

A protein called Reelin keeps popping up in brains that resist aging and Alzheimer's

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A key protein called Reelin may help stave off Alzheimer's disease, according to a growing body of research.

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A key protein that helps assemble the brain early in life also appears to protect the organ from Alzheimer's and other diseases of aging. A trio of studies published in the past year all suggest that the **protein Reelin** helps maintain thinking and memory in ailing brains, though precisely how it does this remains uncertain. The studies also show that **when Reelin levels fall, neurons become more vulnerable.**

There's growing evidence that Reelin acts as a **"protective factor" in the brain**, says Li-Huei Tsai, a professor at MIT and director of the Picower Institute for Learning and Memory.

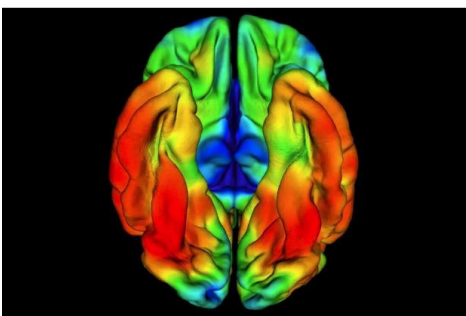
"I think we're on to something important for Alzheimer's," Tsai says.

The research has inspired efforts to develop a **drug that boosts Reelin or helps it function better**, as a way to stave off cognitive decline.

"You don't have to be a genius to be like, 'More Reelin, that's the solution,'" says Dr. Joseph Arboleda-Velasquez of Harvard Medical School and Massachusetts Eye and Ear. "And now we have the tools to do that."

From Colombia, a very special brain

Reelin became something of a scientific celebrity in 2023, thanks to a study of a Colombian man who should have developed Alzheimer's in middle age but didn't. The man, who worked as a mechanic, was part of a large family that carries a very rare gene variant known as Paisa, a reference to the area around Medellin where it was discovered. Family members who inherit this variant are **all but certain to develop Alzheimer's** in middle age. *"They start with cognitive decline in their 40s, and they develop full-blown dementia [in their] late 40s or early 50s,"* Arboleda-Velasquez says.



This PET image shows the brain of a Colombian man whose memory and thinking remained intact in his late 60s, even though he carried a rare gene variant that nearly always causes Alzheimer's in a person's 40s.

Yakeel T. Quiroz-Gaviria and Justin Sanchez/Massachusetts General Hospital

But this man, despite having the variant, remained cognitively intact into his late 60s and wasn't diagnosed with dementia until he was in his 70s. After he died at 74, an autopsy revealed that **the man's brain was riddled with sticky amyloid plaques, a hallmark of Alzheimer's.**

Scientists also found another sign of Alzheimer's — **tangled fibers called tau, which can impair neurons.** But oddly, these tangles were **mostly absent in a brain region called the entorhinal cortex, which is involved in memory.** That's important because this region is usually one of the first to be affected by Alzheimer's, Arboleda-Velasquez says.

The researchers studied the man's genome. And they found something that might explain why his brain had been protected. He carried a rare variant of the gene that makes the protein Reelin. A study in mice found that **the variant enhances the protein's ability to reduce tau tangles.**

Although the research focused on a single person, it reverberated through the world of brain science and even got the attention of the (then) acting director of the National Institutes of Health, Lawrence Tabak.

"Sometimes careful study of even just one truly remarkable person can lead the way to fascinating discoveries with far-reaching implications," Tabak wrote in his blog post about the discovery.

Reelin gets real

After the study of the Colombia man was published, lots of researchers “started to get excited about Reelin,” Tsai says. Tsai’s team, though, had already been studying the protein’s role in Alzheimer’s. In September of 2023, the team published an analysis of the brains of 427 people. It found that **those who maintained higher cognitive function as they aged tended to have more of a kind of neuron that produces Reelin.**

In July of 2024, the group published a study in the journal *Nature* that provided more support for the Reelin hypothesis. The study included a highly detailed analysis of post-mortem brains from 48 people. Twenty-six brains came from people who had shown symptoms of Alzheimer’s. The rest came from people who appeared to have normal thinking and memory when they died.

Interestingly, a few of these apparently unaffected people had brains that were full of amyloid plaques. “*We wanted to know, ‘What’s so special about those individuals?’*” Tsai says. So the team did a genetic analysis of the neurons in six different brain regions. They found several differences, including a surprising one in the **entorhinal cortex**, the same region that appeared to be protected against tau tangles in the man from Colombia.

“*The neurons that are most vulnerable to Alzheimer’s neurodegeneration in the entorhinal cortex, they share one feature,*” Tsai says: “***They highly express Reelin.***”

With early Alzheimer’s in the family, these sisters decided to test for the gene

In other words, **Alzheimer’s appears to be selectively damaging the neurons that make Reelin**, the protein needed to protect the brain from disease. As a result, Reelin levels decline and the brain becomes more vulnerable.

The finding dovetails with what scientists learned from the Colombian man whose brain defied Alzheimer’s. He had carried **a variant of the RELN gene** that seemed to make the protein more potent. So that might have offset any Reelin deficiency caused by Alzheimer’s.

At the very least, the study “***confirms the importance of Reelin,***” Arboleda-Velasques says, “*which, I have to say, had been overlooked.*”

A breakthrough made thanks to a Colombian family

The Reelin story might never have emerged without the cooperation of about 1,500 members of an extended Colombian family that carries the Paisa gene variant. The first members of that family were identified in the 1980s by Dr. Francisco Lopera Restrepo, head of the University of Antioquia’s Clinical Neurology Department. Since then, members have taken part in a range of studies, including trials of experimental Alzheimer’s drugs. Along the way, scientists have identified a handful of family members who inherited the Paisa gene variant but have remained cognitively healthy well beyond the age when dementia usually sets in.