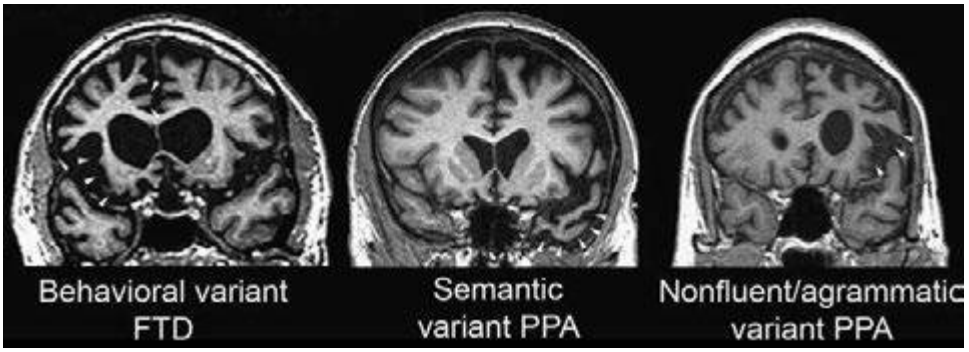

FIGURE 448-3 Three major frontotemporal dementia (FTD) clinical syndromes. Coronal magnetic resonance imaging sections from representative patients with behavioral variant FTD (*left*), semantic dementia (*center*), and progressive nonfluent aphasia (*right*). Areas of early and severe atrophy in each syndrome are highlighted (*white arrowheads*). The behavioral variant features anterior cingulate and frontoinsular atrophy, spreading to orbital and dorsolateral prefrontal cortex. Semantic variant primary progressive aphasia (PPA) shows prominent temporopolar atrophy, more often on the left. Nonfluent/agrammatic variant PPA is associated with dominant frontal opercular and dorsal insula degeneration.

is nearly as prevalent as AD in this age group. Early studies suggested that FTD may be more common in men than women, although more recent reports cast doubt on this finding. Although a family history of dementia is common, autosomal dominant inheritance is seen in only 10–20% of all FTD cases.

The clinical heterogeneity seen in familial and sporadic FTD is remarkable. Three core clinical syndromes have been described (Fig. 448-3). In the behavioral variant (bvFTD), the most common FTD syndrome, social and emotional systems dysfunction manifests as apathy, disinhibition, compulsivity, loss of empathy, and overeating, often but not always accompanied by deficits in executive control. Two forms of primary progressive aphasia (PPA), the semantic and nonfluent/agrammatic variants, are commonly due to FTLD and included under the FTD umbrella. In the semantic variant, patients slowly lose the ability to decode word, object, person-specific, and emotion meaning, whereas patients with the nonfluent/agrammatic variant develop profound inability to produce words, often with prominent motor speech impairment. Any of these three clinical syndromes, but most often bvFTD, may be accompanied by motor neuron disease (MND), in which case the term FTD-MND is applied. In addition, the corticobasal syndrome (CBS) and progressive supranuclear palsy syndrome (PSP-S) can be considered part of the FTLD clinical spectrum. Furthermore, patients may evolve from any of the major syndromes described above to have prominent features of another syndrome.

Findings at the bedside are dictated by the anatomic localization of the disorder. Right hemisphere-predominant or symmetric anterior cingulate/medial prefrontal, orbital, and anterior insular degeneration predicts bvFTD. Patients with nonfluent/agrammatic PPA show left (dominant) frontal opercular and precentral gyrus degeneration, whereas left anterior temporal atrophy presents with semantic variant PPA. Visuoconstructive ability, arithmetic calculations, and navigation may remain normal late into any FTD syndrome. Many patients with nonfluent aphasia or bvFTD later develop PSP-S, as disease spreads into diencephalic and brainstem structures, or CBS-like features, as disease moves into dorsal and lateral perirolandic cortices.

The most common autosomal dominantly inherited mutations causing FTD involve the *C9ORF72* (chromosome 9), *GRN* (chromosome 17), and *MAPT* (chromosome 17) genes. Hexanucleotide (GGGGCC) expansions in the noncoding portion of *C9ORF72* are the most recently identified and represent the most common genetic cause of familial or sporadic FTD (usually presenting as bvFTD with or without MND) and amyotrophic lateral sclerosis (ALS). The expansion is associated with reduced *C9ORF72* mRNA expression, nuclear mRNA foci containing transcribed portions of the expansion and other mRNAs, neuronal cytoplasmic inclusions containing dipeptide repeat proteins translated from the repeat mRNA, and transactive response DNA-binding protein of 43 kDa (TDP-43) neuronal cytoplasmic and glial inclusions. The pathogenic significance of these various features is a topic of vigorous investigation. *MAPT* mutations lead to a change in the alternate splicing of tau or cause loss of function in the tau molecule, thereby altering microtubule binding. With *GRN*, mutations in the coding sequence of the gene encoding progranulin protein result in mRNA degradation due to nonsense-mediated decay, providing a rare example of an autosomal dominant mutation that leads to haploinsufficiency and leads to a ~50% reduction in circulating progranulin protein levels. Intriguingly, a patient with *GRN* mutations on both chromosomes was recently reported to develop neuronal ceroid lipofuscinosis, focusing investigators on the lysosome as a site of molecular dysfunction in *GRN*-related FTD. Progranulin is a growth factor that binds to tumor necrosis factor (TNF) receptors and participates in tissue repair and tumor growth. How progranulin mutations lead to FTD remains unknown, but the most likely mechanisms include lysosomal dysfunction and enhanced neuroinflammation. Both *MAPT* and *GRN* mutations are associated with parkinsonian features, whereas ALS is rare. Infrequently, mutations in the valosin-containing protein (*VCP*, chromosome 9) and charged multivesicular body protein 2b (*CHMP2b,* chromosome 3) genes also lead to autosomal dominant familial FTD. Mutations in the *TARDBP* (encoding TDP-43) and *FUS* (encoding fused in sarcoma [FUS]) genes (see below) cause familial ALS, sometimes in association with an FTD syndrome, although a few patients presenting with FTD alone have been reported.

The gross pathologic hallmark of FTLD is a focal atrophy of frontal, insular, and/or temporal cortex, which can be visualized with neuroimaging studies (Fig. 448-3) and is often profound at autopsy. Despite the appearance of advanced disease, however, imaging studies suggest that atrophy often begins focally in one hemisphere before spreading to anatomically interconnected regions, including basal ganglia. Loss of cortical serotonergic innervation is seen in many patients. In contrast to AD, the cholinergic system is relatively spared in FTD, which accounts for the poor efficacy of acetylcholinesterase inhibitors in this group.

Although early studies suggested that 15–30% of patients with FTD showed underlying AD at autopsy, progressive refinement in clinical diagnosis has improved pathologic prediction accuracy, and most patients diagnosed with FTD at a dementia clinic with expertise in FTD will show underlying FTLD pathology. Microscopic findings seen across all patients with FTLD include gliosis, microvacuolation, and neuronal loss, but the disease is subtyped according to the protein composition of neuronal and glial inclusions, which contain either tau or TDP-43 in ~90% of patients, with the remaining ~10% showing inclusions containing FUS (Fig. 448-4).

The toxicity and spreading capacity of tau aggregates underlies the pathogenesis of many familial cases and is emerging as a key factor in sporadic tauopathies, although loss of tau microtubule stabilizing function may also play a role. TDP-43 and FUS, in contrast, are RNA/DNA binding proteins whose roles in neuronal function are still being actively investigated, but one key role may be the chaperoning of