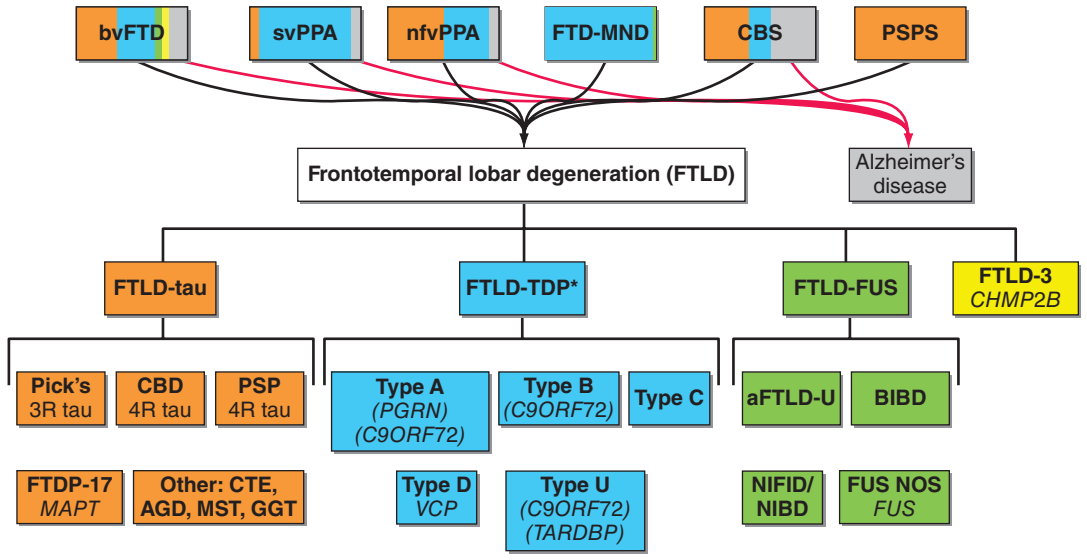

FIGURE 448-4 Frontotemporal dementia syndromes are united by underlying frontotemporal lobar degeneration pathology, which can be divided according to the presence of tau, TPD-43, or FUS-containing inclusions in neurons and glia. Correlations between clinical syndromes and major molecular classes are shown with colored shading. Despite improvements in clinical syndromic diagnosis, a small percentage of patients with some frontotemporal dementia syndromes will show Alzheimer's disease neuropathology at autopsy (*gray shading*). aFTLD-U, atypical frontotemporal lobar degeneration with ubiquitin-positive inclusions; AGD, argyrophilic grain disease; BIBD, basophilic inclusion body disease; bvFTD, behavioral variant frontotemporal dementia; CBD, corticobasal degeneration; CBS, corticobasal syndrome; CTE, chronic traumatic encephalopathy; FTD-MND, frontotemporal dementia with motor neuron disease; FTDP-17, frontotemporal dementia with parkinsonism linked to chromosome 17; FUS, fused in sarcoma; GGT, globular glial tauopathy; MST, multisystem tauopathy; nfvPPA, nonfluent/agrammatic variant primary progressive aphasia; NIBD, neurofilament inclusion body disease; NIFID, neuronal intermediate filament inclusion disease; PSP, progressive supranuclear palsy; PSPS, progressive supranuclear palsy syndrome; svPPA, semantic variant primary progressive aphasia; Type U, unclassifiable type.

mRNAs to the distal neuron for activity-dependent translation within dendritic spines. Because these proteins also form intracellular aggregates and produce similar anatomic progression, protein toxicity and spreading may also factor heavily in the pathogenesis of these FTLD-TDP and FTLD-FUS.

Increasingly, misfolded proteins in neurodegenerative disease are being recognized as having "prion-like" properties in that they can template the misfolding of their natively folded protein counterparts, a process that creates exponential amplification of protein misfolding within a cell and may promote transcellular and even transsynaptic protein propagation between cells. This hypothesis could provide a unifying explanation for the stereotypical patterns of disease spread observed in each syndrome (Chap. 444e).

Although the term *Pick's disease* was once used to describe a progressive degenerative disorder characterized by selective involvement of the anterior frontal and temporal neocortex and pathologically by intraneuronal cytoplasmic inclusions (*Pick bodies*), it is now used only in reference to a specific FTLD-tau histopathologic entity. Classical Pick bodies are argyrophilic, staining positively with the Bielschowsky silver method (but not with the Gallyas method) and also with immunostaining for hyperphosphorylated tau. Recognition of the three FTLD major molecular classes has allowed delineation of distinct FTLD subtypes within each class. These subtypes, based on the morphology and distribution of the neuronal and glial inclusions (Fig. 448-5), account for the vast majority of patients, and some subtypes show strong clinical or genetic associations (Fig. 448-4). Despite this progress, available data do not allow reliable prediction of the underlying FTLD subtype, or even the major molecular class, based on clinical features alone. Molecular PET imaging with ligands chosen to bind misfolded tau protein shows great promise and is already being applied to the study of patients with AD and FTD. Because FTLD-tau and FTLD-TDP account for 90% of FTLD patients, the ability to detect pathologic tau protein deposition in vivo will greatly improve prediction accuracy, especially when amyloid PET imaging is negative.

The burden on caregivers of patients with FTD is extremely high, especially when the illness disrupts core emotional and personality functions of the loved one. Treatment is symptomatic, and there are currently no therapies known to slow progression or improve symptoms. Many of the behaviors that may accompany FTD, such as depression, hyperorality, compulsions, and irritability, can be ameliorated with antidepressants, especially SSRIs. The co-association with motor disorders such as parkinsonism necessitates the careful use of antipsychotics, which can exacerbate this problem.

Progressive supranuclear palsy syndrome (PSP-S; also known as Steele-Richardson-Olszewski syndrome) is a degenerative disorder that involves the brainstem, basal ganglia, limbic structures, and selected areas of cortex. Clinically, PSP-S begins with falls and executive or subtle personality changes (such as mental rigidity, impulsivity, or apathy). Shortly thereafter, a progressive oculomotor syndrome ensues that begins with square wave jerks, followed by slowed saccades (vertical worse than horizontal) before resulting in progressive supranuclear ophthalmoparesis. Dysarthria, dysphagia, and symmetric axial rigidity can be prominent features that emerge at any point in the illness. A stiff, unstable posture with hyperextension of the neck and a slow, jerky, toppling gait are characteristic. Frequent unexplained and sometimes spectacular falls are common secondary to a combination of axial rigidity, inability to look down, and poor judgment. Even once patients have severely limited voluntary eye movements, they retain oculocephalic reflexes (demonstrated using a vertical doll's head maneuver); thus, the oculomotor disorder is supranuclear. The dementia overlaps with bvFTD, featuring apathy, frontal-executive dysfunction, poor judgment, slowed thought processes, impaired verbal fluency, and difficulty with sequential actions and with shifting from one task to another. These features are common at presentation and often precede the motor syndrome. Some patients with a pathologic diagnosis of PSP begin with a nonfluent aphasia or motor speech disorder and progress to classical PSP-S. Response to L-dopa is limited or absent; no other treatments exist. Death occurs within 5–10 years of onset. Like Pick's disease, increasingly the term PSP is used to refer to a specific histopathologic entity within the FTLD-tau class. In PSP, accumulation of hyperphosphorylated 4-repeat tau is seen within neurons and glia. Neuronal inclusions often take the form of NFTs, which may