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Study Suggests Genetics as a Cause, Not Just a Risk, for Some Alzheimers

People with two copies of the gene variant APOE4 are almost certain to get Alzheimer's, say researchers, who proposed a framework under which such patients could be diagnosed years before symptoms.

By Pam Belluck

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Scientists are proposing a new way of understanding the genetics of Alzheimer's that would mean that up to a fifth of patients would be considered to have a genetically caused form of the disease.

Currently, the vast majority of Alzheimer's cases do not have a clearly identified cause. The new designation, proposed in a study published Monday, could broaden the scope of efforts to develop treatments, including gene therapy, and affect the design of clinical trials.

It could also mean that hundreds of thousands of people in the United States alone could, if they chose, receive a diagnosis of Alzheimer's before developing any symptoms of cognitive decline, although there currently are no treatments for people at that stage.

The new classification would make this type of Alzheimer's one of the most common genetic disorders in the world, medical experts said.

"This reconceptualization that we're proposing affects not a small minority of people," said Dr. Juan Fortea, an author of the study and the director of the Sant Pau Memory Unit in Barcelona, Spain. "Sometimes we say that we don't know the

cause of Alzheimer's disease," but, he said, this would mean that about 15 to 20 percent of cases "can be tracked back to a cause, and the cause is in the genes."

The idea involves a gene variant called APOE4. Scientists have long known that inheriting one copy of the variant increases the risk of developing Alzheimer's, and that people with two copies, inherited from each parent, have vastly increased risk.

The new study, published in the journal Nature Medicine, analyzed data from over 500 people with two copies of APOE4, a significantly larger pool than in previous studies. The researchers found that almost all of those patients developed the biological pathology of Alzheimer's, and the authors say that two copies of APOE4 should now be considered a cause of Alzheimer's — not simply a risk factor.

The patients also developed Alzheimer's pathology relatively young, the study found. By age 55, over 95 percent had biological markers associated with the disease. By 65, almost all had abnormal levels of a protein called amyloid that forms plaques in the brain, a hallmark of Alzheimer's. And many started developing symptoms of cognitive decline at age 65, younger than most people without the APOE4 variant.

"The critical thing is that these individuals are often symptomatic 10 years earlier than other forms of Alzheimer's disease," said Dr. Reisa Sperling, a neurologist at Mass General Brigham in Boston and an author of the study.

She added, "By the time they are picked up and clinically diagnosed, because they're often younger, they have more pathology."

People with two copies, known as APOE4 homozygotes, make up 2 to 3 percent of the general population, but are an estimated 15 to 20 percent of people with Alzheimer's dementia, experts said. People with one copy make up about 15 to 25 percent of the general population, and about 50 percent of Alzheimer's dementia patients.

The most common variant is called APOE3, which seems to have a neutral effect on Alzheimer's risk. About 75 percent of the general population has one copy of APOE3, and more than half of the general population has two copies.

Alzheimer's experts not involved in the study said classifying the two-copy condition as genetically determined Alzheimer's could have significant implications, including encouraging drug development beyond the field's recent major focus on treatments that target and reduce amyloid.

Dr. Samuel Gandy, an Alzheimer's researcher at Mount Sinai in New York, who was not involved in the study, said that patients with two copies of APOE4 faced much higher safety risks from anti-amyloid drugs.

When the Food and Drug Administration approved the anti-amyloid drug Leqembi last year, it required a black-box warning on the label saying that the medication can cause "serious and life-threatening events" such as swelling and bleeding in the brain, especially for people with two copies of APOE4. Some treatment centers decided not to offer Leqembi, an intravenous infusion, to such patients.

Dr. Gandy and other experts said that classifying these patients as having a distinct genetic form of Alzheimer's would galvanize interest in developing drugs that are safe and effective for them and add urgency to current efforts to prevent cognitive decline in people who do not yet have symptoms.

"Rather than say we have nothing for you, let's look for a trial," Dr. Gandy said, adding that such patients should be included in trials at younger ages, given how early their pathology starts.

Besides trying to develop drugs, some researchers are exploring gene editing to transform APOE4 into a variant called APOE2, which appears to protect against Alzheimer's. Another gene-therapy approach being studied involves injecting APOE2 into patients' brains.

The new study had some limitations, including a lack of diversity that might make the findings less generalizable. Most patients in the study had European ancestry. While two copies of APOE4 also greatly increase Alzheimer's risk in other ethnicities, the risk levels differ, said Dr. Michael Greicius, a neurologist at Stanford University School of Medicine who was not involved in the research.

“One important argument against their interpretation is that the risk of Alzheimer’s disease in APOE4 homozygotes varies substantially across different genetic ancestries,” said Dr. Greicius, who cowrote a study that found that white people with two copies of APOE4 had 13 times the risk of white people with two copies of APOE3, while Black people with two copies of APOE4 had 6.5 times the risk of Black people with two copies of APOE3.

“This has critical implications when counseling patients about their ancestry-informed genetic risk for Alzheimer’s disease,” he said, “and it also speaks to some yet-to-be-discovered genetics and biology that presumably drive this massive difference in risk.”

Under the current genetic understanding of Alzheimer’s, less than 2 percent of cases are considered genetically caused. Some of those patients inherited a mutation in one of three genes and can develop symptoms as early as their 30s or 40s. Others are people with Down syndrome, who have three copies of a chromosome containing a protein that often leads to what is called Down syndrome-associated Alzheimer’s disease.

Dr. Sperling said the genetic alterations in those cases are believed to fuel buildup of amyloid, while APOE4 is believed to interfere with clearing amyloid buildup.

Under the researchers’ proposal, having one copy of APOE4 would continue to be considered a risk factor, not enough to cause Alzheimer’s, Dr. Fortea said. It is unusual for diseases to follow that genetic pattern, called “semidominance,” with two copies of a variant causing the disease, but one copy only increasing risk, experts said.

The new recommendation will prompt questions about whether people should get tested to determine if they have the APOE4 variant.

Dr. Greicius said that until there were treatments for people with two copies of APOE4 or trials of therapies to prevent them from developing dementia, “My recommendation is if you don’t have symptoms, you should definitely not figure out your APOE status.”

He added, “It will only cause grief at this point.”

Finding ways to help these patients cannot come soon enough, Dr. Sperling said, adding, “These individuals are desperate, they’ve seen it in both of their parents often and really need therapies.”

Pam Belluck is a health and science reporter, covering a range of subjects, including reproductive health, long Covid, brain science, neurological disorders, mental health and genetics. More about Pam Belluck