Update on Recent Molecular and Genetic Advances in Frontotemporal Lobar Degeneration

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Abstract

Great strides have been made in the last 2 years in the field of frontotemporal lobar degeneration (FTLD), particularly with respect to the genetics and molecular biology of FTLD with ubiquitinated inclusions. It is now clear that most cases of familial FTLD with ubiquitinated inclusions have mutations in the progranulin gene, located on chromosome 17. It is also clear that most ubiquitinated inclusions in FTLD with ubiquitinated inclusions are composed primarily of TAR DNA-binding protein-43. Thus, FTLDs can be separated into 2 major groups (i.e. tauopathies and ubiquitinopathies), and most of the ubiquitinopathies can now be defined as TAR DNA-binding protein-43 proteinopathies. Many of the familial FTLDs are linked to chromosome 17, including both the familial tauopathies and the familial TAR DNA-binding protein-43 proteinopathies with progranulin mutations. This review highlights the neuropathologic features and the most important discoveries of the last 2 years and places these findings into the historical context of FTLD.

Keywords

Frontotemporal lobar degeneration; FTDP-17; FTLD-U; Progranulin; TAR-DNA binding protein-43; Tauopathy; Ubiquitinopathy

Historical: Pick Disease

More than 115 years ago, in 1892, Arnold Pick published an article describing 3 patients with clinical aphasia and pathologic circumscribed frontal and temporal atrophy (1). In 1911, Alois Alzheimer subsequently discovered argyrophilic "Pick bodies" in such cases (2), and then in 1922, Gans, one of Arnold Pick's students, coined the term "Pick disease" for frontal disorders with circumscribed atrophy and Pick bodies (3).

Frontal Lobe Dementia of the Non-Alzheimer Type: Pick Disease and Non-Pick Lobar Atrophy/Dementia Lacking Distinctive Histology

Twenty years have passed since Arne Brun defined "frontal lobe dementia of the non-Alzheimer type." In his 1987 article, Brun et al (4) described the clinical presentation of frontal lobe dementia of the non-Alzheimer type as various combinations of alterations in behavior, personality, executive function, or language. He delineated 2 major underlying pathologic entities: the less common Pick disease and the more frequent non-Pick lobar atrophy, which has the same circumscribed frontal and temporal atrophy but lacks Pick bodies. At that point

in the history of frontotemporal dementia, the neuropathology could be simply diagrammed (Fig. 1).

In 1990, Knopman et al (5) described "dementia lacking distinctive histology (DLDH)," which in most cases includes the type of pathology found in "non-Pick lobar atrophy." Dementia lacking distinctive histology has no immunohistochemically labeled inclusions, but does have some distinctive histologic findings, including circumscribed atrophy, variable caudate atrophy, and nigral pallor, both with corresponding neuronal loss and gliosis, and superficial microvacuolation and gliosis in frontal or temporal neocortex, or both. These features are also common to Pick disease (Fig. 2), but, whereas Pick disease has Pick bodies, DLDH has no pathologic inclusions (Fig. 3).

Tau Protein and the *TAU* gene (*MAPT*) in Frontotemporal Lobar Degeneration

In the 1990s, great strides were made in Alzheimer disease (AD) by studying of familial cases, identifying mutations and their effects, and looking for similar mechanisms to occur in sporadic AD (6-8). Specialists noted that up to 50% of clinically defined frontotemporal dementias (FTDs) were familial, and that many of them had insoluble tau deposits and were linked to chromosome 17. Some of these cases were described as familial multiple system tauopathy with dementia (9-11). This led to a consensus statement article designating such cases as "familial tauopathy with dementia linked to chromosome 17" (FTDP-17) (12). In 1998, Hutton et al (13) and Poorkaj et al (14) discovered that mutations in the *MAPT* gene were responsible for FTDP-17 cases with insoluble tau deposits. Like the mutations identified in familial AD, this exciting discovery allowed the development of research projects based on testable hypotheses for sporadic as well as familial tauopathies, with the goal of developing targeted drug therapy (15).

Currently, there are 64 *MAPT* mutations identified worldwide, 42 of which are pathogenic (16). *MAPT* missense mutations seem to result in partial loss of microtubule binding, whereas exon 10 splicing mutations seem to disrupt alternative splicing, thereby disturbing the normal 4R:3R tau isoform ratio (17-22). Both increase the tendency of tau protein to assemble into insoluble fibrils. These discoveries proved that tau dysfunction was sufficient to cause neurodegeneration and were significant because, whereas tau is also the major component of the neurofibrillary tangles of AD (23), no *MAPT* mutations were associated with AD. Tau was also found to be the major protein component of Pick bodies and the insoluble tau deposits typical of other sporadic degenerative disorders, including progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), amyotrophic lateral sclerosis (ALS)-Parkinson disease complex of Guam, and argyrophilic grain disease (24-27). Notably, many of these disorders present either as frontotemporal dementia/aphasia or as a movement disorder (parkinsonism or ALS), or both. The pathology of the FTDP-17s can be unique, or it can be similar to any of the sporadic tauopathies such as Pick disease, PSP, or CBD (Fig. 4). There remained a group of familial cases with clinical frontotemporal dementia that were linked to chromosome 17 but that had no mutations in *MAPT* (28-33).

Ubiquitinopathies

Meanwhile, progress was also being made with regard to frontotemporal lobar degeneration (FTLD) not associated with tau deposits. In 1991, Okamoto et al described ubiquitinated cytoplasmic and intranuclear inclusions in extramotor cortex in ALS (34). In 1992, Wightman et al (35) next found the same inclusions in hippocampus and neocortex in ALS patients with dementia. Two articles in 1995 and 1996 devised simple immunohistochemical means of pathologically subtyping frontotemporal dementia into major subtypes (Table 1) (36,37), and in 2001, Woulfe et al (38) showed the same ubiquitinated inclusions in the hippocampus and neocortex of pathologically defined FTD cases without ALS. At the 2001 meeting of the

American Association of Neuropathologists, Lipton et al (39) reported that FTLD with ubiquitinated inclusions (FTLD-U) was the single most common FTLD variant (Fig. 5). This and a similar article by Josephs et al (40,41) were published in 2004. Most cases of DLDH, formerly thought to be the most common pathologic subtype, have now been shown to be FTLD-U, and DLDH is most likely rare to possibly nonexistent (40,42-45).

The pathology of frontal lobe dementia of the non-Alzheimer type, now preferably termed "frontotemporal lobar degeneration," could now be divided into 2 major categories: tauopathies and ubiquitinopathies (46,47). The FTDP-17 cases without *MAPT* mutations also had ubiquitinated inclusions of the type seen in FTLD-U. The identity of the major protein component of the ubiquitinated inclusions remained elusive, as did the mutation or mutations in the FTDP-17 cases without *MAPT* mutations.

Non-*MAPT* FTDP-17 and Progranulin Mutations

Knowledge regarding FTLD-U "ballooned" beginning in the summer of 2006, with 2 papers published back-to-back in *Nature* in which familial FTLD-U cases linked to chromosome 17 were found to have mutations in the progranulin (*PGRN*) gene (48,49). Work on *PGRN* advanced so quickly that, less than 2 years later, 98 *PGRN* mutations have been identified, 53 of which are known to be pathogenic (16). To date, most pathogenic mutations are nonsense mutations and produce a premature termination codon ("null" mutations) that results in haploinsufficiency (48,49). However, a few missense mutations have been shown to be either pathogenic or major risk factors for FTLD-U; these likely result in low PGRN protein expression or secretion (50-54). Recently, a genomic deletion that included the entire *PGRN* locus was described in a Belgian FTD patient (55). Therefore, whereas mutations in *MAPT* seem to result in toxic gain of function, mutations in *PGRN* apparently result in loss of function (56).

PROGRANULIN was first described in relation to wound healing and tumorigenesis (57,58). It is present in inactive, ramified microglia; in this form, it is anti-inflammatory and likely neurotrophic. Elastase cleaves PGRN into 7 proinflammatory granulin peptides that are present in ameboid microglia (59,60). Serine leukocyte protease inhibitor (SLPI) protects PGRN from elastase cleavage (61). Because of the opposing effects of PGRN and GRN peptides, microglia can have both anti-inflammatory and proinflammatory effects and, therefore, may be involved in either a deficient or an overactive response to injury in the development of FTLD-U (59, 60). Alternatively, the loss of the neurotrophic support of PGRN may underlie FTLD-U, or there may be other, as yet unidentified, factors involved (59,60). Progranulin in murine brain is located in microglia and in neurons of the superficial neocortex, hippocampal granular layer, and cerebellar Purkinje layer (62). Immunostains of human brain with antibodies to PGRN show similar positivity in a subset of cortical neurons and in activated microglia, including those surrounding senile plaques in AD, but no positivity of FTLD-U inclusions (48,59,63).

Progranulin mutations are found in many familial FTLD-U cases and in as many or more familial FTLD cases as are *MAPT* mutations (49,64-66). Progranulin mutations are also found in apparently sporadic FTLD-U cases (64,65). There is much heterogeneity in the clinical presentation even within the same family. Clinical presentation is usually early onset (fifth or sixth decade), but may also be late-onset, behavioral variant FTD or aphasia with or without parkinsonism (66-81). Clinical presentation may also be that of corticobasal syndrome (68, 80-83). Cases with corticobasal syndrome often have prominent parietal atrophy and often right-greater-than-left asymmetry, whereas those with aphasia syndromes often have left-greater-than-right temporal atrophy, both on imaging and on gross pathologic examination (68,70,74,76,83,84). Most report that motor neuron disease (MND) is absent clinically and pathologically in cases with *PGRN* mutations, but a few studies describe sequence variation

or missense mutations of uncertain pathogenicity, but which may affect PGRN protein levels or modify the disease in ALS, causing younger age at onset, shorter survival, or both (85-87). Some cases also have pathologic AD, unusual tau pathology, or α-synuclein pathology (69, 88,89).

A clinicopathologic correlation paper of 12 Northwestern Cognitive Neurology and Alzheimer Disease Center cases with pathologic FTLD-U or FTLD-MND analyzed for *PGRN* mutations was recently published (71). All had clinical cognitive impairment: 7 had clinical behavioral variant FTD, 4 had primary progressive aphasia (PPA), and 1 had "dementia." Three also had clinical and pathologic ALS; final pathologic diagnosis in these cases was FTLD-MND. Based on pathologic and genetic results, the cases can be separated into 3 groups: cases with FTLD-U and *PGRN* mutations (Group 1), cases with FTLD-U but without *PGRN* mutations (Group 2), and cases of FTLD-MND without *PGRN* mutations (Group 3; Table 2). Two of the Group 1 cases had the p.Arg493X mutation that was found to be the most common *PGRN* mutation in a study of 3,405 neurodegenerative diseases (90). Additionally, 1 case had the p.Ser226TrpfsX28 mutation, and 1 had the p.Ala237TrpfsX4 mutation, the same as that reported for the HDDD1 family (69). Unlike the HDDD1 family, however, this p.Ala237TrpfsX4 mutation case did not have AD pathology. On the other hand, disease duration was only 8 years, and age at death was only 61 years. One case in Group 3 (FTLD-MND group) had a likely silent polymorphism, c.708C>T (p.Asn236Asn).

With regard to clinical data, this study found no difference between groups in clinical diagnoses or family history. The Group 1 cases with *PGRN* mutations were split evenly in clinical diagnoses: 2 presented with PPA and 2 with FTDV. With regard to neuropathologic features, there was no difference between groups in regional neuronal loss and gliosis, superficial neocortical microvacuolation, or simple presence of neuronal intranuclear inclusions (NIIs). Group 1 cases had greater caudate atrophy, and, similar to what others have found, Group 1 cases with *PGRN* mutations had more frontal and temporal cytoplasmic inclusions (CIs) and dystrophic neurites and higher densities of frontal and striatal NIIs (63,68,73,91,92). Group 3 cases had more dentate gyrus CIs. Ubiquitinated inclusions in all cases labeled with antibodies to TAR-DNA binding protein-43 (TDP-43).

Since the publication of this article, 11 additional Northwestern Cognitive Neurology and Alzheimer Disease Center cases have been analyzed for PGRN mutations for a current total of 23. Breakdown of the pathology in these 23 cases is as follows: 12 have FTLD-U alone, 7 have FTLD-MND, 1 has FTLD-U with MND pathology but no clinical MND, and 3 have FTLD-U with AD pathology, 2 of these sufficient for the pathologic diagnosis of AD by National Institute on Aging/Reagan criteria (93). Unlike the HDDD1 family (69), none of the cases with combined FTLD-U and AD pathology had *PGRN* mutations. The only additional mutations found in this group (both in FTLD-U cases) are 2 with the IVS6+2 del TGAG mutation that has not yet been proven to be pathogenic.

TDP-43 Is the Major Protein Component of Ubiquitinated Inclusions in FTLD-U

In the fall of 2006, 2 months after the first *PGRN* mutation articles were published, Neumann et al (94) identified TDP-43 as the major protein component of the ubiquitinated inclusions in FTLD-U; this was swiftly confirmed by Arai et al (95). Identification of this protein had previously been hampered by the relative scarcity of the inclusions and their very small size. In preliminary work, however, monoclonal antibodies were generated to the urea-soluble fraction prepared from homogenates of FTLD-U brains, and these were shown to variably label ubiquitinated cytoplasmic and intranuclear inclusions and dystrophic neurites in subsequent sections from FTLD-U brains (91). Neumann et al (94) performed 2-dimensional

polyacrylamide gel electrophoresis on the urea-soluble fraction from FTLD-U brain homogenate and identified spots labeled with certain monoclonal antibodies. They identified the same spots on duplicate Coomassie blue-stained 2-dimensional polyacrylamide gel electrophoresis gels, excised the spots, analyzed them by liquid chromatographyYtandem mass spectrometry, and identified them as amino acid residues belonging to TDP-43. The monoclonal antibodies strongly labeled inclusions in FTLD-U brains, and immunoblots showed that pathologic TDP-43 in FTLD-U has signature 25-kd C-terminal breakdown or cleavage fragments, an approximately 45-kd variant, and a high molecular weight smear. Dephosphorylation of urea fractions collapsed the 45-kd fraction into a 43-kd band and separated the 2 C-terminal fragments into at least 4 TDP-43-immunolabeled bands (94). Frontotemporal lobar degeneration with ubiquitinated inclusion TDP-43 was shown to be ubiquitinated (94). Thus, in FTLD-U, TDP-43 is abnormally phosphorylated, ubiquitinated, and enzymatically hydrolyzed in a manner that produces 2 abnormal C-terminal products of 23 and 27 kd.

TDP-43 Function

At the time TDP-43 was identified in FTLD-U inclusions, the TDP-43 literature was quite sparse; in fact, there were only approximately a dozen articles published regarding TDP-43. Most were related to its role in human immunodeficiency virus infection and cystic fibrosis. TAR-DNA binding protein-43 is a 43-kd highly conserved and widely expressed nuclear protein encoded by the *TARDBP* gene on chromosome 1. Its functions are diverse and incompletely understood, but TDP-43 seems to bind to DNA, RNA, and protein. In human immunodeficiency virus infection, TDP-43 binds to the "transactive response" DNA and represses transcription in infected cells (96). In cystic fibrosis, TDP-43 is part of a complex that is involved in splicing the cystic fibrosis transmembrane conductance regulator (97). It is involved in splicing the apolipoprotein A2 gene (98). TAR-DNA binding protein-43 helps regulate expression of the mouse SP-10 gene involved in spermatogenesis (99). It also likely acts as a scaffold to link nuclear bodies (GEMS) by interacting with survival motor neuron protein (100). Mutants of human and *Drosophila* TDP-43 that lack the C-terminal domain are unable to affect splicing (101). Because the C-terminal fragments are aggregated in the urea-soluble fraction of human brain homogenates, it is likely that TDP-43 aggregates in FTLD-U result in loss of function, rather than a toxic gain of function. TAR-DNA binding protein-43 is likely also involved in microRNA biogenesis, apoptosis, and cell division (102), and binds to and stabilizes human low molecular weight neurofilament (*h*NFL) mRNA (103). Recent evidence emerged that TDP-43 resides in the dendritic-processing body of somatodendrites in the form of RNA granules colocalized with the postsynaptic protein PSD95, where it acts as a translational repressor and thus likely helps regulate neuronal plasticity (104). Restricting nuclear-cytoplasmic trafficking of TDP-43 results in accumulation of TDP-43 as insoluble aggregates (105). Finally, loss of TDP-43 results in dysmorphic nuclear shape, misregulation of the cell cycle, and apoptosis by upregulating cyclin-dependent kinase 6, resulting in increased phosphorylation of retinoblastoma protein pRB and pRb-related protein pRb2/p130 (106). There are currently approximately 60 publications regarding TDP-43 in FTLD-U and ALS, and they continue to accumulate.

TDP-43 in FTLD-U and ALS

The TDP-43 antibody labels ubiquitinated cortical, hippocampal, and striatal inclusions in FTLD-U (107-115) and lower motor neuron and striatal inclusions in ALS (107,108,110, 113-120); it also labels inclusions in FTLD-U white matter (121). Neurons with TDP-43-positive inclusions in either the cytoplasm or the nucleus have absence of normal nuclear TDP-43 positivity, additional information that assists in interpreting immunopositivity. Figure 6 compares ubiquitin to TDP-43 immunohistochemistry (IHC) in an FTLD-U case.

Some investigators have correlated clinical patterns with immunohistochemical TDP-43 patterns as outlined by 2 slightly different schemes (91,92). One study showed that cases with numerous CIs (Sampathu Type 2/Mackenzie Type 3) have shorter survival, increased frequency of semantic dementia/semantic variant of PPA, and dense hippocampal inclusions; cases with numerous neurites (Sampathu Type 1/Mackenzie Type 2) have difficulty with object naming and have dense temporal and hippocampal inclusions; and cases with intranuclear inclusions (Sampathu Type 3/Mackenzie Type 1) have substantial executive deficits with dense frontal inclusions (109). *PROGRANULIN* mutations were found only in Sampathu Type 3/ Mackenzie Type 1 cases (109), as has been reported (92,112).

The absence of nuclear TDP-43 labeling and the presence of granular cytoplasmic TDP-43 positivity have been interpreted as being characteristic of "preinclusions" (107,108,112). Some interpret preinclusions to indicate that abnormal TDP-43 is prevented from relocating to the nucleus, possibly by becoming hyperphosphorylated and therefore remaining in the cytoplasm where it aggregates (107). Additionally, chromosome 9p-linked FTLD-ALS cases seem to have TDP-43-positive granular inclusions in cortical neurons that are not labeled with ubiquitin IHC, corroborating their interpretation as preinclusions that have not yet become ubiquitinated (112).

The Northwestern Cognitive Neurology and Alzheimer Disease Center participated in an international collaborative study analyzing TDP-43 immunopositivity in one of the largest group of FTLD cases published (112). TAR-DNA binding protein-43 IHC was performed using the polyclonal TDP-43 antibody (Proteintech, Chicago, IL) in 193 familial and sporadic FTLD-U and FTLD-MND cases, which included 36 with *PGRN* mutations, 5 with valosin-containing protein (*VCP*) mutations, 4 with charged multivesicular body protein 2B (*CHMP2B*) mutations, 7 with chromosome 9p linkage but no *VCP* mutation, 46 other familial, and 95 sporadic cases. These cases were compared with 49 other non-FTLD-U FTLD cases, including Pick disease, CBD, PSP, basophilic inclusion body disease, neuronal intermediate filament inclusion disease, and FTDP-17; 42 non-FTLD dementia cases, including AD, argyrophilic grain disease, tangle predominant senile dementia, Parkinson disease, DLBD, multiple systems atrophy, trinucleotide repeat disorders, and hippocampal sclerosis; and 19 normal controls. TAR-DNA binding protein-43 was positive in all the familial and sporadic FTLD-U and FTLD-MND cases except those with neuronal intermediate filament inclusion disease (112,122-124) and those with *CHMP2B* mutations, as has been reported (112,125) (see also succeeding sentences). Rare, apparently sporadic FTLD-U cases were found to be TDP-43 negative, and those were termed "atypical FTLD-U" (Fig. 7). These cases are currently being investigated for possible spontaneous *CHMP2B* mutations. Cases of hippocampal sclerosis were also positive with TDP-43 (Fig. 8). There were no TDP-43-positive inclusions in any of the non-FTLD-U dementias, including AD and dementia with Lewy bodies (DLB), or in the controls (112). Of particular interest to studies involving animal models of superoxide dismutase 1 (SOD1)-linked familial ALS (FALS), a large series of ALS cases was studied immunohistochemically for TDP-43. Results showed that, whereas ubiquitinated lower motor neuron inclusions in 59 sporadic ALS cases (SALS) and 11 FALS cases with *SOD1* mutations excluded were labeled with TDP-43, those in 15 FALS cases with *SOD1* mutations were not (Fig. 9) (119). TAR-DNA binding protein-43 negativity of lower motor neuron inclusions in 2 FALS cases with *SOD1* mutations has been confirmed in another study (120).

Clearly, additional clinicopathologic studies are needed to better delineate the pathologic and significance of TDP-43 in FTLD-U and ALS.

Additional FTLD-U-Associated Chromosomes

Although *PGRN* mutations account for many of the familial FTLD-U cases, there are rare mutations in 3 other genes associated with familial FTLD-U. Most, but not all, of these have TDP-43-positive ubiquitinated inclusions (see next two sections).

Chromosome 9 Related

1) Inclusion body myopathy with Paget disease of bone and frontotemporal dementia is due to mutations in the *VCP* gene (126). Twelve mutations, 11 of which are pathogenic, have been identified. The ubiquitinated inclusions in inclusion body myopathy with Paget disease of bone and frontotemporal dementia are predominantly intranuclear and are not primarily composed of VCP (127) but rather of TDP-43 (128). 2) A mutation in intraflagellar transport protein 74 on chromosome 9p has been reported in only 1 family with familial FTD-ALS (129). No pathologic description is available for this family. 3) There are other as yet undefined mutation (s) on chromosome 9p associated with familial FTD-ALS (129-131). These cases have ubiquitinated inclusions that are labeled by TDP-43 (112). 4) Lastly, there is a potential locus on chromosome 9q linked to familial FTD-ALS, although this has not been replicated (132).

Chromosome 3

A large Danish familial FTLD and FTLD-ALS pedigree linked to chromosome 3 was found to have mutations in *CHMP2B* (see previous sentences) (133). Ten mutations have been identified, 4 of which are pathogenic. The ubiquitinated inclusions in *CHMP2B*-related familial FTLD-U are TDP-43 negative (112,125).

TDP-43 in Other Disorders

The discovery that TDP-43 is the major protein component in the ubiquitinated inclusions of FTLD-U has allowed investigation into combined pathologies of FTLD-U with other disorders. For example, in the past, because AD pathology also labels with ubiquitin, cases of AD combined with FTLD-U could only be definitively identified if the FTLD-U component had intranuclear inclusions. Because only a fraction of the AD tangle pathology sometimes labels with TDP-43, combined AD/FTLD-U pathology is now known to be quite common; in some studies, it has been shown to occur in the hippocampus and amygdala in approximately 30% of AD and combined AD-DLB cases, half of pure DLB cases, and in the dentate fascia in 70% of hippocampal sclerosis cases (134-137). Results have been conflicting, however, with some studies finding no TDP-43-positive inclusions in pure DLB (136). Likewise, some have found combined TDP-43 proteinopathy and Pick disease (95,138) with a subset of inclusions positive for both tau and TDP-43, whereas others have not (112). On the other hand, most Guamanian ALS-Parkinson disease complex cases have TDP-43 positivity (139,140). The significance of TDP-43 positivity in hippocampus and amygdala but not in cortex in AD and DLB is unclear. Does it play a role in the patient's cognitive impairment or is it simply a sign of generalized molecular and cellular disarray in medial temporal regions? Interestingly, in an immunohistochemical analysis of TDP-43 in 5 cases of PPA with AD pathology (which might be expected to have concomitant TDP-43-positive inclusions), none did; all had AD pathology only (141). Further studies may shed light on these issues.

Gene Expression Studies in FTLD-U

Mishra et al (142) performed gene expression micro-array analysis on homogenates from superficial frontal cortex of 10 cases of FTLD-U (n = 6) and FTLD-MND (n = 4) and 6 age-matched controls. Three of the FTLD-U cases had *PGRN* mutations. The FTLD-MND cases that had TDP-43-positive inclusions predominantly in the dentate gyrus and not in the frontal cortex had results similar to the controls. Frontotemporal lobar degeneration with ubiquitinated

inclusion cases compared with controls had downregulated synapse-related genes. This is not surprising because normal TDP-43 colocalizes with the postsynaptic protein PSD-95 (104). There was upregulation of cytoskeletal protein-associated, mitochondrial/energy-associated, and kinase family-associated genes (142). Compared with FTLD-MND, FTLD-U also had downregulation of microtubule-/axon-associated genes, including *h*NFL and MAP4 (142). The downregulation of *h*NFL is interesting in view of the recent report that TDP-43 binds to and stabilizes *h*NFL mRNA (103). Several ubiquitin-/proteasome-associated genes were also downregulated (142). Subsequently, another analysis of gene expression in FTLD-U frontal cortex gray matter, hippocampus, and cerebellum showed similar downregulation of synapse-related and upregulation of cytoskeletal protein-associated genes in affected regions (143). However, this study showed dysregulation of more genes than did the study by Mishra et al and identified pathways not involved in other neurodegenerative diseases such as the cell cycle pathway and transforming growth factor β signaling (143). A gene expression analysis in ALS showed downregulation of cytoskeletal protein-related and mitochondrial-/energy-associated genes, but found similar downregulation of signaling-related genes (144). This study used slices of "fresh frozen prefrontal cortex," and it is not clear whether it was full-thickness cortex and white matter or a focused region of cortex that was analyzed (144). One might expect results of gene expression analyses in FTLD-U and ALS to be similar because FTLD-U and ALS seem to be on a clinical and pathologic spectrum (145); additional work in this area may be enlightening.

TDP-43 Gene Analysis

The 2 major recent discoveries in the FTLD field are the *PGRN* mutations in non-tau FTDP-17 dementias (48,49), which have also been called FTDU-17 in recognition of the presence of ubiquitin inclusions, and the identification of TDP-43 as the major protein component of the ubiquitinated inclusions (94). Familial FTLD-U with *PGRN* mutations have insoluble inclusions composed of TDP-43 rather than PGRN protein, ie the insoluble aggregates in these cases are not composed of the mutated gene protein product. This is a distinct contrast from the familial taupathies with *MAPT* mutations which contain insoluble tau protein deposits. Until now, mutations in the *TARDBP* gene have not been found in FTLD-U (146-148) and FALS (148) cases with TDP-43-labeled inclusions, which has leant credibility to those reports that TDP-43 is not truly the major protein component of the ubiquitinated inclusions (149). New reports, however, describe *TARDBP* mutations in FALS (150) and in FALS and SALS (151). The *TARDBP* mutation in the autosomal dominant FALS family is a novel missense mutation, Ala-315-Thr (c.1077 G>A), in exon 6 (150). No member of this family has yet come to autopsy, but it will be crucial to examine such a case for TDP-43-positive insoluble inclusions. In the FALS and SALS cases, 3 single base substitutions in *TARDBP* exon 6 were identified, all near the C-terminal protein-protein interaction region of *TARDBP*, resulting in substitution of valine for methionine (M337V), lysine for glutamine (Q331K), and alanine for glycine (G294A) (151). The M337V mutation segregated with disease in a large autosomal dominant FALS kindred, whereas the Q331K mutation was found in screening 200 British SALS cases (absent in 500 controls) and the G294A mutation in screening 172 Australian SALS cases (absent in 372 controls) (151). Screens of an additional 390 controls revealed no *TARDBP* mutations (151). Chick embryos whose spinal cords were transfected with either the M337V or the Q331K mutant *TARDBP* gene did not develop limb or tail buds (151). It will likely not be long until *TARDBP* mutations are found in familial FTLD-U.

Links Between PGRN and TDP-43

Given that most familial FTLD-U cases with known mutations have *PGRN* mutations, and that the aggregated protein in these brains is composed primarily of TDP-43, it is important to understand the relationship between PGRN and TDP-43 and the roles they play in

neurodegeneration. In one study, in which *PGRN* missense mutations were shown to result in very low PGRN protein levels, investigators asked whether reduced *PGRN* expression would induce accumulation or relocalization of TDP-43 fragments (52). *PROGRANULIN* expression was downregulated in human cell lines and in zebrafish, but neither TDP-43 relocalization nor proteolytic processing to C-terminal fragments occurred (52). Zhang et al (152) recently reported that PGRN mediates caspase-dependent cleavage of TDP-43, generating 25- and 35-kd fragments. Suppression of *PGRN* expression (which is similar to *PGRN* haploinsufficiency related to mutations) results in accumulation of TDP-43 fragments and this can be inhibited by caspase inhibitors (152). Because SLPI, binding to PGRN, inhibits elastase-mediated proteolysis of PGRN (61), the authors speculate that the mechanism involves a complex between SLPI, PGRN, caspase 3, and TDP-43; decreased PGRN and therefore decreased SLPI might free caspase 3 activity to cleave TDP-43, thereby resulting in a cascade of intracellular events that lead to FTLD-U (152). Staurosporine, a protein kinase inhibitor, also induces caspase cleavage and redistribution of TDP-43 from the nucleus to the cytoplasm, which correlates with the findings in FTLD-U and ALS (152). The results suggest a potential role for PGRN in normal TDP-43 function and a link between the two in FTLD-U disease (152).

CONCLUSIONS AND FUTURE DIRECTIONS

The pathology of frontal lobe dementia of the non-Alzheimer type, now preferably termed frontotemporal lobar degeneration, is currently divided into the same 2 major categories, tauopathies and ubiquitinopathies. There now are at least 13 different subtypes (Table 3) (153,154). Much has been learned in 20 years, and the FTD subtype diagram has become much more complex (Fig. 10; compared with Fig. 1). There has been exciting recent progress, but much work clearly remains to elucidate the interactions between PGRN and TDP-43 and the roles they play in FTLD-U and ALS. Individuals at risk must be identified early to prevent or halt progression of the disease. Can TDP-43 be measured in cerebrospinal fluid? Can ligands similar to the Pittsburgh B compound that allow in vivo imaging of amyloid plaques be developed to image FTLD-U pathology? In view of the role of PGRN in tumorigenesis, do individuals with *PGRN* mutations and resulting haploinsufficiency have a decreased incidence of cancer? In view of its role in inflammation, do those with *PGRN* mutations or FTLD-U without mutations have an increased or decreased incidence of autoimmune or chronic inflammatory disorders? Progranulin is upregulated in activated microglial cells, but is it upregulated in neurons, and, if so, is this beneficial or deleterious to the neuron or to the CNS in general? What is the significance, if any, of TDP-43-positive inclusions in medial temporal regions in AD? Do they contribute to cognitive impairment or are they simply markers of general molecular and cellular dysfunction in these regions in AD? *TARDBP* mutations have now been identified in ALS—are *TARDBP* mutations also found in FTLD-U? The 2 discoveries of mutations in *PGRN* and TDP-43 protein in FTLD-U inclusions occurring only months apart offer opportunities to explore and answer these questions and learn more regarding the neurobiology of the brain in the process.

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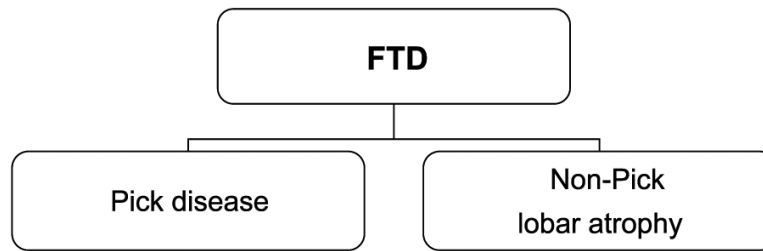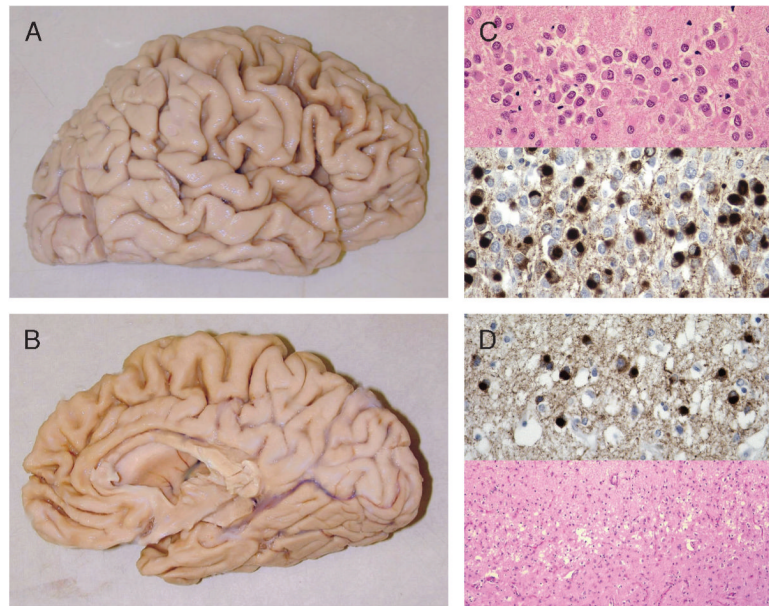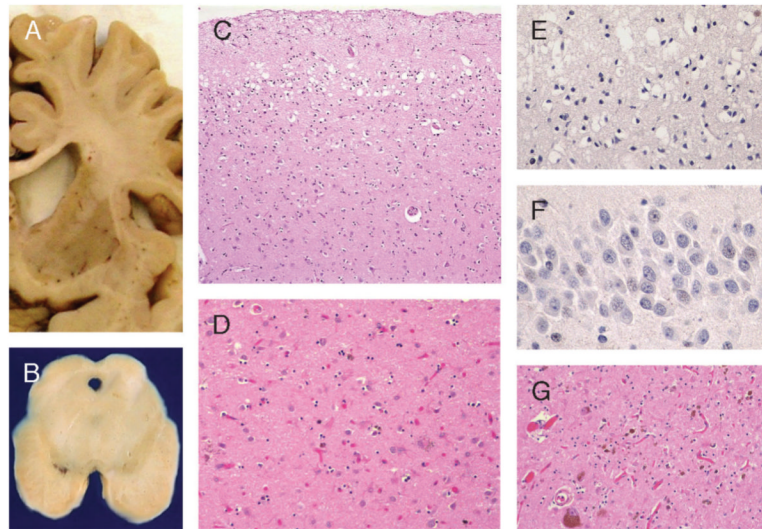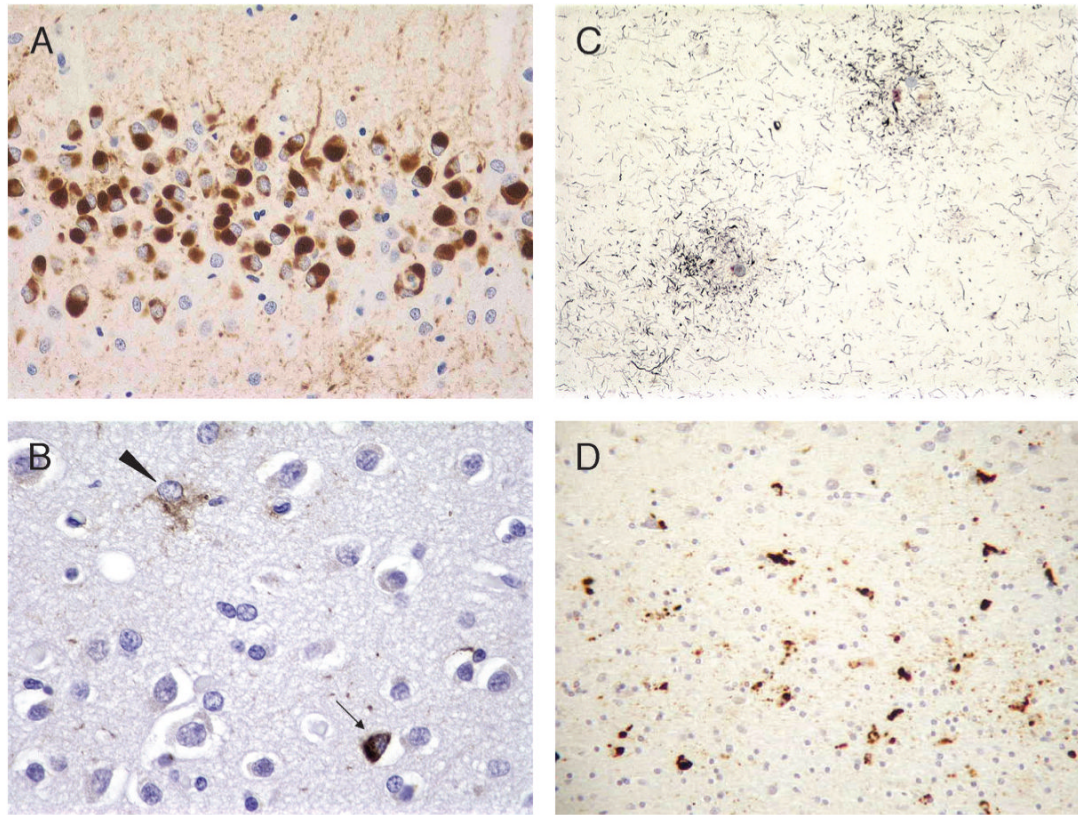
FIGURE 1.
Frontotemporal dementia (FTD) pathologic subtypes, 1987.

FIGURE 2.
Pick disease pathology. **(A, B)** Circumscribed frontal and temporal atrophy. **(C)** Pick bodies in dentate gyrus seen on hematoxylin and eosin (top; 40×) and with paired helical filament 1 immunohistochemistry (IHC) (bottom; 60×). **(D)** Pick bodies seen with paired helical filament 1 IHC (top; 60×) in frontal cortical layer II, which also shows microvacuolation and gliosis on hematoxylin and eosin (bottom; 10×).
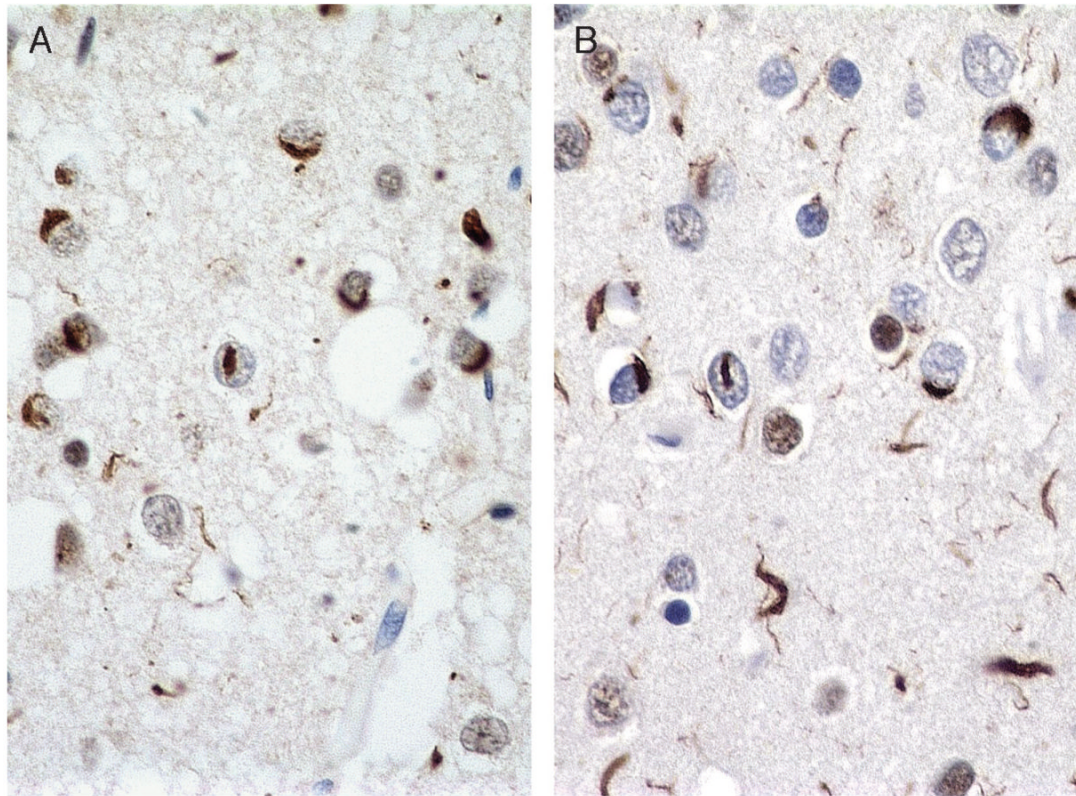
FIGURE 3.
Dementia lacking distinctive histology. Pathology (circumscribed frontal and temporal atrophy, as in Pick disease, is also present). **(A)** Caudate atrophy. **(B)** Pallor of the substantia nigra. **(C)** Superficial microvacuolation and gliosis, cortical layer II, frontal and temporal lobes (hematoxylin and eosin: 20×). **(D)** Neuronal loss and gliosis, caudate nucleus (hematoxylin and eosin: 40×). **(E)** Ubiquitin immunohistochemistry (IHC) of frontal lobe shows no inclusions (40×). **(F)** Ubiquitin IHC of dentate gyrus shows no inclusions (60×). **(G)** Neuronal loss and gliosis in substantia nigra (hematoxylin and eosin: 20×).

FIGURE 4.
Familial tauopathy with dementia linked to chromosome 17 pathology. **(A)** Dentate gyrus with Pick-like bodies, L266V tau mutation (paired helical filament 1 immunohistochemistry [IHC]; 40×). **(B)** Progressive supranuclear palsy (PSP)-like pathology in frontal cortex, with neuronal PSP-type tangle (arrow) and tufted astrocyte (arrowhead; AT8 IHC; 60×). **(C)** Corticobasal degeneration-like cortical pathology with 2 large astrocytic plaques and abundant thread pathology (Gallyas stain; 20×). **(D)** Cortical gray-white junction with unique tau pathology consisting predominantly of globular white matter (oligodendroglial)-insoluble tau deposits (AT8 IHC; 20×).
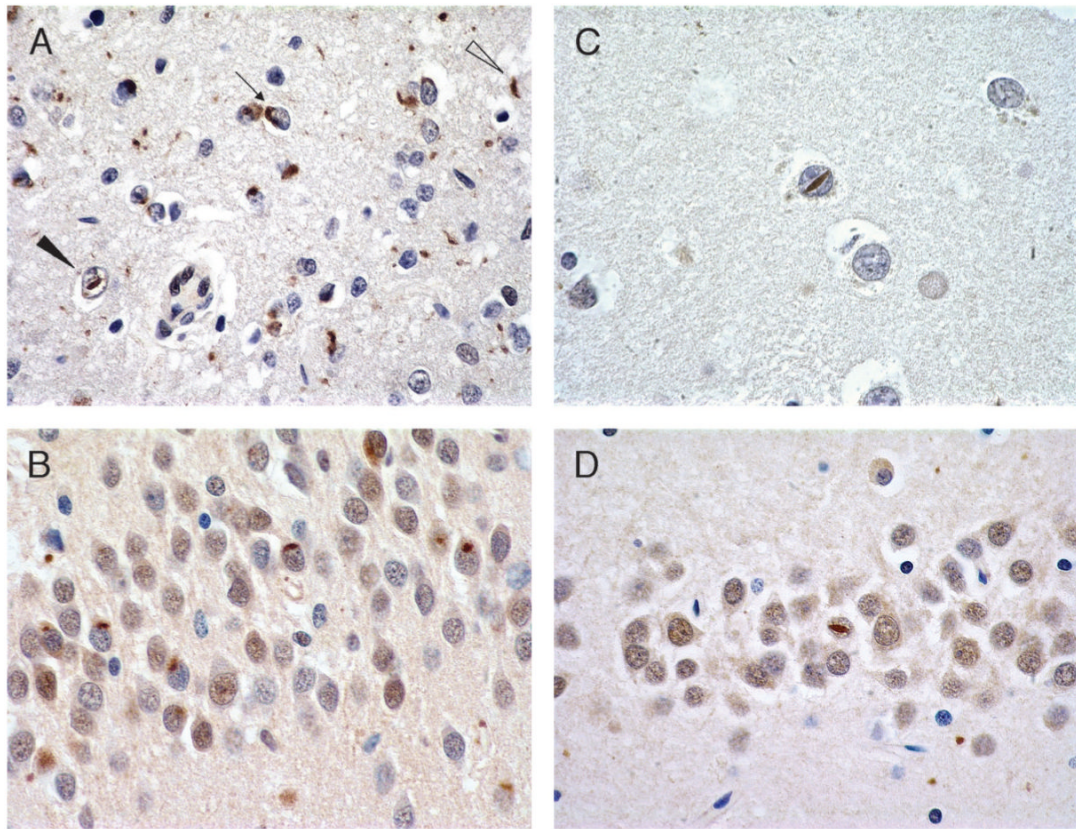
FIGURE 5.
Frontotemporal lobar degeneration with ubiquitinated inclusions pathology. **(A)** Superficial frontal cortex with neuronal cytoplasmic inclusions (arrow), neuronal intranuclear inclusions (NIIs; solid arrowhead), and dystrophic neurites (open arrowhead; 40×). **(B)** Dentate gyrus with neuronal cytoplasmic inclusions (60×). **(C)** Putamen neuron with NII (100×). **(D)** Dentate gyrus neuron with NII (60×). All are ubiquitin immunohistochemistry (Dako polyclonal, Carpinteria, CA).

FIGURE 6.
Ubiquitin and TAR-DNA binding protein-43 (TDP-43) immunohistochemistry (IHC) in frontotemporal lobar degeneration with ubiquitinated inclusions (FTLD-U). Ubiquitin (**A**; ubiquitin IHC, Dako polyclonal; 60×) and TDP-43 (**B**; TDP-43 IHC, Proteintech) in frontal cortex of FTLD-U have similar labeling patterns; **(A)** Ubiquitin IHC (Dako polyclonal). **(B)** TDP-43 (Proteintech).
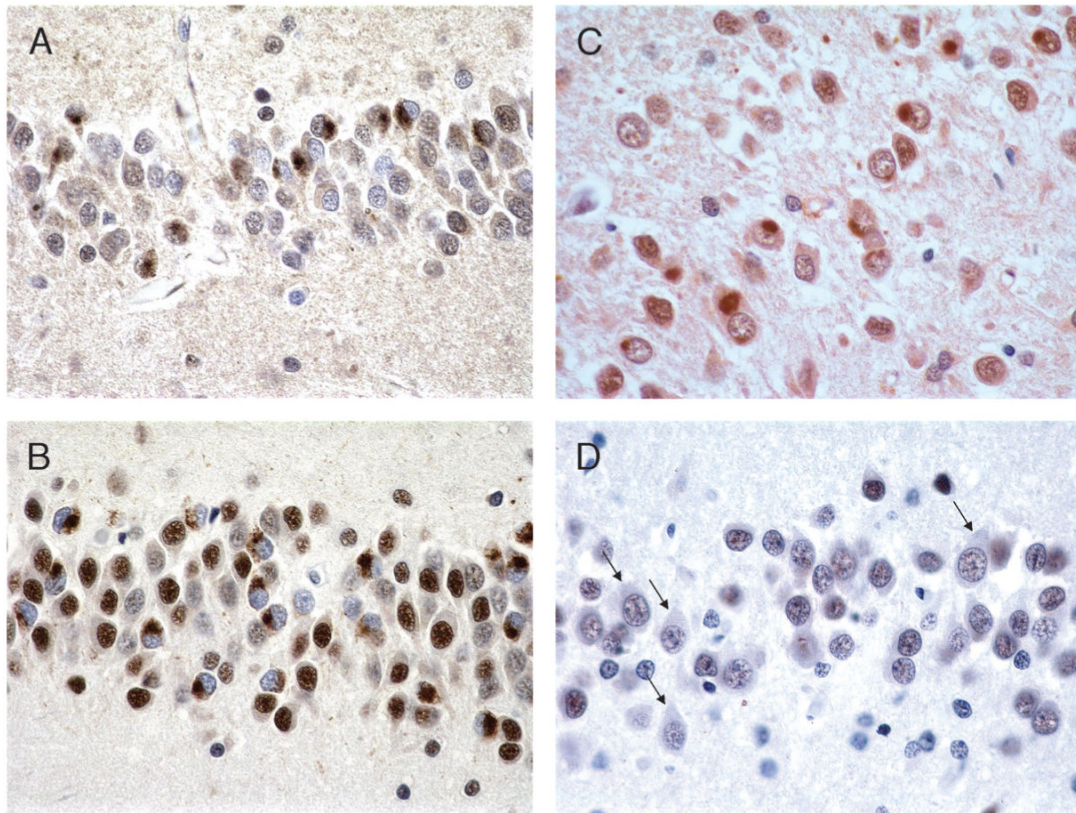
FIGURE 7.
Typical and "atypical" frontotemporal lobar degeneration with ubiquitinated inclusions (FTLD-U). **(A, B)** Typical FTLD-U labeled with ubiquitin (**A**; 40×) and TAR-DNA binding protein-43 (TDP-43; **B**; 40×); both label cytoplasmic inclusions (CIs). **(C, D)** "Atypical" FTLD-U labeled with ubiquitin (**C**; 60×) and TDP-43 (**D**; 60×). Inclusions are ubiquitin positive but TDP-43 negative (note arrows pointing to unlabeled CIs).
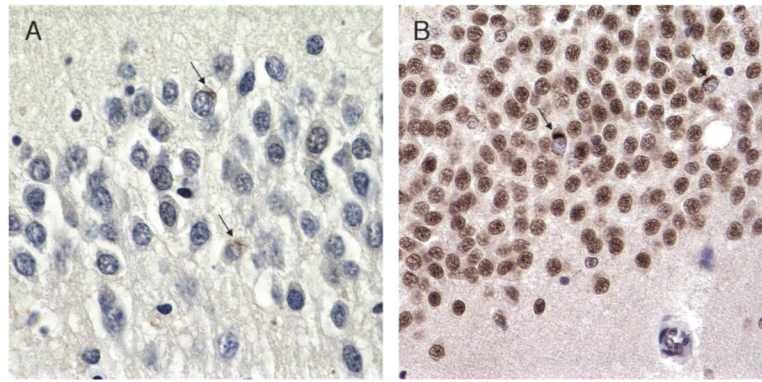
FIGURE 8.
Hippocampal sclerosis, ubiquitin, and TAR-DNA binding protein-43 immunohistochemistry (IHC). **(A)** Ubiquitin IHC of dentate gyrus in hippocampal sclerosis shows 2 equivocal inclusions noted retrospectively (arrows; 60×). **(B)** TAR-DNA binding protein-43 of same case clearly shows 2 positive cytoplasmic inclusions (CIs; arrows; 40×). Note that all nuclei are labeled except those in neurons with CIs.
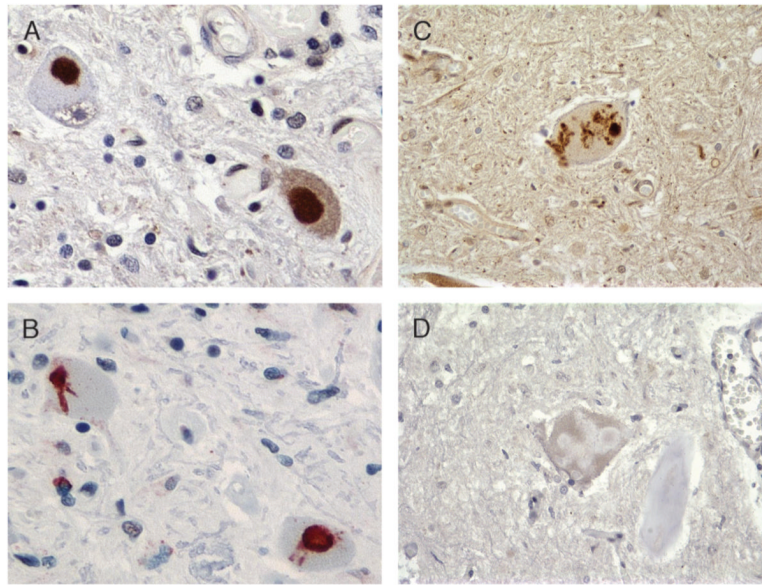
FIGURE 9.
Ubiquitin and TAR-DNA binding protein-43 immunohistochemistry (IHC) in familial amyotrophic lateral sclerosis (FALS) with and without superoxide dismutase 1 (SOD1) mutations. Familial amyotrophic lateral sclerosis cases without SOD1 mutation **(A, B)** and with SOD1 mutation **(C, D)**. Ubiquitin **(A, C)** clearly labels Lewy-like bodies **(A)** and skein-like inclusions **(C)** in FALS cases with **(C)** and without **(A)** SOD1 mutations. TAR-DNA binding protein-43 **(B, D)** labels FALS without SOD1 mutation **(B)** but is negative in FALS with SOD1 mutation **(D)** (all magnifications: 60×).
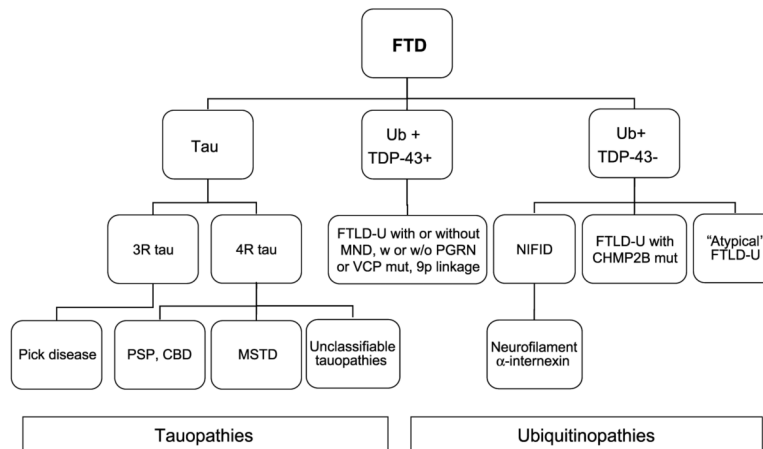
FIGURE 10.
Frontotemporal lobar degeneration (FTLD) pathologic subtypes, 2008. The pathology of frontotemporal dementia (FTD) has become increasingly complex, and pathologic diagnoses now incorporate molecular information compared with Figure 1. CBD, corticobasal degeneration; CHMP2B, charged multivesicular body protein 2B; MND, motor neuron disease; MSTD, multiple system taupathy with presenile dementia; NIFID, neuronal intermediate filament inclusion disease; PGRN, progranulin; PSP, progressive supranuclear palsy; TDP-43, TAR-DNA binding protein-43; VCP, volosin-containing protein.

TABLE 1

Immunohistochemical Features of Neuronal Inclusions in Disorders Causing Frontotemporal Dementia

Disease	Type of Neuronal Inclusion	Major Site	Tau Immunoreactivity	Ubiquitin Immunoreactivity
Pick disease	Pick body	Hippocampal and neocortical neurons	++	+
Corticobasal degeneration	Corticobasal inclusion	Layer II of neocortex, substantia nigra	++	-
Motor neuron disease-type dementia	Motor neuron disease-type inclusion	Layer II of neocortex, hippocampal dentate granule cells	-	++
Alzheimer disease	Neurofibrillary tangles	Hippocampal and neocortical neurons	++	+
Dementia of frontal type	None	-	-	-

This concise table illustrates the simplicity with which tau and ubiquitin immunostains can distinguish pathologic subtypes of frontotemporal dementia based on positivity or negativity and type and distribution of inclusions. Reprinted with permission from *Acta Neuropathol* 1996;91:12734 (Fig. 1).

TABLE 2

Clinicopathologic Correlations in 12 Patients

Group	n	Clinical Diagnoses	Family History	Sex	Average Age at Onset, years	Average Duration, years	NIIs
1	4	2 FTDbv	+/+	M/M	56.5	5.0	+/+
		2 PPA	+/-	M/F			+/+
2	5	3 FTDbv	+/+/+	M/M/F	65.4	7.6	+/+/-
		1 PPA	-	F			+
		1 "dementia"	Unknown	M			+
3	3	All FTD with ALS	+/-/+	M/M/F	62	3.3	+/-/-

Group 1, pathologic FTLD-U with *PGRN* mutations; Group 2, pathologic FTLD-U without *PGRN* mutations; Group 3, pathologic FTLD-MND without *PGRN* mutations.

ALS, amyotrophic lateral sclerosis; F, female; FTDbv, FTD behavioral variant; FTLD, frontotemporal lobar degeneration; FTLD-U, FTLD with ubiquitinated inclusions; M, male; MND, motor neuron disease; NIIs, neuronal intranuclear inclusions; *PGRN*, progranulin; PPA, primary progressive aphasia.

TABLE 3

Frontotemporal Lobar Degeneration: Pathologic Subtypes, 2008

Tauopathies	Ubiquitinopathies
Pick disease	FTLD-U/TDP-43 proteinopathy
Corticobasal degeneration	FTLD-MND
Progressive supranuclear palsy	FTDP-17 with *PGRN* mutations
FTDP-17 with *MAPT* mutations	FTLD-U with *VCP* mutations
Sporadic MSTD	FTLD-U with *CHMP2B* mutations
Tauopathies, unclassifiable	FTLD-MND linked to chromosome 9p
	Atypical FTLD-U (TDP-43 negative)

CHMP2B, charged multivesicular body protein 2B; FTDP, familial tauopathy with dementia linked to chromosome 17; FTLD, frontotemporal lobar degeneration; FTLD-U, FTLD with ubiquitinated inclusions; MND, motor neuron disease; MSTD, multiple system tauopathy with presenile dementia; *PGRN*, progranulin; TDP-43, TAR-DNA binding protein-43; *VCP*, valosin-containing protein.