



NEURODEGENERATIVE DISEASE

A new mouse model to study late-onset Alzheimer's disease

Baglietto-Vargas, D. et al. *Nat. Commun.* **12**, 2421 (2021)

Most mouse models of Alzheimer's disease (AD) consist of transgenic mice that overexpress human genes associated with familial AD, an early-onset form of the disease caused by rare and fully penetrant mutations in the genes *APP*, *PSEN-1* and *PSEN-2*. The *PD-APP* transgenic mouse, which overexpresses human amyloid precursor protein (*APP* 717V→F), was the first APP-based model to reproduce amyloid β -peptide ($A\beta$) pathology in the form of amyloid plaques in mice; since then researchers have created and characterized more than 170 genetically modified mouse models containing AD-linked mutations.

Although these mice have provided valuable insights into disease mechanisms, early-onset AD accounts for less than 5% of AD cases and new mouse models that mimic the late-onset progression seen in sporadic human AD, the most common form of the disease, are needed.

In a new study published in *Nature Communications*, a team of investigators

led by Frank M. LaFerla from University of California, Irvine generated a new mouse model in which they substituted the mouse $A\beta$ peptide for its human counterpart (h $A\beta$). The mice, which carry no familial AD mutation and develop age-dependent behavioral and phenotypic alterations, might represent an important step towards modeling late-onset AD.

The investigators used a knock-in (KI) strategy to humanize the murine *App* gene by changing 3 amino acids within the sequence of the $A\beta$ peptide, a product of APP processing. In these mice, h $A\beta$ -KI allele is integrated in the *App* locus, under the control of endogenous gene-regulatory elements; therefore humanized *App* is expressed at murine physiological levels. "These results are significant because APP is not overexpressed in human sporadic AD, and the h $A\beta$ -KI mouse model recapitulates this salient feature," explain the investigators in their report.

Detailed phenotypic characterization of the mice showed that substitution of

mouse $A\beta$ with the wild-type human isoform was sufficient to produce significant changes in cognition, synaptic plasticity, inflammation, OC+/PAS granule formation and gene expression in h $A\beta$ -KI mice. These changes were associated with an age-associated increase in insoluble $A\beta$ and decrease in soluble $A\beta$ in the brain of the mice. However, the investigators could not detect amyloid aggregates in h $A\beta$ -KI brains, which suggests that additional factors are required for the formation of amyloid plaques.

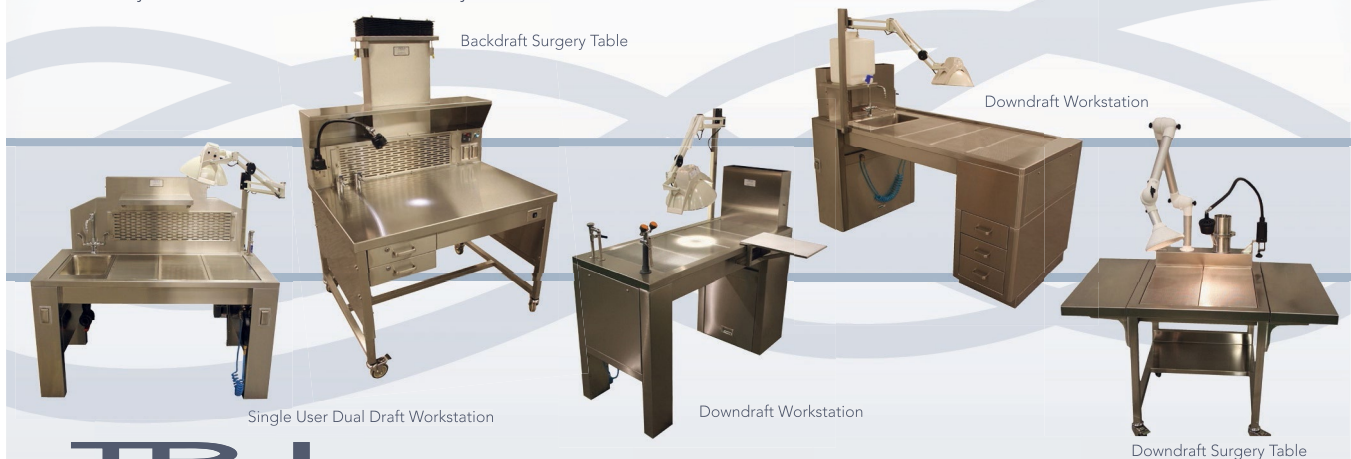
The investigators conclude that the h $A\beta$ -KI mouse line will be a useful platform to investigate the many genetic, aging, and environmental factors that drive the development of AD and lead to formation of plaques.

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