Medical Xpress

New study zeroes in on genetic roots of Alzheimer's

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Scientists have known for more than a decade that individuals with a certain gene are at higher risk for developing Alzheimer's disease. Now a new study helps explain why this is so.

The research, led by scientists at the Oklahoma Medical Research Foundation (OMRF), has uncovered a molecular mechanism that links the susceptibility gene to the process of Alzheimer's disease onset. The findings appear in the April 11 issue of *The Journal of Neuroscience* and may lead to new pathways for development of Alzheimer's therapeutics.

Approximately 15 percent of the population carries a gene that causes their bodies to produce a lipoprotein—a combination of fat and protein that transports lipids (fats) in the blood—known as apolipoprotein (Apo) E4. Studies have found that those who inherit the E4 gene from one parent are three times more likely than average to develop Alzheimer's, while those who get the gene from both parents have a tenfold risk of developing the disease.

In the new study, OMRF's Jordan J.N. Tang, Ph.D., and his colleagues discovered that ApoE4 (along with other apolipoproteins) attaches itself to a particular receptor on the surface of brain cells. That receptor, in turn, adheres to a protein known as amyloid precursor protein. The brain cells then transport the entire protein mass inside.

Once inside, cutting enzymes—called proteases—attack the amyloid precursor protein. These cuts create protein fragments that, when present

in the brain for long periods of time, are believed to cause the cell death, memory loss and neurological dysfunction characteristic of Alzheimer's.

Although researchers have known for more than a decade that ApoE4 was involved—somehow—in development of Alzheimer's, Tang's new study is the first to connect the process of protein fragment formation to ApoE4.

While roughly 1 in 7 people carry the E4 gene, the remainder of the population carry only two variations—known as E2 and E3—of that gene. These individuals have a markedly lower incidence of Alzheimer's than those who carry the E4 gene. The new study found that ApoE4 produced more protein fragments than did E2 or E3.

"ApoE4 apparently interacts better with the receptor than its cousins," said Tang. "This may explain why people who carry the E4 gene have a higher risk of developing Alzheimer's."

"These findings may allow us to investigate the possibility of therapeutic intervention at different points in the process," said Tang. For example, he said, such efforts might focus on developing a compound to interfere with the receptor's ability to adhere to ApoE4.

"There currently is no effective treatment for Alzheimer's disease, so we must explore every possible option to find a way to stop it," he said.

"Dr. Tang's study shows a beautiful biochemical connection between a genetic risk factor and the development of a disease," said OMRF President Stephen Prescott, M.D. "This work opens the door to the development of alternate methods for treating—and perhaps even preventing—Alzheimer's."

ApoE4 also has been linked to coronary artery disease. "Ultimately, this

work could pave the way for similar study of the pathogenesis of other diseases," said Prescott.

Source: Oklahoma Medical Research Foundation