MARY S. EASTON CENTER for Alzheimer's Research and Care at UCLA
DAVID GEFFEN SCHOOL OF MEDICINE AT UCLA

David Geffen School of Medicine

Spring 2023 Newsletter

The Mary S. Easton Center for Alzheimer's Research and Care at UCLA has very active teams working on basic research, drug discovery, biomarkers for early diagnosis and clinical activity including clinical trials, cognitive testing, and patient care.

Clinical Genetics Research at the UCLA Easton Center's Alzheimer's Disease Research Center

By: Ariadna Martinez, MS, CGC, Genetic Counselor

Through efforts taking place around the country and the world, including at the Mary S. Easton Center for Alzheimer's Research and Care at UCLA (Easton Center), scientists have begun to identify the various factors that contribute to the development of Alzheimer's disease (AD) and related conditions. These discoveries have enabled us to identify individuals at increased risk for AD, allowing for early diagnosis, and have paved the way for research aimed at identifying and developing preventive measures and treatments that one day could be tailored to each individual.

The term Alzheimer's disease includes different presentations of the condition that differ in terms of age of onset of symptoms and the presence of a family history of this condition. In the early form of Alzheimer's disease, also known as Early-Onset Alzheimer's Disease (EOAD), individuals tend to show symptoms in their '30s to '60s. Some of these patients have relatives in each generation with the condition and have a form of AD called familial AD. In the late 1980s, with the help of families that participated in research studies, scientists learned that the presence of a damaging genetic change (mutation) in one of three genes, amyloid precursor protein (APP), Presenilin 1 (PSEN1) and Presenilin 2 (PSEN2), was the cause of familial AD in the participating families. Research is currently taking place to identify potential genetic causes of other cases of familial AD and to develop potential treatments to restore the normal functions of the proteins made by these genes.

The most common form of Alzheimer's disease is known as Late-Onset Alzheimer's Disease (LOAD). LOAD tends to appear after the age of 65 years, with or without a family history of AD. A combination of environmental factors and likely many genetic risk factors contribute to the development of both EOAD and LOAD. The first discovery of these genetic risk factors was in the 1990s when scientists learned that individuals with a variant of the APOE gene, called e4, appeared to have an increased risk of developing

AD. As a risk factor for AD, the presence of the e4 version of APOE can contribute to a person's risk of developing LOAD but is insufficient to cause AD. Since then, scientists have identified several additional genetic risk factors for Alzheimer's disease and are working to understand how the presence of different combinations of these factors can translate into a personalized genetic risk for individuals to develop AD. Through some of the clinical trials for AD, scientists are also learning that genetic risk factors may help identify the safest and most efficient treatments for AD in an individualized way.

While getting to this point in the care of Alzheimer's disease may take some time, the work has already begun. These are exciting times at the Easton Center, where we are actively increasing our understanding of the role of the various genetic risk factors already discovered and that have yet to be discovered. In addition, the Easton Center prides itself in conducting inclusive genetic research studies to increase the representation of groups that have previously not been extensively studied, such as people identifying as Hispanic/Latinx, Black, and/or Asian. Several of our clinical research studies include a genetic component, via which we collect blood or saliva samples from participants to carry out comprehensive and state-of-the-art genetic testing and analysis, such as Whole Genome Sequencing (WGS).

Our research efforts also include learning about how to best incorporate the information we learn from genetic research studies into a person's medical care. As part of this effort, the Easton Center recently added me, a genetic counselor, to the team. Genetic counselors are healthcare providers with graduate degrees who undergo training in counseling, medical genetics, and research. Additionally, they specialize in assessing a person's risk of developing a medical condition that has a genetic component and helping people to understand genetic concepts and incorporate this information into their medical care. The role of the genetic counselor in the clinic is to help individuals understand their risk of developing Alzheimer's disease based on the currently available information and explore whether genetic testing for genes associated with AD would be a practical option. If individuals undergo genetic testing, the genetic counselor helps them understand the implications of the test result, their next steps, and available resources. In the research setting, the genetic counselor develops tools to collect genetic information and coordinates research genetic testing. The genetic counselor also meets with research participants to discuss the purpose of the genetic testing in the study and helps them understand the differences between genetic testing information collected through research studies versus clinical care. While we have not yet arrived at a time where we can call AD a condition of the past, by including clinical genetics in our research, our dedicated scientists and staff, with the help of study participants, are helping to get closer to that reality.

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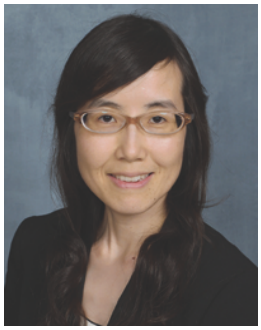
Dementia Brain Bank at the Easton Center




By: Shino Magaki, MD, PhD, Assistant Professor of Neuropathology, and Harry Vinters, MD, Distinguished Professor of Pathology and Laboratory Medicine (Emeritus)

Neuropathologic examination of the brain at autopsy remains the gold standard in diagnosing neurodegenerative diseases such as Alzheimer's disease (AD) despite the many advances in neuropsychological assessment tools and blood and neuroimaging biomarkers since AD was first described over a century ago. The pathogenesis of this uniquely human disease is still not well understood.[1]

At autopsy, the brain is first inspected with the naked eye for any gross abnormalities, such as narrowing of the gyri ("folds in the brain") and widening of the sulci indicating atrophy, the cerebral vessels for hardening or atherosclerotic plaques and for infarcts/haemorrhage (evidence of a "stroke"). If the post-mortem interval (time between death and brain removal) is short and tissue integrity intact, the majority of the brain is frozen for research purposes after sampling specific regions to examine under the microscope. Multiple regions of the brain that have been shown to demonstrate important pathologic changes in AD and other neurodegenerative diseases are dissected out and processed into formalin fixed paraffin embedded blocks. From these blocks, tissue sections mounted on slides are then stained with various methods and evaluated histopathologically. These include the hematoxylin & eosin (H&E) stain, the workhorse of histology, special stains that use chemicals to highlight cellular structures, and immunohistochemical stains using antibodies targeted against proteins relevant to neurodegenerative diseases. Prime examples of these proteins include β –amyloid, the major component of plaques, and tau, which comprises neurofibrillary tangles, both hallmarks of AD. There are often multiple disease processes evident in the brain, which adds layers of complexity to diagnosis and treatment. An individual may have AD but also have severe cerebrovascular disease. The majority of patients with Lewy body disease will also have some degree of AD pathology.

The dementia brain bank at the Easton Center for Alzheimer Disease Research and Care stores and distributes thousands of brain specimens that have undergone this extensive characterization. Many different laboratories at UCLA and other institutions have made important discoveries utilizing tissue from the brain bank. One current project is in collaboration with Timothy Chang, MD, PhD, and Ariadna Martinez, MS, CGC, from the Neurogenetics Core, and Keith Vossel, MD, MSc, Director of the Easton Center, and Kwaku Addo-Osafo, MSc, to examine the brains of centenarians, or individuals who were 100 years or above of age at death. Although the cohort is small, research on these individuals allows a unique opportunity to pathologically and genetically characterize the brains of individuals who live to a very old age. This will lead to a better understanding of how people age and how some may be more susceptible or resistant to dementia.[2] Another project is a multi-institutional study headed by Brittany Dugger, PhD, at UC Davis utilizing the many tissue sections produced in the course of histopathologic examination of dementia brain autopsies. Using a slide scanner, whole slide images are made from the physical slides which can then be examined remotely as well as digitally analysed (Figure 1). Slides from multiple institutions can be categorized to create a digital slide library for research, education and

training accessible to all sites. Furthermore, artificial intelligence is being used to automate and assist in image analysis.

These are a few of the many projects utilizing this tissue resource. It should be emphasized that all of this is only made possible by individuals and their families who have made the ultimate gift in participating in autopsy and brain donation. AD is a distinctly human disease. Although animal models allow for study of some components of the disease replicated in experimental animals, human autopsy tissue continues to be a unique and invaluable source of material that can be used to address the pathogenesis of this tragic ailment. Some autopsy-based studies—in individuals who have received innovative AD treatments—may even provide clues to why some therapies work, while others do not.

References:

1. Vinters HV. Emerging concepts in Alzheimer's disease. Annu Rev Pathol. 2015;10:291-319.
2. Sebastiani P, Federico A, Morris M, et al. Protein signatures of centenarians and their offspring suggest centenarians age slower than other humans. Aging Cell. 2021;20:e13290.

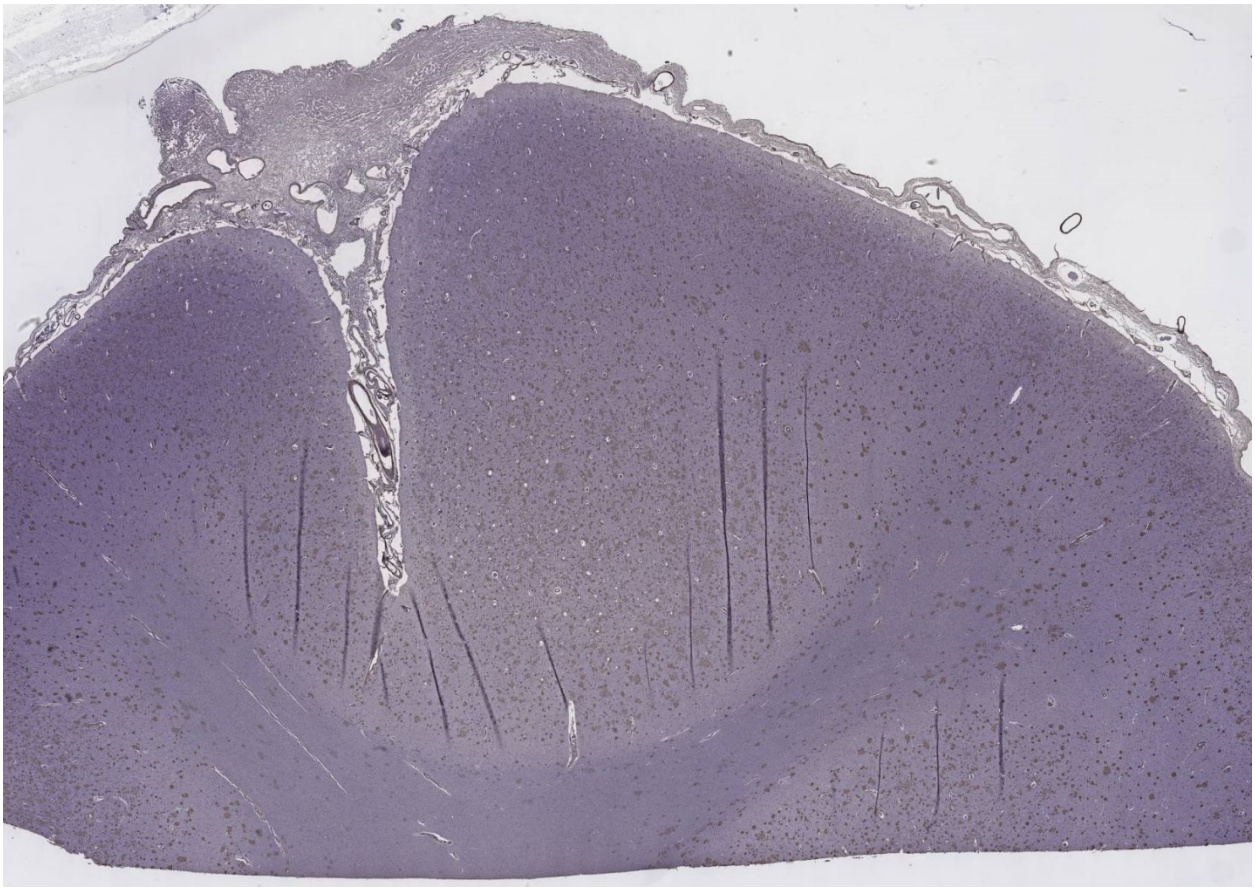


Figure 1. Whole slide image of an abeta42 immunostained frontal lobe from a patient with AD.

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New Additions to the Easton Center

Please join us in welcoming new staff members to the Easton Center.

Photo: Carlos Marroquin, MS, Clinical Research Coordinator, Katherine and Benjamin Kagan Alzheimer's Disease Treatment Development Program

Carlos received his Bachelor's degree in Human Biology and Master's degree in Global Medicine Management track from the University of Southern California in 2022. As an undergraduate student, he worked as a Research Assistant at the USC BRANCH (Brain Regulation of Appetite, Nutrition, Cognition, & Health) lab under the direction of Dr. Katie Page, investigating neural mechanisms for appetite response to high-reward foods. Carlos is excited to join the Kagan Clinical Trials Program at the UCLA Easton Center.

Photo: Gabriela Islas Huerta, Primary Care Champion for the Dementia Screening Project, ELHA Lab

Gabriela Islas Huerta graduated from UC Santa Barbara in 2021 with bachelor's degrees in Psychological and Brain Sciences and Sociology. After graduating, she worked full-time as a Behavior Interventionist for 360 Behavioral Health - California Psychcare. Since then, she has joined Dr. Mirella Diaz-Santos in The Equity for Latinx-Hispanic Healthy Aging Lab to serve as the Primary Care Champion for the Dementia Screening Project. Outside of work, she enjoys reading and traveling. Gabriela is excited to begin her contribution to Alzheimer's research in the ELHA Lab at the UCLA Easton Center.

Clinical Research Opportunities

If you would like to advance Alzheimer's disease research, please consider being a study participant. Below are the current recruiting trials. For a complete list of enrolling studies, visit our website at https://eastonad.ucla.edu/.

OBSERVATIONAL STUDIES:

- Alzheimer's Disease Neuroimaging Initiative 3 (ADNI3) Protocol
- Alzheimer's Disease Research Center - Biomarkers in Neurodegenerative Disease (ADRC-BIND)
- ARTFL-LEFFTDS Longitudinal Frontotemporal Lobar Degeneration (ALLFTD)
- Biomarkers for Vascular Contributions to Cognitive Impairment and Dementia (MarkVCID)
- Longitudinal Early-Onset Alzheimer's Disease Study (LEADS)
- Music Stimulation to Improve Cognition (MUSIC)
- National Institute on Aging Alzheimer's Disease Family Based Study (NIA-AD-FBS)

INTERVENTIONAL STUDIES:

- A Study of JNJ-63733657 in Participants with Early Alzheimer's Disease (Autonomy)
- A Research Study Investigating Semaglutide in People with Early Alzheimer's Disease (EVOKE and EVOKE Plus)
- SUVEN-502 Study

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For more information on our upcoming lectures and events, please visit the Easton Center Community Calendar.

Coping with Cognitive Challenges in Lewy Body Dementia

Date: Wednesday, May 17, 2023
Time: 11:00 AM – 12:15 PM (PDT)
Virtual Platform

Sponsored by the Lewy Body Dementia Association.
This webinar presentation will define the various changes to thinking that may present with Lewy body dementia. Practical suggestions will be highlighted to help cope with how these changes can impact daily life, including strategies for reading and navigating your home. This webinar is intended for our community of individuals, care partners, family members, and friends living with Lewy body dementia; however, we welcome professionals in our community to attend as well.

To register for this free event:
https://us02web.zoom.us/webinar/register/WN_WTUNTrggQk2am3EdxZOA7Q#/registration

For more information, please visit: https://www.lbda.org/event/coping-with-cognitive-challenges-in-lewy-body-dementia/

ONEgeneration 14th Annual Senior Symposium

Date: Saturday, May 20, 2023
Time: 9:00 AM – 12:00 PM (PDT)
Location: One Generation Adult Daycare
17400 Victory Blvd.
Van Nuys, CA 91406

The Mary S. Easton Center for Alzheimer's Disease Research and Care at UCLA is excited to be a part of the 14th annual ONEgeneration Senior Symposium. Easton Center representatives will be on-site with information regarding dementia care, clinical trials, and caregiver support.

Know Your Genes: How Family History Affects Brain Health

Date: Wednesday, June 7, 2023
Time: 3:00 PM – 4:00 PM (PDT)
Virtual Platform

Presenters: Kacie Deters, PhD, Assistant Professor in the Department of Integrative Biology UCLA, and Jessica Rexach, MD, PhD, Assistant Professor of Neurology UCLA.

Join Kensington Senior Living and the Mary S. Easton Center for Alzheimer's Research and Care at UCLA for this educational webinar on the role genetics play in neurodegenerative brain diseases.

To register for this free event:
https://us06web.zoom.us/webinar/register/WN_5sohTjrgQqSiKIplF1f9EA#/registration

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Update on Research

Date: Thursday, July 20, 2023
Time: 10:00 AM – 11:00 AM (PDT)
Location: Cerritos Senior Center at Pat Mixon Park (Community Center)
12340 South Street
Cerritos, CA 90701

Monica Moore, MSG Easton Center Community Health Program manager, will present about the latest findings related to the symptoms and causes of dementia and Alzheimer's disease. Learn about the latest treatments available and what research is currently being conducted to find a cure for this devastating disease.

Newsletter Editorial Team:
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California Alzheimer's Disease Center (CADC) Director: Timothy Chang, MD, PhD
Co-Directors of Training and Education Activities: Monica Moore, MSG and Mirella Díaz-Santos, PhD
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