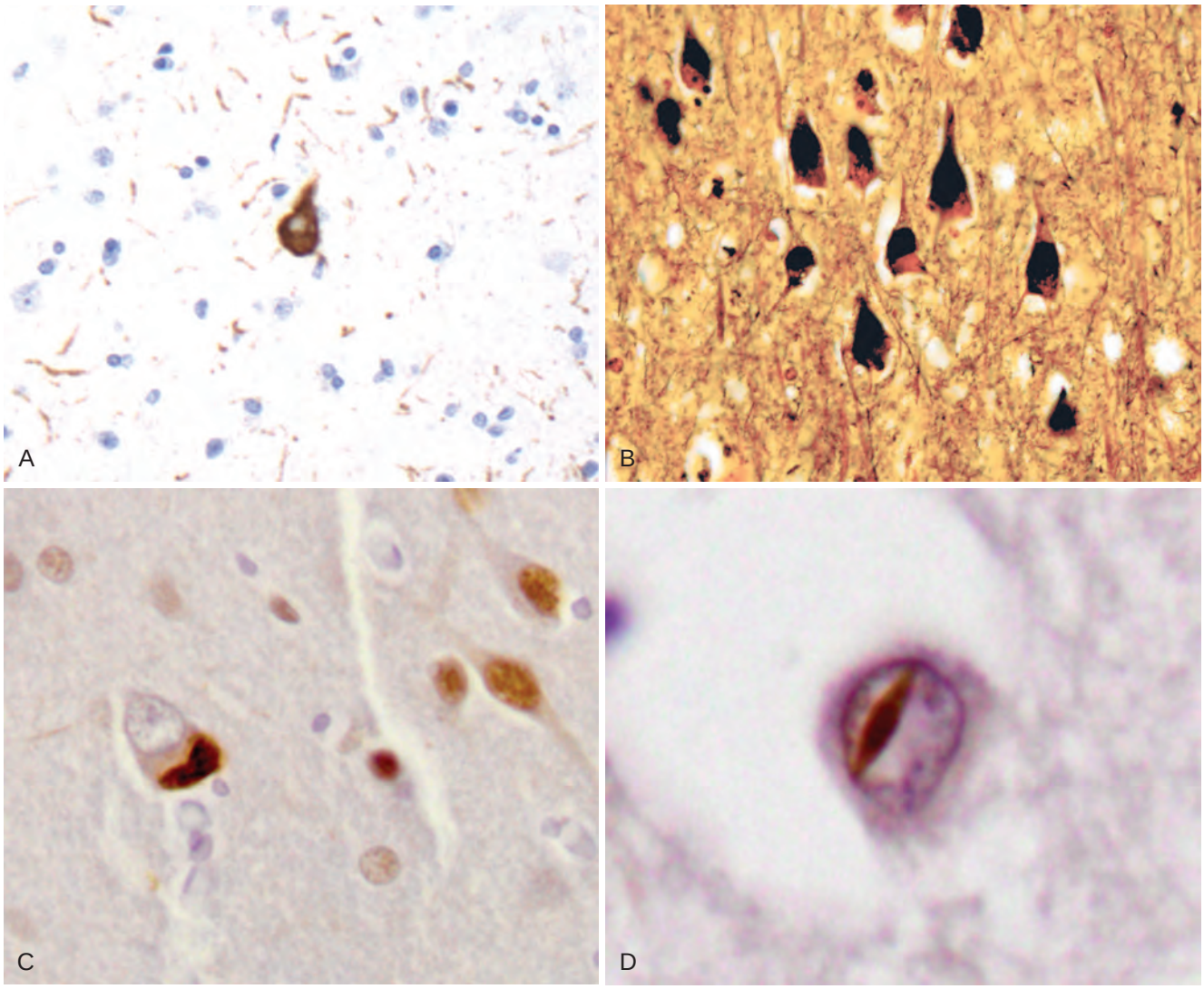

Figure 28-39 Frontotemporal lobar degenerations (FTLDs). **A,** FTLD-tau. A tangle is present along with numerous tau-containing neurites. **B,** Pick disease. Pick bodies are round, homogeneous neuronal cytoplasmic inclusions that stain intensely with silver stains. **C,** FTLD-TDP. Cytoplasmic inclusions containing TDP-43 are seen in association with loss of normal nuclear immunoreactivity. **D,** FLTD-TDP. With progranulin mutations, the TDP-43–containing inclusions are commonly intranuclear.

Microscopically, neuronal loss is most severe in the outer three layers of the cortex. Some of the surviving neurons show a characteristic swelling **(Pick cells)**, while others contain **Pick bodies**, which are cytoplasmic, round to oval, filamentous inclusions that are only weakly basophilic but stain strongly with silver methods and contain 3R tau (Fig. 28-39*B*).

FTLD-TDP

Some individuals with clinically diagnosed FTLD and macroscopic changes of relatively localized cortical atrophy (the 'lobar degeneration' of the term) have inclusions that contain TDP-43, an RNA-binding protein, and do not contain tau. Individuals with this type of neurodegeneration may present with either behavioral problems or language complaints, just as with FTLD-tau.

Molecular Genetics and Pathogenesis. There are three well-established genetic forms of FLTD-TDP, as well as sporadic forms. Three different mutations have been found in the inherited forms of FTLD-TDP.

- The most common genetic form of familial FTLD-TDP is the result of an expansion of a hexanucleotide repeat in the 5′ UTR of C9orf72 (a gene encoding a protein of unknown function). The spectrum of disease associated with C9orf72 expansion also includes amyotrophic lateral sclerosis (ALS). How the repeat expansion results in formation of aggregates of TDP-43 is a mystery at present.
- Mutations in the gene encoding the TDP-43 protein are less common in FTLD-TDP and also occur in some familial cases of ALS. TDP-43 is an RNA-binding protein with roles in RNA processing as well as in the formation of stress granules. Both loss of function and gain of