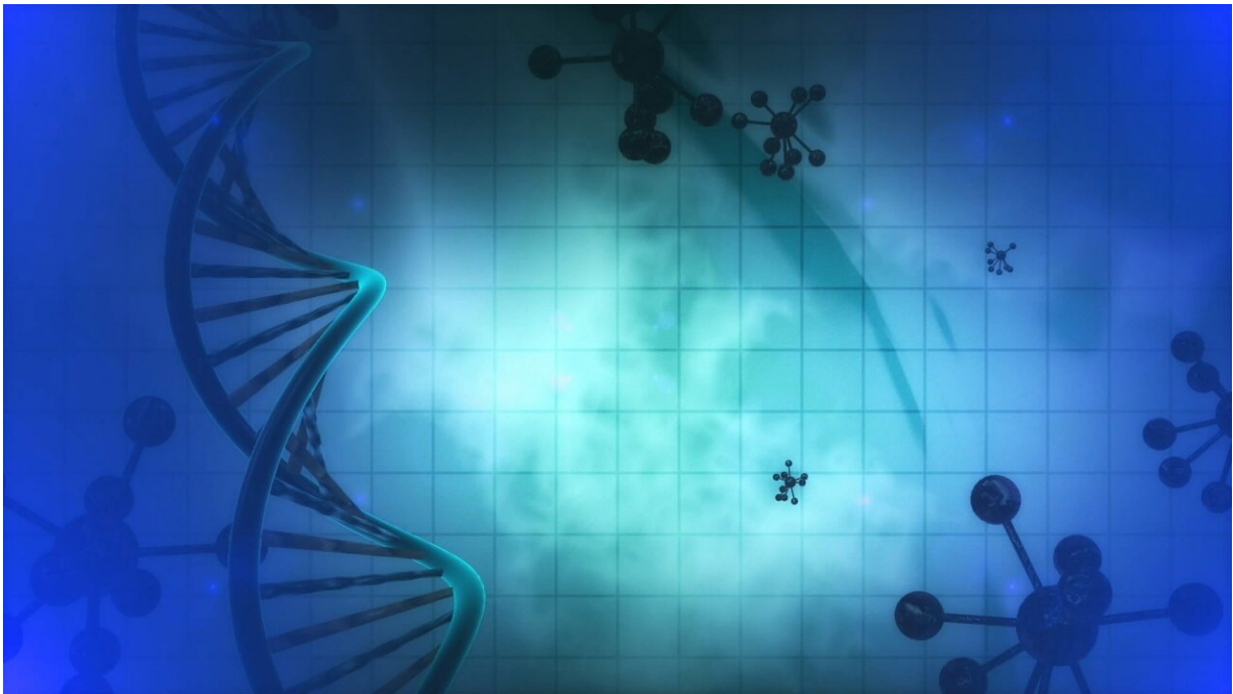# Genetic variants reduce risk of Alzheimer's disease

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A DNA study of over 10,000 people by UCL scientists has identified a class of gene variants that appear to protect against Alzheimer's disease.

The findings, published in *Annals of Human Genetics*, suggest these naturally occurring gene variants reduce the functioning of proteins called tyrosine phosphatases, which are known to impair the activity of a

cell signalling pathway known as PI3K/Akt/GSK-3β. This pathway is important for cell survival.

The research builds on previous studies in mice and rats, which suggested inhibiting the function of these proteins might be protective against Alzheimer's disease, but this is the first time such an effect has been demonstrated in people.

Researchers believe the PI3K/Akt/GSK-3β signalling pathway could be a key target for therapeutic drugs and the findings also strengthen evidence that other genes could be linked to either elevated or reduced risk of Alzheimer's disease.

"These results are quite encouraging. It looks as though when naturally-occurring genetic variants reduce the activity of tyrosine phosphatases then this makes Alzheimer's disease less likely to develop, suggesting that drugs which have the same effect might also be protective," said the study's lead author, Professor David Curtis (UCL Genetics Institute).

In this study, scientists analysed DNA from 10,000 people: half with Alzheimer's disease and half without.

In total, researchers examined all DNA sequence variants in over 15,000 genes, including over one million individual variants, in order to identify genes in which damaging variants were more common in people with or without Alzheimer's disease.

Researchers found that Alzheimer's disease risk is lower in people with damaging variants in a particular class of genes, which code for tyrosine phosphatases. The researchers say the findings suggest that drugs which have the same effect might also be able to reduce the risk of Alzheimer's. Professor Curtis points out there are already some drugs which act on tyrosine phosphatases but they have not yet been tested in

clinical trials.

"Here's a natural experiment in people that helps us understand how Alzheimer's disease develops: as some people have these genetic variants and some don't, we can see that the impact of having particular variants is a reduced likelihood of developing Alzheimer's disease," Professor Curtis added.

The researchers also found suggestive evidence that if there are genetic variants which damage the gene for the PI3K protein, then the risk of Alzheimer's increases.

"There is a consistent story in our results that the activity of the PI3K/Akt/GSK-3β signalling pathway is protective, which is exactly in line with findings from animal studies," said Professor Curtis.

The study also found suggestive evidence to implicate a gene not previously known to affect Alzheimer's risk, called C1R. The gene is known to affect periodontal Ehlers-Danlos syndrome, a disease involving chronic gum inflammation. Some previous research suggests that gum infections may increase the risk of Alzheimer's disease, so Professor Curtis speculates there may be a mechanism whereby genetic variants in C1R lead to some degree of gum disease, which in turn predisposes to Alzheimer's disease.

This study builds on a major 2019 study involving UCL researchers that identified five new risk genes for Alzheimer's disease, adding to UCL's record of world-leading research in dementia and genetics.

"Finding DNA variants which modify the risk of Alzheimer's disease is useful as it may help us develop drugs which target the same proteins. Simultaneously, researchers at UCL and across the globe are finding ways to detect the earliest stages of Alzheimer's disease, before it causes

any problems. As our understanding improves, there may be opportunities to intervene with treatments to prevent the disease from progressing," Professor Curtis said.

Professor Curtis, honorary professor at the UCL Genetics Institute and at Queen Mary University London, conducted the study with a team of undergraduate students in the UCL Genetics Institute. The data was generated by an international collaboration, the Alzheimer's Disease Sequencing Project.

 **More information:** *Annals of Human Genetics*, DOI: 10.1111/ahg.12375

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