Medical Xpress

Alzheimer's disease is partly genetic—studying the genes that delay decline in some may lead to treatments for all

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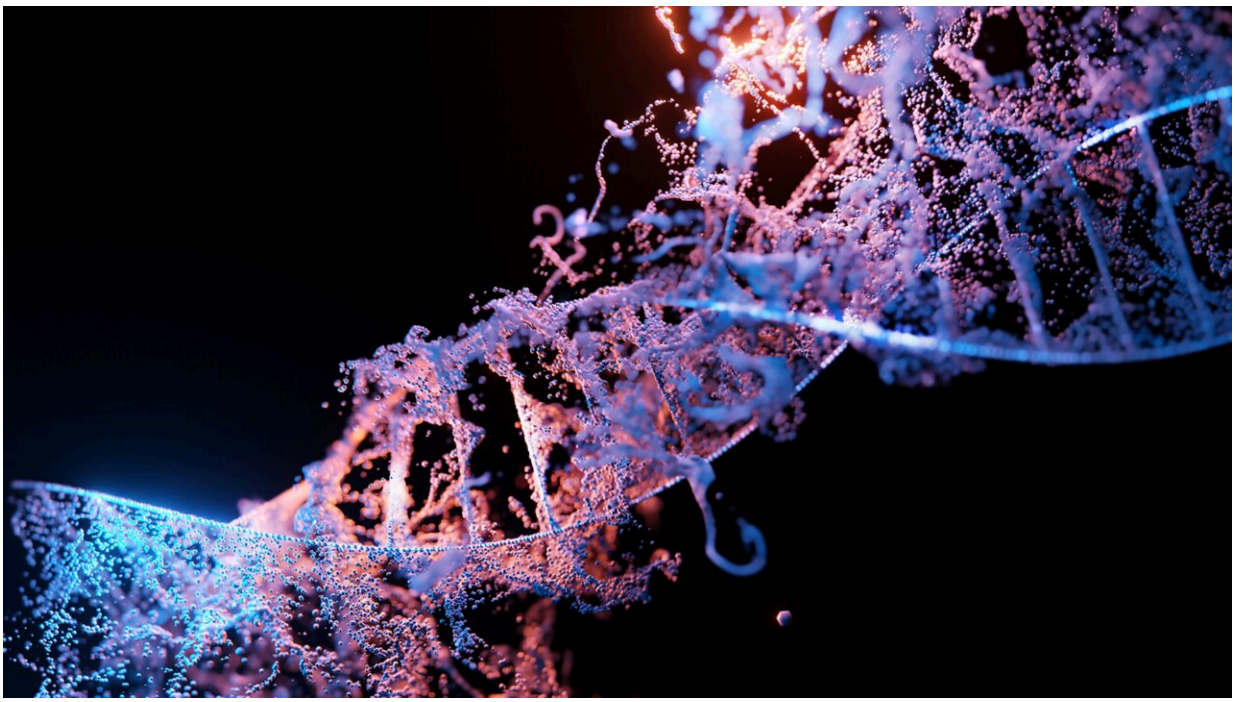

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Diseases that run in families usually have genetic causes. Some are genetic mutations that directly cause the disease if inherited. Others are risk genes that affect the body in a way that increases the chance someone will develop the disease. In Alzheimer's disease, genetic

mutations in any of three specific genes can cause the disease, and other risk genes either increase or decrease the risk of developing Alzheimer's.

Some genetic mutations or variants interact with other genetic alterations that lead to Alzheimer's disease. In some cases, gene alterations can interact with Alzheimer's-causing genetic variants in a way that proves beneficial; they actually suppress the pathological brain changes the other mutations would normally lead to. These protective gene variants can drastically slow or prevent cognitive decline. In two recent case reports on familial Alzheimer's disease, mutations delayed Alzheimer's symptoms for decades.

I am a neurologist and neuroscientist who has spent my career studying Alzheimer's disease and dementia both in the laboratory and in the clinic. Determining how genes affect brain chemistry is vital to understanding how Alzheimer's disease progresses and devising interventions to prevent or delay cognitive decline.

The amyloid hypothesis

In the early 1990s, scientists proposed the amyloid hypothesis to explain how Alzheimer's disease develops. The first neuropathological changes detected in the brain of Alzheimer's disease patients were the formation of amyloid plaques—clumps of protein pieces called beta-amyloid. Other changes in the Alzheimer's brain, such as the accumulation of another type of abnormal protein called neurofibrillary tangles, were thought to develop later in the course of the disease.

Beta-amyloid begins to accumulate in the brain up to 15 years before symptoms emerge. Symptoms correlate with the number of neurofibrillary tangles in the brain—the more tangles, the worse the cognition. Researchers have tried to determine whether preventing or removing amyloid plaques from the brain would be an effective

treatment.

Imagine the excitement of the scientific community in the 1990s when researchers identified three different genes causing familial Alzheimer's disease—and all three were involved with beta-amyloid.

The first was the amyloid precursor protein gene. This gene directs cells to produce the amyloid precursor protein, which breaks down into smaller fragments, including the beta-amyloid that forms amyloid plaques in the brain.

The second gene was termed presenilin 1, or PSEN-1, a protein needed to cut the precursor protein into beta-amyloid.

The third gene, presenilin 2, or PSEN-2, is closely related to PSEN-1 but found in a smaller number of families with familial Alzheimer's disease.

These findings added strength to the amyloid hypothesis explanation of the disease. However, uncertainty and opposition to the amyloid hypothesis have developed over the past several decades. This was in part tied to a recognition that several other processes—neurofibrillary tangles, inflammation and immune system activation—are also involved in the neurodegeneration seen in Alzheimer's.

The hypothesis also got significant pushback after many clinical trials attempting to block the effects of amyloid or remove it from the brain were unsuccessful. In some cases, treatments had significant side effects. Some researchers have come up with strong defenses of the hypothesis. But until a clinical trial based on the amyloid hypothesis could show definitive results, uncertainty would remain.

Genetic discoveries with treatment implications

The vast majority—more than 90%—of Alzheimer's cases occur in late life, with disease prevalence increasing progressively from age 65 and up. Such cases are mostly sporadic, with no clear family history of Alzheimer's.

However, a relatively small number of families have one of the three known genetic mutations that cause the disease to be passed down. In familial Alzheimer's, 50% of each generation will inherit the mutated gene and develop the disease much earlier, usually from their 30s to early 50s.

In 2019 and 2023, researchers identified changes in at least two other genes that markedly delayed the onset of disease symptoms in people with familial Alzheimer's disease mutations. These mutated genes were found in a very large family in Colombia whose members tended to develop Alzheimer's symptoms by their 40s.

A woman in the family carrying a mutated PSEN-1 gene did not have any cognitive symptoms until she was in her 70s. A genetic analysis showed that she had an additional mutation in a variant of the gene that codes for a protein called apolipoprotein E, or ApoE. Researchers believe the mutation, called the Christchurch variant—named after the city in New Zealand where the mutation was first discovered—is responsible for interfering with and slowing down her disease.

Importantly, her brain had a great deal of amyloid plaque but very few neurofibrillary tangles. This suggests that the link between the two was broken and that the suppressed number of neurofibrillary tangles also slowed down cognitive loss.

In May 2023, researchers reported that two siblings in the same large family also did not develop memory problems until their 60s or late 70s and were found to carry a mutation in a gene that codes for a protein

called reelin. Studies in mice suggest that reelin has protective effects against amyloid plaque deposition in the brain. In these patients' brains, as with the patient who had the Christchurch variant, there were extensive amyloid plaques but very few neurofibrillary tangles. This observation confirmed that the tangles are responsible for the cognitive loss and that there are several ways to "disconnect" amyloid and neurofibrillary tangle accumulation.

Finding medicines that might mimic the protective effects of the Christchurch variant or the reelin mutation could help delay Alzheimer's disease symptoms for all patients. Since the vast majority of nonfamilial Alzheimer's manifests after age 70 or 75, a 10-year delay in the emergence of first symptoms of Alzheimer's could have a massive effect in decreasing the prevalence of the disease.

These findings demonstrate that Alzheimer's can be slowed and will hopefully lead to additional new therapies that can someday not only treat the disease but prevent it as well.

Starts and stops

Despite over 20 years of doubts and therapy failures, the past several years have seen positive results from three different treatments—aducanumab, lecanemab and donanemab—that remove amyloid plaques and slow loss of cognitive function to some extent. Although there is still discussion of how much slowing of decline is clinically significant, these successes provide support for the amyloid hypothesis. They also suggest that other strategies will be needed for optimal treatment.

The U.S. Food and Drug Administration's 2021 approval of the first antibody treatment for Alzheimer's, aducanumab, sold under the brand name Aduhelm, was controversial. Only one of the two clinical trials

testing its safety and effectiveness in people yielded positive results. The FDA approved the drug on the basis of that single study through an accelerated approval process in which treatments meeting an unmet clinical need can receive expedited approval.

The second antibody, lecanemab, sold as Leqembi, was approved in January 2023 via the same accelerated approval pathway. It was then fully approved in July 2023.

The third antibody, donanemab, completed a successful phase three clinical trial and is awaiting more safety data. When that is submitted to the FDA, the agency will consider the drug for approval.

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