Various neurological diseases are accompanied by the formation of dense fibrous aggregates within particular classes of neuron in the brain. The abnormal filaments constituting these aggregates are morphologically distinct from any of the normal components of the neuronal cytoskeleton. Little is known about the identity of the molecules that form these filaments or about the reasons for their aberrant assembly. The paired helical filament (PHF), which constitutes the principal component of neurofibrillary tangles in Alzheimer disease, is one of the most intensively studied of these abnormal filaments. The characteristic modulated appearance of the PHF is generated by a double-helical stack of morphological units, each with a C-shaped cross-section displaying three domains