Study explores how life experiences contribute to the biological changes of Alzheimer's

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The National Institutes of Health has awarded Rush University Medical Center approximately $5.5 million in grants to study how epigenetic changes - chemical modifications to genes that result from diet, aging, stress, or environmental exposures - define and contribute to memory formation and cognitive decline. Results from the studies could profoundly alter the way the medical community understands, diagnoses, and treats Alzheimer's disease, according to the researchers.

Every cell in the body has the same genetic information. What makes cells, tissues and organs different are the epigenetic modifications, or marks, that turn genes on or off.

Researchers at the Rush Alzheimer's Disease Center hypothesize that the brain uses epigenetic marks to store memory and are exploring the relationship between life experiences known to affect memory abilities and changes in the epigenetic marks.

The study is motivated, in large part, from the center's work with two large, longitudinal studies of aging and dementia conducted over the past 15 years. Researchers at Rush have identified a wide range of life experiences that are related to loss of cognitive function and a clinical diagnosis of Alzheimer's disease but are not associated with the neuropathologic hallmarks of the disease, the plaques and tangles that accumulate in the brain. These life experiences include socioeconomic

status, psychological distress, and cognitive, physical, and social activities across the life span.

"We have found that while cognitive decline in old age often results from one or more of three common brain diseases, Alzheimer's disease, cerebrovascular disease and Lewy body disease, these conditions only account for about 20% of the variance of cognition in older persons," said Dr. David Bennett, director of the Rush Alzheimer's Disease Center and principal investigator for the studies. "Thus, factors other than neuropathology must make important contributions to cognitive function in old age."

One of those factors may be epigenetic marks. There are currently about 30 known proteins that turn genes on and off. Since it is known that life experiences can affect which proteins are produced, Bennett and his colleagues want to know if the brain is using epigenetic marks as a means of linking experiential factors to long term memory storage.

"A memory trace involves protein production. It is hard to change genes, but it may be easier to manipulate the opening and closing of genes to impact memory," said Bennett.

Researchers will conduct epigenome-wide DNA methylation scans and epigenome-wide histone acetylation scans on brain tissue from participants in two large, longitudinal studies of aging and dementia: the Rush Memory and Aging Project and the Religious Orders Study. These studies include the participation of more than 2,400 older adults from across the country who have agreed to medical and psychological evaluation each year and brain donation after death. Brain tissue is already available from more than 750 participants, and the epigenomic studies will eventually examine brain tissue from more than 1000 participants.

The results of these scans will be used to explore the relation of epigenetic alterations to age-related cognitive decline and point to potential DNA methylation sites and histone modifications linking life experiences to cognitive decline and dementia. Understanding these relationships offer the possibility of therapeutic intervention because a number of drugs are known to affect epigenetic modifications.

In addition, Rush researchers have already been funded by the NIH to conduct a whole genome scan on participants from both studies. Thus, they will be able to examine the interaction between genetic variation and epigenetic marks on cognition and life experiences. Rush is collaborating with the Broad Institute of MIT and Harvard Universty to conduct the genome-wide genotyping and epigenome wide scans.

Recent major advances in technology allow the scientists to look at one million genetic variations in a single human's DNA using a simple blood sample and tens of thousands of epigenomic marks across the genome with a small piece of brain tissue.

A third set of analyses will examine the relation of epigenetic marks to measures of the pathology of Alzheimer's disease, cerebrovascular disease and Lewy body disease found in the brain.

"Together, this integrative study represents a timely, novel and powerful approach that will transform our understanding of epigenetic contributions to age-related loss of cognition and dementia," said Bennett. "We are not aware of any other studies of older men and women of comparable size, relevant life experience, clinical data, and follow-up and autopsy rates, in which these analyses can be performed.

Source: Rush University Medical Center (news : web)