Age-related dementia may begin with neurons' inability to dispose of unwanted proteins

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A team of European scientists from the University Medical Center Hamburg-Eppendorf (UKE) and the Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD) at the University of Cologne in Germany has taken an important step closer to understanding the root cause of age-related dementia. In research involving both worms and mice, they have found that age-related dementia is likely the result of a declining ability of neurons to dispose of unwanted aggregated proteins. As protein disposal becomes significantly less efficient with increasing age, the buildup of these unwanted proteins ultimately leads to the development and progression of dementia. This research appears in the March 2013 issue of the journal *Genetics*.

"By studying disease progression in dementia, specifically by focusing on mechanisms neurons use to dispose of unwanted proteins, we show how these are interconnected and how these mechanisms deteriorate over time," said Markus Glatzel, M.D., a researcher involved in the work from the Institute of Neuropathology at UKE in Hamburg, Germany. "This gives us a better understanding as to why dementias affect older persons; the ultimate aim is to use these insights to devise novel therapies to restore the full capacity of protein disposal in aged neurons."

To make this discovery, scientists carried out their experiments in both worm and mouse models that had a genetically-determined dementia in

which the disease was caused by protein accumulation in neurons. In the worm model, researchers in the lab of Thorsten Hoppe, Ph.D., from the CECAD Cluster of Excellence could inactivate distinct routes used for the disposal of the unwanted proteins. Results provided valuable insight into the mechanisms that neurons use to cope with protein accumulation. These pathways were then assessed in young and aged mice. This study provides an explanation of why dementias exponentially increase with age. Additionally, neuron protein disposal methods may offer a therapeutic target for the development of drugs to treat and/or prevent dementias.

"This is an exciting study that helps us understand what's going wrong at a cellular level in age-related dementias," said Mark Johnston, Ph.D., Editor-in-Chief of the journal *Genetics*. "This research holds possibilities for future identification of substances that can prevent, stop, or reverse this cellular malfunction in humans."

More information: Schipanski, Angela, Sascha Lange, Alexandra Segref, Aljona Gutschmidt, David A. Lomas, Elena Miranda, Michaela Schweizer, Thorsten Hoppe, and Markus Glatzel A Novel Interaction between Aging and ER Overload in a Protein Conformational Dementia *Genetics* March 2013, 193: 865-876.

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