

THE *Current*

November 4, 2019

[Sonia Fernandez](#)

Escaping Alzheimer's

There is, in Colombia, a family with the tragic legacy of forgetfulness.

“People in this large family get Alzheimer's like clockwork at age 45-50,” said UC Santa Barbara neuroscientist [Kenneth S. Kosik](#), the campus's Harriman professor of Neuroscience and co-director of the Neuroscience Research Institute. Their aggressive, genetic form of the disease has been passed down from generation to generation, causing rapid cognitive and physical declines in both the men and the women of this family.

For decades, Kosik and colleagues, including Dr. Francisco Lopera of the University of Antioquia; Dr. Eric Reiman of the Banner Alzheimer's Institute in Phoenix; clinical neuropsychologist Yakeel Quiroz of Massachusetts General Hospital; and Dr. Joseph Arboleda-Vasquez of Massachusetts Eye and Ear, have been studying this family, from their brains right down to their genes. They have [even traced the specific gene mutation](#) of this disease back as far as the time of the Spanish conquistadors.

During their studies the researchers also have witnessed the predictable onset of the disease as members of this family enter into their middle years. Sometimes it happens sooner, sometimes later, but all paths have always led to the same destination.

But one woman has defied the odds. Now in her late 70s, she has the mutant gene — and the plaques of amyloid protein that are the hallmark of Alzheimer's disease — yet she has exhibited no signs of cognitive impairment associated with Alzheimer's.

“When you find an escapee, it’s extremely interesting,” said Kosik, co-author of a [study](#) that appears in the journal Nature Medicine. The woman, and others who are considered outliers in the normal trend of neurodegeneration of this family, may present hints at a new approach for therapy for and even prevention of the disease, he said.

Fire with Fire

The culprit in this version of Alzheimer’s is a mutation to the presenilin 1 gene, called E280A, copies of which are found in every member of this family afflicted with the disease. It is implicated in the high production of those sticky amyloid plaques.

“The mutation is known to cause the onset of the disease at age 45, and it’s really flagrant by the time you’re in your 50s,” Kosik said. The woman, in her late 60s at the time they were conducting their study, was positive for the mutation, but exhibited few symptoms.

“It was amazing,” Kosik said. In the course of their analysis they found that the woman also had another mutation in another gene that is responsible for making lipoproteins in the central nervous system, a gene called apolipoprotein E or APOE. A variant of this gene called the Christchurch variant is exceedingly rare, but its presence in the patient hinted at a protective mechanism. The researchers turned to the Kosik Lab’s extensive collection of genomes to look for other family members with this same variant.

“They asked us especially to look at people who were also outliers — who got it at a very late age,” Kosik said. They found a few others who had the variant, he said. Importantly, however, while there were others who did carry the Christchurch mutation, they all carried one copy, inherited from one parent.

“The key thing about this discovery is that this patient is homozygous for the variant; it came from both the mother and the father,” Kosik explained. The researchers’ lab studies showed that the APOE gene variant might delay the onset of Alzheimer’s by binding to sugars (called heparin sulphate proteoglycans, or HSPG) and preventing the uptake and inclusion of tau proteins in neurons that ultimately lead to the tangles that are a pathological hallmark of the disease. Tau is a common structural protein in the brains of patients with Alzheimer’s and other neurodegenerative diseases that becomes sticky and insoluble.

More work needs to be done to investigate this single patient's resistance to a disease that affects her extended family of 6,000 people, but this promising development could point toward an approach and a therapy for the estimated 44 million people in the world who have Alzheimer's, a number that continues to rise.

"This finding suggests that artificially modulating the binding of APOE to HSPG could have potential benefits for the treatment of Alzheimer's disease, even in the context of high levels of amyloid pathology," said the paper's co-lead author Joseph F. Arboleda-Velasquez, in a press statement.

For Kosik's part, he and Arboleda-Vasquez (who formerly was Kosik's graduate student at Harvard) continue to probe for other genetic one-offs and outliers that may contribute to Alzheimer's resistance.

About UC Santa Barbara

The University of California, Santa Barbara is a leading research institution that also provides a comprehensive liberal arts learning experience. Our academic community of faculty, students, and staff is characterized by a culture of interdisciplinary collaboration that is responsive to the needs of our multicultural and global society. All of this takes place within a living and learning environment like no other, as we draw inspiration from the beauty and resources of our extraordinary location at the edge of the Pacific Ocean.