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Pig model of Huntington's offers advantages for testing treatments

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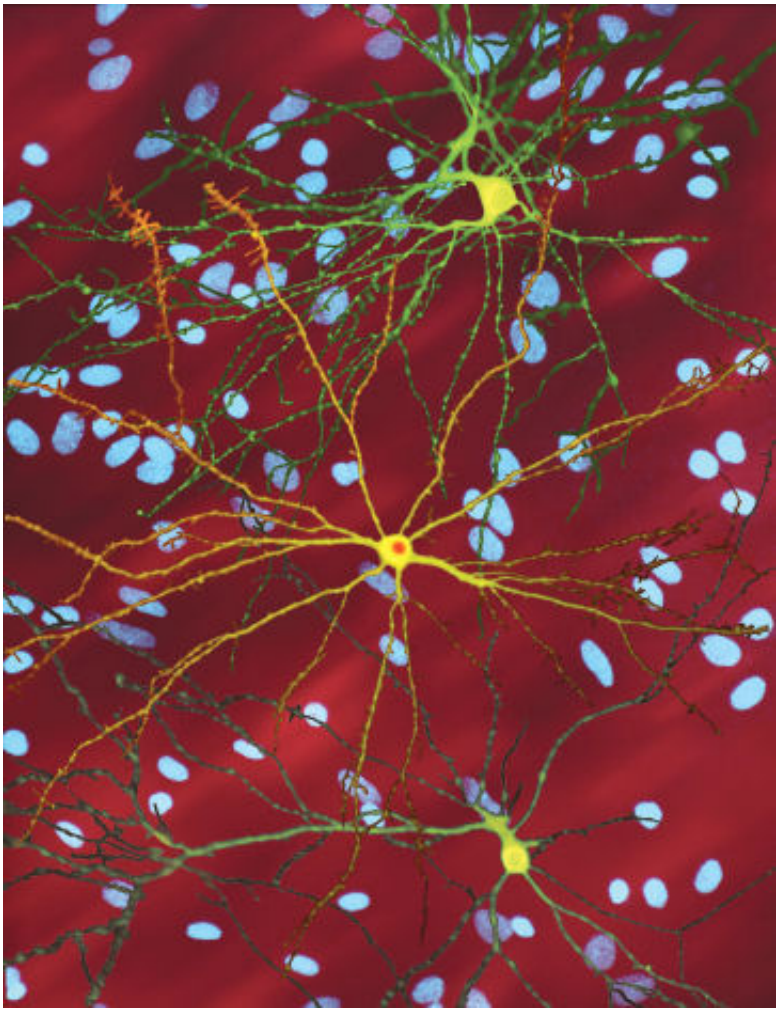

A montage of three images of single striatal neurons transfected with a disease-associated version of huntingtin, the protein that causes Huntington's disease. Nuclei of untransfected neurons are seen in the background (blue). The neuron in the center (yellow) contains an abnormal intracellular accumulation of huntingtin called an inclusion body (orange). Credit: Wikipedia/ Creative

Using genetic engineering technology, a team of scientists has established a pig model of Huntington's disease (HD), an inherited neurodegenerative disease. The researchers anticipate that the pigs could be a practical way to test treatments for HD, which is caused by a gene encoding a toxic protein that causes brain cells to die.

The research is scheduled for publication in *Cell* on March 29th.

Although genetically modified mice have been used widely to model neurodegenerative diseases, they lack the typical neurodegeneration or overt neuronal loss seen in human brains, says corresponding author Xiao-Jiang Li, MD, PhD, distinguished professor of human genetics at Emory University School of Medicine.

The pig HD model is an example that suggests large animal models could better model other neurodegenerative diseases, such as Alzheimer's, Parkinson's and ALS (amyotrophic lateral sclerosis), he says. A HD pig could be an opportunity to test if CRISPR-Cas9 gene editing can work in larger animals before clinical applications in humans.

In comparison with mice, delivery of treatments to affected nervous system tissues can be better tested in pigs, because their size is closer to that of humans. The pig model of HD also more closely matches the symptoms of the human disease. Compared with non-human primate models, the pigs offer advantages of faster breeding and larger litter sizes, the researchers say.

The pig model of HD was established by researchers at Emory University School of Medicine, together with colleagues at Jinan

University and Chinese Academy of Sciences in Guangzhou.

"We think the pig model will fill an important gap," says co-senior author Shihua Li, M.D, professor of human genetics at Emory University School of Medicine. "In pigs, the pattern of neurodegeneration is almost the same as in humans, and there have been several treatments tested in mouse models that didn't translate to human."

Shihua and Xiao-Jiang Li jointly run a lab at Emory, which collaborated with Liangxue Lai, PhD, associate director of the South China Institute of Stem Cells and Regeneration Medicine, Chinese Academy of Sciences. The lead author of the paper is Sen Yan at Jinan University's Guangdong-Hongkong-Macau Institute of CNS Regeneration. Yan was trained in the Li Lab as a visiting PhD student at Emory. The pigs are housed in Guangzhou.

Symptoms displayed by the genetically altered pigs include movement problems. They show respiratory difficulties, which resemble those experienced by humans with HD and are not seen in mouse models of HD. In addition, the pigs show degeneration of the striatum, the region of the brain most affected by HD in humans, more than other regions of the brain.

Huntington's disease is caused by a gene encoding a toxic protein (mutant huntingtin or mHTT). mHTT contains abnormally long repeats of a single amino acid, glutamine. Symptoms commonly appear in mid-life and include uncontrolled movements, mood swings and cognitive decline.

Researchers used the CRISPR/Cas9 gene editing technique to introduce a segment of a human gene causing Huntington's, with a very long glutamine repeat region, into pig fibroblast cells. Then somatic cell

nuclear transfer generated pig embryos carrying this genetic alteration. The alteration is referred to a "knock in" because the changed gene is in its natural context.

Last year, the Li lab published a paper in *Journal of Clinical Investigation* showing that CRISPR-Cas9 gene editing, delivered by viral vector, can reverse signs of HD in a mouse model. Working with Liangxue Lai, the Li lab has generated transgenic—not "knock-in"—pigs that are models for HD. The Li lab also collaborated with Anthony Chan, DVM, PhD at Yerkes National Primate Research Center to generate a transgenic HD monkey model.

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