Table 28-4 Relationship Between Proteins and Neurodegenerative Diseases

Protein	Diseases with Inclusions
Aβ	Alzheimer disease
Tau	Alzheimer disease Frontotemporal lobar degeneration Parkinson disease (with *LRRK2* mutations) Progressive supranuclear palsy Corticobasal degeneration
TPD-43	Frontotemporal lobar degeneration Amyotrophic lateral sclerosis
FUS	Frontotemporal lobar degeneration Amyotrophic lateral sclerosis
α-synuclein	Parkinson disease Multiple system atrophy
Polyglutamine aggregates (distinct proteins per disease)	Huntington disease Some forms of spinocerebellar ataxia Spinal bulbar muscular atrophy

immobile. Patients rarely become symptomatic before 50 years of age; the incidence of the disease increases with age, and the prevalence roughly doubles every 5 years, starting from a level of 1% for the 60- to 64-year-old population and reaching 40% or more for the 85- to 89-year-old cohort. This progressive increase in the incidence with increasing age has given rise to major medical, social, and economic concerns in countries with aging populations. About 5% to 10% of cases are familial forms of AD; these have provided important insight into the pathogenesis of the more common sporadic form of the disease. While pathologic examination of brain tissue remains necessary for the definitive diagnosis of AD, the combination of clinical assessment and modern radiologic methods allows accurate diagnosis in 80% to 90% of cases as confirmed at autopsy.

Molecular Genetics and Pathogenesis. **The fundamental abnormality in AD is the accumulation of two proteins (Aβ and tau) in specific brain regions, likely as a result of excessive production and defective removal** (Fig. 28-36). The two pathologic hallmarks of AD, particularly evident in the end stages of the illness, are *plaques* and *tangles*. Plaques are deposits of aggregated Aβ peptides in the neuropil, while tangles are aggregates of the microtubule binding protein tau, which develop intracellularly and then persist extracellularly after neuronal death. Both plaques and tangles appear to contribute to the neural dysfunction, and the interplay between the processes that lead to the accumulation of these abnormal aggregates is a critically important aspect of AD pathogenesis that has yet to be unraveled.

Several lines of evidence strongly support a model in which **Aβ generation is the critical initiating event for the development of AD**. First, there are diseases in which tau deposits appear, such as frontotemporal lobar degenerations, progressive supranuclear palsy, and corticobasal degeneration (discussed later), but Aβ deposits do not ensue. This suggests that having abnormal deposits of tau in the brain is not a sufficient stimulus to elicit deposition of Aβ. Additionally, multiple lines of genetic evidence point to the likely importance of altered Aβ metabolism; mutations in the protein from which Aβ is derived (APP) cause familial AD, as does increased copy number (either from small duplications or from trisomy 21) of the *APP* gene. Furthermore, point mutations in proteins that are part of the protease complexes that generate Aβ from APP also give rise to AD. In contrast, mutations in the gene for tau do not give rise to AD but rather cause frontotemporal lobar degenerations (discussed later).

The pathogenesis of AD involves not only Aβ and tau but several other genetic and host factors.

- *Role of Aβ.* Amyloid precursor protein (APP) is a cell surface protein with a single transmembrane domain that may function as a receptor, possibly for prion protein (PrP^c) among other ligands. The Aβ portion of the protein extends from the extracellular region into the transmembrane domain (Fig. 28-36). Processing of APP begins with cleavage in the extracellular domain, followed by an intramembranous cleavage. There are two potential pathways, determined by the type of initial proteolytic event. If the first cut occurs at the α-secretase site within the Aβ sequence, then Aβ is not generated (the non-amyloidogenic pathway). This mostly occurs at the cell surface, since the various proteases with α-secretase activity are involved in the shedding of surface proteins. Surface APP can also be endocytosed and may undergo cleavage by β-secretase, which cuts at the N-terminal region of the Aβ sequence (the amyloidogenic pathway). Following cleavage of APP at either of these sites, the γ-secretase complex performs an intramembranous cleavage. When paired with a first cut by α-secretase, it produces a soluble fragment, but when paired with β-secretase cleavage, it generates Aβ. The variation in peptide length ($Aβ_{40}$vs $Aβ_{42}$) arises from alterations in the exact location of the γ-secretase cleavage. The γ-secretase complex—containing presenilin, nicastrin, pen-2, and aph-1—is also responsible for processing of Notch receptors as well as many other membrane proteins. Once generated, Aβ is highly prone to aggregation—first into small oligomers (which may be the toxic form responsible for neuronal dysfunction), and eventually into large aggregates and fibrils.

  As mentioned earlier, part of the support for the central role of Aβ generation as a critical step for at least initiation of AD pathogenesis comes from familial AD. The gene encoding APP, on chromosome 21, lies in the Down syndrome region; AD pathology is an eventual feature of the cognitive impairment of these individuals. Histologic findings appear in the second and third decades followed by neurologic decline about 20 years later. A similar gene dosage effect is produced by localized chromosome 21 duplications that span the *APP* locus in some patients with familial AD. Point mutations in APP are another cause of familial AD. Some mutations lie near the β-secretase and γ-secretase cleavage sites, and others sit in the Aβ sequence and increase its propensity to aggregate. The two loci identified as causes of the majority of early-onset familial AD encode the two presenilins (PS1 on chromosome 14 and PS2 on chromosome 1). These mutations lead to a gain of function, such that the γ-secretase complex generates increased amounts of Aβ, particularly $Aβ_{42}$.