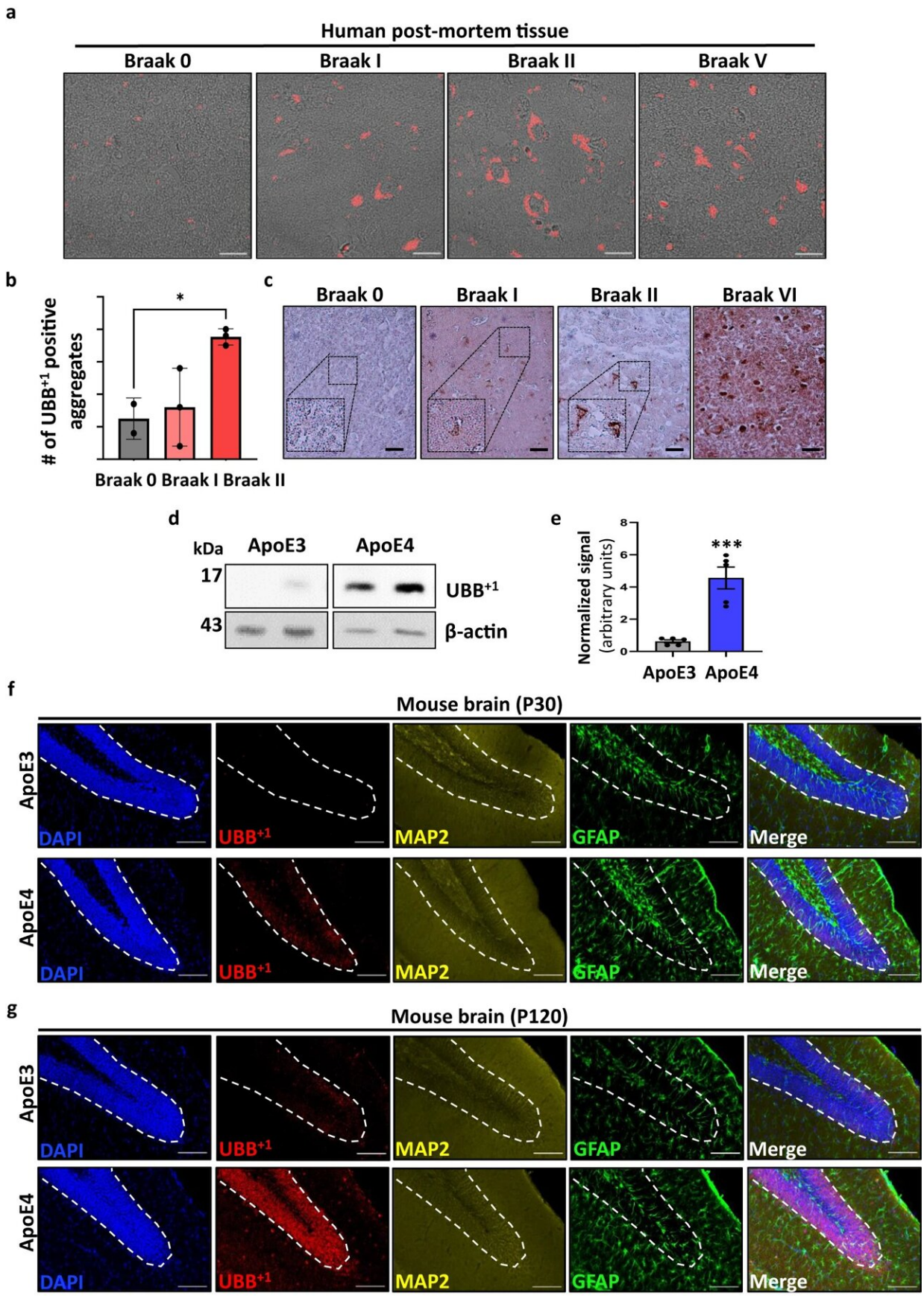
Protein experts show altered ubiquitin signaling induces hallmarks of sporadic Alzheimer's disease

October 3 2023


a
Human post-mortem tissue
Braak 0
Braak I
Braak II
Braak V
b
# of UBB+1 positive aggregates
*
Braak 0 Braak I Braak II
c
Braak 0
Braak I
Braak II
Braak VI
d
kDa
ApoE3
ApoE4
17
43
UBB+1
β-actin
e
Normalized signal (arbitrary units)
***
ApoE3 ApoE4
f
Mouse brain (P30)
ApoE3
ApoE4
DAPI
UBB+1
MAP2
GFAP
Merge
g
Mouse brain (P120)
ApoE3
ApoE4
DAPI
UBB+1
MAP2
GFAP
Merge

UBB^{+1} accumulates in the early stages of AD postmortem tissue. **a** Immunofluorescence staining of human tissue (ER = hippocampal complex, including entorhinal cortex) with an antibody against UBB^{+1} (red). **b** Quantification of UBB^{+1}-positive aggregates counted in different biological samples taken from dentate gyrus (DG) of patients diagnosed at different Braak stages [n = 3 biologically independent samples] (Supplementary information Table 1) (p = 0.038). **c** Immunohistochemistry staining of human postmortem tissue (ER) with anti-UBB^{+1}. **d** Representative immunoblots of proteins isolated from the hippocampus of Apolipoprotein E (ApoE3/4)-TR mice using an anti-UBB^{+1} antibody. **e** Quantification of (**d**) by densitometry and normalized to β-actin [n = 5 mice] (p = 0.00042) **f**, **g** Immunofluorescence staining of hippocampal sections of one (**f**) and 4-month-old (**g**) ApoE (ApoE3/4)-TR mice, showing UBB^{+1} is specifically expressed in neurons (MAP2) and not glial cells (GFAP). *P*-values were determined by unpaired two-tailed Student's *t*-test. Error bars represent ± s.d. Images are representative of three independent wells. All experiments were repeated at least twice. Scale bars: 20 μm (**a**), 50 μm (**c**), 100 μm (**f**, **g**). Credit: *Nature Communications* (2023). DOI: 10.1038/s41467-023-41545-7

New discoveries in the development of Alzheimer's disease in a study led by Professor Michael Glickman and Dr. Inbal Maniv from the Faculty of Biology at the Technion were published in *Nature Communications*.

Alzheimer's disease was named after the German researcher Dr. Alois Alzheimer, who first described it in 1906. The disease is characterized by the degeneration and death of nerve cells, processes that lead to a progressive impairment of cognitive abilities. It occurs typically in adults over the age of 65, but a small percentage of all Alzheimer's patients are hereditary cases that affect younger patients.

Today, Alzheimer's disease is commonly divided into two types—familial and sporadic. Familial Alzheimer's disease is a rare condition, caused by genetic mutations. By contrast, the underlying mechanism of the more prevalent sporadic Alzheimer's disease is unclear and was the focus of the study conducted by Dr. Maniv and Professor Glickman.

Toxic proteins accumulate in the brains of Alzheimer's patients. The mechanism of accumulation in familial patients is clear because there is an obvious link between the known mutations and the proteins that accumulate. In sporadic Alzheimer's disease, on the other hand, the trigger for protein accumulation is unknown.

As protein experts, Prof. Glickman's research group proposed that the accumulation of toxic proteins in the brain is due to a disruption in the protein clearance mechanism, also known as the ubiquitin-proteasome system. To test their hypothesis, the group established a model system of human neurons, that allowed them to examine the involvement of the ubiquitin system in the development of the disease.

In the published article, they describe their results: damage to the ubiquitin system leads to the accumulation of toxic proteins even in healthy tissue, mimicking the typical Alzheimer's pathology.

To assess the importance of their findings, the researchers went on to engineer an RNA molecule that specifically silences one of the components of the ubiquitin system. Treatment with this molecule ameliorated the pathology in their experimental model. The team proposes that this RNA molecule could serve as a prototype for the development of effective treatments.

The past few years have seen major advancements in the packaging and delivery of bio-active RNA molecules as therapies. With proper

modifications and packaging, the interference RNA targeting the component that the team has identified could yield promising results in a clinical setting. This discovery highlights the importance of the ubiquitin system in clearing defective proteins to maintain the cells' health. Disruption in this system could lead to the development of the disease.

The Technion researchers believe that beyond the findings presented in the article, the platform they developed may be used to screen drugs for the treatment and prevention of sporadic Alzheimer's disease. They add that this platform will help reduce animal experiments in the development of new Alzheimer's therapies.

More information: Inbal Maniv et al, Altered ubiquitin signaling induces Alzheimer's disease-like hallmarks in a three-dimensional human neural cell culture model, *Nature Communications* (2023). DOI: 10.1038/s41467-023-41545-7

Provided by Technion - Israel Institute of Technology