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Huntington's disease monkeys display progressive clinical changes and neurodegeneration

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Transgenic Huntington's disease monkeys show similarity to humans with Huntington's in their progressive neurodegeneration and decline of motor control, scientists from Yerkes National Primate Research Center, Emory University, report.

These findings are promising for developing a preclinical, large animal model of Huntington's disease for assessing new therapeutics, which could ultimately provide better treatment options, including altering the course of the disease.

In this first multiyear study on a transgenic nonhuman primate model for Huntington's, lead author Anthony Chan, DVM, PhD, engineered monkeys to develop a slower and more gradual form of the neurodegenerative disease. Chan says, "It was important to recapitulate progressive changes in clinical measurements, such as cognitive behaviors and neural anatomical changes as the Huntington's disease monkeys age. Our finding of similarity in clinical progression between human patients and Huntington's disease monkeys suggests monkeys could become a preclinical, large animal model for the development of new treatments." Chan is associate professor of human genetics at Emory University School of Medicine and a researcher at the Yerkes National Primate Research Center.

The findings are scheduled for online publication in *PLOS ONE* on May

12, 2015.

Although mouse models of Huntington's exist, it is difficult for researchers to study certain aspects of the disease. A nonhuman primate model could eliminate the current gap and allow researchers to better study aspects of fine motor control and cognition in a nervous system that is structurally similar to humans'.

Another potential, says Chan, is "the promise a nonhuman primate model holds for developing treatments that could alter the course of Huntington's disease. Right now, we can address the symptoms of the disease, but we want to do more. A nonhuman primate model should be able to help us better help others."

With support from the Yerkes Research Center and the Office of Research Infrastructure Programs at the National Institutes of Health, Chan and colleagues are establishing a Transgenic Huntington's Disease Monkey Resource to facilitate preclinical research, consisting of a breeding colony, a biomaterial repository and a sperm bank. This resource will be the first of its kind and will be a prototype for other transgenic primate research programs with rhesus monkeys and marmosets.

Huntington's is an inherited disease caused by a gene encoding a toxic protein (mutant huntingtin) that causes brain cells to die. Symptoms commonly appear in the 30s or 40s and include uncontrolled movements, balance problems, mood swings and cognitive decline. There is also a juvenile form of Huntington's disease, which can occur during the teenage years.

In the *PLOS ONE* paper, Chan and colleagues describe how three male rhesus macaques they studied displayed cognitive and motor impairments emerging at 16 months of age, and dystonia and signs of

neurodegeneration on brain imaging at 24 months of age. Rhesus macaques normally go through puberty around 3-5 years of age and can live for 25 or 30 years. Studying these symptoms earlier in the animal model gives researchers more time to monitor the progression of the disease as well as assess the efficacy of potential therapeutics and to determine if and when the course of the disease could be altered.

These three monkeys carried a gene encoding a fragment of mutant human huntingtin. The researchers introduced this extra gene, designed to be regulated in a way that is similar to normal huntingtin genes, by injecting rhesus macaque oocytes with a viral vector.

Beginning at 8 months of age, the researchers tested the animals in an "object retrieval detour task" (retrieval of an M&M candy from a transparent box that is open on one side) and a fine motor task (freeing a Life Saver candy by moving it along a bent metal rod), both well-established tests for cognitive and fine motor control in nonhuman primates. The researchers also used viewed the monkeys' brains via magnetic resonance imaging (MRI), which revealed progressive degeneration of the striatum, a region of the brain known to be affected in humans with Huntington's.

More information: *PLOS ONE*, journals.plos.org/plosone/arti … journal.pone.0122335

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