Deciphering brain somatic mutations associated with Alzheimer's disease

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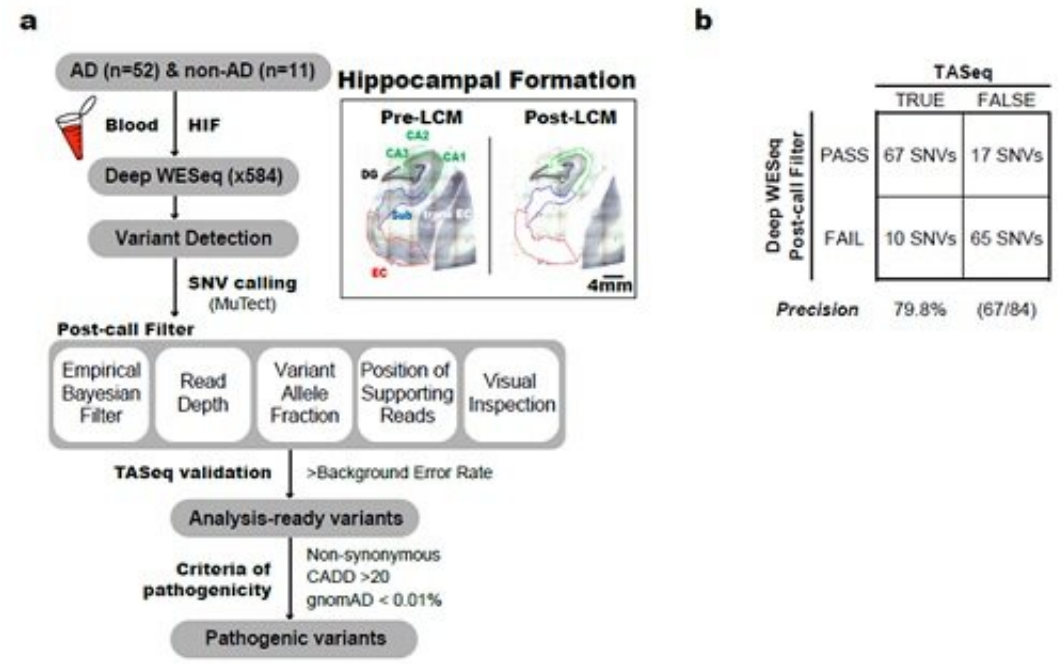


Bioinformatic pipeline for detecting low-level brain somatic mutations in AD and non-AD. Credit: KAIST

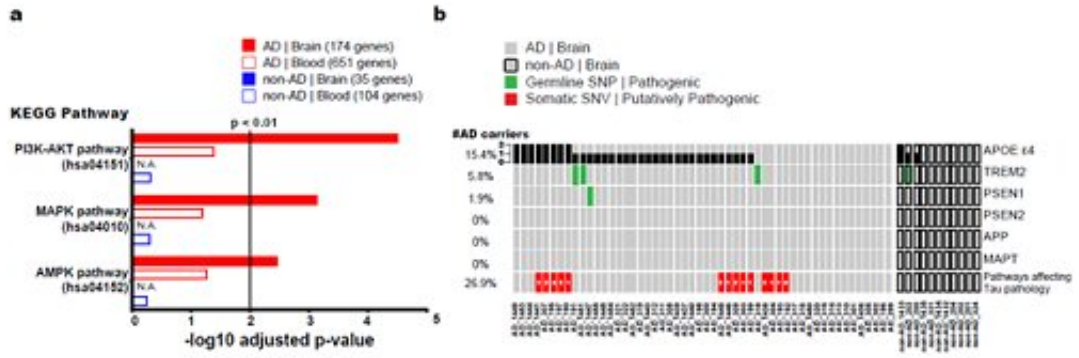
Researchers have identified somatic mutations in the brain that could contribute to the development of Alzheimer's disease (AD). Their findings were published in the journal *Nature Communications* last week.

Decades worth of research has identified inherited mutations that lead to early-onset familial AD. Inherited mutations, however, are behind at

most half the cases of late onset sporadic AD, in which there is no family history of the disease. But the genetic factors causing the other half of these sporadic cases have been unclear.

Professor Jeong Ho Lee at the KAIST Graduate School of Medical Science and Engineering and colleagues analysed the DNA present in post-mortem hippocampal formations and in blood samples from people aged 70 to 96 with AD and age-matched controls. They specifically looked for non-inherited somatic mutations in their brains using high-depth whole exome sequencing.

The team developed a bioinformatics pipeline that enabled them to detect low-level brain somatic single nucleotide variations (SNVs)—mutations that involve the substitution of a single nucleotide with another nucleotide. Brain somatic SNVs have been reported on and accumulate throughout our lives and can sometimes be associated with a range of neurological diseases.



Pathogenic brain somatic mutations associated with tau phosphorylation are significantly enriched in AD brains. Credit: KAIST

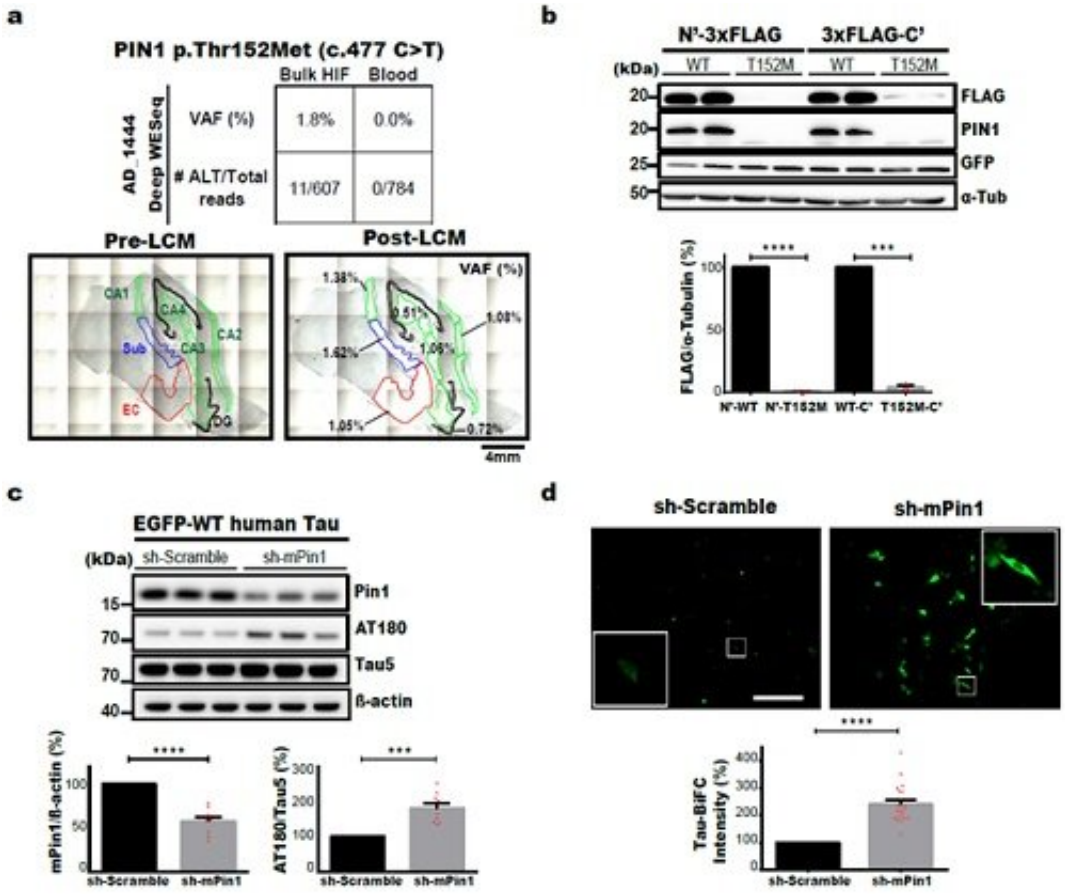
The number of somatic SNVs did not differ between individuals with

AD and non-demented controls. Interestingly, somatic SNVs in AD brains arise about 4.8 times more slowly than in blood. When the team performed gene-set enrichment tests, 26.9 percent of the AD brain samples had pathogenic brain somatic SNVs known to be linked to hyperphosphorylation of tau proteins, which is one of major hallmarks of AD.

Then, they pinpointed a pathogenic SNV in the PIN1 gene, a cis/trans isomerase that balances phosphorylation in tau proteins, found in one AD patient's brain. They found the mutation was 4.9 time more abundant in AT8-positive neurons, a marker for hyper-phosphorylated tau proteins, in the entorhinal cortex than the bulk hippocampal tissue. Furthermore, in a series of functional assays, they observed the mutation causing a loss of function in PIN1 and such haploinsufficiency increased the phosphorylation and aggregation of tau proteins.

"Our study provides new insights into the molecular genetic factors behind Alzheimer's disease and other neurodegenerative diseases potentially linked to somatic mutations in the brain," said Professor Lee.

The team is planning to expand their study to a larger cohort in order to establish stronger links between these brain somatic mutations and the pathogenesis of Alzheimer's disease.



A pathogenic brain somatic mutation in PIN1 (c. 477 C>T) is a loss-of-function and related functional assays show its haploinsufficiency increases phosphorylation and aggregation of tau. Credit: KAIST

More information: Jun Sung Park et al, Brain somatic mutations observed in Alzheimer's disease associated with aging and dysregulation of tau phosphorylation, *Nature Communications* (2019). DOI: 10.1038/s41467-019-11000-7

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