Amyloid β (Aβ) generated from amyloid precursor proteins (APP) is a major component of senile plaque which is a pathogenic hallmark of Alzheimer’s disease (AD). X11-like (X11L), X11 and X11L2 are neuronal adaptor proteins whose association to the cytoplasmic domain of APP suppress the generation of Aβ. Several lines of previous observations indicate that X11 and X11L work to suppress the amyloidogenic metabolism of APP selectively, although it remains unclear how X11 and X11L function in the regulation of APP metabolism in the intact brain. To address these issues, we generated X11 and X11L genes doubly-deficient (X11/X11L double-KO) mice and human APPswe transgenic (hAPP Tg)/X11L-KO mice and analyzed the metabolism of APP. We revealed that X11L mutant mice showed enhanced β-site cleavage of APP along with increased accumulation of Aβ in brain and the dysfunction of X11s enhances the translocation of APP into detergent-resistant membranes (DRMs) where amyloidogenic metabolism of APP is facilitated. Moreover, we elucidated that two carboxyl PDZ domains of X11s have an important function to suppress the APP metabolism, suggesting the possibility of novel procedure to reduce the Aβ generation in brain by regulating the X11s PDZ domain.