Genetic changes in brain cells link aging and Alzheimer's

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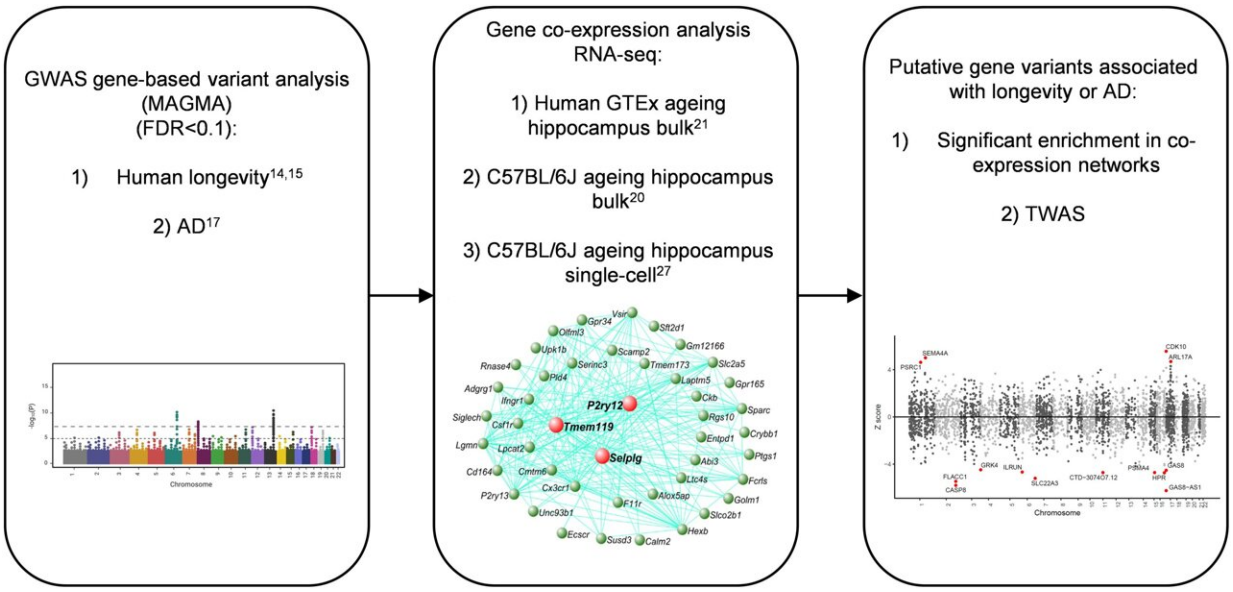

Experimental workflow to integrate human gene variants associated with AD and longevity from GWAS with gene expression networks that show aging-dependent changes. Credit: *Brain* (2025). DOI: 10.1093/brain/awae339

Genetic differences that contribute to how long a person will live and their risk of Alzheimer's disease have been identified by researchers at UCL and the UK Dementia Research Institute (UK DRI).

The study, published in *Brain*, found that genetic variations in brain cells, particularly the immune cells in the brain (microglia) and the cells

that support nerve cells (oligodendrocytes), are linked to both aging and Alzheimer's.

The researchers hope that the findings will highlight potential new targets for treating Alzheimer's and provide a deeper understanding of how our brains age.

Senior author, Dr. Dervis Salih (UCL Queen Square Institute of Neurology and UK Dementia Research Institute at UCL), said, "Our research highlights how genetic variation in certain brain cells can provide new opportunities for drug discovery of novel molecular targets for treatment.

"By understanding how these cells change with age and their role in Alzheimer's, we gain a deeper insight into the aging brain, offering hope for innovative and preventative therapies and a brighter future for families affected by this life-changing disease."

To understand the genetic factors behind aging and Alzheimer's, the team used large datasets of genetic information from people with Alzheimer's (21,982 people) and those without (41,944 people) from the International Genomics of Alzheimer's Projects (IGAP), alongside European ancestry data on aging—including the length of time a person was healthy (300,477 people), their longevity (11,262 people), and the lifespan of their parents (1,012,240 parents from a study from the University of Edinburgh).

The team then analyzed these datasets to find the significance of certain genes with relation to both aging and Alzheimer's.

They also used RNA sequencing data—a technique used to help understand which genes are active and how much they change with aging and disease—from both mice and people to study gene activity (how

cells function and respond to their environment).

The researchers found that genetic differences linked to Alzheimer's are common in microglia and oligodendrocytes, as both change with age and are linked to Alzheimer's risk.

These changes were observed in both humans and mice. However, only humans showed significant genetic links to Alzheimer's, suggesting that aging in human brain cells might make them more susceptible to dementia.

Researchers found that certain genetic variants were linked to how cells respond to aging, while others were linked to dementia. A few gene variants were associated with both aging and dementia, including APOE (a gene that provides instructions for making a protein called apolipoprotein E, which helps transport fats and cholesterol in the bloodstream), which had a strong effect.

This data indicates two sequential processes: aging and then dementia. This suggests that aging gene variants may prime some people for dementia, influencing when and how Alzheimer's develops.

It may also explain why some people develop dementia when they reach 70–80 years of age, and why some people are still mentally sharp when they are much older.

Dr. Salih said, "Genetic differences in microglia and oligodendrocytes affect how the cells function during aging, either in a healthy way or an activated way related to disease.

"By understanding these key genes, we might be able to develop new tests and biomarkers that will help slow brain aging and the progression of Alzheimer's disease."

More information: Andrew C Graham et al, Human longevity and Alzheimer's disease variants act via microglia and oligodendrocyte gene networks, *Brain* (2025). DOI: 10.1093/brain/awae339