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Evaluation of subcortical pathology and clinical correlations in FTLD-U subtypes

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Abstract

Frontotemporal lobar degeneration (FTLD) can be classified as tau-positive (FTLD-tau) and tau-negative FTLD. The most common form of tau-negative FTLD is associated with neuronal inclusions that are composed of TAR DNA binding protein 43 (TDP-43) (FTLD-TDP). Recent evidence suggests that FTLD-TDP can be further subdivided into at least three major histologic variants based on patterns of TDP-43 immunoreactive neuronal cytoplasmic inclusions (NCI) and dystrophic neurites (DN) in neocortex and hippocampus. The aim of this study was to extend the histologic analysis to other brain regions and to determine if there were distinct clinical and pathologic characteristics of the FTLD-TDP subtypes. Thirty-nine FTLD-TDP cases were analyzed (Mackenzie type 1, n = 24; Mackenzie type 2, n = 9; Mackenzie type 3, n = 6). There was a highly significant association between clinical syndrome and FTLD-TDP subtype, with progressive non-fluent aphasia associated with type 1, semantic dementia with type 2, and behavioral variant frontotemporal dementia with types 1, 2 and 3. Semi-quantitative analysis of NCI and DN demonstrated different patterns of involvement in cortical, subcortical and brainstem areas that were characteristic for each of the three types of FTLD-TDP. Type 1 had a mixture of NCI and DN, as well as intranuclear inclusions in most cases and TDP-43 pathology at all levels of the neuraxis, but less in brainstem than supratentorial structures. Type 2 cases were characterized by predominance of long, thick DN in the cortex, as well as numerous NCI in hippocampus, amygdala and basal ganglia, but virtually no NCI and only sparse DN in diencephalon and brainstem. Type 3 had a paucity of DN at all levels of the neuraxis and significantly more NCI in the hypoglossal nucleus than the other types. These findings extend previously described clinicopathological associations of FTLD-TDP subtypes and support the notion that FTLD-TDP subtypes may be distinct clinicopathologic disorders.

Keywords

frontotemporal dementia; frontotemporal lobar degeneration; immunohistochemistry; progressive non-fluent aphasia; semantic dementia; TDP-43

INTRODUCTION

The term frontotemporal lobar degeneration (FTLD) refers to a group of neurodegenerative disorders that are the cause of the clinical syndromes of frontotemporal dementia (FTD)

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[30]. The major pathological disorders included in FTLT include Pick disease, corticobasal degeneration, progressive supranuclear palsy, neuronal intermediate filament inclusion disease, frontotemporal lobar degeneration with ubiquitin-immunoreactive inclusions (FTLD-U), frontotemporal lobar degeneration with motor neuron disease (FTLD-MND) and dementia lacking distinctive histology. Pick disease, corticobasal degeneration, progressive supranuclear palsy are characterized by neuronal and glial inclusions composed of abnormally phosphorylated microtubule associated protein tau and are classified as FTLD-tau [28]. Neuronal intermediate filament inclusion disease is characterized by neuronal inclusions composed in part of intermediate filament proteins [4,17] and is classified as FTLD-IF [28]. FTLD characterized by ubiquitin-positive inclusions composed of the TAR DNA binding protein of 43-kDa (TDP-43) [32] are classified as FTLD-TDP [28]. Some cases of FTLD-TDP are associated with motor neuron disease (MND) [18], and most cases of amyotrophic lateral sclerosis have TDP-43 immunoreactive inclusions at postmortem examination, suggesting that FTLD-MND and amyotrophic lateral sclerosis form a disease spectrum [29].

Recent clinicopathological studies have demonstrated an association between pathologic variants and three main clinical variants of FTD [9,13,22,25]. The three clinical variants include the behavioral variant of FTD (bvFTD), which is characterized by personality change and executive dysfunction; progressive non-fluent aphasia (PNFA), which is characterized by non-fluent speech with agrammatism; and semantic dementia (SD), which is characterized by loss of word and object meaning and poor comprehension [31]. Semantic dementia can be further subdivided into left dominant SD, where loss of word meaning is the dominant feature, and right dominant SD, where loss of facial recognition and behavioral dyscontrol are dominant features [36].

Previous studies have demonstrated good clinicopathological correlations when disorders are simply grouped into tau-positive and tau-negative FTLD [9,22]. More recently, it has been suggested that FTLD-TDP can be subdivided into at least three major subtypes based upon distribution of ubiquitin or TDP-43 immunoreactive inclusions [3,27,34]. In these schemes the pathological analysis is often limited to cortex [34] or to cortex and hippocampus [27]. When multiple brain regions were studied [33], the classification scheme proposed by Mackenzie and co-workers [27] proved to be more useful at differentiating subtypes than that proposed by Sampathu and co-workers [34], probably because of the use of more than one brain region to define the subtype in the Mackenzie classification scheme. Moreover, the scheme proposed by Mackenzie was shown to have specificity with respect to FTD clinical subtypes [27].

The aim of our study was to determine if inclusion of brain regions other than the cortex and hippocampus could be used to support the Mackenzie classification scheme and if the subtypes had correlations with clinical phenotypes of FTD.

METHODS

Subject selection

The neuropathological database at the Mayo Clinic in Jacksonville, Florida, was queried to identify all cases of tau negative FTLD accessioned from 1998 to 2007 that had paraffin blocks from multiple brain regions suitable for further study. A total of 70 cases were identified, and most also had frozen tissue from which DNA had been extracted and screening for mutations in the gene for progranulin had been performed as previously described [1,14]. Cases were excluded if they had a Braak neurofibrillary tangle stage of IV or greater and if they had other major pathologic processes, such as Lewy body disease or argyrophilic grain disease, that might complicate interpretation of neuronal pathology in

subcortical regions. Cases of neuronal intermediate filament inclusion disease [23,38] and TDP-43-negative FTL-D-U [20] were also excluded. Hence inclusion and exclusion criteria were based only on pathologic features. Thirty-nine subjects met these inclusion and exclusion criteria.

Pathological methods

All cases had prior neuropathological evaluation using staining methods and a diagnostic algorithm as previously described [7,37]. The brains had standardized dissection and sampling. Glass mounted sections were studied with hematoxylin and eosin (H&E) and with thioflavin-S fluorescent microscopy to assess Alzheimer type pathology.

Immunohistochemistry was performed using a DAKO Autostainer with the following antibodies: TDP-43 (rabbit polyclonal; 1:3,000, ProteinTech Group, Chicago, IL); ubiquitin (Ubi-1, 1:40,000; EnCor Biotechnology, Alachua, FL); phosphorylated neurofilament (SMI-31, 1:20,000; Sternberger-Meyer, Gaithersburg, MD); phospho-tau (CP-13, 1:100; Peter Davies, Albert Einstein College of Medicine, Bronx, NY); α -synuclein (NACP, 1:3,000) [2,11]; and α -internexin (1:100; EnCor Biotechnology, Alachua, FL). The presence or absence of motor neuron degeneration was assessed and defined as previously described, with additional assessment using immunohistochemistry for activated microglia to assess tract degeneration and motor neuron loss [21].

Semiquantitative analysis of TDP-43 immunohistochemistry

For each case, 10 sections were processed for TDP-43 immunohistochemistry, including the following regions: cortex – midfrontal gyrus (MF), superior temporal gyrus (ST), inferior parietal gyrus (IP) and entorhinal cortex (ERC); subcortical areas – hippocampal dentate fascia, hippocampal CA1 pyramidal layer, amygdala, putamen and thalamus; and brainstem – midbrain tectum, substantia nigra, inferior olivary nucleus, hypoglossal nucleus and cerebellar dentate nucleus. Abnormal TDP-43 immunoreactivity was scored on a 5 point scale by two observers (AS, DWD) as 0 = absent; 0.5 = rarely observed; 1 = sparse; 2 = moderate and 3 = frequent. For each of the brain regions, the density of neuronal cytoplasmic inclusions (NCI) and dystrophic neurites (DN) were scored separately. The presence or absence of thin neurites, as recently described by Hatanpaa and co-workers [12], was assessed in the CA1 region of the hippocampus. In addition, the presence or absence of neuronal intranuclear inclusions (NII) was assessed in all brain regions, except the hippocampal dentate cell layer and CA1 region and cerebellar dentate.

Criteria for subclassification

The Mackenzie scheme [6,27] was used to classify the cases, as this was found to be the most reliable scheme when subcortical brain regions were studied [33]. The subtypes proposed by Mackenzie [27] map approximately to those proposed by Sampathu [34] as follows: Mackenzie type 1 corresponds to Sampathu type 3; Mackenzie type 2 corresponds to Sampathu type 1; Mackenzie type 3 corresponds to Sampathu type 2.

Type 1 cases had moderate to numerous TDP-43 immunoreactive NCI, as well as thin and short DN predominantly in layer II of neocortex and variable density of pleomorphic NCI in the dentate gyrus of the hippocampus. Type 2 cases had predominance of TDP-43 immunoreactive large and thick DN not restricted to any layer of the neocortex with absent, or at most sparse, NCI and no NII in neocortex. Type 3 cases had NCI in neocortex and in dentate granule cells of hippocampus with absent to sparse DN.

Clinical information

In all cases, one experienced behavioral neurologist (KAJ) blinded to any pathological data, reviewed the available medical records and abstracted demographic and clinical information. Medical records were sparse on seven cases. Published research criteria for the clinical diagnosis of FTD [31] were applied to each case utilizing clinical features at presentation. Parkinsonism was defined as the presence of at least any two of the following: resting tremor, bradykinesia, postural instability or cogwheel rigidity. A positive family history was defined as at least one first degree relative with a diagnosis of parkinsonism, dementia or MND.

Statistical methods

Statistical analyses were performed utilizing SigmaStat (ver 3.0.1 Systat Software Inc, San Jose, CA). Binary data were compared across the three histological types with Chi-square test. Analysis of variance was used to compare the three groups for normally distributed continuous variables (e.g., brain weight, disease duration); when significant differences were detected, pairwise comparisons were made with Student-Newman-Keuls Method. For ordinal data (e.g., Braak stage, NCI or DN scores) Kruskal-Wallis analysis of variance on ranks was used; when significant differences were detected, pairwise comparisons were made with Dunn's Method. Since statistical analyses of lesion densities across the three types were exploratory (i.e. hypothesis generating and not hypothesis testing), we did not adjust for multiple comparisons.

RESULTS

Demographic, pathological, clinical and genetic information is shown in Table 1. There were no significant differences in demographics across three types, but there was a difference in disease duration, with type 3 having significantly shorter disease duration than both types 1 and 2. In addition, type 2 had significantly longer disease duration than type 1. The presence of a family history of a neurodegenerative disorder was not different across the three histological types, but tended to be more frequent in type 1.

Pathological findings

By experimental design Alzheimer type pathology was minimal in all cases, but several had sparse cerebrovascular lesions or cortical diffuse type amyloid plaques with minimal neurofibrillary degeneration. The presence of these concurrent pathologies did not differ between the three types. Brain weight tended to be greater in type 3 than in types 1 and 2, but this did not reach statistical significance. Hippocampal sclerosis is common in tau-negative FTLN [15], and it was detected in 27 of the 39 cases (69%), with no significant difference in frequency of hippocampal sclerosis between the three types. Pathologic evidence of MND was more frequent in type 3 and this was significantly different compared to type 1.

Clinical features

There was a significant difference in the syndromic diagnoses across all three types for those cases in which sufficient clinical information was available to unequivocally assign an FTD clinical variant. Behavioral variant FTD accounted for 58% of the syndromic diagnoses in type 1 and 100% of the diagnoses of type 3. A diagnosis of PNFA was only identified in type 1 (42%), and 71% of type 2 fulfilled criteria for SD, a diagnosis that was only identified in type 2. Two of the type 2 subjects that were clinically classified as having a SD phenotype had features that were consistent with right dominant SD. There were no significant differences in the frequency of other clinical features. Eight of the 36 cases that

underwent genetic analysis (22%) were found to have a mutation in the gene for progranulin, but there was no statistically significant difference between subtypes due to the small sample size. One the type 2 cases carried a mutation in the gene for leucine rich repeat kinase [5].

When we combined all three types we found a significant association between the presence of Parkinsonism and lesser DN in substantia nigra, and midbrain tectum ($p < 0.05$), as well as an association between the presence of aphasia and increased deposition of NCI in the temporal cortex ($p < 0.05$). We did not find any association between behavioral/personality changes and frontal lobe pathology.

Semi-quantitative analysis of NCI

Graphical display of the data for NCI in neocortical regions is shown in Figure 1 in bar charts showing the median and 25th and 75th percentile. Cortical NCI tended to be greater in type 1 than in type 2 in all regions and was significant in the frontal, temporal and entorhinal cortices (Table 2). Greater variance of data for type 1 in the parietal lobe eliminated significance for this region. The cortical region that tended to have the most NCI in type 3 was the frontal lobe and least in the temporal and parietal lobes, and type 3 cases had significantly fewer NCI in the temporal lobe compared to in type 1. Figure 2 shows that all subcortical regions were affected to some degree in all FTLD-TDP subtypes. There was no significant difference in density of NCI across the three types, except that the thalamus had almost no NCI in type 2 cases. Subcortical involvement was most consistent in all subcortical areas in type 1. Type 2 had NCI in basal ganglia, but not thalamus. Type 3 tended to have more NCI in limbic structures (hippocampus and amygdala) than in basal ganglia and thalamus. Brainstem NCI were sparse in all types (Figure 3), but significantly more in the substantia nigra and inferior olive in type 1 and in the hypoglossal nucleus in type 3 (Table 2).

Semi-quantitative analysis of DN

Figure 4 shows that cortical DN were abundant in both types 1 and 2, but significantly less in type 3 in all regions. Subcortical areas also have fewer DN in type 3 compared to both types 1 and 2 (Figure 5), but the differences were not as striking as for cortical regions (Table 3). Of the subcortical areas studied, the amygdala had significantly more DN than the hippocampus and thalamus for type 2. Brainstem DN were sparse in all FTLD-TDP subtypes (Figure 6), but significantly greater in type 1 than type 2 for the substantia nigra, and for the inferior olive compared to type 3.

Qualitative summary of TDP-43 immunohistochemistry

Morphology of NCI—There were notable differences in the FTLD-TDP subtypes in terms of distribution and morphologic features of the inclusions. In type 1, almost all regions were found to have at least some inclusions. The NCI in type 1 cases were often granular (Figure 7a) or crescent shaped (Figure 7d). In type 2 there were often many NCI in dentate gyrus, amygdala and putamen and these most often were round, dense Pick body-like inclusions (Figure 7b). In type 3 NCI were poorly defined granular inclusions in the hippocampus (Figure 7c) and cortex (Figure 7f) and similar to what has been termed “pre-inclusions.” On the other hand, NCI in the hypoglossal nucleus were more typical of those seen in MND (Figure 7e).

Morphology of DN—In type 1 cases DN were usually short processes of variable length (Figure 8a), while DN in type 2 cases were usually thicker and longer (Figure 8b). DN were sparse or absent in type 3. An additional type of neurite was characterized by delicate thin processes in the CA1 sector of the hippocampus (Figure 8d). The presence of these

hippocampal neurites was related to age ($p=0.007$) and FTLT-TDP subtype ($p=0.006$). A logistic regression model for these two variables showed an odds ratio for hippocampal neurites and age to be 0.84 (0.74, 0.95; 5th and 95th confidence intervals) and for FTLT-TDP type 0.10 (0.02, 0.51; 5th and 95th confidence intervals). These fine hippocampal neurites were largely limited to type 1 patients and often those dying at relatively young ages. It has been suggested that hippocampal neurites may be a precursor to hippocampal sclerosis, given the similar distribution of the two pathologies [12], but in this series of cases, the presence of hippocampal sclerosis was not related to either age or FTLT-TDP subtype. The presence of hippocampal neurites did not correlate with any of the clinical FTD syndromic diagnoses or with the presence of PGRN mutations. More cases without PGRN mutations (61%) had hippocampal neurites than cases with PGRN mutations (50%) for type 1 subjects only.

Intranuclear inclusions—NII (Figure 8c) were detected in 24 of the 39 cases in at least one of the regions studied. The presence of NII was significantly associated with FTLT-TDP type ($p<0.001$). A logistic regression model for NII and FTLT-TDP type showed an odds ratio for type to be 0.02 (0.003, 0.19; 5th and 95th confidence intervals). In fact, NII were detected in 96% of type 1 cases compared to 16% of type 3 and none in type 2. NII were detected in the entorhinal cortex in one type 3 case

DISCUSSION

In this study we have confirmed and extended the clinicopathological findings associated with the proposed histological variants of tau-negative FTLT originally proposed by Mackenzie and co-workers [27]. We found clinical FTD syndromic diagnoses to be strongly associated with the three different histological variants [35]. Specifically, we found PNFA subjects only in type 1 and SD only in type 2. Behavioral variant FTD accounted for all subjects in type 3. Similar associations between SD and type 2 (Sampathu type 1) have been reported [10,27]. We also found a trend for disinhibition to be more frequent in type 2, although this did not reach statistical significance. We did not find any difference across the three variants in either the presence of a positive family history of neurodegenerative disease or the presence of mutations in the progranulin gene; however, the present study was under-powered to address this issue rigorously. Nevertheless, as previously suggested [26], mutations in progranulin were only detected in FTLT-TDP type 1.

Type 3 cases tended to be youngest at death and to have significantly shorter disease duration. This may be explained by the fact that half of the subjects with FTLT-TDP type 3 had pathologic evidence of MND, and subjects with FTLT-MND have been shown in previous studies to die at a younger age and to have a shorter disease duration (approximately 2.3 years) [19]. The shorter disease duration may in part account for less brain atrophy in type 3 cases with tendency for brain weights to be in the normal range (1200 ± 180 grams). Type 2 cases had the longest survival of approximately 10 years, which is consistent with findings recently reported in another study [10].

Cases with pathological evidence of MND were limited to FTLT-TDP type 2 and type 3; however, we found that type 3 cases more often had lower motor neuron pathology, while type 2 cases more often had upper motor neuron pathology (i.e. FTLT-primary lateral sclerosis [8,16]) (not shown). While the former association has been previously reported [27], the latter is a novel finding that needs to be confirmed in a larger series. We also found an association between Parkinsonism and DN in substantia nigra and midbrain tectum, and between aphasia and NCI in temporal cortex which requires further analysis. Although Parkinsonism would be expected to be associated with substantia nigra pathology and

aphasia to be associated with temporal cortical pathology, the association with DN in the former and NCI in the latter is unclear.

Findings from semi-quantitative analysis of neocortical and limbic regions were similar to that reported by Mackenzie et al. confirming that our typing scheme fits well with that previously reported [27]. Type 1 variant was characterized by a mixture of NCI and DN; type 2 variant by predominance of DN; and our type 3 variant by predominance of NCI. We also observed, however, that the type 2 variant had a moderate to frequent NCI in the dentate gyrus of the hippocampus, amygdala and putamen, although NCI were minimal in neocortical regions. Extending the semi-quantitative analysis to subcortical gray and brainstem regions demonstrated differences between neocortical and limbic, and subcortical gray and brainstem regions in terms of abnormal TDP-43 immunoreactive lesion burden and distribution. Of importance, is the fact that DN do not predominate in subcortical gray and brainstem structures in type 2 cases, as they do in neocortical regions, which argues against considering FTLN-TDP type 2 to be a subtype of FTLN-TDP associated predominantly with DN. Another important finding observed with subcortical analysis was that although NCI are prominent in limbic regions and basal ganglia in FTLN-TDP type, NCI are absent to scant in thalamus and brainstem regions.

Type 3 is considered to be predominantly associated with NCI, but sparse neurites were detected in most regions studied. Nevertheless, the density of DN was significantly less than in types 1 and 2 in the cortex and a number of subcortical regions. The most significant difference in regional pathology with type 3 was the selective involvement of the motor neurons in the brainstem, which was nearly completely absent in types 1 and 2.

The presence of hippocampal neurites was driven by at least two factors, FTLN-TDP type and age. It was not associated with hippocampal sclerosis with a multiple logistic regression model that included age, FTLN-TDP type and dentate fascia NCI score. Hippocampal neurites tended to be most frequent in type 1; they were virtually absent in type 2 cases. Logistic regression showed that younger age was a risk factor for hippocampal TDP-43-immunoreactive neurites. The average age for cases with hippocampal neurites was 70 (± 8 years) compared to 78 (± 10 years) for cases without neurites ($p=0.015$). There was only a weak trend for an inverse relationship between the presence of hippocampal neurites and neuronal loss in the CA1 region of the hippocampus making it unlikely that hippocampal neurites is a precursor to hippocampal sclerosis as suggested by Hatanpaa [12]. Since the presence of HpScl in FTLN is associated with an older at death [15], younger FTLN subjects are less likely to have HpScl, hence less likely to have neuronal loss in the CA1 region of the hippocampus and more likely to have retain neuronal elements with abnormal TDP-43 immunoreactivity.

As previously reported NII were associated with the type 1 variant, being found in 96% of the cases, although we also found sparse NII in the entorhinal cortex in type 3 variant. Therefore, NII are not completely specific to any one variant, as previously alluded to [6,27]. As we previously noted, the presence of NII is not highly specific to progranulin mutations [14].

We also observed that morphology of the NCI is associated with histological type. We observed that inclusions in FTLN-TDP type 1 are most often granular [24], while those in type 2 are Pick body like [24]. Inclusions in the type 3 variant are also different, being neither granular nor Pick body like, and appearing a diffuse cytoplasmic TDP-43 immunoreactivity consistent with “pre-inclusions.” This is an intriguing finding that suggests that the formation of abnormal TDP-43 immunoreactive inclusions is not entirely arbitrary. This fact, along with the differences in the distribution and nature of TDP-43

pathology suggests that the three FTLT-DTP subtypes may be distinct clinicopathologic entities.

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Figure 1. Distribution and density of NCI in cortical regions. * = $p < 0.05$ compared to type 1. (MF = midfrontal; ST = superior temporal; IP = inferior parietal; ERC = entorhinal cortex)

Figure 2. Distribution and density of NCI in subcortical regions. * $p < 0.05$ compared to type 1 (Hp = hippocampus, dentate fascia; Amg = amygdala; BG = basal ganglia, putamen; Thal = thalamus)

Figure 3.

Distribution and density of NCI in brainstem regions * $p < 0.05$ compared to type 2; # $p < 0.05$ compared to types 1 and 2. (MB = midbrain, tectum; SN = substantia nigra; XII = hypoglossal nucleus; IO = inferior olivary nucleus)

Figure 4. Distribution and density of DN in cortical regions. * $p < 0.05$ compared to type 1. (MF = midfrontal; ST = superior temporal; IP = inferior parietal; ERC = entorhinal cortex)

Figure 5. Distribution and density of DN in subcortical regions. * $p < 0.05$ compared to type 1; # $p < 0.05$ compared to types 1 and 3. (Hp = hippocampus, dentate fascia; Amg = amygdala; BG = basal ganglia, putamen; Thal = thalamus)

Brainstem DN

Figure 6. Distribution and density of DN in brainstem regions. * $p < 0.05$ compared to type 2; # $p < 0.05$ compared to type 3. (MB = midbrain, tectum; SN = substantia nigra; XII = hypoglossal nucleus' IO = inferior olivary nucleus)

Figure 7. Morphology of NCI in FTLD-TDP subtypes. Hippocampal dentate fascia in type 1 (a), type 2 (b) and type 3 (c). Note striking difference of inclusions in type 2, with a dense round, Pick body-like appearance. Pleomorphic cortical NCI in type 1 (d); Skein-like NCI in motor neuron in type 3 (e) and pre-inclusions in entorhinal cortical neurons in type 3 (f). (all x400)

Figure 8. Morphology of DN in FTLD-TDP subtypes. Cortical DN in type 1 (a) and type 2 (b). Note much thicker and longer neurites in type 2. NII (arrow) in cortex in type 1 (c). Delicate, thin neurites in hippocampal CA1 sector in type 1 (inset higher magnification) (d). (all x400, except inset, x800)

Table 1

Summary of clinical and pathologic features of FTLN-U

	Type 1	Type 2	Type 3	p value
DEMOGRAPHICS				
Sex M:F	14:10	5:4	3:3	0.93
Age at death (years)	76 ± 10	74 ± 10	70 ± 8	0.41
Age at onset (years)	66 ± 9.0	64 ± 12	67 ± 9	0.80
Disease duration (years)	7.4 ± 2.6	10 (3.2) [#]	3.7 (1.5) [*]	0.005
Positive family history	52%	29%	33%	0.39
PATHOLOGIC				
Brain weight (grams)	950 ± 170	970 ± 180	1200 ± 180	0.055
Braak NFT stage	1.0 (0.25, 2.5)	2.0 (0.0, 2.0)	1.0 (0.0, 2.0)	0.95
Cortical amyloid plaques	8%	25%	0%	0.72
Cerebrovascular lesions	8%	22%	0%	0.34
Hippocampal sclerosis	75%	56%	67%	0.55
Motor neuron disease	0%	25%	50% [#]	0.001
CLINICAL				
bvFTD/PNFA/SD (%)	58/42/0	29/0/71 [#]	100/0/0	0.002
Parkinsonism	61%	20%	40%	0.21
Apathy	19%	0%	25%	0.50
Disinhibition	42%	80%	75%	0.21
GENETIC				
Progranulin mutation	35%	0%	0%	0.055

bvFTD = behavioral variant frontotemporal dementia; PNFA = progressive non-fluent aphasia; SD = semantic dementia, MND = motor neuron disease.

* = p<0.05 compared to types 1 and 2

** = p<0.05 compared to type 2

[#] = p<0.05 compared to type 1.

Table 2

Results of semi-quantitative analysis of NCI in FTL-D-U subtypes

	Type 1	Type 2	Type 3	p value
Cortical				
Mid-frontal gyrus	1.6 ± 0.2 [*]	0.6 ± 0.2	0.9 ± 0.5	0.01
Superior temporal cortex	1.5 ± 0.2 ^{*#}	0.6 ± 0.2	0.3 ± 0.2	0.002
Inferior parietal cortex	1.1 ± 0.2	0.2 ± 0.1	0.3 ± 0.3	0.004
Entorhinal cortex	1.5 ± 0.2 [*]	0.6 ± 0.2	0.8 ± 0.3	0.014
Subcortical				
Dentate fascia	1.2 ± 0.2	2.1 ± 0.3	2.2 ± 0.5	0.012
Amygdala	1.3 ± 0.2	1.7 ± 0.3	2.2 ± 0.5	0.17
Putamen	1.2 ± 0.2	1.8 ± 0.4	0.7 ± 0.3	0.14
Thalamus	1.2 ± 0.2 [*]	0.1 ± 0.1	0.5 ± 0.2	<0.001
Brainstem				
Midbrain tectum	0.4 ± 0.1	0.1 ± 0.1	0.2 ± 0.1	0.09
Substantia nigra	0.8 ± 0.1 [*]	0.06 ± 0.06	0.6 ± 0.2	<0.001
Hypoglossal nucleus	0.02 ± 0.02	0 ± 0	0.8 ± 0.2 ^{**}	<0.001
Inferior olive	1.1 ± 0.2 [*]	0 ± 0	0.8 ± 0.6	<0.001

* = p<0.05 compared to type 2

= p<0.05 compared to type 3

** = p<0.05 compared to types 1 and 2

Table 3

Results of semi-quantitative analysis of DN in FTLN-U subtypes

	Type 1	Type 2	Type 3	p value
Cortical				
Mid-frontal gyrus	1.8 ± 0.2	2.1 ± 0.3	0.3 ± 0.2 *	0.003
Superior temporal cortex	1.8 ± 0.2	2.1 ± 0.3	0.2 ± 0.1 *	<0.001
Inferior parietal cortex	1.1 ± 0.2	1.8 ± 0.3	0.1 ± 0.1 *	<0.001
Entorhinal cortex	1.7 ± 0.2	2.0 ± 0.2	0.3 ± 0.2 *	0.002
Subcortical				
CA1	0.6 ± 0.1	0.1 ± 0.1	0.2 ± 0.2	0.023
Amygdala	1.4 ± 0.2	2.6 ± 0.3 #	0.8 ± 0.5	0.003
Putamen	1.2 ± 0.2 ##	1.0 ± 0.3	0.2 ± 0.1	0.034
Thalamus	1.3 ± 0.2 ***	0.2 ± 0.1	0.2 ± 0.1	<0.001
Brainstem				
Midbrain tectum	0.8 ± 0.1	0.4 ± 0.2	0.2 ± 0.1	0.033
Substantia nigra	0.8 ± 0.1 **	0.4 ± 0.1	0.8 ± 0.3	0.010
Inferior olive	0.8 ± 0.1 ##	0.3 ± 0.1	0.1 ± 0.1	0.001
Cerebellar dentate	0.1 ± 0.04	0.3 ± 0.1	0 ± 0	0.037

* = p<0.05 compared to types 1 and 2

= p<0.05 compared to types 1 and 3

** = p<0.05 compared to type 2

= p<0.05 compared to type 3

*** = p<0.05 compared to types 2 and 3