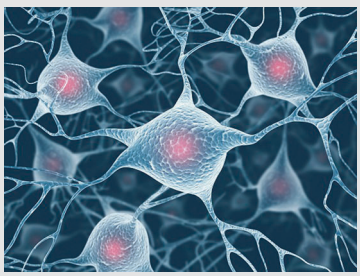
NEWS

Promising gene therapy for Krabbe disease



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Globoid cell leukodystrophy (GLD), also known as Krabbe disease, is a progressive neurodegenerative disorder that in its most severe form leads to compromised myelination, paralysis, and death by 2 years of age. Variants in the *GALC* gene, which encodes galactosylceramidase, a catabolic enzyme critical to normal myelin turnover, underlie the condition. Currently, the sole treatment—hematopoietic stem cell transplantation—is generally indicated only for presymptomatic patients, has high procedure-related morbidity, and is not a cure. In a recent article published in *The Journal of Clinical Investigation* (https://doi.org/10.1172/JCI133953), Bradbury and colleagues report effective treatment of GLD in a naturally occurring canine model. A missense variant in canine *GALC* leads to tremors and pelvic limb paralysis in GLD dogs, symptoms that mirror GLD in humans. The researchers administered a single intrathecal injection of either a high or low dose of adeno-associated virus serotype 9 (AAV9) encoding canine *GALC* (AAV9-cGALC) to presymptomatic 2-week-old or postsymptomatic 6-week-old GLD dogs. All GLD dogs also received prednisone. Untreated GLD dogs reached endpoint disease, defined as pelvic limb paralysis, between 11 and 16 weeks of age. In contrast, presymptomatic GLD dogs that received high-dose AAV9-cGALC remain neurologically normal and are still under evaluation at 1.5 to 2.5 years of age. Postsymptomatic dogs treated with low-dose AAV9-cGALC suffered pelvic limb paralysis and endpoint disease between 14 and 32 weeks of age, while high-dose treatment in postsymptomatic GLD dogs further extended survival. Magnetic resonance imaging scans of untreated GLD dogs showed changes consistent with myelin loss and brain atrophy. However, the brains of GLD dogs that received high-dose AAV9-cGALC at 2 weeks old appeared similar to those of normal dogs. This was not the case for presymptomatic dogs given low-dose treatment or postsymptomatically treated GLD dogs. Hematoxylin and eosin staining revealed that globoid cell accumulation—the hallmark GLD pathology—was widespread throughout white matter in untreated dogs. However, GLD dogs treated presymptomatically with high-dose AAV9-cGALC showed globoid cell accumulation only in the centrum semiovale, the pathological origin of GLD, and in the corona radiata in one of four dogs. Demyelination was also isolated to these regions in this cohort. Altogether, the results indicate that high-dose presymptomatic treatment significantly improved neurological outcomes while high-dose postsymptomatic treatment delayed disease progression. The authors conclude that high-dose AAV9-GALC gene therapy warrants translation to the clinic. —*V. L. Dengler, News Editor*

X chromosome bolsters against Alzheimer disease in a mouse model

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Men with Alzheimer disease (AD) suffer greater cognitive deficits and die younger than do women with AD, indicating that males, defined as individuals harboring an XY complement, are disadvantaged against the disorder. In a recently reported study in *Science Translational Medicine* (https://stm.sciencemag.org/content/12/558/eaaz5677), Davis and colleagues show that X chromosome dosage may modulate AD disease vulnerability in a mouse model. To assess the effects of sex chromosomes in AD, the researchers generated XX and XY mice with either ovarian or testicular development by transposing the *Sry* gene onto an autosome. They then crossed these mice with mice expressing human amyloid precursor protein (hAPP) to yield four sex genotypes with or without hAPP. After sexual maturation, the mice were gonadectomized to recapitulate human reproductive aging and their survival and cognition were assessed. XX-hAPP mice of either gonadal phenotype outlived all XY-hAPP mice, although XY-hAPP mice that retained *Sry* survived longer than XY-hAPP mice that did not. In a test of learning, all nontransgenic mice performed similarly well, while male and female XY-hAPP mice did more poorly than male or female XX-hAPP mice. XY-hAPP mice also fared worse in tests of memory retention and fear memory than XX-hAPP mice. To determine whether the lack of the second X chromosome or the presence of the Y chromosome disadvantaged XY-hAPP mice, the researchers generated mice with genotypes comparable to XX and XO mice with ovaries and XY and XXY mice with testes. After crossing with hAPP mice, the researchers found that mice with one X chromosome (XY-hAPP and XO-hAPP) died younger and exhibited poorer memory than mice with two X chromosomes (XX-hAPP and XXY-hAPP). To investigate how a second X chromosome may confer resilience against AD-related deficits, the team probed a role for *KDM6A*, an X chromosome–encoded demethylase that escapes X inactivation and leads to cognitive decline in humans with loss-of-function variants. Protein and messenger RNA (mRNA) analysis revealed that hippocampal *KDM6A* expression was significantly higher in mice with two X chromosomes regardless of gonadal phenotype or hAPP status. When the researchers overexpressed *KDM6A* in XY-hAPP mice, the animals displayed marked improvements in learning and memory compared with XY-hAPP control mice. The researchers conclude that a second X chromosome may facilitate cognitive resilience against AD in both sexes. —*V. L. Dengler, News Editor*

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