

Genes linking Alzheimer's and Down syndrome discovered

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Scientists are a step closer to understanding which genes are responsible for early onset Alzheimer's disease in people with Down syndrome, thanks to a new study led by researchers at the Francis Crick Institute and UCL along with an international group of collaborators.

The findings could pave the way for future medicines to prevent the

disease in these individuals, and provide insights into the mechanisms that cause dementia in the general population.

Around 1 in 800 people are born with Down syndrome, which arises in people carrying an extra copy of chromosome 21. By the time they reach their 60s, around two thirds of those with Down syndrome will have early onset Alzheimer's.

The high rates of Alzheimer's in people with Down syndrome were previously thought to be caused by a particular gene on chromosome 21 called APP. Chromosome 21 contains 231 [genes](#), but APP was the prime suspect because it produces amyloid precursor proteins. These are involved in generating amyloid beta proteins, which build up in the brain in Alzheimer's patients.

In this study, published in the journal *Brain*, researchers found that extra copies of other genes on chromosome 21 increase Alzheimer's-like brain pathology and cognitive impairments in a mouse model of Down syndrome.

Dr. Frances Wiseman, Senior Research Fellow at UCL, and first author of this study, said: "We've shown for the first time that genes other than APP are playing a role in early-onset Alzheimer's disease in our model of Down Syndrome. Identifying what these genes are, and what pathways are involved in the earliest stages of neurodegeneration, could help us to one day intervene with these pathways to prevent the disease in people with Down syndrome."

The team compared [mice](#) that produce APP amyloid protein with, and without, the presence of human chromosome 21, to tease apart the contributions of APP and other genes in Alzheimer's disease.

They found that mice with an extra copy of all the genes on chromosome

21 had more signs of Alzheimer's disease than mice without. The mice with extra copies of all genes on chromosome 21 had greater levels of amyloid beta and more protein clumps or 'plaques' inside part of the brain that controls memory, and performed worse on memory tests.

The team then looked at what was causing the increased build-up of amyloid-beta and plaques in the brains of mice with [extra copies](#) of all the genes on human chromosome 21. They found that these mice produced more of a particular type of amyloid beta protein that is more prone to forming clumps.

Dr. Victor Tybulewicz, Group Leader at the Francis Crick Institute and co-senior author of the paper, said: "Down syndrome has historically been very difficult to model in a mouse, because the genes that we have on chromosome 21 are spread across three different [chromosomes](#) in mice. Only after years of refining our mouse models can we study the earliest stages of Alzheimer's, and other diseases, in the context of Down syndrome."

Elizabeth Fisher, Professor of Neurogenetics at UCL, and co-senior author of the paper, added: "Although we're looking at Alzheimer's disease through the lens of Down [syndrome](#), this international collaboration provides insight into the earliest stages of disease progression, which may be applicable to modulating Alzheimer's [disease](#) in the general population."

More information: *Brain* (2018). [DOI: 10.1093/brain/awy159](https://doi.org/10.1093/brain/awy159)

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