NEWS IN FOCUS

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A volunteer in the Alzheimer's study at the University of Antioquia, Colombia, who is unsure whether she carries a genetic mutation that causes the disease.

NEUROSCIENCE

Alzheimer's study zeroes in on enigmatic protein

Researchers in Colombia hope to uncover new drug targets.

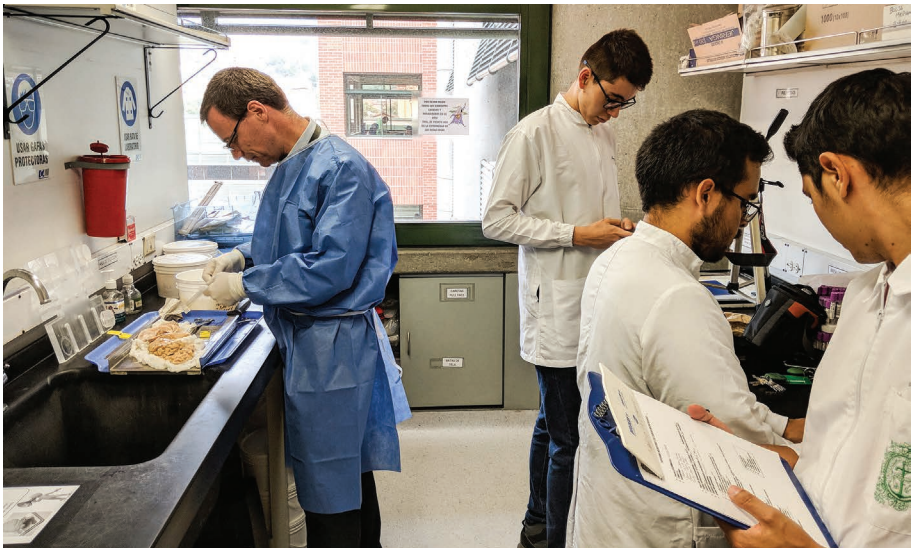
BY SARA REARDON, MEDELLÍN, COLOMBIA

Jhon Kennedy was building a house for his family when he realized that his 45-year-old father was beginning to struggle with daily life. His father tried to help with the construction project but often forgot to complete simple tasks. And he kept getting lost on the way home from work.

Jhon Kennedy wasn't surprised: his four uncles had also started to lose their memories, one by one. But their doctors in Colombia's rural Antioquia region, which is known for its mountainous terrain and coffee plantations, had never heard of early-onset dementia. It wasn't until a cousin learned about a study of Alzheimer's disease at the University of Antioquia in Medellín that Jhon Kennedy's relatives understood the illness they faced. For more than three decades, researchers there have been tracking a genetic mutation — common in the region — that causes Alzheimer's to strike people in their 40s and 50s.

Later this year, a team at the university will begin scanning the brains of some of the study participants using a technique that is available only in a few major medical centres worldwide. It will allow the researchers to track a protein called tau, which accumulates rapidly in the brains of people with Alzheimer's as symptoms begin to emerge. Watching tau form in real time could reveal the part it plays in the disease, says Francisco Lopera, the neurologist who is leading the research.

Many scientists have long thought that the disease is triggered by another protein, ▶



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The University of Antioquia Brain Bank stores brains from people who had Alzheimer's disease.

amyloid, that builds up in the brains of people with Alzheimer's. But several drugs that reduce amyloid levels have failed to relieve the symptoms of the disease in clinical trials, increasing interest in the role of tau.

If all goes well, Lopera's team will soon be the first in Colombia with the ability to scan people's brains for tau. In February, he and his colleagues published the results of a pilot study in which they brought 24 people from Colombia to Boston, Massachusetts, and used positron-emission tomography (PET) to search their brains for tau. The researchers showed for the first time that tau begins to accumulate in the brains of people with the Antioquia mutation six years before they begin to show signs of disease[1].

"This is a very definitive paper," says Bruce Miller, a behavioural neurologist at the University of California, San Francisco. "I think it's another piece of evidence that tau is very important and has a strong correlation with clinical symptoms."

The genetic mutation that affected Jhon Kennedy's father and uncles is well known in the field of Alzheimer's research. It probably arrived in South America with Spanish conquerors 375 years ago, and now affects 25 extended families in Antioquia with some 5,000 members. Researchers have published dozens of papers about this group, including some of the clearest evidence that amyloid plaques can accumulate in the brain decades before symptoms of Alzheimer's appear[2].

But because questions have emerged about amyloid's role in Alzheimer's, scientists have taken a closer look at tau. The protein normally helps to stabilize the structures that enable neurons to communicate with one another. People with Alzheimer's make too much dysfunctional tau, causing these structures to collapse into tangles. The amount of tau seems to increase in step with a person's symptoms.

In the past several years, researchers have developed radioactive biomarkers that allow them to detect tau in living people using PET. Studies have shown that tau accumulation in the brain's language centres correlates with speech problems, for instance[3]. Several research groups are beginning clinical trials of drugs that scrub tau from the brain, although this work is at an early stage.

Jhon Kennedy and his 11 siblings each have a 50% chance of inheriting the Alzheimer's mutation from their father. Eight have enrolled in Lopera's study and could be among the first people to undergo tau imaging in Colombia; none know whether they carry the mutation.

The study, which began in 2013, was designed to test whether crenezumab, a drug that clears amyloid plaques from the brain, could lessen symptoms of Alzheimer's. In the past five years, Lopera's team has recruited 252 participants who were between 30 and 60 years old. Those who carry the Alzheimer's mutation will begin accumulating amyloid in their brains during their early 30s, on average.

Each participant in the study will receive infusions of crenezumab or a placebo every other week, for five years. Lopera's team is also testing their cognitive abilities, scanning their brains for amyloid and searching for blood proteins and other biomarkers that could be early indicators of disease.

The scientists hope to begin mapping the tau in participants' brains in the coming months, after they receive final permission from regulators to produce the crucial radioactive marker GTP1. When that happens, the team will join a handful of researchers worldwide that are using the technology. "It's quite remarkable that a population that lives in such a remote area is getting access to some of the most advanced technology for understanding Alzheimer's," says Kenneth Kosik, a neuroscientist at the University of California, Santa Barbara.

Lopera and his colleagues want to determine how tau spreads in the brains of young people with Alzheimer's, and whether that pattern mirrors the distribution of tau seen in elderly people with the disease. They hope to compare their results with data from two clinical trials of anti-amyloid drugs in the United States that have begun scanning participants' brains for tau. Lopera, Kosik and other scientists are also beginning to identify families in Colombia with different genetic mutations that cause dementia or neurological disorders linked to tau, in the hope of imaging their brains too.

Lopera says that his team will not release data from the crenezumab study until it finishes in 2022. But if the results are promising, he adds, the researchers might give the drug to people under 30 who carry the mutation for early-onset Alzheimer's. The scientists have identified almost 500 young people who might be carriers, including Jhon Kennedy's 15-year-old daughter. "She's not worried about it," Jhon Kennedy says. "She's like me — she lives day by day." ■

1. Quiroz, Y. T. *et al. JAMA Neurol.* http://dx.doi.org/10.1001/jamaneurol.2017.4907 (2018).
2. Reiman, E., *et al. Lancet Neurol.* **11,** 1048–56 (2012).
3. Ossenkoppele, R. *et al. Brain.* **139,** 1551–1567 (2016).

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CORRECTION

The News story 'Alzheimer's study zeroes in on enigmatic protein' (*Nature* **555,** 567-568; 2018) misstated the radioactive marker that will be used in the tau scans. It is GTP1, not GPT1.