APP mutations at or around codon 693 are located within the Aβ sequence and usually result in a clinical picture that is distinct from classical AD and characterized by frequent intracerebral hemorrhages. In contrast, patients carrying the so-called Arctic (E693G) and the recently reported E693Δ APP mutations develop an early-onset AD-like clinical phenotype. To investigate the effects of the two intra-Aβ APP mutations, E693G and E693Δ, on Aβ generation and deposition in vivo, we have generated a novel transgenic mouse model expressing the E693Δ APP mutation together with the K670N/M671L (Swedish) double mutation. These so-called E22ΔAβ mice were compared to our recently published ArcAβ mouse model with the combined expression of the Swedish and Arctic mutations and to the wild type Aβ producing Tg2576 mice that express the Swedish mutation alone. Sequential extractions of Aβ from brains of both ArcAβ and E22ΔAβ mice showed early decreases in soluble Aβ levels when compared to the Tg2576 mice. Interestingly, histopathological analyses in 15 month-old mice revealed a complete absence of extracellular amyloid deposition in the E22ΔAβ mice in contrast to the ArcAβ mice which were characterized by an aggressive amyloidosis with pronounced cerebral amyloid angiopathy. The preliminary results of this study indicate both similarities and striking differences of the in vivo phenotype of two codon 693 APP mutations. Our findings are in agreement with recently published data in human E693Δ carriers and a related mouse model expressing the E693Δ mutation on a wild type APP background.