Amyloid β-protein (Aβ) accumulation in neurons has been demonstrated to precede its formation as amyloid plaques in the extracellular space in Alzheimer’s Disease (AD) patients. Consequently, intraneuronal Aβ accumulation is thought to be a critical first step in the fatal cascade of events that leads to neurodegeneration in AD. Understanding the structural basis of neuronal binding and uptake of Aβ might lead to potential therapeutic targets that could block this binding and the subsequent neurodegeneration that leads to the pathogenesis of AD. Previously, we demonstrated that mutation of the two adjacent histidine residues of Aβ40 (H13,14G) resulted in a significant decrease in its binding to PC12 cells and mouse cortical/hippocampal neurons (Poduslo et al., PLoS One, 5(1):e8813, 2010). We now demonstrate that the decreased neuronal binding follows the mutation order of H13G< H14G< H13,14G which suggests that the primary domain for neuronal binding involves histidine at position 13. A novel APP mutation (E693D) that produced variant Aβ lacking glutamate-22 (E22D) in Japanese pedigrees and showed AD-type dementia has enhanced oligomerization without both fibrillation and amyloid plaque formation but contains extensive intraneuronal Aβ (Tomiyama et al, J. Neuroscience, 30:4845, 2010). Our PC12 assay showed that deletion of glutamate-22 of Aβ resulted in a six-fold enhancement of neuronal binding. This enhanced binding explains the high level of intraneuronal Aβ seen in this pedigree. Blocking the binding of Aβ to neurons may provide a novel therapeutic approach for preventing neurodegeneration in AD.