the core cognitive, behavioral, neuropsychological, and neuroimaging features that cases with c9FTD/ALS frequently exhibit.

A right-handed male began experiencing depression and apathy at age 49. He is patient III.2 in the report by Boxer and colleagues [16]. His father developed ALS at age 35 and died after a two-and-a-half-year course. His paternal aunt presented with behavioral variant frontotemporal dementia (bvFTD) features at age 46 and shortly thereafter with parkinsonism and ALS and died after a nine-year course. His brother had bvFTD, which was diagnosed at age 49, and parkinsonism, which was diagnosed four years later, and is currently residing in a skilled nursing care facility after a seven-year course. Five other relatives have or had FTD, ALS, or parkinsonism or a combination of these disorders.

The patient presented to our institution at age 53, complaining of severe depression and 'lack of pep'. He had lost his job because of apathy and poor decisions. He lived in a rural area and remarked that, owing to boredom since he could not find work, a favorite activity was to sit in a lawn chair in his yard with a cooler of beer adjacent to him, hold a rifle in each arm, and 'shoot anything that moves'. The targets included squirrels, birds, and insects. Despite his wife's best efforts to curb this activity and keep him from consuming alcohol, he continued to do so. This eventually led to a drunk driving charge, and as a result, all weapons were removed from his residence. His driver's license was temporarily suspended, yet he was able to evade the local police and drive his own or friends'

*Correspondence: bboeve@mayo.edu
[1]Department of Neurology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA
Full list of author information is available at the end of the article

cars, apparently never getting lost or having any accidents. After a six-month period with no driving privileges, he successfully completed a driving safety examination. On one occasion, he picked up a hitchhiker who was seeking shelter, brought him home, but refused to allow the hitchhiker in his home and an altercation ensued.

The patient became increasingly suspicious of his family, neighbors, and local police and health-care providers. Owing to his obstinacy, his wife chose to reside in a separate home and his children chose to no longer interact with him. He remarked that he often heard voices, but other than stating that the Lord was telling him to do good deeds, he would not elaborate on the content of these auditory hallucinations as 'you guys will lock me up and throw away the keys'.

His only source of income was disability benefits. His home was in disarray, and he would drive around town obtaining food from fast-food restaurants, but he managed to live independently. He gained more than 50 pounds since the onset of his symptoms because of hyperphagia and the tendency to consume large quantities of potato chips. His family has worked with the local legal authorities in an attempt to transfer oversight of his medical and financial affairs to his wife, but when he went before a judge, the patient successfully argued that he was competent and absolutely did not want anyone overseeing his affairs.

The longitudinal clinical, behavioral, neuropsychological, and neuroimaging findings in this patient are shown in Figures 1 to 3. His presenting features were typical of bvFTD, followed shortly thereafter with left hemiparkinsonism that has evolved to an asymmetric akinetic-rigid syndrome without tremor. Asymmetric corticospinal tract signs have also evolved but without features of lower motor neuron dysfunction. His course has been remarkably slowly progressive. As reflected in his neuropsychological performance over time, his episodic memory and visuospatial functions have remained relatively preserved and this likely has allowed him to live independently despite his psychomotor slowing, executive dysfunction, delusions, hallucinations, apathy, and mild parkinsonism.

Neuroimaging findings mirror this remarkably slow clinical progression. Very minimal atrophy has evolved over the course of seven years of serial magnetic resonance imaging (MRI) scans. A flourodeoxyglucose positron emission tomography (FDG-PET) scan image of the brain, performed eight years after the onset of his symptoms, shows relatively mild frontal, parietal, and cingulate cortex hypometabolism.

Literature review

We reviewed reports with ample numbers of cases having a dementia-predominant phenotype, published through March 2012. Reports focused on ALS with cognitive and behavioral data were also included. We identified nine recent publications meeting these criteria [20-28], and a summary of the core features associated with c9FTD/ALS is shown in Table 1.

Cohort characteristics

More than 250 subjects among more than 230 kindreds with sufficient cognitive/behavioral data are included in these reports to be summarized and reviewed for general consistencies [20-22,24-29]. This accumulation of hundreds of subjects is in itself striking given that these data have been published within seven months since the publication of the landmark papers on the *C9ORF72* mutation [18,19]; similar data exist for FTD associated with mutations in the gene encoding *MAPT* among 134 kindreds since the original report on *MAPT* mutations in 1996 [1] and in the gene encoding *PGRN* among 231 kindreds since the original reports on *PGRN* mutations in 2006 [2,3,30].

Among those series in which the frequency of the *C9ORF72* mutation was assessed (some also compared this frequency with the frequency of mutations in *MAPT* and *PGRN*), the frequency was calculated as sporadic or familial or both; also, the frequency of FTD ± parkinsonism ± ALS was calculated [21,22,24-29]. Most reports state that the *C9ORF72* mutation frequency is in the 7% to 12% range compared with the 6% to 10% range for *MAPT* and the 4% to 7% range for *PGRN*. These frequencies increase to 13% to 26% for *C9ORF72*, 11% to 22% for *MAPT*, and 6% to 22% for *PGRN* when the frequencies of mutations among familial FTD cases are considered. Importantly, despite the recruitment and analyses of familial FTD cases during at least the past 20 years among several teams focused on this issue, the frequency of familial cases without an identified genetic mechanism is in the 45% to 66% range, thereby providing ample reasons to continue research in familial FTD.

Demographic characteristics

The male-to-female ratio on cumulative cases among FTD ± parkinsonism ± ALS suggests a slight male predominance (129:105 or 1.23:1). In different series, the mean/median age of onset is in the 52- to 65-year age range, and the range of age of onset is wide (33 to 78 years). Survival mean/median values are in the 5- to 9-year range, and the range of survival also is wide (1 to 22 years). The illustrative case above exemplifies the slow course and long survival of some individuals. In the reports in which this was assessed, those with FTD and concomitant ALS tended to have shorter survival, as one would expect.

Inheritance characteristics

The disorder of c9FTD/ALS is inherited in an autosomal dominant fashion with high but not complete penetrance,

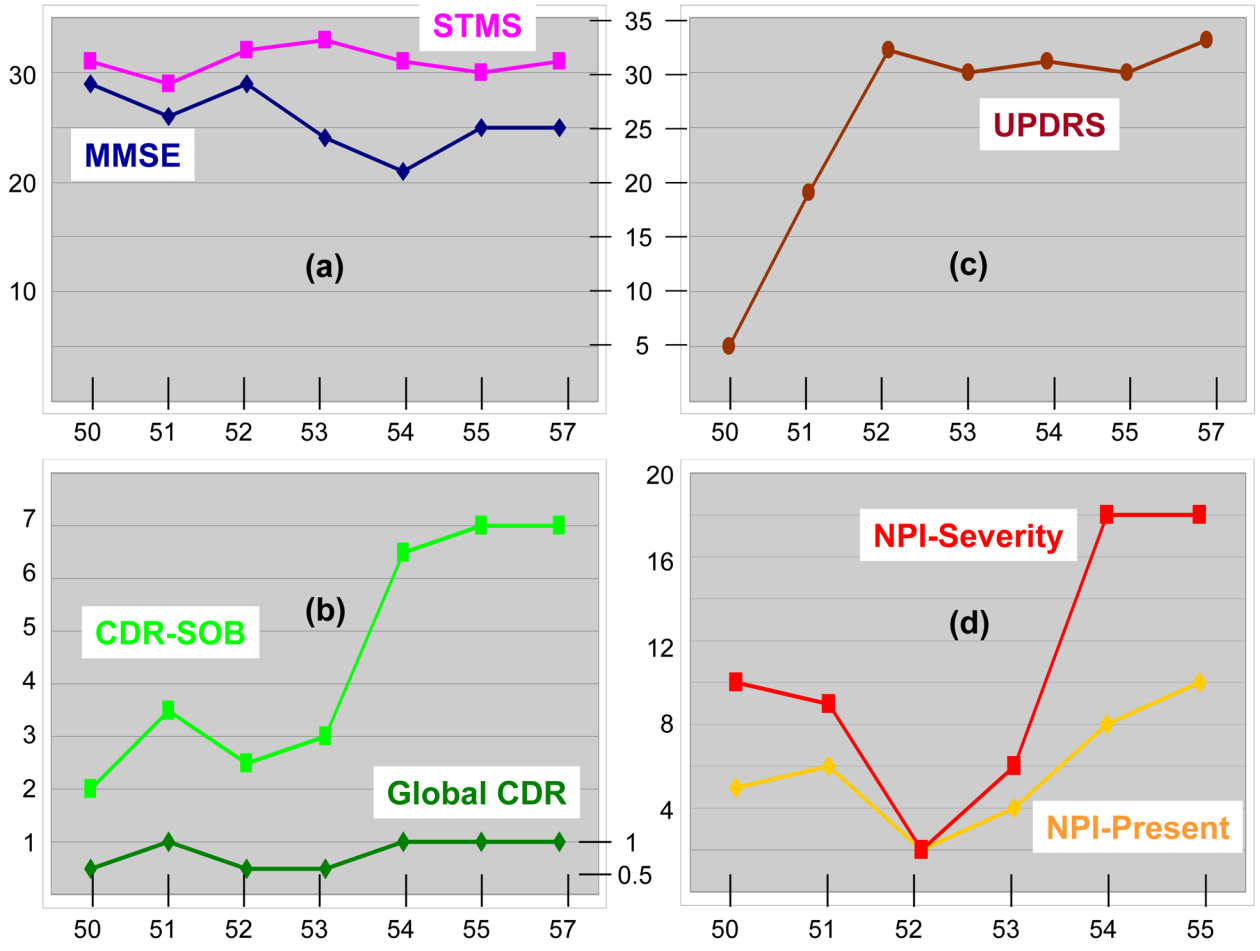

Figure 1. Longitudinal cognitive, motor, functional, and neuropsychiatric data in an illustrative case in the VSM-20 kindred with c9FTD/ALS. (a) Graphs of longitudinal scores on the Mini-Mental State Exam (MMSE) (maximum of 30) and Kokmen Short Test of Mental Status (STMS) (maximum of 36) of a patient from ages 50 to 57. **(b)** Global scores on the Clinical Dementia Rating (CDR) scale (maximum of 3) and CDR sum of the boxes (CDR-SOB) (maximum of 18) from ages 50 to 57. **(c)** Longitudinal summed scores for each assessment on the motor subtest of the Unified Parkinson's Disease Rating Scale (UPDRS) (maximum of 108) from ages 50 to 57. **(d)** Longitudinal scores and Neuropsychiatric Inventory (NPI) from ages 50 to 55. (At age 57, the patient was estranged from his wife.) The NPI-Present score represents the summed score for the presence (score = 1) or absence (score = 0) of each domain across the 12 domains (maximum of 12), and the NPI-Severity score represents the summed score for the severity rating by the informant (mild = 1, moderate = 2, and severe = 3) for each domain across the 12 domains (maximum of 36). Given that scores of less than 24 on the MMSE and of less than 29 on the STMS are viewed as abnormal, this patient has declined minimally on these screening/global measures of mental status. He has hovered in the very mild (0.5) to mild (1) range on the global CDR, whereas the CDR-SOB score shows the accumulating functional impairment across the six domains measured on the CDR. The UPDRS graph reflects that, at age 50, the patient had subtle parkinsonism that increased in severity through age 52 and that has registered scores of around 30 to 33 in the past five years. His parkinsonian features began as left hemiparkinsonism, which has since evolved to an asymmetric akinetic-rigid syndrome without tremor. None of his parkinsonian features responded to carbidopa-levodopa (750 mg of levodopa per day in divided doses). As reflected in the NPI graph, apathy, depression, and appetite/eating change have been confirmed by his wife to have been present throughout his course (he has gained more than 50 pounds over his illness due to hyperphagia), and the severity of most features has increased in recent years. The dips in frequency and severity on the NPI at age 52 may reflect the effects of quetiapine, which was commenced at age 51. However, despite upward titrations of this agent and many other pharmacologic adjustments, his neuropsychiatric morbidity continues to escalate. c9FTD/ALS, frontotemporal dementia or amyotrophic lateral sclerosis (or both) linked to chromosome 9; VSM-20, Vancouver-San Francisco-Mayo Clinic family 20.

and sporadic cases have been identified in every report published to date. Many reports document families in which succeeding generations appear to have a younger age of onset; hence, these reports suggest genetic anticipation [21,25,29]. Given that c9FTD/ALS involves a polynucleotide repeat expansion mechanism, it stands to reason that anticipation could occur. The challenge among geneticists is to resolve the technical aspects of quantifying the number of repeats in this mutation but this has been difficult. One can easily hypothesize that, with increasing numbers of repeats, an earlier age of onset would occur, but this awaits confirmation.

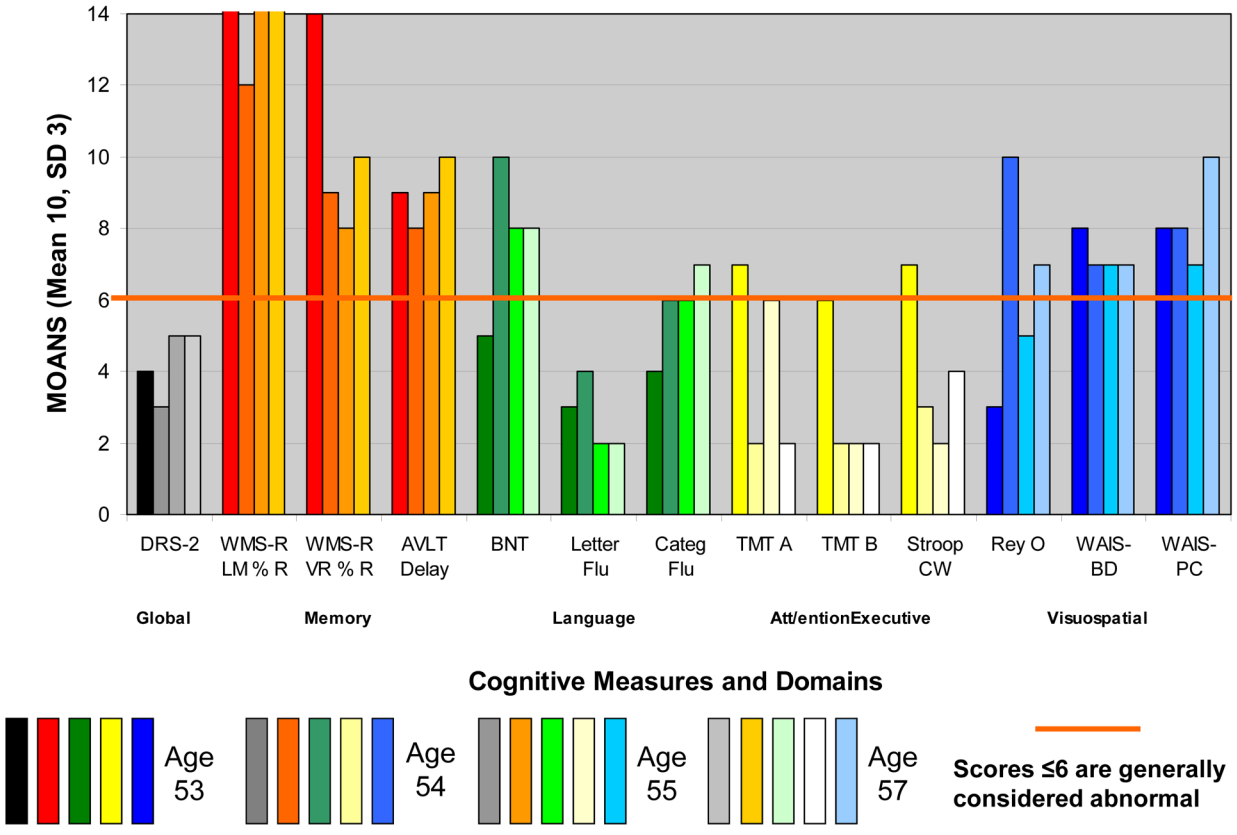

Figure 2. Graph of the neuropsychological test scores of the patient at ages 53, 54, 55, and 57. Note the poorer performance on measures of attention/executive functioning and letter fluency, which are typically impaired in those with behavioral variant frontotemporal dementia. Note also the relative stability of performance across most measures. He has been at the 'floor' in letter fluency and Trail Making Test (TMT) forms A and B for the past few years. AVLT, Auditory Verbal Learning Test; BNT, Boston Naming Test; Categ flu, category fluency; DRS 2, Dementia Rating Scale 2; Letter flu, letter fluency; MOANS, Mayo Older American Normative Studies; Rey O, Rey-Osterreith Complex Figure; SD, standard deviation; Stroop CW, Stroop Color-Word Test; WAIS-BD, Wechsler Adult Intelligence Scale-Block Design; WAIS-PC, Wechsler Adult Intelligence Scale-Picture Completion; WMS-R LM % R, Wechsler Memory Scale-Revised, Logical Memory, percentage retention; WMS-R VR % R, Wechsler Memory Scale-Revised, Visual Reproduction, percentage retention.

Clinical phenotype

Clearly, the predominant dementia phenotype is the classic bvFTD syndrome [31,32]. Many have some degree of parkinsonism, which is typically of the akinetic-rigid type without tremor and is levodopa-unresponsive [21]. Others have elements or the full clinical picture of ALS. This phenotype has not yet been reported in c9FTD/ALS, in contrast to FTD with or without parkinsonism associated with *MAPT* and *PGRN* mutations, in which a primary parkinsonian phenotype can occur. Most series do not have any cases with a primary progressive aphasia (PPA) phenotype, although this has been encountered rarely in some series [25-28]. Only one case of the corticobasal syndrome phenotype [33] has been reported in c9FTD/ALS [16]. Though rare, the amnestic presentation diagnosed clinically as probable Alzheimer's disease has been observed across many in the series [20,21,25,26], including one analysis focused on late-onset Alzheimer's disease [34]. The phenotype of dementia with Lewy bodies was reported in a few cases in one series [20]. These observations suggest that the *C9ORF72* mutation can manifest as a variety of dementia phenotypes as well as pure ALS, but the vast majority have the core syndrome of bvFTD ± parkinsonism ± ALS.

Cognitive features

The classic bvFTD phenotype involves executive dysfunction and word retrieval difficulties with relative sparing of memory and visuospatial functioning [31,32], as

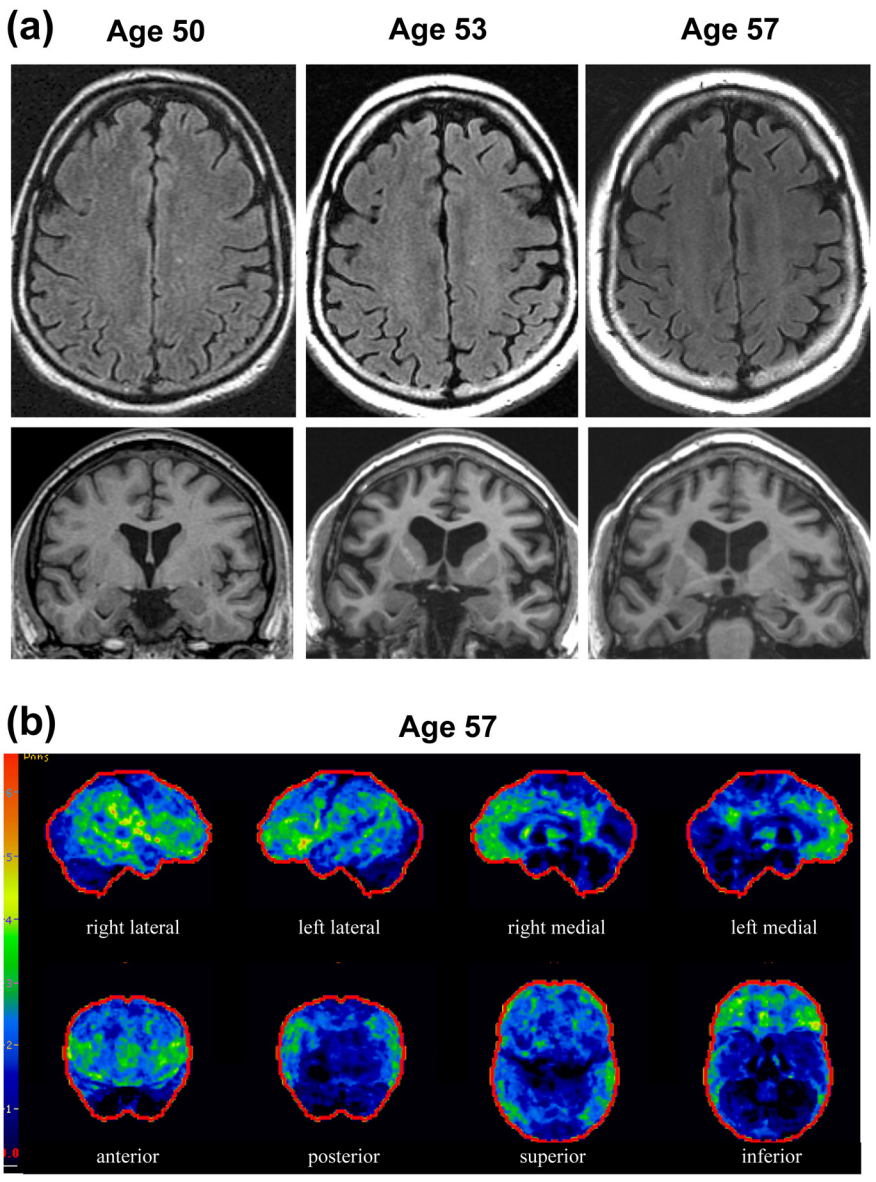

Figure 3. Neuroimaging findings in an illustrative case in the VSM-20 kindred with c9FTD/ALS. (a) Axial fluid attenuation inversion recovery magnetic resonance images (top row) and coronal T1-weighted magnetic resonance images (bottom row) demonstrating the minimal atrophy in the frontal and temporal lobes at ages 50, 53, and 57. **(b)** Flourodeoxyglucose positron emission tomography scan images of the brain at age 57. The color scheme on the left side of the set of images shows the relative degree of hypometabolism. Areas in black and blue are considered to be within normal limits, areas in green are considered mildly abnormal, areas in yellow are considered moderately abnormal, and areas in orange and red are considered markedly abnormal. Note the relatively mild and symmetric hypometabolism in the frontal, temporal, parietal, and cingulate cortices; this is remarkable given that this scan was performed eight years after the onset of symptoms. c9FTD/ALS, frontotemporal dementia or amyotrophic lateral sclerosis (or both) linked to chromosome 9; VSM-20, Vancouver-San Francisco-Mayo Clinic family 20.

exemplified by our illustrative case. Degeneration of the dorsomedial and dorsolateral cortices and their afferent and efferent connections – two of the critical frontosubcortical neural networks involved in executive functioning, word retrieval, psychomotor speed, motivation, and so on – is the likely substrate underlying the typical bvFTD cognitive features. In some c9FTD/ALS cases, this classic phenotype is not always exhibited, owing mainly to memory being impaired [20,21,25-28]. Visuospatial dysfunction is present in a minority of cases [21,25-28]. In addition to bifrontal and cingulate cortex atrophy, parietal cortex atrophy is part of the signature pattern on MRI [35] and this likely explains visuospatial dysfunction, but memory impairment is harder to explain.

Table 1. Key features of c9FTD/ALS due to the GGGGCC hexanucleotide repeat expansion in *C9ORF72* across published series with ample numbers of cases with the FTD ± ALS phenotype

Feature	Mayo Clinic	Mayo Clinic Brain Bank	Manchester	Vancouver	Dutch	London	Flanders-Belgian	NIH/NINDS	Irish	Total
Reference in text	[21]	[20]	[28]	[25]	[27]	[26]	[24]	[29]	[21]	
Cohort characteristics										
Number of cases examined (with mutation)	53 (63)	13 (13)	32 (32)	30 (30)	42 (42)	19 (19)	41 (41)	4 (4)	10 (10)	254
Number of kindreds identified	43	20	32	16	37	18	25	4	39	234
Percentage of all FTD ± ALS cases with mutation due to *C9ORF72/PGRN/MAPT*	12/4/6	NA	8/0/0	55/24/NA	9/7/10	7/7/6	8/7/1	8% for *C9ORF72*	9% for *C9ORF72*	Most in 7%-12% range
Percentage of familial FTD ± cases with mutation due to *C9ORF72/PGRN/MAPT*	20/6/11	NA	?	70/30/NA	18/14/22	13/14/14	26/22/4	NA	NA	Most in 13%-26% range
Percentage of FTD cases not due to known genes	66	NA	?	?	46	45	56	NA	NA	45%-66% range
Demographics										
Males/Females	33/30	8/5	18/14	21/8	20/22	11/8	8/7	?	10/11	129/105
Age of onset in years, mean or median	52	65	58	54	57	55	55	58	56	52-65 range
Age of onset in years, range	33-72	50-78	46-72	34-74	39-76	43-68	38-71	?	?	33-78 range
Survival in years, mean or median	5	5	?	5	7	9	5	?	?	5-9 range
Survival in years, range	1-17	3-11	1-11	1-16	1-22	1-22	2-17	?	?	1-22 range
Inheritance										
Inheritance pattern	AD	AD	AD	AD	AD	AD	AD	AD	AD	AD
Frequency of sporadic cases	++	++	++	++	++	++	++	++	+	++
Penetrance	High	High	High	High	High	High	High	High	High	High
Anticipation suggested	++	?	?	++	?	?	?	+	?	Many reports
Clinical phenotype										
bvFTD phenotype	+++	++	+++	+++	+++	+++	+++	++	0	Frequent
ALS phenotype	++	NA	NA	++	++	NA	++	0	+++	Often
FTD/ALS phenotype	++	0	++	++	++	++	++	++	++	Often
Primary parkinsonian phenotype	0	0	0	0	0	0	0	0	0	None reported
Non-fluent/agrammatic subtype of PPA	0	0	+	++	++	+	0	0	0	Rare

Continued overleaf

Table 1. Continued

Feature	Mayo Clinic	Mayo Clinic Brain Bank	Manchester	Vancouver	Dutch	London	Flanders-Belgian	NIH/NINDS	Irish	Total
Semantic subtype of PPA	0	0	+	0	+	0	0	0	0	Rare
Corticobasal syndrome phenotype	0	0	NA	0	0	0	0	0	0	None reported
Alzheimer's disease-like phenotype	+	++	NA	+	0	+	0	0	0	Rare
Cognitive features										
Memory impairment	++	+++	++	+++	+++	+++	?	?	0	Often to frequent
Executive functioning impairment	+++	+++	+++	+++	+++	+++	Presumably	Presumably	++	Frequent
Language impairment (aphasia)	++	++	+++	+++	++	+++	?	?	0	Frequent and usually late feature
Visuospatial impairment	+	?	+	+	+	+	?	?	?	Rare
Neuropsychological profile of executive/generation deficits with relative sparing of memory and visuospatial functions	++	Presumably in some	++	++	?	++	Presumably in many	Presumably in many	++	Often but certainly not frequent
Behavioral features										
Early behavioral disinhibition	+++	Presumably	+++	+++	++	+++	Presumably	Presumably	Presumably	Frequent
Early apathy or inertia	+++	Presumably	+++	+++	++	+++	Presumably	Presumably	Presumably	Frequent
Early loss of sympathy or empathy	+++	Presumably	+++	+++	?	++	Presumably	Presumably	Presumably	Frequent
Hyperorality and dietary changes	+++	Presumably	+++	?	?	+++	Presumably	Presumably	Presumably	Frequent
Pseudobulbar affect	+	?	?	?	?	?	?	?	?	Insufficient data
Psychosis (delusions or hallucinations)	++	?	++	+	+	++	?	?	?	Often
Other clinical features										
Frontal release signs	++	?	++	?	?	?	?	?	?	Insufficient data
Parkinsonism	++	++	++	++	?	++	?	?	?	Often
Upper or lower (or both) motor neuron dysfunction not fulfilling ALS criteria	++	?	+	++	?	+++	?	?	?	Often
ALS	++	0	++	++	++	++	++	0	+++	Often in FTD
Limb apraxia	0	?	0	+	+	0	?	?	?	Rare

The Manchester series only included cases with a frontotemporal dementia (FTD) spectrum dementia syndrome and not amyotrophic lateral sclerosis (ALS) or parkinsonism. In the Vancouver series, cases of FTD or ALS or both had progressive non-fluent aphasia plus frontal features and ALS. The percent breakdowns of chromosome 9 open reading frame 72 (C9ORF72) and progranulin (PGRN) are based on autopsied cases with TDP-43^{+} pathology, not all FTD cases. The Irish series involved mostly ALS cases, of which 10 had FTD or ALS or both. 0, feature reported as not present; +, feature reported as present infrequently (<10% of cases); ++, feature reported as often present (10% to 50% of cases); +++, feature reported as frequently present (>50% of cases); ?, feature not discussed sufficiently in the report to make any determinations. AD, Alzheimer's disease; bvFTD, behavioral variant frontotemporal dementia; c9FTD/ALS, frontotemporal dementia or amyotrophic lateral sclerosis (or both) linked to chromosome 9; GGGGCC, (the hexanucleotide expansion of) guanine-guanine-guanine-guanine-cytosine-cytosine; MAPT, microtubule-associated protein tau; NA, not applicable; NIH/NINDS, National Institutes of Health/National Institute of Neurological Disorders and Stroke; PPA, primary progressive aphasia.

The determination of whether memory is impaired varies on the basis of clinical evaluation, neuropsychological testing, and which tests are used. For example, one can consider the older and more simplistic rubric that memory impairment is due to an encoding versus retrieval deficit. A deficit in encoding implicates the mesial temporal lobe structures with or without other structures in the limbic system such as the medial thalamus, whereas a retrieval deficit implicates the frontosubcortical neural networks. Most cases of c9FTD/ALS have clinical, neuropsychological, and neuroimaging features implicating the frontosubcortical neural networks, and thus a retrieval deficit would be expected, and in one study in which neuropsychological tests were performed in many c9FTD/ALS subjects, performance on delayed recall measures was usually normal [21]. Yet many cases exhibit poor performance on delayed recall measures as well as on recognition of stimuli [26-28], suggesting an encoding deficit, yet the medial temporal lobes tend to be relatively spared, according to neuroimaging studies conducted thus far [21,26,35]. However, pathologic studies show that hippocampal sclerosis is frequent and associated with those presenting with an amnestic disorder [20]. This issue is reviewed in more detail in the section on 'Neuropathologic features and their clinical relevance'.

Another challenge is understanding the executive dysfunction in mutation carriers who have the bvFTD phenotype yet no apparent frontotemporal atrophy on MRI or hypometabolism on FDG-PET [21]. The pathologic findings, however, provide evidence that frontal atrophy is indeed more frequent with this phenotype. One hypothesis is that the executive deficits are due, in part, to primary cerebellar dysfunction akin to the cerebellar cognitive affective syndrome [36-38]. All pathologic studies in c9FTD/ALS have shown widespread ubiquitin-positive inclusions in the cerebellum, and this could contribute to 'frontal' dysfunction (see section on 'Neuropathologic features and their clinical relevance'). Furthermore, while neuroimaging studies clearly include the cerebellum as part of the signature pattern of atrophy [26,35], cerebellar degeneration per se tends to be minimal on pathologic analyses, and other clinical features of cerebellar dysfunction, such as limb or truncal ataxia, limb dysmetria, ataxic dysarthria, and nystagmus, have not been appreciated in affected cases. Understanding the mechanism for executive dysfunction in c9FTD/ALS cases with minimal or no frontotemporal atrophy will require further study.

Language impairment is relatively common in c9FTD/ALS but is rarely the predominant phenotype; aphasia typically evolves as the illness progresses. When the primary progressive aphasia syndrome is the predominant phenotype, it is typically of the non-fluent/agrammatic type [25-28]. Non-fluent/agrammatic aphasia relates to degeneration of Broca's area or the insula in the dominant hemisphere or both, and in those with a predominant non-fluent/agrammatic PPA phenotype, neuroimaging studies demonstrate this topography of atrophy or hypometabolism [39-44]. However, such PPA phenotype cases in c9FTD/ALS have not been well characterized with detailed speech/language assessments and neuroimaging studies, and so this remains to be seen. Furthermore, symmetric neuroimaging abnormalities are the rule and asymmetric findings are the exception [21,26,35], and so these PPA cases could be the exceptions with focal/asymmetric dominant hemisphere degeneration. One might also predict that if a bilateral and relatively symmetric pattern of degeneration has ensued and if the key anterior language networks are affected, then a non-fluent/agrammatic phenotype could be present. Also, the dominant hemisphere supplementary motor area has recently been implicated in the primary progressive apraxia of speech phenotype [45,46], and this could easily be construed to represent non-fluent aphasia; mesial frontal atrophy/hypoperfusion/hypometabolism is part of the signature pattern of topography in c9FTD/ALS [21,26,35], and so this mechanism is quite plausible. This is yet another area worthy of further research.

Behavioral features

The overwhelming majority of cases with a dementia syndrome-predominant phenotype as part of c9FTD/ALS manifest the full spectrum of the bvFTD features [31,32]: early behavioral disinhibition, early apathy or inertia, early loss of sympathy or empathy, and hyperorality and dietary changes. The dorsolateral prefrontal cortex, orbitofrontal cortex, and anterior cingulate cortex are typically affected, according to neuroimaging and neuropathologic studies [20,21,26,35], and this topography readily explains the full bvFTD spectrum of behavioral features. Yet there are those who do not have neuroimaging evidence of frontal atrophy or hypometabolism [21], and as noted above, perhaps the cerebellar degeneration contributes to these behavioral features similar to the hypothesis that such degeneration might explain executive dysfunction. These 'frontally impaired but frontally normal on neuroimaging' cases clearly deserve ample study, as understanding the neuroanatomic correlates of their impairment will not only aid in understanding the disease of c9FTD/ALS but also enhance our understanding of brain-behavior correlations in general.

A few investigators have observed that some c9FTD/ALS cases exhibit the most bizarre behavioral manifestations they have ever witnessed among all of the bvFTD patients they have cared for [21,28]. Psychotic features, obsessive-compulsive behaviors, odd ritualistic behaviors, and so on are often striking. A summary of observations by clinicians is presented in Table 2.

Table 2. Descriptions of dramatic behavioral manifestations associated with c9FTD/ALS

Delusions
• The patient believed that others were spying on her and required all blinds to be closed in the home and doors to be locked.
• The patient believed that pieces of plastic were emanating from his head, leading him to pick repetitively at his scalp to remove the 'plastic bits' embedded in his skin.
• The patient believed that someone was about to harm her and carried a knife and pistol for self-defense.
• The patient believed he had a weakness of the gluteal muscles and that he therefore had to keep his finger in his anus to prevent incontinence.
• The patient believed that he was under surveillance.
• The patient believed that he was infested by mites, which crawled under his skin and into his extremities. He reported that the mites congregated in his earlobe and that he could reduce their number by pinching his earlobe at regular 10-minute intervals.
• The patient believed that his son was trying to kill him, so the patient barricaded himself in his home.
• The patient believed he was being contacted by letter or phone by dead friends and hatched plans to meet them.
• The patient believed that characters on the television screen were communicating with her.
• The patient believed that someone's wife was trying to harm him and threatened to shoot her.
• The patient believed that people around him and on the television screen were talking about him and calling him names.
Hallucinations
• The patient had visions of the devil.
• The patient heard the voice of God.
• The patient perceived that men, including a man dressed in a gorilla outfit, were hiding in her garden and saw disembodied faces, which she believed to be spirits. As a result, the police were contacted.
Other
• The patient sat in the yard, held rifles in both arms, and 'shot anything that moved' (illustrative case).
• The patient spoke in a high-pitched and child-like voice and behaved as if she was a child.
• The patient underwent a dramatic change in religious beliefs and arranged ritualistic and candle-lit meetings with spirits.
• The patient felt the need to carry a handgun in her purse. When her husband hid the gun, she proceeded to purchase another (and was able to do so without raising the suspicion of the gunshop owner).
• The patient threw lit fireworks though his neighbor's letterbox.
• The patient complained of excessive heat. He threw open doors and windows, refused to allow any heating in the home, and dressed in summer attire in mid-winter. He took to pouring cold water over tepid food to 'cool it down'.
• The patient combed his hair repetitively and vigorously, leading to bleeding of the scalp. The patient wore multiple watches on his arm and donned clothes on the wrong part of his body (for example, trousers on his head and underpants on his arms). He used objects inappropriately (for example, a spoon to clean his teeth and a toilet brush to brush his hair).
• The patient constantly wiped surfaces and washed pots and carried with him a cloth to wipe his shoes before getting into his car and plastic bags to wipe his hands.
• The patient washed his hands, filed his nails, and combed his hair repetitively and drank excessive quantities of water as a remedy for her symptoms, leading to hyponatremia.
• The patient cleaned the house obsessively and followed his dog around, cleaning the surfaces that it had walked on.

Examples were compiled from the clinical series of the authors [21] and that of Snowden and colleagues [28]. c9FTD/ALS, frontotemporal dementia or amyotrophic lateral sclerosis (or both) linked to chromosome 9.

Other clinical features

Whereas the documentation of other clinical features varied across reports, many cases with frontal release signs, parkinsonism, upper or lower motor neuron dysfunction (or both) not fulfilling criteria for ALS, and the full ALS phenotype were observed. Limb apraxia was rarely documented.

Atypical features

Atypical features are already emerging. A very interesting (and, for many clinicians, somewhat frightening) finding is the identification of the *C9ORF72* mutation in rare cases of the FTD phenocopy syndrome [47]. The FTD phenocopy refers to those individuals who clearly exhibit cognitive and behavioral changes suggestive of bvFTD, but neuropsychological tests and neuroimaging studies tend to be more normal than not during the initial years of symptoms [48,49]. The 'typical' FTD phenocopy patient does not show progression on longitudinal clinical, neuropsychological, and neuroimaging evaluations, and such cases are now considered to usually have a non-degenerative substrate for their features. When

Table 3. Salient features of the FTD-predominant phenotype of c9FTD/ALS due to the GGGGCC hexanucleotide repeat expansion in *C9ORF72*

Frequency
• The mutation is as frequent as or more frequent than microtubule-associated protein tau (*MAPT*) or progranulin (*PGRN*) in most clinical cohorts with FTD ± parkinsonism ± ALS.
Demographics
• There is a slight male predominance.
• Age of onset is between 33 and 78, and most patients present in the 40- to 70-year age range.
• Survival is variable but typically is in the 5- to 9-year range.
• Survival is shorter when the ALS phenotype is present.
Inheritance
• Inheritance is autosomal dominant.
• Many examples of incomplete penetrance exist.
• Sporadic cases clearly exist.
• Some kindreds appear to exhibit an anticipation-like phenomenon.
Clinical phenotype
• The characteristic phenotype is bvFTD ± parkinsonism ± ALS.
• The primary progressive aphasia and Alzheimer's disease-dementia phenotypes are uncommon but do exist.
• The primary parkinsonism and corticobasal syndrome phenotypes are rare to nonexistent.
Cognitive features
• Executive dysfunction is very common, as would be expected in an FTD-spectrum disorder, but the underlying substrate for this cognitive feature is not fully understood in those with no frontotemporal changes on neuroimaging studies.
• Memory impairment is frequent, but the underlying substrate for this is not fully understood.
• Aphasia is frequent but is typically a manifestation as the disease evolves after the predominant bvFTD phenotype. The underlying substrate for aphasia in not fully understood.
• Visuospatial dysfunction in uncommon, but in view of the known parietal atrophy and hypometabolism in such cases, this feature is adequately explained.
• Because memory dysfunction or visuospatial dysfunction or both are present in many cases with c9FTD/ALS, such cases will not fulfill the neuropsychological criterion for bvFTD.
Behavioral features
• Almost all cases with a dementia phenotype have early behavioral disinhibition, early apathy or inertia, early loss of sympathy or empathy, and hyperorality and dietary changes and thus fulfill the bvFTD behavioral criteria.
• Psychosis and other dramatic/bizarre behavior changes can occur.
• The underlying substrate for the bvFTD features in those with minimal or no frontotemporal changes on neuroimaging studies is poorly understood.
Other clinical features
• Many with the bvFTD-predominant phenotype have evidence of parkinsonism or upper or lower motor neuron involvement or a combination of the three.

ALS, amyotrophic lateral sclerosis; bvFTD, behavioral variant frontotemporal dementia; c9FTD/ALS, frontotemporal dementia or amyotrophic lateral sclerosis (or both) linked to chromosome 9; *C9ORF72*, (gene encoding the mutation in) chromosome 9 open reading frame 72; FTD, frontotemporal dementia; GGGGCC, (the hexanucleotide expansion of) guanine-guanine-guanine-guanine-cytosine-cytosine.

first encountering patients who clearly have bvFTD features but no corroborating evidence of an underlying neurodegenerative disorder, the clinician is faced with the obvious challenge of establishing a confident diagnosis and predicting what the future holds. And since so few cases have come to autopsy, the underlying substrate for their symptoms has not been well characterized. The two cases recently reported with the FTD phenocopy associated with the *C9ORF72* mutation are very intriguing [47], not only because such atypical FTD cases do have a neurodegenerative disorder underlying their symptoms but also because of the number of atypical FTD cases who have surely been suspected by seasoned clinicians to have a primary psychiatric disorder. Clinical testing is now commercially available for *C9ORF72* mutation detection, and more FTD phenocopy and other atypical neurobehavioral syndromes will undoubtedly be identified with this mutation.

Neuropathologic features and their clinical relevance

Neuropathologic studies in c9FTD/ALS have shown many consistent findings yet also some unexpected,

Table 4. Clues that should alert clinicians to suspect the hexanucleotide repeat expansion in *C9ORF72* in individual patients

Demographics
• Age of onset in the 30- to 70-year age range
Inheritance
• Apparent autosomal dominant pattern of inheritance of dementia or ALS or both[a]
Clinical phenotype
• Presence of the phenotype of bvFTD ± parkinsonism ± ALS in the patient and his or her relatives[a]
• Absence of any of the focal/asymmetric focal cortical degenerative syndromes (for example, primary progressive aphasia and corticobasal syndrome) in the patient and his or her relatives[a]
Cognitive/Neuropsychological features
• Presence of executive dysfunction and word retrieval deficits[a]
• The presence of memory impairment or visuospatial impairment or both should not dissuade the suspicion of the mutation if many other clues are present.
• Normal or minimally abnormal performance on neuropsychological tests early in the course of behavioral changes should not dissuade the suspicion of the mutation if many other clues are present.
Behavioral features
• Presence of the 'classic bvFTD features' in the patient, including behavioral disinhibition, early apathy or inertia, early loss of sympathy or empathy, and hyperorality and dietary changes[a]
• Presence of psychosis and other dramatic/bizarre behavior changes in the patient ± his or her relatives
Neuroimaging features
• Presence of symmetric bilateral frontal (often mesial more so than dorsolateral) ± temporal ± parietal atrophy or hypometabolism[a]
• Normal or minimally abnormal neuroimaging findings early in the course of behavioral changes should not dissuade the suspicion of the mutation if many other clues are present.
Neuropathologic features
• Presence of TDP-43-, ubiquitin-, ubiquilin-, and p62-positive inclusions in the cerebellum in the patient or any of his or her relatives[a]

[a]This feature is a primary clue for considering the *C9ORF72* mutation. ALS, amyotrophic lateral sclerosis; bvFTD, behavioral variant frontotemporal dementia; *C9ORF72*, (gene encoding the mutation in) chromosome 9 open reading frame 72.

variable, and curious findings. All cases studied to date – except one (see below) – have had TDP-43 pathology associated with frontal and variable parietal or temporal cortical atrophy (or both) and microscopic evidence of neurodegeneration [20,21,25-28,50-55]. Many have evidence of upper or lower motor neuron degeneration (or both) that may or may not have been appreciated antemortem, but this finding underscores the involvement of the brain and spinal cord motor systems in this disease and also emphasizes the overlapping spectrum of FTD and ALS. Degeneration of the substantia nigra is also common and likely explains the presence of parkinsonism in the significant minority of cases who have parkinsonism. A few cases have had coexisting Alzheimer's disease pathology. One case with an apparent hexanucleotide expansion has been described in association with corticobasal degeneration pathology [28]; hopefully, additional details will be presented in the future to better understand this single case with non-TDP pathology.

Unexpected findings in c9FTD/ALS are the variable histologic features across cases [20,21,25,27,51-53]. Earlier studies suggested that all chromosome 9-linked FTD/ALS cases had a moderate degree of cortical neurons with neuronal cytoplasmic inclusions and relatively few dystrophic neurites across all cortical layers (which is characteristic of Mackenzie type 3, Sampathu type 2, and harmonized type B FTLD-TDP pathology) [56,57], yet approximately half of c9FTD/ALS cases have had many neurons with neuronal cytoplasmic inclusions and many dystrophic neurites in the cortex, especially in layer 2 (which is characteristic of Mackenzie type 1, Sampathu type 3, and harmonized type A FTLD-TDP pathology and most often associated with mutations in *PGRN*) [20,21,57]. Why this variability exists is not understood, but this finding suggests that there is not a distinctive set of histologic features for c9FTD/ALS based on TDP-positive inclusions alone.

One of the most unexpected and still curious findings in c9FTD/ALS cases is the predominance of ubiquitin-positive inclusions in the cerebellum, which far exceeds the density of TDP-positive inclusions [20,21,50,51,53,58]. The ubiquitin-positive inclusions also stain positively for ubiquilin and p62 immunohistochemistry, suggesting a pathophysiological link between *C9ORF72* expansions and ubiquilin proteins in ALS and FTLD-TDP

Table 5. Issues worthy of further study in c9FTD/ALS

Demographic and inheritance issues
• Is there a slight male predominance in the dementia-predominant phenotype of c9FTD/ALS? If so, why?
• Is the *C9ORF72* mutation present across races and continents? If not, does the mutation represent a common founder?
• Why are there such variable ages of onset and durations of disease across affected individuals?
• Does genetic anticipation occur in c9FTD/ALS? If so, does the age of onset decrease as the expansion repeat number increases?
• What explains incomplete penetrance in some families?
• What is the mechanism for explaining sporadic cases?
Clinical phenotype
• Why are the bvFTD or ALS phenotypes or both so consistently expressed?
• Why are the syndromes of primary progressive aphasia, corticobasal syndrome, and primary parkinsonism so uncommon in the *C9ORF72* mutation whereas the frequencies of these syndromes are higher in mutations associated with microtubule-associated protein tau (*MAPT*) and progranulin (*PGRN*)?
• Does the hexanucleotide repeat length impact the topography of degeneration and therefore the phenotype?
Cognitive features
• What is the underlying substrate for executive dysfunction and word retrieval impairment in those with no frontotemporal changes on neuroimaging studies? Does cerebellar dysfunction contribute to the 'frontal' cognitive features?
• What are the qualitative features of memory impairment on neuropsychological assessment?
• What is the underlying substrate for memory impairment in those with no frontotemporal changes on neuroimaging studies?
• What is the underlying substrate for aphasia, particularly in those with no frontotemporal changes on neuroimaging studies?
• How will c9FTD/ALS cases be viewed for experimental drug trial participation if they do not meet the neuropsychological profile criteria of bvFTD?
Behavioral features
• Why are psychosis and other dramatic/bizarre behavior changes relatively common in c9FTD/ALS? What is the underlying substrate for these behavioral features?
• What is the underlying substrate for the prominent behavioral features in those with minimal or no frontotemporal changes on neuroimaging studies? Does cerebellar dysfunction contribute to these prominent behavioral features?

ALS, amyotrophic lateral sclerosis; bvFTD, behavioral variant frontotemporal dementia; c9FTD/ALS, frontotemporal dementia or amyotrophic lateral sclerosis (or both) linked to chromosome 9; *C9ORF72*, (gene encoding the mutation in) chromosome 9 open reading frame 72.

[20,50,51,53,58]. Yet the degree of neuronal loss in cerebellar structures has been mild to negligible and this may explain why classic cerebellar signs such as ataxia, dysmetria, and nystagmus have not been appreciated or reported. However, the finding of ubiquitin-, ubiquilin-, and p62-positive inclusions in the cerebellum has been present in almost every case in which such immunohistochemistry has been used. Hence, these cerebellar inclusions are now viewed as a highly sensitive and specific marker for the presence of the *C9ORF72* mutation.

The cognitive and behavioral features and their known or presumed neuropathologic substrates are described above in the respective sections, but again, the typical cognitive features (executive dysfunction and word retrieval deficits) likely relate to degeneration in the dorsomedial and dorsolateral frontosubcortical networks, and the typical behavioral features (impaired social cognition, prominent apathy, and so on) likely relate to these and other frontosubcortical networks such as the orbitomedial frontal and anterior cingulate circuits. Furthermore, the von Economo neurons in the anterior cingulate and insular regions have been implicated in impaired social cognition [59-61]. These clinical-topography associations are very plausible when abnormalities on MRI, single-photon emission computed tomography, or PET correspond to the specific features that are present in individual cases.

The more challenging circumstance is when obvious cognitive or behavioral changes or both are present and the neuroimaging studies are normal regardless of whether any patient has an obvious neurologic cause or has the less obvious FTD phenocopy syndrome. Memory impairment is not typical of the bvFTD syndrome but is often present in c9FTD/ALS cases; as discussed above, this could relate to hippocampal sclerosis or a retrieval-based deficit due to frontosubcortical dysfunction. Also, even when hippocampal sclerosis is not present, an encoding deficit could relate to dysfunction associated with ubiquitin-, ubiquilin-, and p62-positive inclusions in the hippocampus [53]. Dysfunction associated with these inclusions in the cerebellum as part of the cerebellar cognitive affective syndrome is also possible. This will be challenging to prove or disprove until radioligands that tag these key proteins are available for functional neuroimaging studies [47].

Summary

A summary of the salient features of the FTD-predominant phenotype of c9FTD/ALS due to the GGGGCC hexanucleotide repeat expansion in *C9ORF72* is presented in Table 3.

Clues for the clinician to suspect the *C9ORF72* mutation

An important consideration for any clinician evaluating a patient for changes in cognition, behavior, or neuromuscular functioning is when to be suspicious of the mutation in *C9ORF72*. Clinical clues that should raise suspicion are listed in Table 4.

Future directions

With any discovery, 'one question answered poses ten new questions' and this is clearly the case in many aspects of c9FTD/ALS. A list of some issues worthy of further study is presented in Table 5. Our hope is that the observations in this review based on what has been published thus far help steer investigators to answer these and other questions associated with this fascinating disorder.

Abbreviations

ALS, amyotrophic lateral sclerosis; bvFTD, behavioral variant frontotemporal dementia; c9FTD/ALS, frontotemporal dementia or amyotrophic lateral sclerosis (or both) linked to chromosome 9; *C9ORF72*, (gene encoding the mutation in) chromosome 9 open reading frame 72; FDG-PET, flourodeoxyglucose positron emission tomography; FTD, frontotemporal dementia; FTD/ALS, frontotemporal dementia or amyotrophic lateral sclerosis or both; FTLD-MND, frontotemporal lobar degeneration with motor neuron disease; FUS, fused in sarcoma; GGGGCC, (the hexanucleotide expansion of) guanine-guanine-guanine-guanine-cytosine-cytosine; MAPT, microtubule-associated protein tau; MRI, magnetic resonance imaging; PET, positron emission tomography; PGRN, progranulin; PPA, primary progressive aphasia; TARDBP, TAR DNA-binding protein.

Competing interests

This paper was supported by P50 AG016574. Ronald C Petersen is the principal investigator. BFB declares that he has no competing interests. He has served as an investigator for clinical trials sponsored by Cephalon, Inc. (Frazer, PA, USA), Allon Pharmaceuticals Inc. (Vancouver, BC, Canada), and GE Healthcare (Little Chalfont, Buckinghamshire, UK). He receives royalties from the publication of a book entitled the *Behavioral Neurology of Dementia* (Cambridge: Cambridge University Press; 2009). He has received honoraria from the American Academy of Neurology. NRG-R declares that he has no competing interests. He is on the scientific advisory board of Codman (part of DePuy Orthopaedics, Inc, Warsaw, IN, USA) and is chair of the data and safety monitoring board of Baxter (Deerfield, IL, USA) regarding an IGIV (immune globulin administered intravenously) trial in Alzheimer's disease, an editor for the *Neurologist*, and part of multicenter trials for Allon Pharmaceuticals Inc. (progressive supranuclear palsy), Janssen (Titusville, NJ, USA), Pfizer Inc (New York, NY, USA) (bapineuzumab for Alzheimer's disease), and Forest Laboratories, Inc. (New York, NY, USA) using memantine in frontotemporal dementia.

Authors' contributions

Both authors contributed to the analysis and views expressed in this review. BFB drafted the manuscript, and NRG-R revised it critically. Both authors read and approved the final manuscript.

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Author details

[1]Department of Neurology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA. [2]Department of Neurology, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224, USA.

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