A second X chromosome contributes to resilience in a mouse model of Alzheimer's disease

Emily J. Davis, Lauren Broestl, Samira Abdulai-Saiku, Kurtresha Worden, Luke W. Bonham, Elena Miñones-Moyano, Arturo J. Moreno, Dan Wang, Kevin Chang, Gina Williams, Bayardo I. Garay|, Iryna Lobach, Nino Devidze, Daniel Kim, Cliff Anderson-Bergman, Gui-Qiu Yu, Charles C. White, Julie A. Harris, Bruce L. Miller, David A. Bennett, Arthur P. Arnold, Phil L. De Jager, Jorge J. Palop, Barbara Panning, Jennifer S. Yokoyama, Lennart Mucke, Dena B. Dubal

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Major sex differences are observed in Alzheimer's disease (AD). Men typically have more age-related cognitive deficits and die earlier than women from AD. Using mouse models expressing the human amyloid precursor protein to model AD and varying the sex chromosome and gonadal sex independently, Dubal and colleagues found that the presence of two X chromosomes delayed cognitive defects and mortality. The hypothesized mechanism was elevated expression in XX compared to XY cells of genes that escape X chromosome inactivation. Dubal et al. determined that the expression of the X escape gene Kdm6a is higher in XX compared to XY mouse neuronal nuclei, and in the temporal cortex of women with AD compared to men with AD. Importantly, increasing Kdm6a expression in the hippocampus in XY male mice to levels typically seen in XX female mice led to improved performance in learning/memory tasks. Finally, genetic variation in KDM6A was associated with increased expression levels and less cognitive decline in aging and precnical AD in humans. These findings suggest that XX chromosome complement and corresponding increased KDM6A levels reduces vulnerability of females compared to males for age-related neurodegeneration and mortality in AD.