Background: Individuals who have Down syndrome frequently develop early onset Alzheimer's disease, a neurodegenerative condition caused by the build-up of aggregated amyloid-β and tau proteins in the brain. Amyloid-β is produced by APP, a gene located on chromosome 21. People who have Down syndrome have three copies of chromosome 21 and thus also an additional copy of APP; this genetic change drives the early development of Alzheimer’s disease in these individuals.

Methods: Here we use a combination of next-generation mouse models of Down syndrome (Tc1, Dp3Tyb Dp(10)2Yey and Dp(17)3Yey) and a knockin mouse model of amyloid-β accumulation (AppNL-F) to determine how chromosome 21 genes other than APP modulate APP/amyloid-β in the brain when in three copies.

Results: We demonstrate that three copies of other chromosome 21 genes are sufficient to partially ameliorate amyloid-β accumulation in the brain. We go on to identify a subregion of chromosome 21 that contains the gene genes causing this decrease in amyloid-β accumulation and investigate the role of two lead candidate genes Dyrk1a and Bace2.

Conclusion: Thus an additional copy of chromosome 21 genes, other than APP, can modulate APP/amyloid-β in the brain under physiological conditions. This work provides critical mechanistic insight into the development of disease and an explanation for the typically later age of onset of dementia in people who have AD-DS compared to those who have familial AD caused by triplication of APP.
