What is *APOE*?

The *APOE* gene provides instructions for the production of the ApoE protein. The ApoE protein helps transport fats and cholesterol in particles called lipoproteins (lipo = lipids or fats) from the blood to the organs. Fats and cholesterol have to form lipoproteins to be carried through the water-based environment of the bloodstream.

Although cells in different parts of the body produce ApoE proteins, **about 75% of plasma ApoE is made by the liver, whereas the rest comes mostly from glial cells in the brain** [R]. However, plasma ApoE proteins do not cross the blood-brain barrier, so all ApoE in the brain is produced by cells in the nervous system [R]. But the spleen, kidneys, reproductive organs, and macrophages also produce small amounts of ApoE [R].

Apoε2/3/4 are some of the most studied variants that can strongly impact our bodies' responses to diet and lifestyle changes. **APOE variations are the most important known risk factor for Alzheimer's disease and a major contributor to cardiovascular disease** [R].

Although these variants affect some biochemical processes, scientists have discovered a great deal about how to counter the potential imbalances. Diet, supplements, and lifestyle can all reduce the odds of developing a full-blown disease in those at risk.

This report seeks to comprehensively summarize the research regarding the ApoE genes available to date, along with your genotype and what studies say about it. Keep in mind that this information is based on your ApoE genotype and the scientific research only, as we do not have information about your health history, current health status, lifestyle, and symptoms. When making health decisions, it is important to take into these factors in addition to your genes. Therefore, please consult your healthcare professional before making drastic changes in your health habits.

What Are The ε2/3/4 Alleles?

There are three different versions (alleles) of the ApoE genes, including ε2, ε3 and ε4. Globally, the prevalence of these alleles is estimated to be:

- ε2: 7%
- ε3: 79%,
- ε4: 14%

The frequency of each genotype varies by ethnicity.

Each person has two copies of the APOE gene. Each gene copy can be any of the above three alleles, so **there are six possible genotypes: ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4, and ε4/ε4**[R].

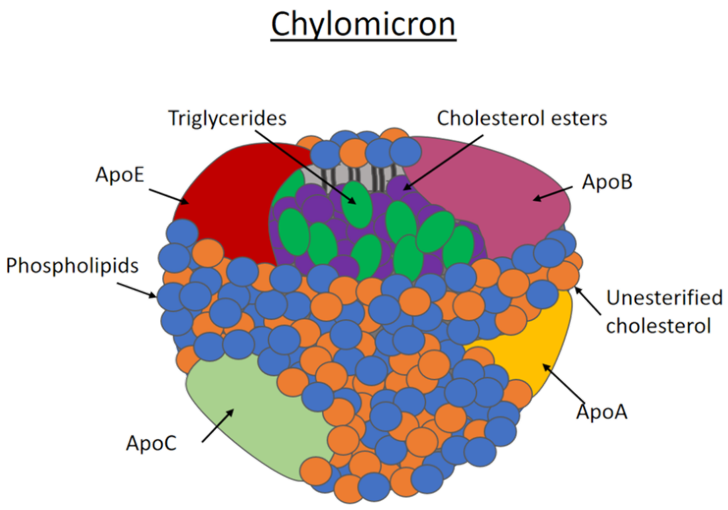
The SNPs inside the *ApoE* gene (rs429358 and rs7412) change only two amino acids inside the ApoE protein, which changes the way it works. ApoE3, the most common variant, has a cysteine as the amino acid 112 and arginine as the amino acid 158. These two amino acids are important for lipid binding and neuroprotective functions. ApoE2 has cysteine at both sites, whereas ApoE4 has arginine at both sites [R].

The Roles of ApoE Protein

1) Fat Metabolism and Transport

Intestinal cells package the fats that we eat into chylomicrons, a type of lipoprotein [R]. These are microscopic particles that contain fats in the middle, along with phospholipids, cholesterol, and Apolipoproteins on the outside. Once packaged into chylomicrons, dietary fats can be transported from the gut to other parts of the body.

In addition, the liver produces other types of lipoproteins, such as low-density lipoproteins (LDL), very low-density lipoproteins (vLDL), and high-density lipoprotein (HDL) [R, R]. vLDL and chylomicrons bring fats (triglycerides), whereas LDL brings cholesterol to the cells and organs. Target cells in these organs have receptors to grab onto the apolipoprotein on the LDL particles. Specifically, **ApoE binds to LDL receptors (and similar receptors in the brain), allowing target cells to take up cholesterol and vLDL from the blood or cerebrospinal fluid** [R].



ApoE affects how fast LDL and fats get taken up by target cells, including those in muscles and fat [R]. A better-functioning ApoE generally enhances LDL uptake and lowers blood lipid levels. A malfunctioning ApoE, on the other hand, can increase blood lipids and LDL [R].

2) Protecting neurons and the brain

Neurons and brain immune cells produce ApoE and ApoE receptors in abundance [R]. ApoE **transports fats and cholesterol** into nerves to build up new and repair old neurons and their myelin insulation [R, R].

In a cell-based study, ApoE3 packed into lipoprotein particles **stimulated the outgrowth of new neuronal branches called neurites**, whereas ApoE4 blocked it [R, R]. ApoE mostly supports neurite outgrowth by stabilizing the proteins that build neuron structures (cytoskeleton), such as microtubules [R]. By **stabilizing microtubules**, it supports the formation of new neuronal structures and prevents the neuronal destruction process that leads to Alzheimer's.

Tau proteins stabilize microtubules under normal conditions. But as Alzheimer's disease develops, too many phosphate groups get added to tau proteins (they become hyperphosphorylated). This disrupts their ability to stabilize microtubules, which results in neurofibrillary tangles found in the brains of Alzheimer's patients [R].

Another protein called APP (Amyloid Precursor Protein) protects neurons from injuries, toxins, and oxidative damage [R]. Protein-digesting enzymes in the brain can convert beneficial APP into the harmful amyloid beta, which can build up in the brain.

Amyloid beta peptide plaques and neurofibrillary tangles may cause Alzheimer's, as both are found in the brains of Alzheimer's patients [R, R]. ApoE prevents Alzheimer's by **blocking the conversion of APP to amyloid beta** [R]. In addition, ApoE3 along with fat molecules helps **destroy amyloid beta and phosphorylated Tau** proteins before they form plaques and kill neurons [R, R].

ApoE also **maintains blood-brain barrier integrity,** which is typically compromised in neurodegenerative diseases [R]. In mice with traumatic brain injury, ApoE3 could inhibit inflammatory proteins that breach the blood-brain barrier [R]. Mice without the ApoE gene or those with ApoE4 have a severely compromised blood-brain barrier [R].

3) Protecting Against Infections

Immune cells also produce ApoE, suggesting that **proper ApoE function may protect against some viral infections**. At the same time, certain infections, such as those caused by the Herpes Simplex Virus, may increase the risk of Alzheimer's disease in people with the ApoE4 genotype.

The Herpes Simplex Virus (HSV) and HIV recognize host cells by binding to the same LDL receptors as ApoE -- meaning that their surface proteins are somewhat biochemically similar to ApoE. In a small study, Alzheimer's patients with ApoE4 were much more likely to have HSV

than those without the ApoE4 allele [R]. ApoE4 carriers appear to have an increased risk of HSV infections, which additionally increase their risk of Alzheimer's[R].

HIV patients with ApoE4 have a faster progression of the disease than those with ApoE3 [R]. However, ApoE4 does not increase the risk of acquiring HIV infections.

Mice without ApoE have a compromised immune system, especially to bacterial infections (including to *Listeria monocytogenes* and *Klebsiella* pneumonia) [R, R].

4) Controlling Immune Function

Macrophages produce ApoE and high ApoE levels can inhibit an exaggerated immune response, making it an anti-inflammatory protein [R]. APOE4/E4 mice mount a more severe inflammatory immune response than APOE3/E3 mice when LPS (a bacterial toxin often present in the blood due to leaky gut) is injected into their brains [R].

Lipoproteins can stop lymphocytes from over-dividing [R]. Specifically, ApoE-containing lipoproteins can suppress the Th1 cytokine called interleukin-2 [R]. Mice without ApoE are Th1 dominant and more predisposed to autoimmune diseases [R].

Nitric oxide is an important activator of the inflammatory response in macrophages. Activated macrophages and microglial cells carrying ApoE4 produce more nitric oxide than macrophages carrying ApoE3 [R, R].

5) Reducing Oxidative Stress

Oxidative stress is a major contributor to Alzheimer's disease, traumatic brain injuries, and cardiovascular disease. Ultimately, it triggers chronic diseases and shortens the lifespan. As Alzheimer's develops, amyloid beta damages neurons, partly by increasing hydrogen peroxides in the brain. Antioxidants like vitamin E can stop this oxidative injury [R, R].

ApoE can act as an antioxidant. Neurons produce ApoE in the presence of stressors, which can be anything from aging oxidative stress, and trauma to amyloid beta deposition, or a lack of oxygen [R]. In a cell-based study, ApoE protected rat neurons from oxidative stress, with ApoE2 being the most protective, followed by ApoE3, and ApoE4, respectively [R].

The antioxidant activity of ApoE is multifold. It increases blood antioxidant levels and the activity of enzymes that break down oxidants. For example, mice without ApoE have lower brain vitamin E levels in the brain than mice with normal ApoE, even if the mice are not vitamin E deficient [R, R]. In humans with ApoE4, vitamin E intake from foods does not reduce the risk of Alzheimer's, whereas in those without ApoE4 vitamin E intake *does* reduce the risk [R].

But ApoE4 carriers have a different, beneficial response to other antioxidant nutrients. For example, higher serum beta-carotene is associated with a lower risk of cognitive decline in high-functioning older apoE4 carriers [R].

ApoE4 carriers also have less active enzymes that break down oxidants and increase antioxidant defense, such as glutathione peroxidase and catalase [R].

Therefore, if you carry ApoE4, it may be beneficial to consume more antioxidants in your diet and lead a healthy lifestyle that increases your natural antioxidants.

The Differences between Apoε2, 3, and 4

Both ApoE2 and ApoE4 variants reduce ApoE function but in different ways. Due to the amino acid differences, ApoE2 functions differently and confers different disease risks than ApoE4. **ApoE2 typically protects against dementia, while ApoE4 is a major risk factor for dementia [R]. Whereas, both ApoE2 and ApoE4 are associated with an increased risk of cardiovascular disease** [R, R].

ApoE4 makes a less stable protein, reducing ApoE blood levels in ApoE4 gene carriers [R]. ApoE2, on the other hand, is significantly more stable, resulting in high levels of ApoE in the blood and the brain [R, R]. This may explain why ApoE2 is a more protective allele, even though it is actually the least efficient in lipoprotein binding [R].

ApoE4 was the first allele of ApoE that ever existed, as all great apes carry this allele [R]. In humans, ApoE3 is the most common allele, especially in agrarian cultures. Yet ApoE4 remains high in regions where humans depend on foraging or where food supplies are often scarce. ApoE4 may be a thrifty gene that allows us to survive longer in times of famine, when humans are less likely to reach the age of Alzheimer's onset R]. In times of famine, the brain with ApoE4 is also more dependent on ketone bodies as a fuel source [R]. Sensibly, the modern diet and lifestyle seem to affect ApoE4 carriers during old age more than others.

Benefits of the ApoE4 Allele

Although ε4/ε4 individuals experience earlier cognitive decline than others, young individuals with the ε4 allele have better cognitive functions. For example, their nervous system is more efficient at episodic memory [R]. They also have better processing speed, attention, verbal fluency, and prospective memory well into middle age [R, R].

ApoE Health Risks

Mild Cognitive Impairment

Since ApoE4 impairs neuroprotection and lipid metabolism in the body, it is strongly linked to mild cognitive impairment and Alzheimer's disease.
Essentially, the brains of ε4 adult carriers age more poorly and use less energy than those of non-ε4 carriers [R]. Older ε4 individuals experience increased myelin breakdown and a greater loss of brain volume in two crucial areas for cognition: the cortex and hippocampus [R, R]. On the other hand, Apoε2 preserves brain volume in old age better than ε3.

Mild cognitive impairment (MCI) is a state in between a healthy brain and full-blown dementia [R], which can occur decades before a diagnosis is made. MCI patients with ApoE4 experience cognitive decline at a younger age than those without ApoE4, with a more severe decline in cognition and day-to-day function [R, R, R].

Late-Onset Alzheimer's Disease

The ApoE ε4 allele is a strong risk factor for late-onset Alzheimer's disease, where the diagnosed in people over 65 years of age. Approximately 60% of Alzheimer's patients have at least one ε4 allele [R].

Having 1 copy of the ε4 allele increases the risk by about 2 - 3-fold, whereas having both copies of this allele increases the risk of late-onset Alzheimer's by about 15 fold [R]. The ε2 allele is protective against Alzheimer's disease, reducing the risk by about 40% compared to the neutral-risk ε3 allele [R].

The effect of the ε4 allele is dependent on race and gender. Women with ApoE4 are at a higher risk of developing Alzheimer's disease than men, especially post-menopause due to aging, hormonal and metabolic changes [R]. African Americans and hispanics who carry the ε4 allele are less likely to develop Alzheimer's, whereas the Japanese and Caucasian people are more likely to develop Alzheimer's if they carry this allele [R].

The ε4 allele also reduces the age of onset of Alzheimer's disease by about 8 years per allele. The mean age of onset for people with two ε4 alleles is 68 years, for those with one ε4 allele 76 years, and for those without the ε4 allele 84 years [R].

Traumatic Brain Injury

Neurons produce ApoE to protect themselves and support regeneration in the presence of injuries and oxidative stress. The ApoE4 allele reduces ApoE levels, which hinders neuronal

repair and defense mechanisms, explaining why people with this allele recover more poorly from traumatic brain injury.

ApoE4 is associated with poorer outcomes following traumatic brain injury (TBI) compared with ApoE2 and ApoE3, regardless of how severe the initial injury was [R]. A large meta-analysis found that ApoE4 is not associated with the severity of the initial injury but more to the actual outcome 6 months after [R]. In addition, traumatic brain injury alone is a predisposing factor for Alzheimer's disease but even more so in ApoE4 carriers, who have amyloid beta plaques in the brain following TBI [R].

Other Neurological Disorders

Vascular cognitive impairment and dementia refer to cognitive disturbances due to problems with blood vessels in the brain, affecting 8 - 15% of elderly individuals with cognitive dysfunction [R]. ApoE4 confers significant risk for vascular dementia, accounting for about 20% of vascular dementia in the population [R].

Parkinson's disease is, in many ways, similar to Alzheimer's disease as both are neurodegenerative diseases caused by protein misfolding inside the neurons [R]. ApoE4 may increase the risk and accelerate the development of Parkinson's disease [R].

ApoE4 might also increase the risk of frontotemporal dementia, but not that of Huntington's disease or amyotrophic lateral sclerosis [R, R, R].

Cardiovascular Disease Risk

ApoE helps transport and deliver lipids from one type of cells to another. It also controls how much fat and lipoproteins get metabolized by delivering them to the cells or back to the liver, and influencing the activities of fat-digesting enzymes.

ApoE2 is associated with higher triglycerides and ApoE levels, and lower total cholesterol [R]. Whereas, ApoE4 is associated with decreased ApoE and triglyceride levels, but increased cholesterol levels [R].

In general, ε2 lowers total cholesterol by ~14 mg/dL, whereas, each ε4 raises it by ~8 mg/dL [R].

The elevated cholesterol associated with ApoE4 predicts an increased risk of cardiovascular disease. ApoE2 generally reduces the risk [R]. However, meta-analyses (combined analyses of multiple large-scale studies) of the effects of these alleles show mixed effects, ranging from no effects to 20% decreased risk from ApoE2, and 42% increased risk from ApoE4 [R, R, R]. This variability could be due to factors other than the ApoE gene that strongly influence cardiovascular disease risk, such as diet, lifestyle, stress, and other genes.

Type III Hyperlipoproteinemia

Type III hyperlipoproteinemia (HLP) or dysbetalipoproteinemia is a genetic disorder of lipid metabolism that can predisposes people to premature hardening of the arteries (atherosclerosis) at a young age [R].

ApoE2 binds poorly to lipoprotein receptors, making it less efficient than ApoE3 and ApoE4 at producing and transferring vLDLs and chylomicrons from the plasma to the liver [R, R]. But people with ApoE2 alleles have several mechanisms that compensate for this. For one, APOE2 produces a more stable APOE protein, which increases its levels in the blood [R, R]. Their APOE proteins may be less efficient, but their high number and stability make up for it, which is why most people with two APOE2 alleles (ε2/ε2 genotype) end up having low blood lipids [R].

Additional factors such as obesity, hypothyroidism, diabetes, or low estrogen can perturb these compensatory mechanisms and precipitate HLP in people who have two ApoE2 alleles or one of the other very rare forms of ApoE (other than ε2, ε3, and ε4). As a result, they may have cholesterol levels over 300 mg/dL, which significantly increases their risk of cardiovascular disease [R].

Age-Related Macular Degeneration:

ApoE2 alleles may increase the risk of age-related macular degeneration by about 20%, which can result in vision loss. Conversely, ApoE4 is associated with 38% reduction in the risk of age-related macular degeneration [R, R].

Kidney Disease

ApoE-deficient mice have kidney damage, possibly due to high inflammation, oxidative stress, and cholesterol levels [R]. The ApoE2 allele increases the risk of chronic kidney diseases, whereas ApoE4 decreases the risk, even after accounting for other factors (race, gender, diabetes, and hypertension) [R].

Longevity

The ApoE2 allele is powerfully associated with extreme longevity. This is possibly due to improved brain health in old age, reduced oxidative stress, and reduced risk of cardiovascular disease compared to people with the other alleles [R]. Centenarians have a higher frequency of ApoE2 and a lower frequency of ApoE4 than people with normal lifespans of the same ethnicity [R, R].

Therefore, you're more likely to attain extreme longevity if you have the ApoE2/E2 or ApoE2/E3 genotypes, and less likely to if you have the ApoE4 alleles [R, R].

Does ApoE4 Always Lead to Alzheimer's? The Nigerian Paradox

We call ApoE the most significant genetic contributor, but not necessarily a cause, of Alzheimer's because of the Nigerian Paradox. Nigerians have the highest prevalence of the ApoE4. However, Nigerians who carry the ApoE4 allele and reside in Nigeria do not have a higher risk of Alzheimer's disease than those with other forms of ApoE [R, R]. Interestingly, ApoE4 is a significant contributor to Alzheimer's among African Americans [R]. In fact, people of African descents who reside in Western countries develop Alzheimer's diseases at the same rates as people of other races [R].

One of the factors that may account for this difference is the cholesterol levels. Native Nigerians have very low cholesterol levels, even when accounted for ApoE4, due to their diet [R]. High cholesterol increases the risk of Alzheimer's disease and may contribute to the formation of amyloid plaques [R, R]. In mice, supplementation with phytosterols reduces the amount of cholesterol available to neurons and reduces amyloid plaques, aiding in Alzheimer's prevention [R].