



## Gene Mutation May Help Cause Alzheimer's It's only the second gene with proven links to late-onset disease

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WEDNESDAY, March 2 (HealthDay News) -- Another piece of the Alzheimer's puzzle has fallen into place, as researchers report the identification of a gene associated with the mind-robbing disease.

Mutations in the gene, called *UBQLN1*, may raise risks for the common, late-onset form of the disease that comprises more than 90 percent of Alzheimer's cases. The gene, located on chromosome 9, is only the second gene ever linked to late-onset disease, researchers said.

Even though truly effective treatments for Alzheimer's remain elusive, identifying genetic factors in the disease should prove crucially important in the not-so-distant future, in both the diagnosis and treatment of the illness.

"It's really a two-pronged attack: First, we find all the genes involved to help identify those at risk, and then, from the other side, we learn from the genes what's going wrong," explained lead researcher Rudolph Tanzi, a professor of neurology at Harvard Medical School, and director of the Genetics and Aging Research Unit at Massachusetts General Hospital.

The findings appear in the March 3 issue of the *New England Journal of Medicine*.

Alzheimer's is the leading cause of age-related dementia in the United States, affecting more than 4.5 million Americans, according to the Alzheimer's Association. As the population ages, experts expect that number to reach 16 million by 2050.

As tough as it is on patients and their caregivers, Alzheimer's has been just as tough for researchers bent on discovering its exact cause and cure. One avenue of research that's slowly bearing fruit, however, is genetics. Over the past 10 years, investigators have pinpointed three genes whose mutations are involved in familial, early onset disease (a rare form of the illness affecting about 10 percent of patients), and just one gene -- called *APOE4* -- that's linked to the much more widespread, late-onset disease type.

Tanzi, who in 1996 identified one of the early onset genes, *Presenilin 2*, now believes his team at Harvard has isolated a second gene associated with late-onset disease.

Working first with a group of 437 families, each with two first-degree relatives affected by Alzheimer's, the researchers specifically looked at genes on chromosome 9. They eventually zeroed in on genes producing a protein called ubiquilin.

"The reason we specifically looked at ubiquilin was because it binds to and interacts with the early onset gene, *Presenilin 2*," Tanzi explained.

The researchers hit pay dirt: Variants in a ubiquilin-linked gene, *UBQLN1*, were significantly associated with incidence of late-onset Alzheimer's in affected families.

A separate analysis, this time in 217 sibling pairs -- where one had Alzheimer's but the other didn't -- further strengthened the association, as did autopsy evidence from brains affected by Alzheimer's, the

researchers found.

"What the Tanzi group has done is identify another gene which, like *APOE4*, probably results in an increased risk in developing Alzheimer's disease," said William J. Netzer, a research associate at Rockefeller University in New York City, and scientific liaison for the Fisher Center for Alzheimer's Research Foundation.

Both Tanzi and Netzer agree that *UBQLN1* is probably about half as potent as *APOE4* in triggering Alzheimer's. But they say the goal is not the identification of one or two genes, but a much larger collection of mutations that together might better predict a person's overall risk.

"The only way to reliably predict early on who's at greatest risk is by having all the genes on one [computer] chip, so you can have some comprehensive screen to reliably tell someone, 'Here's your risk relative to the rest of the population,'" Tanzi said.

Of course, that information isn't much good if there are no treatments available to prevent or treat Alzheimer's. But genetics has a big role to play there, too.

"Remember, each of these genes represents the possibility of a pharmacological target," Netzer said. "Each discovery like this makes it increasingly likely that effective therapies will be made. Then, when they are made, you might want to intervene at an earlier stage, before a person actually presents with symptoms. That's where genetic screening might come in."

In the case of *UBQLN1*, Tanzi said his team already knows ubiquilin may have links to the slow buildup of beta-amyloid plaque deposits in brain tissues that are a hallmark -- and possibly, a cause -- of the disease. There are also indications the gene may interact with presenilin to impede the natural clearance of beta amyloid proteins that otherwise clump up to form these plaques.

"I like to use a kitchen sink metaphor -- you either make too much of this stuff, or you can't clear it away fast enough," Tanzi said, noting that *UBQLN1* may be involved in both processes.

In a second, related study, published in the March 3 issue of *Neuron*, researchers at the University of California, Irvine, said they have identified a molecular "trigger" for the kind of memory decline that characterizes early Alzheimer's.

Working with mice genetically engineered to develop Alzheimer's disease, the researchers found that the buildup of the protein beta amyloid in and around brain cells in the hippocampus, amygdala and cerebral cortex coincide with noticeable lapses in the mice's ability to navigate a maze they had successfully navigated in the past.

Both of these studies offer new reason for hope, Netzer said.

"We live in a very exciting time," he said. "We've already defined several major [drug] targets now, and we're on the brink of being able to produce drugs that actually significantly lower beta amyloid. Some of them are under development right now at pharmaceutical companies, and probably will be tested in humans within about two years."

### More information

Learn much more about ongoing research into Alzheimer's at the [Fisher Center for Alzheimer's Research Foundation](#).

SOURCES: Rudolph Tanzi, Ph.D., professor, neurology, Harvard Medical School, and director, Genetics and Aging Research Unit, Massachusetts General Hospital, Boston; William J. Netzer, Ph.D., research associate, Rockefeller University, and scientific liaison, Fisher Center for Alzheimer's Research Foundation, New York City; March 3, 2005, *New England Journal of Medicine*; March 2, 2005, University of California, Irvine, news

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