A Reassessment of the Neuropathology of Frontotemporal Dementia Linked to Chromosome 3

Ida Elisabeth Holm, MD, DMSc, Elisabet Englund, MD, Ian R. A. Mackenzie, MD, PhD, Peter Johannsen, MD, PhD, and Adrian M. Isaacs, DPhil*

Abstract

A large Danish family has previously been reported in which autosomal dominant frontotemporal dementia (FTD) is genetically linked to chromosome 3 (FTD-3). A mutation was recently identified in the CHMP2B gene that is probably responsible for causing disease in this family. Because of its neuropathologic findings, FTD-3 was originally categorized as a subtype of frontotemporal lobar degeneration, termed “dementia lacking distinctive histopathology.” We now report a reevaluation of the neuropathologic changes in this family. Postmortem material from 4 affected family members was available for examination. Gross examination revealed generalized cortical atrophy that was most severe in frontal and temporal cortices. Microscopy showed loss of cortical neurons, microvacuolation of layer II, mild gliosis, and demyelination of the deep white matter. Results of immunohistochemistry revealed generalized cortical atrophy that was most severe in frontal and temporal cortices. Microscopy showed loss of cortical neurons, microvacuolation of layer II, mild gliosis, and demyelination of the deep white matter. Results of immunohistochemical staining for α-synuclein, prion protein, neurofilament, and tau protein were unremarkable. Variable numbers of small, round, ubiquitin-positive cytoplasmic inclusions were present in the dentate granule layer of the hippocampus in all 4 cases. Rare ubiquitin-positive inclusions were also found in frontal and temporal cortical neurons. These inclusions were also positive for p62 but not for TDP-43. The finding of ubiquitin- and p62-positive, TDP-43-negative cytoplasmic inclusions in the hippocampus and neocortex suggests reclassification of the neuropathology of FTD-3 as a unique subtype of frontotemporal lobar degeneration with ubiquitin-positive inclusions that are TDP-43-negative.

Key Words: Chromosome 3, Dementia lacking distinctive histopathology, Frontotemporal lobar degeneration, Ubiquitin.

INTRODUCTION

Frontotemporal dementia (FTD) is the second most common form of presenile dementia after Alzheimer disease, accounting for 10% to 20% of cases (1, 2). The clinical picture is heterogeneous and is dominated by abnormalities in personality, behavior, and language, whereas episodic memory is relatively preserved (3–5). In some cases of FTD, parkinsonian features also develop, and FTD can also co-occur with motor neuron disease (FTD-MND) (3, 6). FTD shows familial clustering in approximately 40% of cases (7), and genetic analyses are providing important insights into the disease. Mutations were first identified in the microtubule-associated protein tau (MAPT) gene in 1998 (8–10), but MAPT mutations account for only approximately 5% to 10% of all cases of FTD (11). Recently, mutations in the progranulin gene (PGRN) have been shown to account for 5% to 10% of all cases of FTD (12–14). A genetic locus for FTD-MND has been identified on chromosome 9p (15, 16); however, the gene has yet to be discovered. Mutations in the gene encoding valosin-containing protein (VCP) were identified in patients with inclusion body myopathy associated with Paget disease of bone and FTD (17), in which a proportion of patients develop FTD. We have recently identified mutations in the CHMP2B gene in a large Danish pedigree with autosomal dominant FTD linked to chromosome 3 (FTD-3) (18).

The neuropathologic changes associated with clinical FTD are heterogeneous, but the common feature is cortical degeneration of the frontal and temporal lobes, termed frontotemporal lobar degeneration (FTLD) (3, 4, 19). Approximately 45% of cases of FTLD are characterized by abnormal accumulation of hyperphosphorylated tau protein in neurons and glial cells (tauopathy) (20, 21), and some familial tauopathy is associated with mutations in the tau (MAPT) gene. Many of the remaining 55% of tau-negative cases were previously referred to as “dementia lacking distinctive histopathology,” because of the absence of any specific histochemically identifiable change (22). However,
Recent studies using sensitive immunohistochemical stainings for ubiquitin have revealed that the great majority of these cases show the presence of ubiquitin-reactive (ub-ir) neurites and neuronal cytoplasmic inclusions (NCI) in the cerebral cortex and hippocampus (FTLD-U) (23-25). Tau-negative ubiquitin-positive inclusions were first recognized as the pathologic substrate in most cases of FTD-MND (26, 27) but were subsequently identified in patients with FTD in the absence of motor abnormalities (28). In a very small proportion of cases of FTD, the ub-ir NCI are also immunoreactive for neurofilament and α-internexin; this condition has been termed neuronal intermediate filament inclusion disease (29, 30).

Among the cases of FTLD-U, 3 distinct histologic subtypes have recently been described on the basis of morphology and anatomical distribution of ub-ir pathology (31). Moreover, novel monoclonal antibodies have been produced that distinguish the ub-ir inclusions in each of the 3 subtypes, suggesting that either different disease proteins or modifications of a single protein could underlie the disease variants (32). Recently, the TAR DNA-binding protein TDP-43 has been shown to be the major ubiquitinated pathologic protein in FTLD-U, FTD-MND, and amyotrophic lateral sclerosis (33). TDP-43 is a nuclear protein that might have a role in transcriptional repression or exon skipping (34-36). Other evidence suggests that it act as a scaffold for nuclear bodies via interactions with the survival motor neuron protein (37). TDP-43 is normally localized to the nucleus, but under pathologic conditions such as FTLD-U, TDP-43 relocates to the cytoplasm and accumulates with the ubiquitin inclusions (33).

FTLD-3 is a rare form of familial frontotemporal dementia. The disease has so far been reported in a single large Danish family (38). Recently, a mutation associated with the disease was identified in the CHMP2B gene, encoding a component of the endosomal sorting complex required for transport-III (ESCRT-III) (18). Symptoms typically begin in the late 50s, with changes in behavior and personality, including disinhibition, apathy, ritualized behavior, loss of emotion, changed eating habits, dyscalculia, and progressive aphasia leading to mutism. In some patients, extrapyramidal motor symptoms develop after more than 4 years (asymmetric akinesic rigid syndrome with arm and gait dystonia) (38).

The neuropathologic findings in FTLD-3 have previously been described as dementia lacking distinctive histopathology (38). However, here we report that the neuropathologic findings in the most recently deceased FTD-3 family member and the reevaluation of 3 other family members suggest that FTLD-3 is a specific subtype of FTLD-U.

**MATERIALS AND METHODS**

We report the neuropathologic findings of the most recently deceased affected member of the FTD-3 family (Table 1, case III-22) in addition to a retrospective review of the neuropathology of 3 other affected family members (Table 1, cases II-12, III-13, and III-17). Two postmortem examinations (Table 1, cases II-12 and III-13) were previously described before identification of the CHMP2B gene mutation (38) and the paraffin blocks were obtained for reexamination of these cases. An additional case (Table 1, case III-17) was found for which an autopsy report and paraffin blocks were available, enabling reexamination of this case.

Routine histochemical staining included hematoxylin and eosin, Luxol fast blue, periodic acid-Schiff, and the Bielschowsky silver method. Immunohistochemistry was performed on 3-µm sections of formalin-fixed, paraffin-embedded tissue representing frontal, temporal, parietal, and occipital neocortex, hippocampus, striatum, lower brainstem and spinal cord, when available. All immunohistochemistry was performed using the automated staining system Autostainer (DAKO, Glostrup, Denmark). The primary antibodies recognized the following proteins: glial fibrillary acidic protein (anti-GFAP, 1:500, after microwave antigen retrieval with Tris-EDTA, pH 9; DAKO), ubiquitin (anti-ubiquitin, 1:500, after microwave antigen retrieval with Tris-EDTA, pH 9; Novocastra, Newcastle upon Tyne, UK), nonphosphorylated neurofilament (anti-neurofilament protein, 1:2000, after microwave antigen retrieval with Tris-EDTA, pH 9; DAKO), hyperphosphorylated tau (tau protein, 1:1500 without antigen retrieval; DAKO), α-synuclein (AB2SYN, 1:50, after microwave antigen retrieval with Tris-EDTA, pH 9; Novocastra, Newcastle upon Tyne, UK), amyloid-β protein (anti-β amyloid 1-40, 1:75, after microwave antigen retrieval with Tris-EDTA, pH 9; Neomarkers, Fremont, CA), amyloid-β protein (anti-prion protein 3F4, 1:50, after microwave antigen retrieval with 2 M HCl; DAKO), p62 (p62, 1:50, after microwave antigen retrieval with Tris-EDTA, pH 9; Transductions Laboratories, Lexington, KY), and TDP-43.

**TABLE 1. Age, Disease Duration, and Gross Changes**

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<tr>
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<th>II-3</th>
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<tr>
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<td>+</td>
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<td>++</td>
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<tr>
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<td>+</td>
<td>++</td>
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(TARDBP-43, 1:500 after microwave antigen retrieval with Tris-EDTA, pH 9; Proteintech Group, Chicago, IL). Sections were developed using Envision-DAB (DAKO) and counterstained with hematoxylin. Additional immunohistochemical staining for ubiquitin, TDP-43, and tau was also carried out on sections from frontal cortex and hippocampus from all 4 cases at Vancouver General Hospital (I.R.A.M.). Immunohistochemical staining for ubiquitin was also performed on sections of frontal cortex and hippocampus of 4 age-matched controls with no history of dementia or MND.

Ubiquitin-positive pathologic changes were graded using the semiquantitative system developed by Mackenzie and Feldman (39). According to this classification scheme the following grades were applicable: 0, none; +, rare (pathologic lesions were only found in a small proportion of 20× microscopic fields examined); ++, mild (a small number of pathologic structures were present in most 20× fields); ++++, moderate (moderate numbers of pathologic structures were present in virtually every 20× field examined); and +++, severe (large numbers of pathologic structures were present in virtually every 20× field examined). The final score was an estimated average for the entire anatomical region being assessed. The degree of microvacuolization (spongiosis) and chronic degeneration (neuronal loss and gliosis) was also graded using a similar semiquantitative method: 0, none; +, minimal; ++, mild; +++, moderate; and +++++, severe. Senile plaque and neurofibrillary tangle pathologies were scored according to the Consortium to Establish a Registry for Alzheimer’s Disease and Braak staging methods, respectively (40, 41).

RESULTS

Gross Appearance

The brains weighed between 900 and 980 g after fixation (Table 1). All brains showed global atrophy with a frontal and temporal preponderance (Fig. 1). The degree of atrophy varied slightly among cases as seen in Table 1. The white matter appeared pale and the ventricular system, particularly the anterior horns of the lateral ventricles, was dilated. There was no convincing atrophy of amygdala, hippocampi, or basal ganglia, and the substantia nigra showed normal pigmentation. In 1 case, a small ischemic infarct was present in the occipital lobe.

Microscopy

Nonspecific chronic degenerative changes were most marked in the frontal neocortex and consisted of microvacuolization (spongiosis), neuronal loss, and astrocytic gliosis (Fig. 2). In some regions these were limited to the supragranular layers but in many areas it involved the entire cortical thickness. The degree of degeneration was fairly constant between cases (Table 2). Milder degeneration was found in the inferomesial temporal cortex but spared the amygdala and hippocampus. There was no hippocampal sclerosis. The white matter showed moderate widespread

![FIGURE 1. Case III-22: Gross appearance showing cerebral atrophy of frontal and temporal cortex and dilatation of 3rd ventricle. Scale bar = 5 cm.](http://jnen.oxfordjournals.org/)

![FIGURE 2. Hematoxylin and eosin (A) and glial fibrillary acidic protein (B) immunohistochemical staining of sections from frontal cortex. Pronounced microvacuolization and gliosis are the most characteristic features. Scale bar = 50 μm.](http://jnen.oxfordjournals.org/)
TABLE 2. Microscopic Changes

<table>
<thead>
<tr>
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<th>II-12</th>
<th>III-13</th>
<th>III-17</th>
<th>III-22</th>
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<tr>
<td>Frontal cortex spongiosis</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
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</tr>
<tr>
<td>Frontal cortex degeneration</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
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<tr>
<td>Temporal cortex spongiosis</td>
<td>++</td>
<td>++</td>
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<td>Temporal cortex degeneration</td>
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<tr>
<td>NCI hippocampus</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>NII hippocampus</td>
<td>0</td>
<td>0</td>
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<td>0</td>
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<tr>
<td>Neurites hippocampus</td>
<td>0</td>
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<tr>
<td>NCI frontal cortex</td>
<td>0</td>
<td>+</td>
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<tr>
<td>NII frontal cortex</td>
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<td>Neurites frontal cortex</td>
<td>0</td>
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<tr>
<td>NCI temporal cortex</td>
<td>0</td>
<td>+</td>
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<td>+</td>
</tr>
<tr>
<td>NII temporal cortex</td>
<td>0</td>
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<td>0</td>
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<tr>
<td>Neurites temporal cortex</td>
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<td>0</td>
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<tr>
<td>NCI striatum</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>NII striatum</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Neurites striatum</td>
<td>0</td>
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<tr>
<td>NCI lower motor neuron</td>
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<tr>
<td>NII lower motor neuron</td>
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<tr>
<td>Neurites spinal cord</td>
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<td>3b</td>
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<tr>
<td>TDP-43</td>
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NCI, neuronal cytoplasmic inclusions; NII, neuronal intranuclear inclusions.

loss of myelin staining with astrocytosis but without macrophages. Numerous corpora amyelica were present in the white matter, and a few vessels showed fibrohyaline arteriosclerosis. The regional distribution of the white matter changes largely paralleled that of the cortical degeneration. The striatum, thalam, and substantia nigra were normal.

Bielschowsky staining showed the presence of neurofibrillary tangles in all 4 cases in the hippocampus, entorhinal cortex, and transentorhinal cortex corresponding to Braak stage IV, but there were no neuritic plaques, dystrophic neurites, or argyrophilic inclusions. Immunohistochemical staining for tau did not show any Pick bodies or glial inclusions but confirmed the presence of the neurofibrillary tangles. Immunohistochemical staining for α-synuclein revealed no Lewy bodies or Lewy neurites in the substantia nigra, hippocampus, or cortex, and staining for β-amyloid confirmed the absence of neuritic plaques. The cerebellar cortex was largely preserved although there was mild age-related loss of Purkinje cells. The spinal cords were normal without loss of anterior horn neurons or myelin.

Immunohistochemical staining for ubiquitin (Figs. 3, 4) showed a highly consistent pattern of pathology (Table 2). The most characteristic feature was the presence of ub-ir NCIs in the hippocampal dentate granule cells (Fig. 3). The inclusions were present in all 4 cases and were equally frequent in 3 of the cases, but less frequent in 1 case (Table 2, case III-17). They most often appeared well-defined, round, and solid, but a few granular NCIs were also seen occasionally. Cortical ub-ir NCI were mostly granular and were very few in number. They were only seen in layer II of the frontal and temporal cortex of 2 of the patients (Table 2, cases III-13 and III-22) and were absent from other cortical areas. No NCI were encountered in the striatum or in lower motor neurons including the hypoglossal nucleus. No ub-ir neuronal intranuclear inclusions or ub-ir neurites were present in any of the sections. In the sections from the 4 age-matched controls, no ub-ir NCI, neuronal intranuclear inclusions, or neurites were seen. Nonspecific ub-ir grains were scattered in the neuropil of all 4 cases from the FTD-3 family and in the controls. These grains had a smaller size and more irregular shape than the NCI.

Immunohistochemical staining for p62 (Figs. 3, 4) revealed inclusions of the same number, morphology, and anatomical distribution as for ubiquitin. However, immunohistochemistry for TDP-43 (Fig. 5) showed normal labeling of neuronal nuclei in all areas with no staining of NCI or other pathologic structures.

DISCUSSION

In the present study, we report the neuropathologic findings in 4 cases from the Danish family with FTD-3. The finding of ub-ir NCI in the hippocampal dentate granule cells in all 4 cases and less consistently in layer II neurons of the frontal and temporal cortex suggests reclassification of the neuropathology of FTD-3 as FTLD-U.

Two recent studies have characterized the histologic heterogeneity of FTLD-U and defined 3 subtypes based on the anatomical and cellular localization of the ubiquitin deposits (31, 32). The distribution of ub-ir NCI in FTD-3, i.e. cytoplasmic staining (rather than nuclear or neuritic), which is predominantly in the hippocampus (rather than the
cortical layers), corresponds most closely to type 3b in the classification of Mackenzie et al (31) but does not fit into the classification scheme of Sampathu et al (32) that is based on cortical pathology. The observation of ub-ir in FTD-3 in a distribution similar to that in other cases of FTLD-U strongly suggests that this is a bona fide example of FTLD-U.

In the previous report (38) the neuropathologic examination of cases II-12 and III-13, including immunohistochemical staining for ubiquitin, was performed in Lund, Sweden, in 1987 and 1995. With the exception of the ubiquitin immunohistochemistry, the present findings correspond very well with the previous description. The discrepancy between the present reassessment and the previously published results (38) is not surprising in view of other studies in which reexamination has resulted in a change of diagnosis from dementia lacking distinctive histopathology to FTLD-U (23–25, 42, 43). The differences in sensitivity of the immunohistochemical staining for ubiquitin can be readily explained by variation in the staining technique applied at different centers.

The number of NCI in the hippocampal dentate granule cells in FTD-3 are at the lower end of the spectrum compared with other cases of FTLD-U, but the localization and number of ub-ir inclusions correlated well with that of p62-positive inclusions in neighboring sections. P62 is a ubiquitin binding protein that has been found in ubiquitinated inclusions in a range of neurodegenerative diseases including Pick disease, Parkinson disease, Alzheimer disease, neurofilament inclusion body disease, and argyrophilic grain disease (44–46) and will be discussed further below.

We have examined sections from hippocampus and frontal cortex from 4 age-matched controls with no history of MND or dementia and only found the age-related, nonspecific changes previously described (47), whereas no ub-ir inclusions were seen in either hippocampal dentate granule cells or neurons in frontal cortex. We, therefore, do not doubt the specificity of the ub-ir NCI, albeit their relatively small number.

The presence of neurofibrillary tangles in all 4 cases with a distribution and number corresponding to Braak and Braak stage IV needs to be commented on because such findings are characteristic of the neuropathology of tangle-only dementia (48). The clinical picture of the latter is a sporadic form of late-onset dementia that mimics Alzheimer disease (AD) and the neuropathology is characterized by neurofibrillary tangles with a distribution and number equivalent to “limbic AD,” i.e. Braak and Braak stage II or IV (48, 49). Because FTD-3 is familial and present in the 50s with behavioral changes rather than AD-like dementia, we believe that tangle-only dementia can be ruled out in the present cases.

We have recently shown that the causative mutation in FTD-3 is likely to be a splice site mutation in the CHMP2B gene (18). CHMP2B is part of the ESCRT-III, which is required for formation of the multivesicular body (MVB).

**FIGURE 4.** Immunohistochemical staining for ubiquitin (A) and p62 (B) in the frontal cortex showing occasional neuronal cytoplasmic inclusions in layer II neurons. Scale bar = 25 μm.

**FIGURE 5.** Immunohistochemical staining for TDP-43 in hippocampal dentate granule cells (A) and frontal cortex (B). The staining is exclusively located in the neuronal nuclei with no cytoplasmic translocation. Scale bar = 25 μm.
MVBs are late endosomal compartments that allow degradation of endocytosed proteins (generally transmembrane proteins and cell surface receptors) via fusion with the lysosome (51). The MVB is formed when the outer membrane of the endosome invaginates inward, pinching off to form an internal vesicle. An endosomal compartment with a number of internal vesicles within its lumen is termed an MVB. The selection of proteins for internalization into the membrane of the endosome invaginates inward, pinching off to form an internal vesicle. An endosomal compartment with a number of internal vesicles within its lumen is termed an MVB. The selection of proteins for internalization into the MVB is orchestrated by 4 multiprotein complexes termed ESCRT-0 to ESCRT-III (51). The splice site mutation we identified in CHMP2B led to the production of 2 aberrant transcripts that when overexpressed led to the formation of abnormal endosomal structures (18), a consistent cellular phenotype when ESCRT protein function is impaired (50). How this leads to the neurodegeneration observed in FTD-3 is presently unclear.

An important question that arises from the current work is what role the ub-ir inclusions may play in the disease process in FTD-3 and whether this is related to the function of CHMP2B. Whether such inclusions in neurodegenerative diseases are protective, toxic, or both (protective initially by sequestering toxic proteins, but toxic if they cannot be removed) is still being openly debated (52). In either case the presence of inclusions suggests an impairment of protein degradation, leading to the build-up of aggregated protein. An impairment of protein degradation could be caused by an alteration in either of the 2 systems responsible for the degradation of most cellular proteins: the ubiquitin-proteasome system and autophagy. Inhibition of either system can lead to the formation of ubiquitinated aggregates in vivo (53–55), and it is plausible that affecting the MVB pathway could have an effect on either process.

Evidence from cell culture experiments showed that when the FTD-3 mutant forms of CHMP2B (but not wild-type CHMP2B) were overexpressed, autophagic clearance was impaired, which led to the formation of large p62-positive but TDP-43-negative ubiquitinated inclusions (A. Simonsen, personal communication, 2007). The presence of p62-positive, TDP-43-negative ubiquitin inclusions in both patient brains with the CHMP2B mutation and in cells overexpressing the mutant CHMP2B proteins strongly suggests that the findings described here are specific and dependent upon the CHMP2B mutation. These findings also implicate altered autophagy as a potential disease mechanism in FTD-3.

A second possibility is that the ubiquitin-proteasome system is affected because both the MVB pathway and the ubiquitin-proteasome system use ubiquitin for targeting, such that if impairment of either reduced the levels of free cellular ubiquitin, the other could be affected; indeed, it has been shown that impairing the ubiquitin-proteasome system affects MVB function (56, 57). A monoubiquitin tag targets proteins to the ESCRT for eventual degradation via the MVB and lysosome (58), and so a third possibility is that an impairment of MVB function leads directly to the accumulation and aggregation of monoubiquitinated proteins. Finally, the inclusions could be aggregates of mutant CHMP2B protein itself. There is precedent in neurodegenerative diseases for inclusions that contain the protein product of the causative mutant gene, e.g. α-synuclein in Parkinson disease (59), familial FTD with MAPT mutations, and prion protein in inherited prion diseases (60). Whether the CHMP2B mutants can self-aggregate is not presently known. Antibodies that can specifically identify endogenous CHMP2B by Western blot or immunohistochemistry are not currently available, but we are in the process of developing these reagents.

If the inclusions described here are a result of CHMP2B dysfunction and have a role in the disease, the question arises as to why they are mostly seen in the dentate granule cells of the hippocampus, which is not a site of neurodegeneration in FTD-3. Given the general scarcity of the inclusions in the FTD-3 brain, one possibility is that the inclusions do not play an active role in the disease process but are indicative of a more global cellular stress, possibly due to impaired protein degradation that only manifests itself as inclusion formation in these particular cells. If the inclusions were protective they would be less likely to be seen in vulnerable areas of the brain, which could explain their distribution.

A major advance in our understanding of FTLD-U was the identification of TDP-43 as a common component of the ubiquitinated inclusions (33). We now report the first example of a case of FTLD-U that is TDP-43-negative. It seems likely, based on the original description, for which all subtypes of FTLD-U characterized were positive for TDP-43 (33), that the majority of FTLD-U will be TDP-43-positive. Our findings suggest, however, that TDP-43 is not the ubiquitinated pathologic protein in all cases of FTLD-U and that FTLD-U comprises a group of diseases that are similar by ub-ir pathology but may have subtle differences in their molecular neuropathology. Whether these differences mean that distinct cellular pathways lead to neurodegeneration in FTD-3 compared with TDP-43-positive FTLD-U is difficult to assess, as it is not clear what role TDP-43 plays in disease pathogenesis. It will be very interesting to determine whether other inclusions in cases of FTD that are not typical FTLD-U are TDP-43-positive. The α-internexin-positive inclusions in neuronal intermediate filament inclusion disease were reported to be negative (33), whereas the ubiquitin-positive inclusions in inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia are positive for TDP-43 (61). The inclusions described here, although negative for TDP-43, were positive for p62. p62 is an ubiquitin binding protein that has been found in ubiquitinated inclusions in a range of neurodegenerative diseases as mentioned briefly above. Therefore, it is not clear whether p62 is simply a general marker of such inclusions, or whether it has a more specific role in disease pathogenesis. p62 has been implicated in autophagy (62), and several intracellular signaling pathways (63–65), so it possible that its sequestration in ubiquitinated inclusions has a more active role in the disease process.

In conclusion, we have shown that upon reevaluation patients with FTD-3 have ubiquitinated inclusions, and, thus, their disease should be considered to represent a specific subtype of FTLD-U in which the ub-ir inclusions are TDP-43-negative.
ACKNOWLEDGMENTS

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