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Alzheimer's patients show striking individual differences in molecular basis of disease

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Alzheimer's disease is thought to be caused by the buildup of abnormal, thread-like protein deposits in the brain, but little is known about the molecular structures of these so-called beta-amyloid fibrils. A study published by Cell Press September 12th in the journal *Cell* has revealed that distinct molecular structures of beta-amyloid fibrils may predominate in the brains of Alzheimer's patients with different clinical histories and degrees of brain damage. The findings pave the way for new patient-specific strategies to improve diagnosis and treatment of this common and debilitating disease.

"This work represents the first detailed characterization of the molecular structures of beta-amyloid fibrils that develop in the brains of patients with Alzheimer's disease," says senior study author Robert Tycko of the National Institutes of Health. "This detailed structural model may be used to guide the development of chemical compounds that bind to these fibrils with high specificity for purposes of diagnostic imaging, as well as compounds that inhibit fibril formation for purposes of prevention or therapy."

Tycko and his team had previously noticed that beta-amyloid fibrils grown in a dish have different molecular structures, depending on the specific growth conditions. Based on this observation, they suspected that fibrils found in the brains of patients with Alzheimer's disease are also variable and that these structural variations might relate to each patient's clinical history. But it has not been possible to directly study the structures of fibrils found in patients because of their low abundance in

the brain.

To overcome this hurdle, Tycko and his collaborators developed a new experimental protocol. They extracted beta-amyloid fibril fragments from the brain tissue of two patients with different clinical histories and degrees of brain damage and then used these fragments to grow a large quantity of fibrils in a dish. They found that a single fibril structure prevailed in the brain tissue of each patient, but the molecular structures were different between the two patients.

"This may mean that fibrils in a given patient appear first at a single site in the brain, then spread to other locations while retaining the identical molecular structure," Tycko says. "Our study also shows that certain fibril structures may be more likely than others to cause Alzheimer's disease, highlighting the importance of developing imaging agents that target specific fibril structures to improve the reliability and specificity of diagnosis."

More information: *Cell*, Lu et al.: "Molecular structure of beta -amyloid fibrils in Alzheimer's disease brain tissue." dx.doi.org/10.1016/j.cell.2013.08.035

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