Alzheimer’s Risk Gene Discovered Using Imaging Method That Screens Brain’s Connections

By Mark Wheeler
University of California, Los Angeles

Scientists at UCLA have discovered a new genetic risk factor for Alzheimer's disease by screening people's DNA and then using an advanced type of scan to visualize their brains' connections.

Alzheimer's disease, the most common cause of dementia in the elderly, erodes these connections, which we rely on to support thinking, emotion and memory. With no known cure for the disease, the 20 million Alzheimer's sufferers worldwide lack an effective treatment. And we are all at risk: Our chance of developing Alzheimer's doubles every five years after age 65.

The UCLA researchers discovered a common abnormality in our genetic code that increases the risk of Alzheimer's. To find the gene, they used a new imaging method that screens the brain's connections — the wiring, or circuitry, that communicates information. Switching off such Alzheimer's risk genes (nine of them have been implicated over the last 20 years) could stop the disorder in its tracks or delay its onset by many years.

The research is published in the March 4 online edition of the journal Proceedings of the National Academy of Sciences.

"We found a change in our genetic code that boosts our risk for Alzheimer's disease," said the study's senior author, Paul Thompson, a UCLA professor of neurology and a member of the UCLA Laboratory of Neuro Imaging. "If you have this variant in your DNA, your brain connections are weaker. As you get older, faulty brain connections increase your risk of dementia."

The researchers, Thompson said, screened more than a thousand people's DNA to find the common "spelling errors" in the genetic code that might heighten their risk for the disease later in life. The new study was the first of its kind to also give each person a "connectome scan," a special type of scan that measures water diffusion in the brain, allowing scientists to map the strength of the brain's connections.

The new scan reveals the brain's circuitry and how information is routed around the brain, in order to discover risk factors for disease. The researchers then combined these connectivity scans with the extensive genomic screening to pinpoint what causes faulty wiring in the brain.

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Hundreds of computers, calculating for months, sifted through more than 4,000 brain connections and the entire genetic code, comparing connection patterns in people with different genetic variations. In people whose genetic code differed in one specific gene called SPON1, weaker connections were found between brain centers controlling reasoning and emotion. The rogue gene also affects how senile plaques build up in the brain — one of the hallmarks of Alzheimer’s disease.

"Much of your risk for disease is written in your DNA, so the genome is a good place to look for new drug targets," said Thompson, who in 2009 founded a research network known as Project ENIGMA to pool brain scans and DNA from 26,000 people worldwide. "If we scan your brain and DNA today, we can discover dangerous genes that will undermine your ability to think and plan and will make you ill in the future. If we find these genes now, there is a better chance of new drugs that can switch them off before you or your family get ill."

Developing new therapeutics for Alzheimer's is a hot area for pharmaceutical research, Thompson said.

It has also been found that the SPON1 gene can be manipulated to develop new treatments for the devastating disease, Thompson noted. When the rogue gene was altered in mice, it led to cognitive improvements and fewer plaques building up in the brain. Alzheimer’s patients show an accumulation of these senile plaques, which are made of a sticky substance called amyloid and are thought to kill brain cells, causing irreversible memory loss and personality changes.

Screening genomes has led to many new drug targets in the treatment of cancer, heart disease, arthritis and brain disorders such as epilepsy. But the UCLA team’s approach — screening genomes and performing brain scans of the same people — promises a faster and more efficient search.

"With a brain scan that takes half an hour and a DNA scan from a saliva sample, we can search your genes for factors that help or harm your brain’s connections," Thompson said. "This opens up a new landscape of discovery in medical science.


Other UCLA authors on the paper included Neda Jahanshad, Priya Rajagopalan, Xue Hua, Derrek P. Hibar, Talia M. Nir and Arthur W. Toga.

The project had multiple funding sources, including the National Institutes of Health (grant R01 HD050735). Please see the paper for other authors and additional funding.

The Laboratory of Neuro Imaging at UCLA, which seeks to improve understanding of the brain in health and disease, is a leader in the development of advanced computational algorithms and scientific approaches for the comprehensive and quantitative mapping of brain structure and function. It is part of the UCLA Department of Neurology, which encompasses more than a dozen research, clinical and teaching programs. The department ranks in the top two among nationwide in National Institutes of Health funding.
Hypertension Could Bring Increased Risk for Alzheimer’s Disease

By Emily Martinez
University of Texas at Dallas

A study in the Journal of the American Medical Association Neurology suggests that controlling or preventing risk factors, such as hypertension, earlier in life may limit or delay the brain changes associated with Alzheimer’s disease and other age-related neurological deterioration.

Untreated Blood Pressure, Genetics Present Risk

A research team has found that the combination of genetic predisposition and non-medicated high blood pressure can lead to a protein buildup that some scientists believe is linked to Alzheimer’s.

![Graph showing mean levels of amyloid and protein buildup]

Dr. Karen Rodrigue, assistant professor in the UT Dallas Center for Vital Longevity (CVL), was lead author of a study that looked at whether people with both hypertension and a common gene had more buildup of a brain plaque called amyloid protein, which is associated with Alzheimer’s disease. Scientists believe amyloid is the first symptom of Alzheimer’s disease and shows up a decade or more before symptoms of memory impairment and other cognitive difficulties begin. The gene, known as APOE 4, is carried by 20 percent of the population.

Until recently, amyloid plaque could be seen only at autopsy, but new brain scanning techniques allow scientists to see plaque in living brains of healthy adults. Findings from both autopsy and amyloid brain scans show that at least 20 percent of typical older adults carry elevated levels of amyloid, a substance made up mostly of protein that is deposited in organs and tissues.

“I became interested in whether hypertension was related to increased risk of amyloid plaques in the brains of otherwise healthy people,” Rodrigue said. “Identifying the most significant risk factors for amyloid deposition in seemingly healthy adults will be critical in advancing medical efforts aimed at prevention and early detection.”

Based on evidence that hypertension was associated with Alzheimer’s disease, Rodrigue suspected that the combination of hypertension and the presence of the APOE-e4 gene might lead to particularly high levels of amyloid plaque in healthy adults.

Rodrigue’s research was part of the Dallas Lifespan Brain Study, a comprehensive study of the aging brain in a large group of adults of all ages funded by the National Institute on Aging. Rodrigue’s group recruited 147 participants (ages 30–89) to undergo cognitive testing, magnetic resonance imaging (MRI) and PET imaging using Amyvid. Amyvid is a compound that when injected travels to the brain and binds with amyloid proteins, allowing the scientists to visualize the amount of amyloid plaque. Blood pressure also was measured at each visit.

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Rodrigue classified participants in the study as hypertensive if they reported a current physician diagnosis of hypertension or if their blood pressure exceeded the established criteria for diagnosis. The participants were further divided into groups based on whether they were taking anti-hypertensive medications or if they were unmedicated and showed blood pressure elevations consistent with a diagnosis of hypertension. Finally, study subjects were classified in the genetic risk group if they were in the 20 percent of adults who had one or two copies of an APOE ε4 allele, a genetic variation linked to dementia.

The most striking result of the study was that nonmedicated hypertensive adults who also carried a genetic risk factor for Alzheimer’s disease showed much higher amyloid levels than all other groups. Adults with medication-controlled hypertension, even those with genetic risk, had levels of amyloid plaque equivalent to participants without hypertension or genetic risk.

The study suggests that controlling hypertension may significantly decrease the risk of developing amyloid deposits, even in those with genetic risk. Rodrigue noted that long-term studies are needed to be certain that the use of hypertensive medications decreased amyloid deposits. Nevertheless, this early finding provides a window into the potential benefits of controlling hypertension that goes beyond lowering the risk of strokes and other cardiovascular complications.

Scientists cannot fully explain the neural mechanisms underlying the effect of hypertension and APOE ε4 on amyloid accumulation. But earlier research in animal models has shown that chronic hypertension may enable easier penetration of the blood-brain barrier, resulting in more amyloid deposition.

The recent study is significant because it focuses on a group of healthy and cognitively normal middle-aged and older adults, which enables the examination of risk factors and amyloid burden before the development of preclinical dementia. The team plans for long-term, longitudinal follow-up with participants to determine the proportion of the subjects who eventually develop the disease.

The study’s co-authors included Dr. Denise Park, director of the Dallas Lifespan Brain Study and co-director of the Center for Vital Longevity, Dr. Kristen Kennedy and doctoral student Jennifer Rieck, all from The University of Texas at Dallas. The team also included Dr. Michael Devous and Dr. Ramon Diaz-Arrastia from UT Southwestern Medical Center and the Uniformed Services University of the Health Sciences. In addition to the National Institute on Aging support, the Alzheimer’s Association provided funds for the study and Avid Radiopharmaceutical provided doses of Amyvid used in scanning.

Dr. Karen Rodrigue, assistant professor for the Center for Vital Longevity

“Identifying the most significant risk factors for amyloid deposition in seemingly healthy adults will be critical in advancing medical efforts aimed at prevention and early detection.”
Researchers at the University of Michigan have found a new potential benefit of a molecule in green tea: preventing the misfolding of specific proteins in the brain.

The aggregation of these proteins, called metal-associated amyloids, is associated with Alzheimer's disease and other neurodegenerative conditions.

A paper published recently in the Proceedings of the National Academy of Sciences explained how Life Sciences Institute faculty member Mi Hee Lim and an interdisciplinary team of researchers used green tea extract to control the generation of metal-associated amyloid-β aggregates associated with Alzheimer's disease in the lab.

The specific molecule in green tea, (—)-epigallocatechin-3-gallate, also known as EGCG, prevented aggregate formation and broke down existing aggregate structures in the proteins that contained metals—specifically copper, iron and zinc.

"A lot of people are very excited about this molecule," said Lim, noting that the EGCG and other flavonoids in natural products have long been established as powerful antioxidants. "We used a multidisciplinary approach. This is the first example of structure-centric, multidisciplinary investigations by three principal investigators with three different areas of expertise."

The research team included chemists, biochemists and biophysicists.

While many researchers are investigating small molecules and metal-associated amyloids, most are looking from a limited perspective, said Lim, assistant professor of chemistry and research assistant professor at the Life Sciences Institute, where her lab is located and her research is conducted.

"But we believe you have to have a lot of approaches working together, because the brain is very complex," she said.

The PNAS paper was a starting point, Lim said, and her team's next step is to "tweak" the molecule and then test its ability to interfere with plaque formation in fruit flies.

"We want to modify them for the brain, specifically to interfere with the plaques associated with Alzheimer's," she said.

Lim plans to collaborate with Bing Ye, a neurobiologist in the LSI. Together, the researchers will test the new molecule's power to inhibit potential toxicity of aggregates containing proteins and metals in fruit flies.

Other authors of the paper, all from U-M, are: Sanghyun Lee and Jung-Suk Choi of the Life Sciences Institute; Alaina DeToma, Suk-Joon Hyung, Akiko Kochi and Brandon Ruotoloa of the Department of Chemistry; and Jeffrey Breder, Ayyalusamy Ramamoorthy and Subramanian Vivekanandan of the Department of Chemistry and Biophysics.

The work was supported by the National Institutes of Health, Alzheimer's Association, Alzheimer's Art Quilt Initiative, American Heart Association, and a Graduate Research Fellowship from the National Science Foundation.
Sleep Loss Precedes Alzheimer’s Symptoms

By Michael Purdy,
Senior Medical Sciences Writer
Washington University in St. Louis

Sleep is disrupted in people who likely have early Alzheimer’s disease but do not yet have the memory loss or other cognitive problems characteristic of full-blown disease, researchers at Washington University School of Medicine in St. Louis report March 11 in JAMA Neurology.

The finding confirms earlier observations by some of the same researchers. Those studies showed a link in mice between sleep loss and brain plaques, a hallmark of Alzheimer’s disease. Early evidence tentatively suggests the connection may work in both directions: Alzheimer’s plaques disrupt sleep, and lack of sleep promotes Alzheimer’s plaques.

“This link may provide us with an easily detectable sign of Alzheimer’s pathology,” says senior author David M. Holtzman, MD, the Andrew B. and Gretchen P. Jones Professor and head of Washington University’s Department of Neurology. “As we start to treat people who have markers of early Alzheimer’s, changes in sleep in response to treatments may serve as an indicator of whether the new treatments are succeeding.”

Sleep problems are common in people who have symptomatic Alzheimer’s disease, but scientists recently have begun to suspect that they also may be an indicator of early disease. The new paper is among the first to connect early Alzheimer’s disease and sleep disruption in humans.

For the new study, researchers recruited 145 volunteers from the University’s Charles F. and Joanne Knight Alzheimer’s Disease Research Center. All of the volunteers were 45 to 75 years old and cognitively normal when they enrolled.

As a part of other research at the center, scientists already had analyzed samples of the volunteers’ spinal fluids for markers of Alzheimer’s disease. The samples showed that 32 participants had preclinical Alzheimer’s disease, meaning they were likely to have amyloid plaques present in their brains but were not yet cognitively impaired.

Participants kept daily sleep diaries for two weeks, noting the time they went to bed and got up, the number of naps taken on the previous day, and other sleep-related information.

The researchers tracked the participants’ activity levels using sensors worn on the wrist that detected the wearer’s movements.

“Most people don’t move when they’re asleep, and we developed a way to use the data we collected as a marker for whether a person was asleep or awake,” says first author Yo-El Ju, MD, assistant professor of neurology. “This let us assess sleep efficiency, which is a measure of how much time in bed is spent asleep.”

Participants who had preclinical Alzheimer’s disease had poorer sleep efficiency (80.4 percent) than people without markers of Alzheimer’s (83.7 percent). On average, those with preclinical disease were in bed as long as other participants, but they spent less time asleep. They also napped more often.

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“When we looked specifically at the worst sleepers, those with a sleep efficiency lower than 75 percent, they were more than five times more likely to have preclinical Alzheimer’s disease than good sleepers,” Ju says.

Ju and her colleagues are following up with studies in younger participants who have sleep disorders.

“We think this may help us get a better feel for the way this connection flows — does sleep loss drive Alzheimer’s, does Alzheimer’s lead to sleep loss, or is it a combination?” Ju says. “That will help us determine whether we can change the course of disease with pharmaceuticals or other treatments.”

This study was funded by an Ellison Medical Foundation Senior Scholar award and NIH grant P01NS074969 from the National Institute of Neurological Disorders and Stroke.

The goal of the Alzheimer's Disease Neuroimaging Initiative Study is to learn how to stop the progression of mild cognitive impairment (MCI) and Alzheimer's disease in future generations. Information from the study might, in the future, lead to new treatments.  http://adcs.org/Studies/ImagineADNI.aspx.

ADNI II Study

The Dominantly Inherited Alzheimer Network (DIAN). DIAN is an international research partnership of leading scientists determined to understand a rare form of Alzheimer's disease that is caused by a gene mutation. Understanding of this form of Alzheimer's disease may provide clues to decoding other dementias and developing dementia treatments.

Funded by a multiple-year research grant from the National Institute on Aging, DIAN currently involves thirteen outstanding research institutions in the United States, United Kingdom, Germany and Australia. John C. Morris, M.D., Friedman Distinguished Professor of Neurology at Washington University School of Medicine in St. Louis, is the project’s principal investigator.

DIAN is currently enrolling study participants who are biological adult children of a parent with a mutated gene known to cause dominantly inherited Alzheimer’s disease. Such individuals may or may not carry the gene themselves and may or may not have disease symptoms (click here for information about genetic testing).

To register for DIAN drug trials or DIAN, visit www.DIANExpandedRegistry.org.

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