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Modified pigs as new experimental platform to test ALS gene and cell therapies

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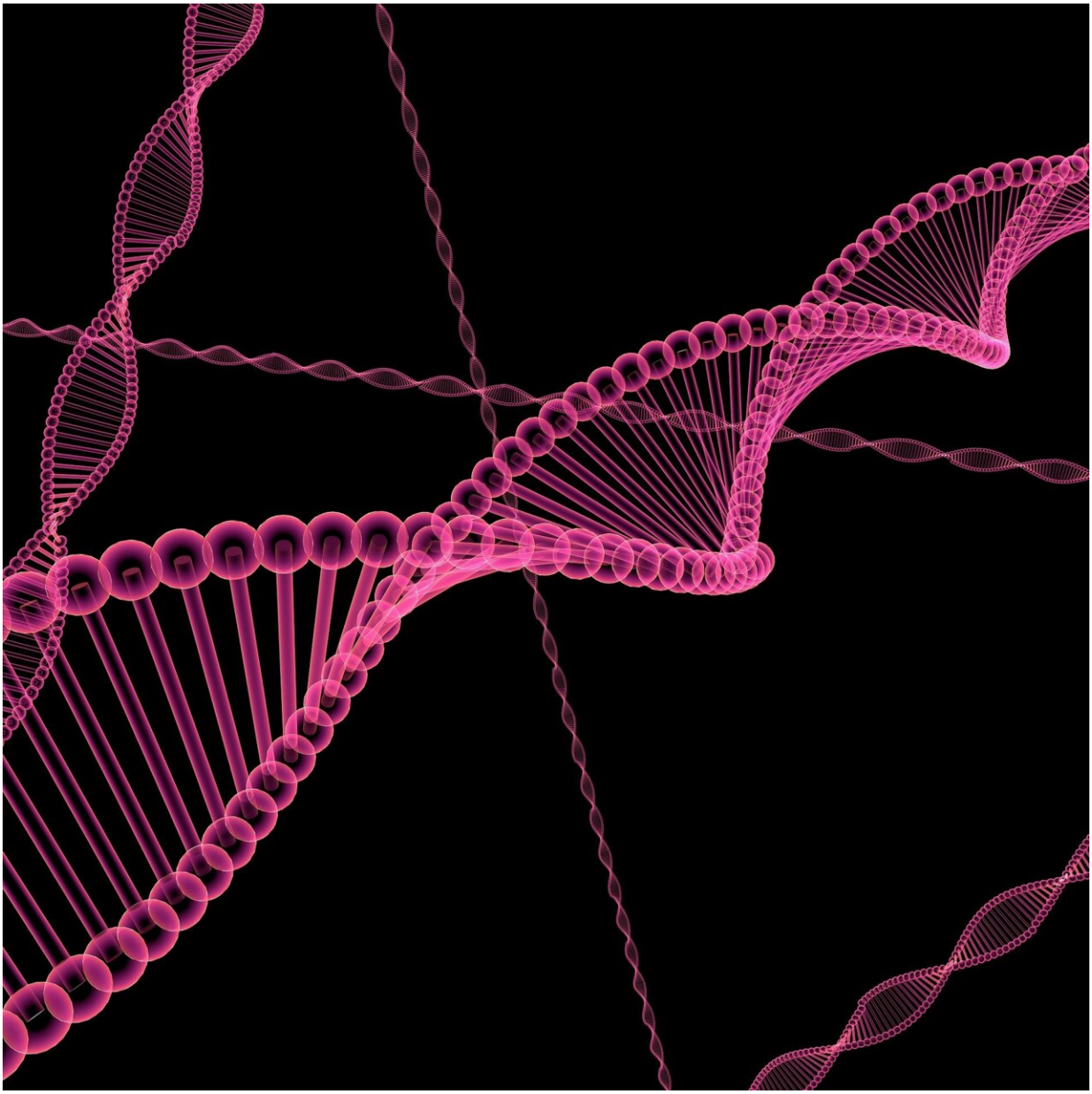

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A research team led by Professor Haruhisa Inoue of CiRA and Professor Hiroshi Nagashima of Meiji University has created a new porcine ALS model by introducing the human superoxide dismutase 1 (SOD1) gene with a mutation associated with familial ALS into the pig genome.

ALS is a neurodegenerative disease that predominantly affects motor neurons and causes limb paralysis and bulbar palsy, often culminating in death due to dysphagia or respiratory paralysis. More than 30 ALS-associated genes have been reported to date. Among them, SOD1 was identified as the most common causative gene of familial ALS in 1993 and the overexpression of mutant human SOD1 proteins in animal models such as mice and rats has been demonstrated to cause ALS-like symptoms, including motor neuron degeneration and shortened life span.

However, the relatively tiny bodies of rodents make them less suitable for the testing of gene and cell therapies required prior to human clinical trials. Thus, a new animal model that more closely resembles human anatomy—in particular, the size and structure—was necessary.

In order to address this problem, the scientists decided to model the devastating disease in pigs. The team generated a porcine model of ALS by expressing the disease-causing human SOD1 G93A mutant protein in pigs using the endogenous human SOD1 gene promoter.

Similar to observations made from human patient samples, they found accumulations of the misfolded SOD1 protein and severe axonal degeneration within the spinal cord and nerve roots of the porcine ALS model. This new animal model with anatomical characteristics more comparable to humans, especially in the spinal cord, provides a much

improved platform for developing gene and cell therapies against ALS.

The results of this study were published online in *Laboratory Investigation* on January 11, 2023.

More information: Takayuki Kondo et al, A Transgenic Pig Model With Human Mutant SOD1 Exhibits the Early Pathology of Amyotrophic Lateral Sclerosis, *Laboratory Investigation* (2023). DOI: 10.1016/j.labinv.2022.100013

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