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

David Geffen School of Medicine

Summer 2022

E-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.

Brief Screening Tool Helps Identify Patients with Dementia

By: Timothy Chang, MD, PhD, and Samantha Shah, BS

Asking older patients three quick questions may lead to earlier detection and timely diagnosis of cognitive decline. For people with dementia and their loved ones, taking early action to manage the challenges of the condition can lead to an improved quality of life. Yet many with dementia are not diagnosed until the later stages. Delay in the diagnosis may occur due to the stigma attached to Alzheimer's disease or people thinking cognitive decline is part of normal aging. Another reason is that primary care providers (PCPs) do not have enough time to ask about cognitive health. To address the latter issue, we have developed a brief dementia screening tool to help PCPs evaluate possible dementia in less than five minutes. This summer, it will be introduced at the UCLA Family Health Center in Santa Monica. The longer-term goal is to expand its use to all UCLA Health primary care clinics.

The screening tool was designed in order to be easy to use and seamlessly integrated into a patient's electronic health record. This will allow PCPs to access relevant information quickly when making clinical decisions and reference results over the years.

The questionnaire consists of three yes/no questions. They ask about changes in memory/thinking, language and mood/personality within the last five to ten years. Each question comes with examples of changes to prompt accurate responses. For instance, when asked about changes in memory/thinking, an example on having trouble recalling important events is included. The questionnaire has a version for the patient, and an additional one for an informant. The informant version is designed to be completed by someone who knows the patient well, such as a family member (Figure 1). Screening will be completed once a year in patients ages 60 and older at visits like an annual check-up.

Some patients with early cognitive issues might not believe or say they have noticed changes. Having input from an informant who knows the patient well can be very helpful. But because an informant is not always available, the PCP can also conduct a very short neuropsychological test called the Mini-Cog, which is available in English and Spanish. The Mini-Cog is already well-established in clinical use and can be administered quickly.

People who identify as Hispanic/Latinx and Black are 1.5 to 2 times more likely than their white counterparts to have dementia. Yet many are not diagnosed or not diagnosed until later in the disease. By that time, functional decline and caregiver burden may already be taking a heavy toll.

One aim of the new screening tool is to improve the detection of dementia in these underserved groups. UCLA Family Health Center serves a racially and ethnically diverse population, where about 20% of patients are Hispanic/Latinx. We have developed a version of the screening tool specifically for Hispanic/Latinx community members. The questionnaire was translated into Spanish and then adapted for Hispanic/Latinx culture to more accurately assess cognitive health.

Furthermore, inclusive dementia screening may give more underrepresented racial and ethnic patients a chance to participate in biomarker research. These are biological changes that may offer very early clues to dementia risk. In the past, such patients have been underrepresented in medical research.

A "yes" answer to a question (or a positive Mini-Cog score) cannot diagnose dementia alone. But it does inform the clinicians that further assessment is needed. The PCP can then choose to do additional workup or refer the patient to a specialist.

Timely diagnosis of dementia is important for patients and their caregivers. There are medications that can delay some symptom progression and there are also many drugs in clinical trials. Additionally, there is evidence that controlling conditions such as heart disease and high blood pressure can help delay the progression of certain types of dementia. This may give patients further encouragement to stay on top of their health.

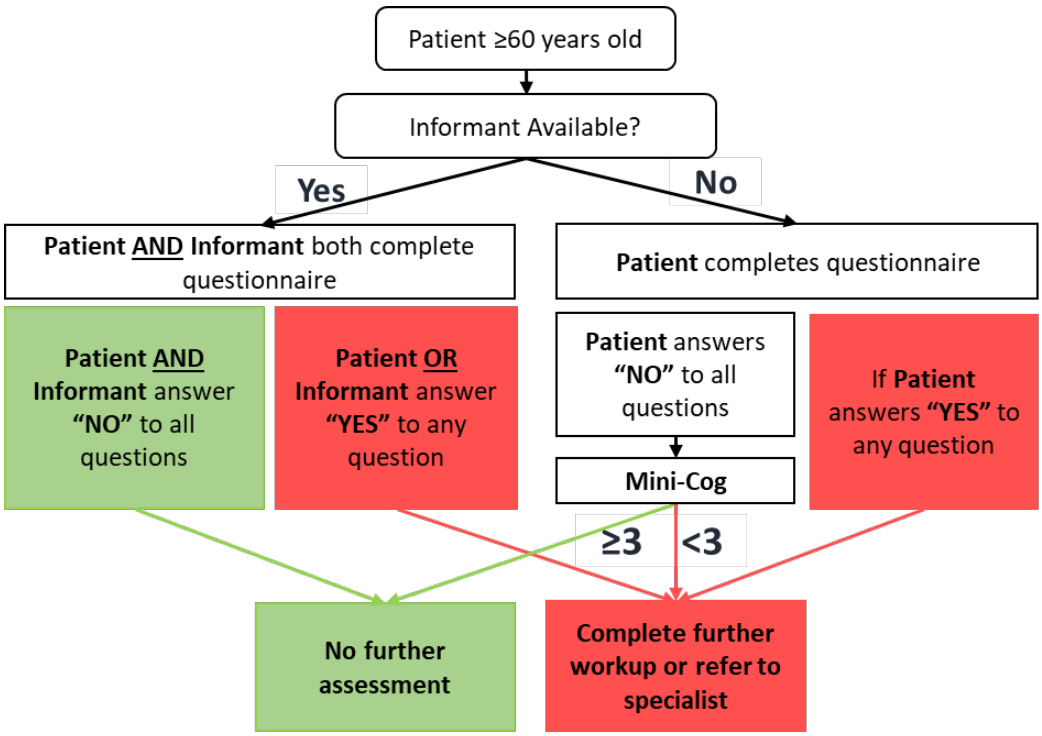

Figure 1. Flowchart of Dementia Screening Toolkit

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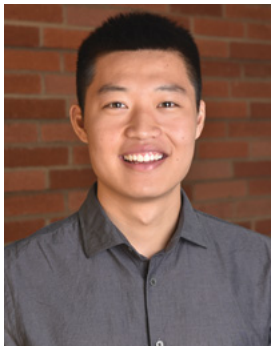
An Unexpected Discovery: TMEM106B Fibrils in Frontotemporal Lobar Degeneration



By: Yi Xiao (Sean) Jiang, Molecular Biology Institute PhD Candidate, David S. Eisenberg, HHMI Investigator, Paul D. Boyer Professor of Biochemistry and Molecular Biology

Frontotemporal lobar degeneration (FTLD) is the third most common dementia, following only Alzheimer's and Parkinson's diseases. FTLD causes young-onset dementia, typically affecting 45-64 year-olds. Clinically, FTLD presents with behavioral changes and regression in language ability. Pathologically, the majority of FTLD cases are defined by deposits in the post-mortem brain, containing TAR DNA-binding protein (TDP-43), thus termed FTLD-TDP.

Cryogenic-electron microscopy (cryo-EM) is a structural biology technique that allows for the imaging and visualization of macro-molecular particles. Cryo-EM has been instrumental in pushing our understanding of protein aggregates to the atomic level. In 2017, scientists extracted amyloid fibrils composed of the protein tau from Alzheimer's disease brains and determined their structures by cryo-EM. These structures provided insight into the molecular endpoint of disease and inspired development of structure-informed therapeutics that aim to prevent, delay, or reverse the aggregation of proteins in amyloid disorders.

We set out to investigate the amyloid fibrils accumulated in brains of FTLD-TDP patients. Collaborating with the Mayo Clinic Brain Bank, we obtained autopsied brains from patients neuropathologically confirmed as having FTLD-TDP. We used a mild detergent-based method to isolate amyloid fibrils from brain tissues, imaged them via cryo-EM, reconstructed their 3D shape, and built atomic models. Knowing the pathological definition of FTLD-TDP and the well-established propensity of TDP-43 proteins to form aggregates in the lab, we were expecting to observe fibrils made up of TDP-43. However, these amyloid fibrils were composed not of TDP-43, but rather of transmembrane protein 106B (TMEM106B), stunning both our team and fellow researchers in the field.

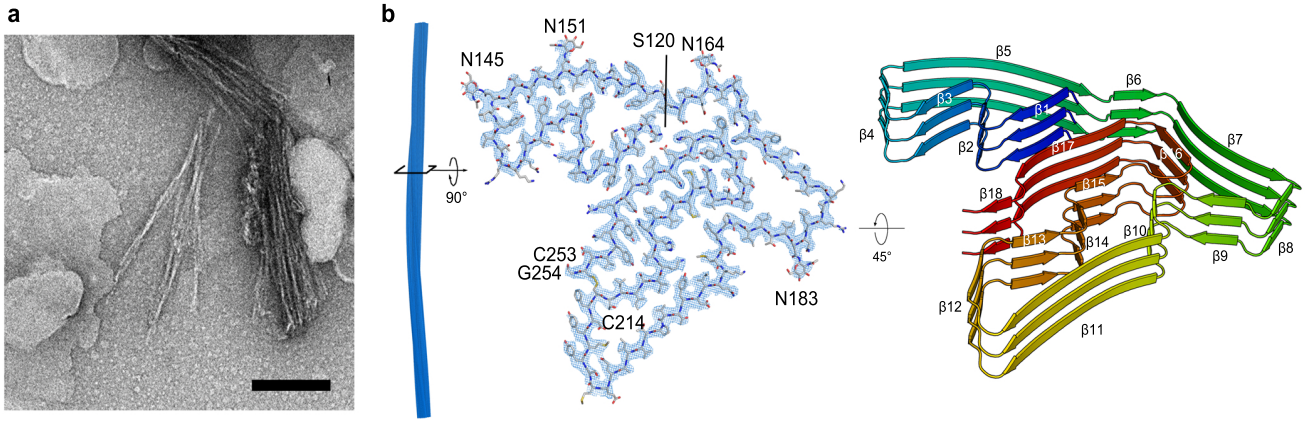


Figure 1. Structure of TMEM106B amyloid fibrils extracted from FTLD-TDP patient brains determined by cryo-EM. a) Negative stain transmission electron microscopy micrograph of TMEM106B fibrils extracted from FTLD-TDP patient using mild detergent-based protocol. Scale bar 200 nm. b) Cryo-EM map and atomic model of TMEM106B fibrils composed of TMEM106B luminal fragment Ser120 to Gly254 (left). Glycosylated asparagines (N145, N151, N164, N183) and cysteines forming disulfide bond (C214, C253) are labeled. Cartoon model of the conserved protofilament fold of TMEM106B fibrils features 18 β-strands (right).

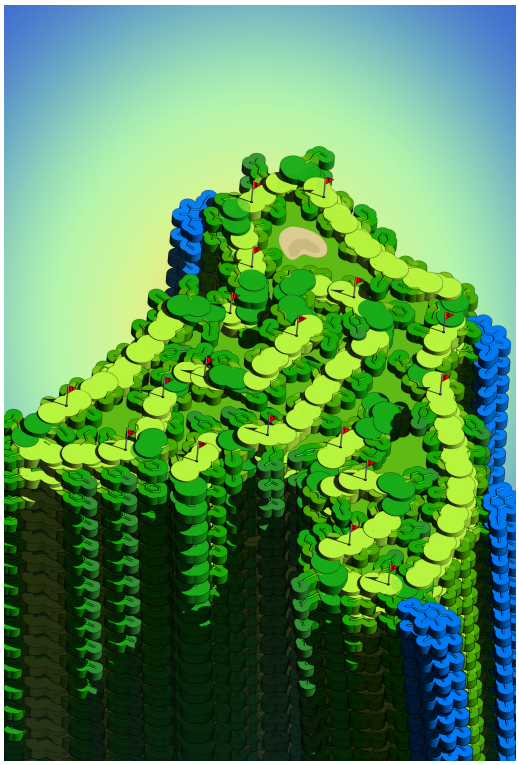


Figure 2. The golf-course-like fold of TMEM106B fibrils from FTLD-TDP.

We performed cryo-EM study on four FTLD-TDP patients (of four different subtypes, A through D). In all four cases, we observed that copies of TMEM106B fragments stack on top of each other to form rod-like "protofilaments", which can either be single or twisting pairs (Figure 1). The fibrils share a conserved arrangement, featuring 18 β-strands of varying length and curvature which we've named a "golf-course-like fold" (Figure 2).

TMEM106B was previously identified as a genetic risk factor for FTLD-TDP, however its connection to disease had been unclear and it was not suspected to form amyloid fibrils. TMEM106B is a protein that spans the membrane surfaces of lysosomes, which are acidic trash disposal systems in cells. We've learned that one end of this protein, called the C-terminal luminal domain, undergoes cleavage by an unknown enzyme before forming fibrils, reminiscent of the aggregation pathway of amyloid-β peptide in Alzheimer's disease. Clues gathered from the structure suggest that the acidic environment of the lysosome may favor fibril formation, but many questions about the mechanism of TMEM106B aggregation, spread, and disease contributions remain to be answered.

First, are TMEM106B fibrils causative of disease, or are they inconsequential by-products ancillary or unrelated to the main disease pathway? If TMEM106B fibrils cause disease, that could arise from either a gain- or loss-of-function toxicity. TMEM106B is normally involved in endo-lysosomal regulation and trafficking; its function could be compromised by fibril formation and lead to problems in removing other abnormal proteins. Second, what is the effect of TMEM106B aggregation on TDP-43? We did not observe fibrillar TDP-43, however shapeless TDP-43 aggregates were co-purified in the detergent-insoluble samples. There may be cross-reactivity between the two proteins, such as one inducing the aggregation of the other. TDP-43 plays an essential role in RNA metabolism, and its aggregation could be a driver of FTLD-TDP disease.

Our discovery introduces TMEM106B as a new player in neurodegeneration and raises intriguing questions to be addressed in future research. Read more about our findings in Nature.

Figure 3. Dr. David Eisenberg (back row, 3rd from left) with his talented laboratory team.

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New Addition to the Easton Center

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

Photo: Vishnu Shandilya, PhD, Postdoctoral Researcher, Vossel Lab

Dr. Vishnu Shandilya is a Postdoctoral Researcher in Dr. Keith Vossel's lab. He did his Ph.D. at University of Hyderabad, where his behavioral and molecular neuroscience work was on the synaptic plasticity gene Arc and memory. He is excited to contribute to the Alzheimer's disease research in the Vossel Lab and Easton Center.

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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 www.eastonad.ucla.edu.

OBSERVATIONAL STUDIES:

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

INTERVENTIONAL STUDY:

- Autonomy Study

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

Update on Alzheimer's Disease Research

Date: Monday, July 11, 2022
Time: 10:30 AM – 12:00 PM (PDT)
Virtual Forum

In partnership with OPICA Adult Day and Counseling Services.
Monica Moore, MSG, Community Health Program Manager will discuss latest findings related to the symptoms and causes of dementia and Alzheimer's disease as well as research related to risk reduction. She will also discuss the latest treatments available and what research is being currently conducted to find a cure for this devastating disease.

Registration required: https://uclahs.zoom.us/meeting/register/tJ0pcu-grjktHtaOsajTjmdqKovVB0KipSUv
for more information, please email **Monica Moore** mrmoore@mednet.ucla.edu or **Pam Schwimmer** Pam@opica.org.

Update on Alzheimer's Disease Research

Date: Wednesday, July 13, 2022
Time: 10:00 AM - 11:30 AM (PDT)
Location: Cerritos Senior Center
12340 South Street
Cerritos, CA 90701

Monica Moore, MSG, Community Health Program Manager will discuss latest findings related to the symptoms and causes of dementia and Alzheimer's disease as well as research related to risk reduction. She will also discuss the latest treatments available and what research is being currently conducted to find a cure for this devastating disease.

To RSVP or for more information, please send an email to **Efren Moreno** emoreno@alzla.org.

Beyond Alzheimer's: The Other Types of Dementia

Date: Monday, August 8, 2022
Time: 10:30 AM - 11:30 AM (PDT)
Virtual Forum

In partnership with OPICA Adult Day and Counseling Services.
While Alzheimer's Disease is the most common form of dementia, it is not the only kind. This presentation will discuss other forms of dementia, such as Vascular Dementia, Dementia with Lewy Bodies, and Frontotemporal Dementia, and how they differ from Alzheimer's in progression, treatment, and diagnosis.

Registration required: https://uclahs.zoom.us/meeting/register/tJ0pcu-grjktHtaOsajTjmdqKovVB0KipSUv
for more information, please email **Monica Moore** mrmoore@mednet.ucla.edu or **Pam Schwimmer** Pam@opica.org.

Senior Briefing & Health Fair by the Office of Congresswoman Nanette Diaz Barragán (CA-44)

Date: Tuesday, August 23, 2022
Time: 9:00 AM - 2:00 PM (PDT)
Location: Carson Community Center
801 E. Carson Street
Carson, CA 90745

Dr. Mirella Díaz-Santos and her ELHA Lab partnered with Office of Congresswoman Nanette Diaz Barragán (CA-44) to engage her constituents in conversations about brain health, healthy aging, Alzheimer's disease, and research participation in ADRD clinical studies. Engagement materials will be offered in both English and Spanish.

***The event also includes free lunch to the attendees.**
For more information about the event or to RSVP, please call **Congresswoman Nanette Diaz Barragán office** at **310-831-1799**. For more information about ELHA's Lab educational program, please contact **Stephanie Ovalle Eliseo** at SOvalle@mednet.ucla.edu.

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