A Protective Genetic Mutation against Alzheimer's Disease: APOE Christchurch Variant; a Potential Advancement in Alzheimer's through Gene Therapy.

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disease with genetic, biological and environmental factors playing a role in its development. The accumulation of amyloid-beta (Aβ), for a long time considered one of the most important aspects of AD, has been associated with several other pathways that are presented in individuals with the rare variant of APOE3 Christchurch , such as tau pathology and neuroinflammation. This paper looks at the Christchurch variant and how it may give some resistance to cognitive decline in people with high genetic indices to AD and its possible application in gene therapy. A study of families in Colombia with PSEN1 E280A mutation found that a person, who had two copies of Christchurch, remained cognitively preserved for decades after significant accumulation of amyloid. Additional analysis indicates that Christchurch likely regulates the binding of apolipoprotein E to heparan sulfate proteoglycans and thus restricts the cellular uptake and distribution of tau. Recent experimental studies have explored gene delivery strategies that recapitulate the protective properties of Christchurch such as liver-directed AAV and astrocyte-based protein expression.This has been proven successful for the reduction of amyloid pathology, neuroinflammation and neurodegeneration in animal models. But studies within humans are currently ongoing as clinical trials recently started. In conclusion, the Christchurch variant offers a valuable model to explore genetic protection against AD and may be incorporated in future AD therapies that aim to change rather than simply treating AD symptoms.

Key Words

Alzheimer's disease, Gene therapy, APOE, Christchurch

Introduction: What is AD, statistics of people with AD, and introduction to the case report Medellín, Colombia.

AD, is an irreversible type of dementia that can be inhabited through complicating genetic and/or environmental lifestyle, affects approximately 55 million people worldwide and is expected to rise to 78 million by 2030 (Zhang et al., 2024). The exact cause of AD isn't known, but a build up from amyloid plaques and tau tangles is a primary reason. Amyloid plaques is a protein caused by beta-amyloid and when clump up can disrupt communication in the brain cell. Tau tangles carry nutrition through the brain cell and when disrupted can cause messy tangles that cause damage to the brain cell.

Genetics, environment, and lifestyle habits can help differentiate the types of AD cases and the severity of someone diagnosed with AD. Familial AD (fAD) represents 1-5% of cases, age of onset occurs at 30-60 years old, and is caused by autosomal mutations in the amyloid beta precursor protein (APP), presenilin-1 (PS1), and/or presenilin-2 (PS2) genes. In contrast, Sporadic AD (SAD) accounts for over 95% of cases, often appearing after age 65 and is influenced by a combination of genetics, and environmental factors and comorbidities. While rare, there are cases of fAD in Columbia, Medellin, where researchers identified over 1,200 diagnoses. This group of people were born with a rare PSEN1 gene variant known to predict AD later in life (mean onset age between 44-47). Aliria Rose Piedrahita de Villegas was one of two people with the PSEN1 gene variant who didn't show any cognitive impairment until the age of 72, about 28 years after the typical age of onset. In 2019, identified APOE3ch, or the Christchurch variant, a genetic mutation that helped delay Aliria Rosa Piedrahita de Villegas cognitive impairment. The rediscovering of the rare genetic mutation showed that even though her amyloid plaques were high, her tau tangles didn't show much damage, helping keep her cognition. Of the thousands of people that have the PSEN1 mutation, twenty-seven people with the PSEN1 mutation had one copy of the Christchurch variant. Those 27 people did not begin experiencing cognitive impairment until 52 (median; Arboleda-Velasquez et al., 2019). The APOE3ch Christchurch mutation is an important biological model which can be used to prove the efficacy of targeting genetic modifiers to protect the brain from neurodegeneration. To explore this we will investigate the mechanism of the Christchurch mutation, its protection against tau pathologies and how these findings can be used as a form of gene therapy.

Introduction of Gene Therapy

While traditional medicines have to be taken regularly and mostly manage symptoms of a disease, gene therapy is designed to target the biological cause of a disease. Gene therapy may also elicit long-lasting or even permanent changes in biological processes by repairing or replacing disease-related genes, unlike traditional treatments which only help alleviate symptoms. Given the significant genetic component to AD, scientists are optimistic that gene therapy could slow the disease process before general neuronal damage has begun. In this paper, I focus on the rare Christchurch variant as a useful tool for understanding Alzheimer's due to insights about genetic protection against Aβ toxicity and tau pathology and their potential for turning into future gene therapies. Knowing more about the biology behind this mutation may help develop treatments that slow or prevent Alzheimer's disease.

Symptoms of AD, who does it affect, what gene does it affect.

When clinically diagnosed with AD, it typically takes 8-12 years for it to fully develop in a person. AD is characterized by impairment in praxis–knowing how to use tools and how to use them and being able to plan and execute an act– short term memory loss, executive function, and visual

based problems (Zvěřová, 2019). Over time, AD symptoms worsen, from mild cognitive impairment to severe memory loss, neuropsychiatric symptoms, and loss of function skill. Sporadic Alzheimer's Disease is the most common after age 65. Risk factors of Sporadic AD can include a stressful environment and unhealthy lifestyle, as well as the APOE4 gene variant. The APOE gene product (apolipoprotein) binds to lipids, forming lipoproteins, and then acts as a transporter of lipids through the bloodstream and brain fluid. APOE is cord shaped and is located on chromosome 19 –known to be important for cholesterol health–and is mainly expressed in the liver, kidney, spleen and then is synthesized and secreted in the central nervous system (Wu, 2016).

The role of APOE is important for determining risk of AD because there are three types of APOE or isoform genes in the human body. APOE genes are numbered from lowest risk of AD to highest, where APOE4 is the highest and causes the greatest incidence of AD. APOE2 is the most uncommon with about 14% incidence (Williams et al., 2026). It acts as a protective agent,decreasing risk of AD where amyloid-beta plaque has consistently been milder in AD cases and there is a lower risk of neurofibrillary tangles of carriers of this gene. APOE2 resistance to AD risk is due to plaque being driven out of the brain very efficiently and it can clear up Aβ out of the brain barrier and into the bloodstream instead of building up (Jackson, 2024). APOE3 is the most common gene variant of all, as about 95 percent of the population have this isoform (Williams et al., 2026). Although the APOE3 gene is neutral with a lower risk of developing Alzheimer's it's still possible to develop AD with an APOE3 allele. APOE3 astrocytes (majority of brain cells) physiologically regulate lipid homeostasis and can therefore "save" or prevent the type of structural abnormalities in neurons that are typical of AD. APOE3 is very good at facilitating normal synaptic plasticity and removing Aβ (Halim et al., 2026). Where APOE3 is readily recycled in the brain, maintaining steady cholesterol efflux and maintaining neuronal homeostasis, APOE3 can become trapped in cell compartments (Rellin et al., 2008). APOE4 increases risks for AD. It is estimated that over 28% of the population share this allele (Williams et al., 2026). The chance of a person with one copy developing AD is 3 times higher than those without a copy, whereas a person is 15 times more likely to develop AD if they inherit both copies from their parents. APOE4 causes toxic protein buildup and persistent inflammation by interfering with the removal of Aβ plaques, impairing lipid metabolism, and interfering with microglia function. APOE4 enhances tau hyperphosphorylation and speeds up the production of neurotoxin amyloid-beta oligomers, which results in tangle neurons (Najm, 2020). The APOE4 gene causes disruption in the fat distribution process, which causes the buildup of sticky plaque causing the brain to swell due to wasted proteins. The brain swelling constantly causes stress to tau protein. This in turn causes the tau protein to twist and form knots called neurofibrillary tangles that suffocate the brain cell, slowly killing it.

Most fAD causes are due to mutations in APP gene, PSEN1 gene, and PSEN2 genes. These genes encode proteins that are required to build and break down Aβ, a protein that builds up in the brains of AD patients. Mutations in these genes cause an excess of abnormal amyloid-beta, which causes the formation of plaques that harm the neurons and interfere with

communication between them. This process does not directly lead to symptoms of AD, but in time they do. (NIA, 2024; Jack et al., 2024). PSEN1 gene mutations are the most common causes of fAD, associated with about 70-80% of genetically confirmed cases. This type of mutation will present symptoms earlier than other genetic mutations. Mutations in PSEN1 are often more aggressive and progressive forms of the inherited AD. There are over 300 different mutations of PSEN1 in people all over the world, suggesting an important function in the path to fAD (Bateman et al., 2011; NIA, 2024). The distinction of the mutation shows that with slight alteration it can change the genetic sequence causing cascade effect toward fAD.
About 10-15% of the fAD cases are linked to the APP gene. The gene is on chromosome 21, providing instruction on how to make amyloid precursor protein. Mutations in APP lead to higher levels of the Aβ 42 peptide, which is likely to aggregate into plaques in the brain. APP mutations generally develop between the ages of 45-65, but due to the type of mutation, the age of onset varies (NIA, 2024; Bird, 2023).
PSEN2 gene mutations are linked to a rare form of AD, consisting of less than 5% of all inherited AD. Symptoms of PSEN2 mutations tend to occur at a later age of onset and display a higher degree of variability in the impairment. In some cases, the symptoms of PSEN2 AD mutations are not seen in people until very late in diagnosis, so there is likely to be an environmental impact and other genetic influences. Why there is a greater clinical variability with mutations in PSEN2 than with the other genes that causes fAD is still being studied (Bird, 2023; Jack et al., 2024). With fAD being rare, it helped researchers determine the genetics of AD in general. Recent studies of APP, PSEN1, and PSEN2 mutations have a large body of evidence pointing to the amyloid cascade hypothesis in which the accumulation of amyloid-beta is the initiating event in the disease process. This understanding has helped develop treatments to slow the accumulation of amyloid in the brain and enhanced the genetic counseling of families with inherited AD. People whose families have mutations might consider genetic testing to see if they have inherited the mutation; however, testing is not recommended unless after professional genetic counseling for emotional and medical reasons (NIA, 2024; Bird, 2023).

What Christchurch is, who does it affect, how it's important.
The Christchurch variant (APOE3ch, R136S) is a rare protective genetic mutation of the APOE3 gene that was discovered in 2019 by a group of scientists studying a familial case of early genetically predisposed Alzheimer's or PSEN1 E280A mutation. PSEN1 E280A mutation was found within a cohort of over 1,000 people in Medellin, Colombia. The fAD genetic mutation had a 100% certainty that carriers of PSEN1 E280A mutation would have AD. (Quiroz, 2024). Carriers of the PSEN1 E280A mutation would develop mild cognitive impairment around their mid-40s and expected death in their late 50s. A woman named Aliria Rose Piedrahita de Villegas was in her 70s and was a carrier of the PSEN1 mutation and didn’t have any general symptoms that come with AD. It took over 30 years for symptoms to appear. Studies that took

place before and after her death showed that she had inherited two copies of the APOE3 Christchurch mutation, which means that she was genetically protected from developing AD symptoms despite her inherited risk (Arboleda-Velasquez et al., 2019).

Although tau pathology is the direct cause of neurodegeneration, the Christchurch variant seems to limit it entirely while the amyloid accumulation is still high. The Christchurch variant is a mutation of the APOE allele. The APOE3ch variant is protective against AD pathology and is competitively binding, where a competitive molecule tries to attach to receptors, which prevents the uptake of tau protein into neurons and microglia. The Christchurch mutation alters the way APOE proteins bind to other molecules in the brain. APOE is usually attached to a protein known as a heparan sulfate proteoglycan (HSPG) which is located on the surface of brain cells. The HSPGs serve as “docking stations” that facilitate the uptake of harmful tau proteins by neurons and supporting brain cells called microglia. The Christchurch mutation helps to disrupt the ability of APOE to bind to these docking stations. The protein APOE which normally binds to tau protein does not bind as well, so less tau protein can enter brain cells and spread throughout the brain. The Christchurch protein binds to these sites, but doesn’t attach effectively, so it doesn’t move the toxic tau proteins. Although amyloid plaques continue to build up, the spread of tau (the proteins most closely linked to memory loss and brain cell death) is greatly slowed. This in part explains why women with the mutation may maintain normative cognitive functioning for years despite having high amounts of amyloid plaques (Arboleda-Velasquez et al., 2019; Shi et al., 2023).

Many different scientific methods were used to gain insight into why this mutation was protective. Neurological exams were administered, along with the Mini-Mental States Examination (MMSE) and the Clinical Dementia Rating (CDR) in Spanish to assess memory and thinking skill over time. To identify genetic differences, DNA samples were analyzed by PCR, Sanger sequence, whole-exome sequencing and whole genome sequencing. Brain imaging assessment consisted of structural MRIs, amyloid plaque evaluations using Flobetapir PET scans, tau tangle evaluations using FDG-PET scans. Scientists also captured measurements of array (Simoa) technology. Arboleda-Velasquez studies uses enzyme-linked immunosorbent assays (ELISA) and heparin affinity chromatography to physically measure and separate APOE3 Christchurch mutation binding with heparin, providing unique measure of its molecular signature compared to normal APOE3 proteins. Combined, these techniques enable researchers to tie the gene mutation to changes to the brain structure, and to account for the markedly slower rate of disease progression (Arboleda-Velasquez et al., 2019). The Christchurch mutation shows that the ability of APOE to interact with HSPGs can slow down neurodegeneration even in the presence of abundant amyloid plaques.

Complementary evidence was observed via brain imaging and laboratory tests. PET scans revealed one of the highest burdens of amyloid-beta plaques in an individual without dementia reported. Imaging, however, did not show much tau accumulation, primarily in one small region of the brain, and very little shrinkage of the brain, compared to other PSEN1 mutation carriers. Blood markers, which assess the damage to nerve cells, or neurofilament light chain (Nfl), also

indicated less than expected nerve degeneration. This clinical case directly shows that the plaque buildup is uncorrelated with cognitive deterioration, proof that neurodegeneration can be halted even in the face of extensive amyloid burden (Arboleda-Velasquez et al., 2019). All other rare mutations identified by genetic testing (whole-exome sequencing and whole genome sequencing) did not account for the late age of onset of her disease. Laboratory experiments showed that the Christchurch variant binds to heparin and HSPGs much less tightly than normal APOE3, consistent with the idea that this is the reason for the protection. (Arboleda-Velasquez et al., 2019; Chen et al., 2022).
The Christchurch mutation is a change in the APOE3 version and is postulated to cause the protein to function much more protectively than the normal APOE3 protein.
Arboleda-Velasquez and researchers' findings have inspired researchers to create new treatments that mimic the protective properties of APOE3 Christchurch, without having to be a carrier for the rare mutation.

How can Christchurch be used in gene editing, showing how it reduces amyloid pathologies and drugs?

Gene therapy is a new branch of medicine that seeks to combat or prevent disease by altering individuals genes, rather than simply controlling symptoms pharmacologically. Cell replacement, repair, and transfection with genes are done with technologies like viral vectors and CRISPR-Cas9 gene editing.There is also an interest in gene therapy in AD since there are numerous genetic risk factors that are directly involved in the accumulation of toxins in the brain. As for AD, the APOE gene is among the most promising targets in that it affects cholesterol processing, removal of amyloid beta proteins, and inflammation. By creating a protective form of APOE, specifically the Christchurch variant, disease progression prior to permanent brain damage may be greatly reduced (Arboleda-Velasquez et al., 2019; Wang & Bu, 2026).
The Christchurch mutation has gained worldwide attention because it is a naturally occurring mutation that allows a person with a highly aggressive Alzheimer's to not have much of a cognitive decline and be able to live longer. It is different from many of the existing Alzheimer’s drugs, which work to remove amyloid plaques once they are already present. There are currently multiple approaches to gene therapy that are being explored to mimic the Christchurch mutation’s protective effects. One strategy is to use the CRISPR-Cas9 genome editing system, which can make targeted modifications to DNA in living cells. Scientists hope that one day, a person’s APOE3 or APOE4 gene may be replaced with a protective version of the gene, APOE3 Christchurch, which would enable brain cells to continually make the modified protein. Another approach is to inject the APOE3 Christchurch gene into specific tissues using adeno-associated viruses (AAVs), which do not permanently affect the patient’s DNA. They are widely used owing to their ability to deliver therapeutic genes into cells with relatively low immune response to the virus. After being taken up by cells, the introduced gene provides instructions to those cells to produce the protective protein in this case the Christchurch. These therapies are experimental

stages but are an important step in developing treatments to modify the disease process, which is the goal, rather than treat symptoms. (Raulin et al., 2026; Tang et al., 2026).

The biggest breakthrough came in 2026 with the testing of liver-directed APOE3 Christchurch gene therapy in mice genetically modified to develop Alzheimer's diseases and to be high-risk for the disease due to their APOE genotype. Researchers have engineered liver cells with adeno-associated viral vector to express the protective gene, the Christchurch gene, instead of introducing it directly into the brain. The liver then synthesized in large quantities the protective Christchurch protein which is released into the bloodstream and which affects processes throughout the body. This method was developed in the wake of increasing evidence that the liver is a crucial organ in the clearance of amyloid-beta proteins from the blood before they deposit in the brain. The treatment was effective at reducing Alzheimer's pathology, even though it didn't alter the brain cells directly, suggesting a much greater role for peripheral organs, like the liver, in AD than had been thought (Tang et al., 2026).

The liver gene therapy study results were very promising. In the brains of mice with Christchurch, there was significantly fewer amyloid-beta plaque, decreasing immune cell activation, decreased neuronal damage, and better cognitive memory test performance than in the untreated animals. They found that the Christchurch protein enhanced the clearance of amyloid-beta from the bloodstream, before it could enter the brain, in both liver cells and circulating monocytes. This enhanced peripheral clearance decreased the concentration of amyloid for deposition in the brain tissue and indirectly decreased tau pathology and neurodegeneration in the downstream regions. The results indicate that futureAlzheimer's treatments might not target the brain directly, which would decrease risk accompanied by invasive neurological treatments (Tang et al., 2026; Wang & Bu, 2026).

The liver-directed APOE3 Christchurch therapy primarily decreases amyloid-beta accumulation, but important effects on tau pathology were also observed that are more closely linked to memory loss and cognitive decline than amyloid plaques. The protection is thought to be due to the Christchurch mutation reducing the ability of APOE to bind to HSPGs on the surface of neurons and microglia. Normally, HSPGs facilitate the transfer of noxious tau proteins between brain cells, enabling the disease to spread through the brain. The Christchurch mutation interferes with this interaction, making it much more difficult for tau proteins to move between cells. Consequently, tau pathology progresses slower and spares neurons and postpones the appearance of symptoms of dementia. This is a very special mechanism that has set the course for Christchurch to be one of the most promising therapeutic targets being studied for AD (Arboleda-Velasquez et al., 2019; Wang & Bu, 2026).

A recent report suggests that astrocytes harbouring the Christchurch variant decreased several types of detrimental amyloid-beta, such as Aβ40, oligomeric Aβ and BACE1, which is associated with damaged neurites in the vicinity of amyloid plaques. The researchers also noted that the remaining plaques shrank and caused less damage to neighboring nerve cells. This is because soluble Aβ oligomers are thought to be more toxic than plaques and are implicated in disrupting communication between neurons and in memory loss. The Christchurch variant

blocks the AD process before existing treatments which primarily attack existing plaques, not only by removing these harmful APP-related amyloid proteins, but also by bloating the inflammation and damage of neurites. The results indicate that potential therapies using Christchurch may prevent damage to neurons by changing the way the amyloid proteins, derived from APP, accumulate in the brain and harm it, thus offering a promising approach for future Alzheimer's gene therapy (Raulin et al., 2026).

Another significant advantage of the Christchurch variant is its capacity to decrease neuroinflammation, a significant factor that is being associated with the progression of AD. Recent studies revealed that microglial activity is influenced by APOE particularly in APOE4 carriers. The Christchurch mutation seems to be able to affect the interaction of APOE and receptors and HSPGs in such a way that it helps to keep microglia in a healthier star, while still allowing them to take out harmful proteins. In mice models, this anti-inflammatory effect was linked to improved synapses and fewer neurons lost as well as better learning and memory. These results indicate that Christchurch could act to protect the brain by several pathways, not just one pathway that targets AD. (Raulin et al., 2026; Tang et al., 2026).

Currently, only moderate effects in the treatment of AD have been observed, and no drugs have been shown to prevent the disease process. The drug donepezil, rivastigmine and memantine temporarily improves memory or cognitive symptoms, but they do not prevent degeneration of neurons. Recent years have seen the approval of anti-amyloid monoclonal antibodies, like lecanemab and and donanemab, which can be used to remove amyloid plaques from the brain. These medications are able to lower amyloid levels and can, in some cases, slow cognitive deterioration slightly, but they are administered via frequent intravenous infusions, must be closely monitored by MRI and can cause brain swelling, bleeding, and other side effects known as amyloid-related imaging abnormalities (ARIA). Moreover, these treatments have no direct effect on tau pathology or neuroinflammations, both of which contribute to the loss of neurons even when amyloid levels are lowered. Due to these restrictions, scientists are looking for drugs that could stop the disease process before it starts and offer more protection against many forms of brain damage (Wang & Bu, 2026; van Dyck et al., 2023).

If Christchurch is a revolutionary variant, it's one that tackles multiple biological processes. Christchurch does more than just clear amyloid plaque, limit the spread of tau, reduce neuroinflammation, and protect neurons from degeneration. This mutation could be used for gene therapy, would allow for protection after just one treatment and would allow the production of protective Christchurch protein throughout the body's lifetime. If the mutation could be safely introduced in that way with the help of gene editing technology like CRISPR or viral vectors, persons with high risk genes like APOE4 or PSEN1 might be able to postpone the onset of Alzheimer's for many years or even avoid it altogether. These treatments are still experimental, but they hold promise for tackling the disease before it causes permanent brain damage as opposed to trying to fix the damage when a symptom is noticed (Tang et al., 2026; Wang & Bu, 2026).

Although gene therapy with Christchurch shows great promise, there are still a number of challenges to be addressed before it can become a mainstream therapy. Researchers will need to find the safest way to deliver the protective gene, make sure the gene editing doesn't alter the rest of the genome, and assess the potential dangers of permanently altering APOE function. Further large clinical trials will also be required to see if the protection seen in mice models and Villages can be replicated in larger populations of both familial and sporadic Alzheimer's patients. But there are ethical questions about gene editing, its accessibility and cost, among others, that needs to be discussed before it can be used clinically. However, the finding of the Christchurch mutation has completely transformed the study of AD, by showing that it can be substantially slowed even in people who are genetically predisposed to developing dementia. Christchurch is the first variant of APOE to be identified, and as scientists work towards a new generation of gene therapies and a deeper understanding of how the gene functions in the body, it could be the basis for a new generation of treatments that can help prevent AD (Arboleda-Velasquez et al., 2019; Wang & Bu, 2026; Tang et al., 2026).

Conclusion

By establishing that the Christchurch variant of the APOE3ch, even persons carrying the most potent genetic risk factor can be intellectually normal for many years, the identification of that gene has revolutionised thinking relative to understanding AD. However, instead of removing amyloid plaques, or providing a temporary benefit for symptoms, these therapies could target several disease pathways, and do so at a much earlier stage in AD, prior to any irreversible damage to the brain (Arboleda-Velasquez et al., 2019; Tang et al., 2026; Wang & Bu, 2026). Recent advancement by Dr. Ronald Crystal translating basic science to clinic. In 2026, Weill Cornell Medicine received a large grant from the National Institute on Aging to continue developing a gene therapy that will be able to strengthen the protective activity of the APOE2 allele and the Christchurch mutation. This therapy involves an AAV vector for delivery to the brain of the engineered protective gene, and is being developed for Phase 1 clinical trials in people who are homozygous for the high-risk APOE4 genotype. The purpose of this study is to assess the safety of the therapy, and to see if it lowers Alzheimer's markers and slows down cognitive decline in people with the highest genetic risk for developing AD (Weill Cornell Medicine, 2026).

While experiment as gene therapy is at the moment, the Christchurch gene, the PSEN2 mutation still needs more research to establish the long term safety of gene editing, refine ways to deliver protective genes and check to see if this proactive mutation can protect patients of all different types of mutation. However, the Christchurch variant is one of the most promising Alzheimer's discoveries; that there is a genetic way to protect against dementia. With ongoing research into gene therapy treatment, this type of treatment could someday change the trajectory of Alzheimer's treatment from symptom reduction to disease prevention.

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