‘The Hemsworth Alzheimer’s disease gene’: Revisiting the nature-nurture debate

It’s frightening when your future health seems indelibly determined, and the prospects are not good. That’s what Chris Hemsworth, the star of Thor and Extraction, has been struggling with — what he calls his “biggest fear” — not being able to recognize or remember his loved ones as he ages.

While working last fall on *Limitless,* his National Geographic docuseries about prolonging life and combating aging. the 39-year-old actor underwent a genetic test, discovering that he has an elevated risk of developing Alzheimer’s, the single most cause of dementia.

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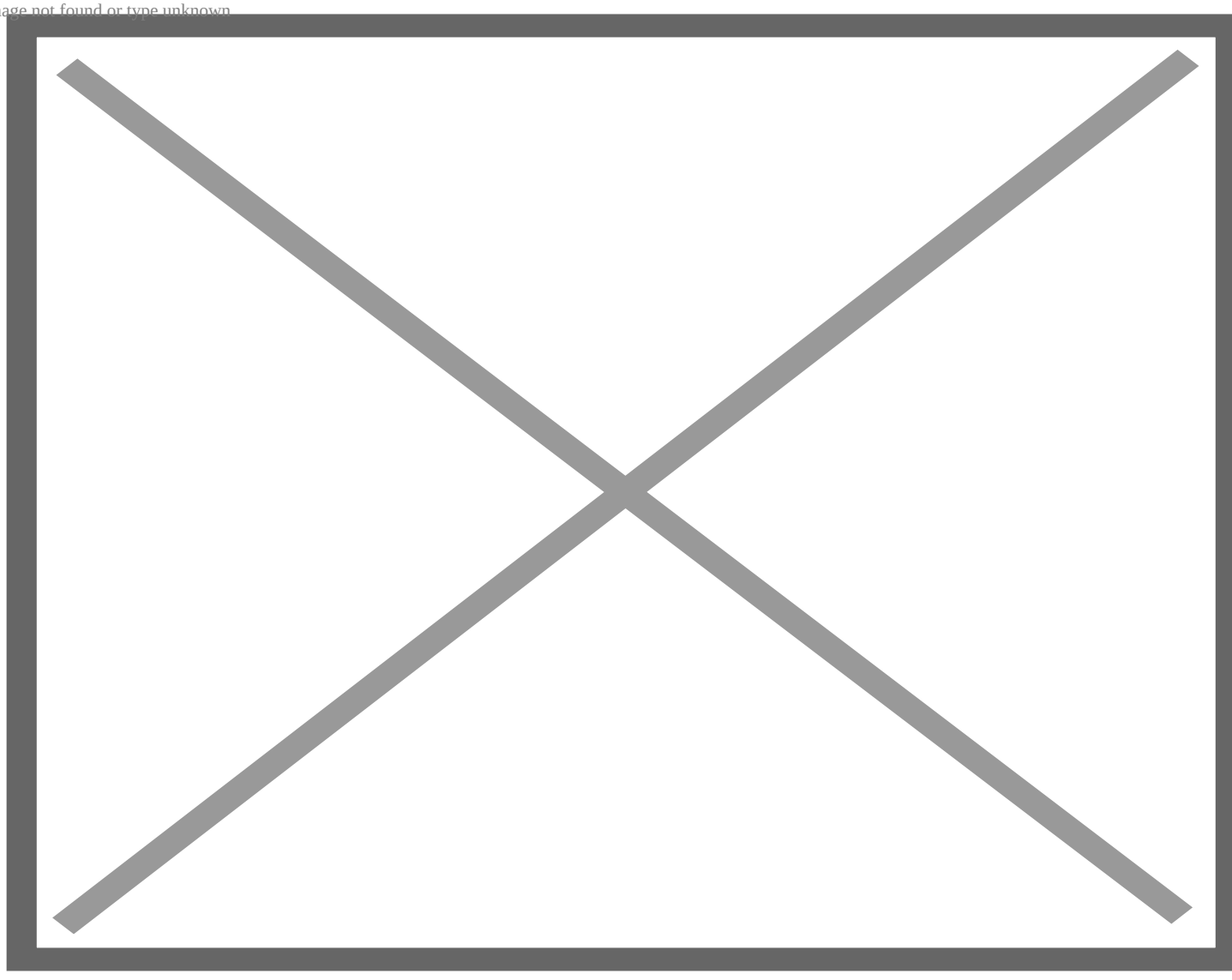

Credit: Journal of Neurology, Neurosurgery & Psychiatry

Hemsworth was found to carry two copies of a gene called APOE4, one each from his father and mother, a major genetic risk factor. Only 2 to 3% of the population have two copies of APOE4, according to a 2021 study

by the National Institutes of Health. It's also associated with early onset, which can happen anytime between someone's 30s and mid-60s.

Hemsworth was diagnosed during the filming of episode five of his docuseries. During filming, the show's longevity doctor first told Hemsworth about the finding off-camera. That "was pretty shocking," he told *Vanity Fair* in an interview.

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Credit: Disney

Alzheimer's disease is the single most common cause of dementia with one in 9 people over 65 living with AD globally. It is, however, not all bad news for Hemsworth and others like him. Last year was a landmark time for Alzheimer's research with two treatments gaining FDA approval.

Furthermore, a recent trial for using gene therapy to mitigate the potentially damaging effects of APOE4 gene expression has returned promising early data. The study, which was labelled as "a very provocative, very intriguing approach," by the director of the neuroscience division at the National Institute on Aging, is a collaboration between the Alzheimer's Drug Discovery Foundation and Weill Medical College of Cornell University. It involved injecting a low dose of gene therapy to promote the production of a protective protein in cerebrospinal fluid.

Administration of the treatment to a small cohort of patients resulted in a marked drop in the main toxic drivers of AD; amyloid and tau. The results were so promising that the trial has now advanced to the next stage.

However, there is another critical factor to consider when we discuss the links between genetics and AD. Alzheimer's is not a genetic disorder in the same way, say, cystic fibrosis or Huntington's disease is, where carrying the disease-associated genes always results in manifestation of the illness. Those are called Mendelian or single-gene diseases.

Alzheimer's is more complex genetically. Genes have a role but not just a single gene, and genetics is only part of a larger equation. This is a fortunate biological situation because it is estimated that at least 25% of the global population carry at least one copy of the APOE4 gene. If AD worked like Huntington's we would have a serious epidemic on the horizon.

So, what else drives the development of AD? And what role do genetic variations in Alzheimer's patients play in its development? Let's take a dive into the mechanics of AD's most common genetic risk factor.

How APOE4 increases AD risk

APOE stands for apolipoprotein E. It can be found in various forms in the human body depending on an individual's genome. The protein plays a key role in cholesterol metabolism; specifically, the 'packaging' and clearance of cholesterol to maintain normal levels within the body. The E4 variant of the gene gives rise to a form of the protein that exhibits impaired function in relation to cholesterol metabolism. This is a critical change because cholesterol metabolism in the brain has to be tightly regulated as Dr. Allison B. Reiss, an associate professor of medicine at NYU Long Island School of Medicine explains:

> *The brain is full of cholesterol and needs cholesterol to develop and produce nerve cells. The balance and transport of cholesterol within the brain are carefully controlled, and lipids are very important in brain function. Most prominent of the lipid-related proteins in the brain is ApoE, a protein that transports lipids in the brain and elsewhere.*

If an individual carries two copies of the APOE4 gene, the control of cholesterol levels in the brain can become impaired. The exact mechanism behind how this can lead to the development of Alzheimer's disease is yet to be fully understood but studies suggest cholesterol metabolism has an impact on one of the two key pathogenic hallmarks of AD: Amyloid beta plaque formation.

Further light was shed on this mechanism with the release of a University of Virginia School of Medicine study that tied the mechanism to a specific cell type in the brain. Astrocytes (the most abundant cell type in the brain) play an important role of maintaining a biochemical balance in the brain. The researchers analyzed the effect of APOE4 mutations on astrocyte behavior and what they found was compelling.

Astrocytes were found to drive amyloid beta plaque formation by manufacturing excess cholesterol and distributing it to the surrounding brain cells. The increase in surrounding cholesterol triggers an upturn in amyloid beta production, thus driving an acceleration in the formation of amyloid beta plaques.

“This study helps us to understand why genes linked to cholesterol are so important to the development of Alzheimer’s disease,” said Heather A. Ferris, MD, PhD at UVA’s Division of Endocrinology and Metabolism:

> *Our data point to the importance of focusing on the production of cholesterol in astrocytes and the transport to neurons as a way to reduce amyloid beta and prevent plaques from ever being formed.*

It all sounds like an ironclad mechanism on paper. APOE4 expression results in defective protein production. This causes dysfunctional cholesterol manufacture which, in turn, drives amyloid aggregation leading to AD. So why doesn’t carrying the APOE4 gene result in a 100% risk of developing AD? It’s not even close to that figure.

What additional risk factors are in play here?

The development of AD is greatly influenced by external factors. The most obvious is age; Alzheimer’s is mostly a disease of the elderly. It takes decades to manifest, and the older you are, the greater the risk. Age is, however, not the only ‘non-genetic’ contributor to the development of AD and the key to the other factors in play lies partly in the major role APOE plays in the human body.

The role of genetics can be summarized by a phrase that has become almost dogmatic among many medical practitioners: “Your genes load the gun, but lifestyle often pulls the trigger”. The CDC highlights eight key contributing factors to AD risk that are not genetic: lack of exercise, smoking, excessive alcohol consumption, obesity, diabetes, hypertension, depression, and hearing loss.

Credit: CDC

The CDC went on to conduct a study on adults over 45 to investigate how integral these factors are to the development of AD. There was one key take home message: Adults with 4 or more of the aforementioned risk factors were significantly more likely to experience cognitive decline with (1 in 4 versus 1 in 25).

The CDC and many other medical authorities since created webpages promoting lifestyle choices to reduce the risk of developing AD, and they all echo the same theme: Eat healthily, exercise avoid alcohol in excess and avoid smoking. And avoid saturated fat — the kind that sends your cholesterol through the roof. This is particularly important if you carry the APOE4 variant. The jury is out on to what extent consuming saturated fat and cholesterol increases your risk. In APOE4 carriers, however, avoiding saturated fats and cholesterol can help to moderate the amount of cholesterol in the brain, potentially reducing the risk of kick-starting the pathology.

There remains a lack of a universally agreed understanding of the relative roles of diet and lifestyle to contracting AD. If you look online, you will find a wealth of claims from one extreme to the other. The contributing factors and their relative contribution to contacting the disease remain murky. So, what can each of us do proactively?

Dr. Darren Gitelman, senior medical director of the Advocate Memory Center at Advocate Lutheran General Hospital in Park Ridge, Ill explains:

> *There's no sure-fire way to prevent Alzheimer's disease, so knowing whether you have ApoE4 won't lead to better treatment at this time. We encourage everyone, regardless of their E4 status, to lead a healthy lifestyle to reduce their risk of dementia.*

Rare case of genetic AD

While 99% of Alzheimer cases appear caused by a combination of genes and other external factors, there is a rare hereditary form of AD called familial Azheimer's that breaks all the genetic rules, giving patients no room for prevention. It is mediated by mutations in one of a variety of genes; presenilin 1 (PSEN1), the most common; presenilin 2 (PSEN2); and amyloid precursor protein (APP) genes. A mutation in one of these three genes and sadly, like carrying the gene for Hutington's, your fate is locked in: AD is not only guaranteed. It is also more likely to hit you earlier in life.

Scientists will continue to write the genetic story of Alzheimer's disease as we search for a cure. Genes may not be the only contributing factor to its development, but they are the driving factors and will be the focus of research for years to come.

Sam Moxon has a PhD in tissue engineering and is currently a research fellow in the field of regenerative medicine. He is a freelance writer with an interest in the development of new technologies to enhance medical therapies. Follow him on Twitter @DrSamMoxon