**Breakthrough: Researchers fix Alzheimer's gene**

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Groundbreaking research shows, for the first time, how the most well-known genetic risk factor for Alzheimer's disease causes signs in human brain cells. Also, the scientists managed to correct the gene and erase its harmful effects.

Scientists fix the faulty gene that most likely causes Alzheimer's.

The complex role of the [apolipoprotein (APOE) gene](https://ghr.nlm.nih.gov/gene/APOE" \t "_blank) in the development of Alzheimer's has been studied extensively.

For instance, researchers know that having one copy of the APOE4 gene variant raises the risk of Alzheimer's by [two to three times](https://www.ncbi.nlm.nih.gov/pubmed/25217293).

And, having two copies of this genetic variant puts people at a 12-fold higher risk.

Normally, APOE's role is to provide instructions for creating the protein of the same name.

In combination with fats, APOE creates lipoproteins, which help to transport and regulate levels of [cholesterol](https://www.medicalnewstoday.com/articles/9152.php) throughout our bloodstream.

However, the E4 version of the gene seems to be particularly damaging to the brain, with several [studies](https://www.medicalnewstoday.com/articles/319492.php) showing that this genetic variant increases the risk of [toxic amyloid beta and tau](https://www.alz.org/braintour/plaques.asp) buildup.

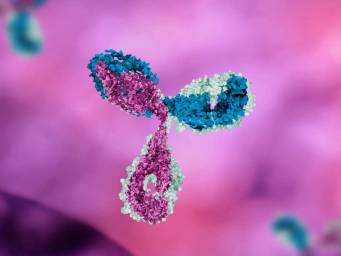
But why is that? What makes the E4 variant of this gene so much more harmful than other variants?

Researchers at the Gladstone Institutes in San Francisco, CA, wanted to find out. Their findings have just been [published](https://www.nature.com/articles/s41591-018-0004-z) in the journal *Nature Medicine.*

**APOE4 studied in human cells for first time**

More specifically, the researchers wanted to locate and understand the fine yet crucial difference between the E3 and E4 variants that makes the APOE4 gene so devastating.

Is it a case, the researchers wondered, of the E4 variant making APOE3 lose some of its functions? Or is it the case that more APOE4 has toxic effects?

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Lead investigator Dr. Yadong Huang — a professor of neurology and pathology at the University of California, San Francisco — explains the importance of this question.

"It's fundamentally important," he says, "to address this question because it changes how you treat the problem. If the damage is caused due to the loss of a protein's function, you would want to increase protein levels to supplement those functions."

"But if the accumulation of a protein leads to a toxic function, you want to lower production of the protein to block its detrimental effect."

**To find out, the researchers modeled the disease in human cells, examining the effect of APOE4 on human brain cells for the first time. Dr. Huang explains why changing the disease model was, in itself, a huge step for Alzheimer's research.**

"Many drugs," he explains, "work beautifully in a mouse model, but so far they've all failed in clinical trials. One concern within the field has been how poorly these mouse models really mimic human disease."

**Of mice and humans: Study finds differences**

Applying [stem cell](https://www.medicalnewstoday.com/info/stem_cell/) technology to skin cells from people with Alzheimer's who had two copies of the APOE4 gene, Dr. Huang and his team created neurons.

The researchers also created brain cells using skin cells from people who didn't have Alzheimer's and had two copies of the APOE3 gene.

The scientists found that in human brain cells, the APOE4 protein has a "pathogenic conformation" — meaning that it has an abnormal form that prevents it from functioning properly, leading to a series of disease-causing problems.

Namely, "APOE4-expressing neurons had higher levels of tau phosphorylation," the authors write, which was "unrelated to their increased production of amyloid-[beta] peptides, and [...] they displayed [GABAergic neuron](https://www.sciencedirect.com/science/article/pii/S0959438813000378) degeneration."

**Importantly, they also found that "APOE4 increased [amyloid-beta] production in human, but not in mouse, neurons."**

"There's an important species difference in the effect of APOE4 on amyloid beta," explains first study author Chengzhong Wang.

"Increased amyloid beta production is not seen in mouse neurons and could potentially explain some of the discrepancies between mice and humans regarding drug efficacy. This will be very important information for future drug development."

Chengzhong Wang

**Correcting the faulty gene**

Next, Dr. Huang and team wanted to see whether it was the loss of APOE3 or the accumulation of APOE4 that caused the disease.

So, they compared neurons that did not produce either the E3 or the E4 variant of the protein with cells that had APOE4 added to them.

The former continued to behave normally, while adding APOE4 led to Alzheimer's-like pathologies. This confirmed the fact that it is the presence of the APOE4 that causes the disease.

As a final step, Dr. Huang and his team looked for ways in which to fix the faulty gene. To this end, they applied a previously developed APOE4 "structure corrector."

The so-called structure corrector has been shown in previous research, led by the same Dr. Huang, to change the structure of APOE4 so that it looks and behaves more like the inoffensive APOE3.

**Applying this compound to human APOE4 neurons corrected the defects, thereby eliminating signs of the disease, restoring normal cell function, and helping the cells to live longer.**

The researchers conclude:

"Treatment of APOE4-expressing neurons with a small-molecule structure corrector ameliorated the detrimental effects, thus showing that correcting the pathogenic conformation of APOE4 is a viable therapeutic approach for APOE4-related [[Alzheimer's disease](https://www.medicalnewstoday.com/articles/159442.php)]."