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Certain patients with type 2 diabetes (T2D) may have specific genetic risk factors that put them at higher risk for developing Alzheimer’s disease (AD), according to a study conducted at the Icahn School of Medicine at Mount Sinai and published recently in Molecular Aspects of Medicine.

Under the leadership of Giulio Maria Pasinetti, MD, PhD, Saunders Family Chair and Professor of Neurology at the Icahn School of Medicine at Mount Sinai and Director of Biomedical Training in the Geriatric Research Education and Clinical Centers at J.J. Peters Bronx VA Medical Center, the study team used recent genome wide association study (GWAS) findings to investigate whether T2D and AD share common genetic etiological factors and the potential impact of these genetic factors on the cellular and molecular mechanisms that may contribute to the development of both of these diseases.

GWAS look at differences at many points in the genetic code to see if, across a population, one or more variations in the code are found more often in those with a given trait (for example, high risk for a disease). Even the smallest genetic variations, called single nucleotide polymorphisms (SNPs), can have a major impact on a trait by swapping just one of the 3.2 billion “letters” that make up the human DNA code.

One of the major long-term complications of T2D is an increased risk for developing AD. While previous studies strongly suggested a causative role of diabetes in the onset and progression of AD dementia, the specific mechanistic interactions connecting diabetes and AD had not been previously described.
We identified multiple genetic differences in terms of SNPs that are associated with higher susceptibility to develop type 2 diabetes as well as Alzheimer’s disease,” says Dr. Pasinetti. “Many of these SNPs are traced to genes whose anomalies are known to contribute to T2D and AD, suggesting that certain diabetic patients with these genetic differences are at high risk for developing Alzheimer’s. Our data highlights the need for further exploration of genetic susceptibility to Alzheimer’s disease in patients with T2D.”

An estimated 312 million people suffer from T2D worldwide, exerting enormous burdens on individuals and on health care systems. Similarly, AD affects nearly 45 million people worldwide and is costly to both individuals and healthcare systems. There is currently no cure for either condition.

Mounting evidence suggests that AD dementia can be traced back to pathological conditions, such as T2D, that are initiated several decades before clinical AD onset. Since T2D is one of the potentially modifiable risk factors for AD, it is critically important for scientists to uncover the genetics of this complex connection so that new therapeutic interventions may be developed and targeted to at-risk individuals with T2D prior to the onset of AD dementia.

This study will support ongoing research applications to further explore genetic susceptibility in patients with T2D for developing AD and help improve the design of future novel treatments for a subpopulation of T2D subjects with genetic predisposition to AD, which could benefit T2D and reduce the risk for subsequent development of AD. Outcomes from these studies identifying cellular abnormalities common to both T2D and AD can lead to the development of T2D therapies that may also help prevent subsequent development of AD in genetically predisposed individuals.

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“Shared genetic etiology underlying Alzheimer’s disease and type 2 diabetes,” by Ke Hao, Antonio Fabio Di Narzo, Lap Ho, Wei Luo, Shuyu Li, Rong Chen, Tongbin Li, Lauren Dubner, and Giulio Maria Pasinetti (DOI: 10.1016/j.mam.2015.06.006), published online in Molecular Aspects of Medicine by Elsevier.
NEW REPORTS FROM THE ALZHEIMER’S ASSOCIATION INTERNATIONAL CONFERENCE® 2015:

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Courtesy of the Alzheimer’s Association

WASHINGTON, DC, July 23, 2015 – Exciting new research results presented at the Alzheimer’s Association International Conference® 2015 (AAIC® 2015) cover a wide range of Alzheimer’s and dementia studies. The data demonstrate a diversity of treatment-related findings, advances in early detection, risk factors in young people, and the impact of Alzheimer’s on the Baby Boomers. Also reported at AAIC 2015 were study results highlighting the disproportionate effect of Alzheimer’s on women and the benefits of physical exercise for people with Alzheimer’s and other dementias.

AAIC is the premier annual forum for presentation and discussion of the latest Alzheimer’s and dementia research. Bringing the world closer to breakthroughs in dementia science, AAIC 2015 brought together approximately 4,500 leading experts and researchers from nearly 70 countries around the world, and featured more than 2,200 scientific presentations.

Promising new data results for treatment of Alzheimer’s disease

Results from more than a dozen experimental drug studies at AAIC show the research community attacking Alzheimer’s disease from multiple angles, targeting the underlying causes and some of the most pernicious symptoms. These advances show a clear maturation of the Alzheimer’s research field, a recognition of the need for a broader attack, and hint at future possibilities for combination therapy. New reports included advanced trials and new analyses in three drugs targeting the abnormal amyloid protein that forms plaques in the brain (one of the hallmarks of Alzheimer’s), plus three drug trials that target other pathways and symptoms in the disease, including psychiatric symptoms such as agitation.

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Taking a longer term vision, another set of studies at AAIC 2015 reviewed early-stage results on three types of investigational drugs that suggest they have the potential to work across brain diseases that cause dementia, including Alzheimer’s, Parkinson’s and Lewy Body dementia, based on small preliminary studies in animal models and test tubes.

**28 Million Baby Boomers will get Alzheimer’s disease**

At AAIC 2015, projections reported by The Lewin Group for the Alzheimer’s Association show that 28 million American baby boomers will get Alzheimer’s by midcentury -- a deluge that will consume nearly 25 percent of Medicare spending in 2040 -- unless there are significant advances in treatment and prevention. A study by the same group released earlier this year suggested that a treatment that delays the onset of Alzheimer’s by five years could save $220 billion within the first few years of its introduction.

**Type 1 diabetes identified as a risk factor for Alzheimer’s disease**

The first study of dementia risk, including Alzheimer’s disease, in older adults with type 1 diabetes (T1D) was reported at AAIC 2015. The study looking at a healthcare database of more than 490,000 people over 60 years old found that participants with T1D were 60 to 93 percent more likely to get dementia compared with people without diabetes, even when the diabetes is treated. More research is needed to validate this finding and investigate the biological reasons for the increased risk in T1D. Both type 1 and type 2 diabetes are rapidly increasing worldwide, and people with type 1 are living longer than ever before.

**Early education impacts future risk for Alzheimer’s disease**

Two studies from Sweden presented at AAIC 2015 suggest a correlation between childhood school performance (ages 9-10) and the development of late life dementia. Both studies analyzed the impact that early schooling, secondary education and occupational complexity have on the risk of developing dementia. In the first study of more than 7,500 individuals aged 65+, dementia risk was elevated 21 percent in people who were in the lowest 20 percent of childhood school grades, and dementia risk was reduced 23 percent among individuals in occupations characterized by high complexity with data and numbers. Importantly, high occupational complexity could not compensate for the effect of low childhood school marks. Results from the second study also found significant correlations between grades/work complexity and dementia risk. In this population of 440 men and women age 75 and older, dementia risk was elevated more than 50 percent in individuals over 75 with the lowest 20 percent of early-life school grades, even if they had more formal education or a job was associated with significant complexity. According to the Alzheimer’s Association’s 10 Ways to Love Your Brain, formal education in any stage of life will help reduce your risk of cognitive decline and dementia.
Women are at greater risk for cognitive decline and dementia

Women are at the epicenter of Alzheimer’s disease. According to Alzheimer’s Association 2015 Alzheimer’s Disease Facts and Figures, almost two-thirds of American seniors living with Alzheimer’s disease are women. Women are also more likely to be caregivers of those with Alzheimer’s. The most recent data show that 63 percent of all unpaid Alzheimer’s and dementia caregivers are women.

At AAIC 2015, two studies revealed how the pace and impact of Alzheimer’s and cognitive decline may be different between the sexes. One study of about 400 people with mild cognitive impairment (141 women, 257 men), mostly in their mid-seventies, showed that women deteriorate twice as fast as men with the condition in both cognitive and functional abilities. Additionally, women declined much more dramatically than men in cognition, function and brain size following surgery with general anesthesia, according to a separate study presented at the conference that reviewed 527 older adults from two different research program databases examining cognitive aging. There is a clear need to investigate why this is the case. Is it simply that women live longer than men, or is there something different in the anatomy, biology and/or genetics that contributes to higher prevalence and faster decline?

Researchers report new ways to predict the development of Alzheimer’s disease

Studies reported at AAIC 2015 indicate that brain scans, memory tests and body fluids may hold the keys to understanding a person’s likelihood of developing Alzheimer’s, even among those who don’t have memory and thinking problems associated with the disease. Especially intriguing is a small study that suggests it could someday be possible to detect Alzheimer’s-like changes in saliva, which is simple to obtain, easily transportable and has been successfully used in diagnosing a variety of diseases and conditions. Another study suggests positron emission tomography (PET) scans of brain inflammation could one day be used to detect the disease and track the impact of treatment.

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Physical exercise may be an effective treatment for Alzheimer’s disease and vascular dementia

We know that regular physical activity may reduce the risk of cognitive decline, Alzheimer’s disease and other dementias. Three new research studies reported at AAIC 2015 demonstrated the value of moderate to high intensity aerobic exercise for people with Alzheimer’s and other dementias, finding that this type of exercise may help them live better with the disease. One study of 200 people with Alzheimer’s age 50-90 showed that study participants who completed a 4-month high intensity aerobic exercise program had fewer psychiatric symptoms, such as anxiety, irritability and depression. Those who exercised hardest also had improvements on mental speed and attention. A second study of moderate-to-high intensity aerobic exercise in 65 sedentary adults 55-89 years old with mild cognitive impairment found that exercise may reduce levels of abnormal proteins in cerebrospinal fluid and increase blood flow in the brain's memory and processing centers. This aerobic exercise program appears to improve attention, planning and organizing abilities. Finally, a six-month study of 71 adults 56-96 years old with vascular cognitive impairment found that participating in a supervised aerobic exercise program was associated with improvements in memory and attention. These studies highlight the potential value of non-drug therapies for Alzheimer's and other dementias and remind us that research ought to adamantly pursue multiple approaches to Alzheimer’s therapy and prevention.

About AAIC

The Alzheimer’s Association International Conference (AAIC) is the world’s largest gathering of leading researchers from around the world focused on Alzheimer’s and other dementias. As a part of the Alzheimer’s Association’s research program, AAIC serves as a catalyst for generating new knowledge about dementia and fostering a vital, collegial research community.

AAIC 2015 home page: www.alz.org/aaic/
AAIC 2015 newsroom: www.alz.org/aaic/press.asp
A protein signature of Alzheimer’s could emerge as soon as early middle age, suggests a study led by Anne Fagan, Ph.D., Washington University School of Medicine, St. Louis. In the July 6 JAMA Neurology, Fagan and colleagues report longitudinal trends in cerebrospinal fluid (CSF) markers and brain amyloid in cognitively healthy volunteers. People as young as 45 had profiles that could portend dementia.

“We have learned a lot about AD pathogenesis by studying biomarkers in cross-sectional studies,” wrote Kaj Blennow, University of Gothenburg, Sweden. “The key in this study is the longitudinal data. Given that we might have anti-Aβ disease-modifying drugs in the near future, these findings are important.”

Previous cross-sectional studies have detected ups and downs in AD-related biomarkers—especially Aβ42 in the CSF and amyloid in the brain—when people are about 50 years old. These changes occur about 20 to 30 years before Alzheimer’s symptoms are apparent, but how early they begin has not been clearly determined. Longitudinal studies in familial AD suggest that CSF Aβ42 begins to fall as early as 25 years before onset in AD mutation carriers, and cerebral amyloid pathology begins to accumulate 15 years earlier. Fagan and colleagues wondered how far back in life those changes start for people at risk for late-onset disease. They also wondered at what age clear longitudinal changes in marker levels might emerge. That knowledge could help clinicians establish prevention trial selection criteria.

First author Courtney Sutphen and colleagues examined data from middle-aged enrollees in the Adult Children Study at WashU. Volunteers in this study have parents who had AD, and are considered at increased risk for dementia. All were cognitively healthy at baseline, though 61 carried at least one copy of the ApoE4 allele, a genetic risk factor for AD. Between January 2003 and November 2013, 169 of these participants gave a sample of cerebrospinal fluid (CSF) every three years. Some gave a total of two samples, others three or four. At each visit, a clinician assessed their clinical dementia rating (CDR). Serial positron emission tomography amyloid scans with Pittsburgh compound B (PiB-PET) were taken for 74 of the subjects. The researchers divided the volunteers into early (age 45 to 54), mid (55 to 64), and late (65 to 74) middle age bins for analysis.

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Using ELISA, Sutphen and colleagues determined whether CSF levels of Aβ40, Aβ42, total tau, and tau phosphorylated at position 181 (p-tau181) changed over time. They also examined two more recently proposed Alzheimer’s biomarkers: visinin-like protein 1 (VILIP-1), a marker of neuronal death, and chitinase-3-like protein 1 (YKL-40), which indicates gliosis and neuroinflammation.

In people whose biomarkers changed, the researchers saw a stereotypical progression. First, CSF Aβ dropped, sometimes as far back as early middle age. In mid middle age, people with lower CSF Aβ42 levels tested positive on PiB-PET scans. Then in mid to late middle age, total and p-tau181 crept up, along with VILIP-1. YKL-40 rose over time in all age groups. All of these biomarker changes were more pronounced, and occurred earlier, in people carrying one copy of the ApoE4 allele, and more so for those with two.

Fourteen people in the cohort scored 0.5 or higher on the CDR at some point in the study, indicating that their cognition had started to decline. Most of these people had low Aβ42 measurements from baseline and high total tau later on (see image below). The authors suggest that these biomarker changes foretell dementia, but write that they will need to follow these people further to test that hypothesis.

Sutphen pointed out that some of the youngest participants in this study already fell below the cutoff for Aβ42 positivity—1041 pg/mL—at baseline, implying that their CSF levels dropped at even younger ages. “It looks like we may need to go earlier than 45 to catch the very beginning of Aβ42 changes,” Sutphen told Alzforum. She also explained that the ultimate goal is to be able to predict who will develop dementia on an individual level to help decide who would benefit from anti-amyloid therapy. The authors noted that the CSF Aβ levels fall before PiB-PET scans become positive, meaning CSF levels could be an earlier biomarker for AD.

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Midlife CSF Crisis cont’d…….

The author made some other interesting observations. For example, total tau rose more slowly in late middle age than mid middle age in ApoE4 carriers (see image below). The authors interpreted this to mean that either neurodegeneration slows at older ages, after an initial phase of rapid neuronal die-off, or that something disrupts the normal pattern of secretion of these proteins in older age. Fagan reported that CSF tau eventually dropped in people enrolled in the DIAN study of familial AD, but those volunteers had symptomatic disease. Clifford Jack of the Mayo Clinic in Rochester, Minnesota, said that alternatively, the slower rise in tau in the older group could result from a cohort effect, whereby those in late middle age happened to be cognitively normal, have little neurodegeneration, and hence produce less CSF tau. They may just be biologically different from the people who started the study when they were 10 years younger, he said.

Pieter Jelle Visser, VU University Medical Center, the Netherlands, pointed out that overall the data support the idea that the ApoE4 allele has an impact on markers of neuronal injury as well as amyloid-related ones. He also agreed with the authors that the results relating these biomarker changes to dementia are preliminary, and require longer follow-up and more rigorous statistical analysis. —Gwyneth Dickey Zakaib

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For information on the following studies please visit:

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**NOBLE** A Study for People with Mild to Moderate Alzheimer’s Disease

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