Researchers identify potential biomarker for AD

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Researchers from Boston University School of Medicine (BUSM) report variants in a new gene, PLXNA4, which may increase the risk of developing Alzheimer's disease (AD). The discovery of this novel genetic association may lead to new drug treatment options that target PLXNA4 specifically. These findings appear in the *Annals of Neurology*.

AD is the most frequent age-related dementia affecting 5.4 million Americans including 13 percent of people age 65 and older, and more than 40 percent of people age 85 and older. Genetic factors account for much of the risk for developing AD with heritability estimates between 60 percent and 80 percent. However much of the genetic basis for the disease is unexplained. Less than 50 percent of the genetic contribution to AD is supported by known common genetic variations.

Using data from the Framingham Heart Study, the researchers obtained strong evidence of an association with several single nucleotide polymorphism in PLXNA4, a gene which had not been previously linked to AD. They then confirmed this finding in a larger dataset from the Alzheimer's Disease Genetics Consortium and other datasets. Next, they performed a series of experiments in models that pinpointed the mechanism by which this gene affects AD risk. "Importantly, this is one of few single studies which go from gene finding to mechanism," explained corresponding author Lindsay Farrer, PhD, Chief of Biomedical Genetics and professor of medicine, neurology, ophthalmology, epidemiology and biostatistics at BUSM.

According to the researchers a form of the protein encoded by this gene promotes formation of neurofibrillary tangles consisting of decomposed tau protein, one of the two pathological hallmarks of the disease. "We showed that PLXNA4 affects the processing of tau as it relates to neurofibrillary tangles, the primary marker of AD. Most drugs that have been developed or that are in development for treating AD are intended to reduce the toxic form of beta-amyloid, a sticky substance that accumulates in the brain of persons with AD, and none have been very effective. Only a few drugs have targeted the tau pathway," added Farrer.

Provided by Boston University Medical Center