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Huntington's disease monkeys display full spectrum of symptoms seen in humans

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Transgenic Huntington's disease monkeys display a full spectrum of symptoms resembling the human disease, ranging from motor problems and neurodegeneration to emotional dysregulation and immune system changes, scientists at Yerkes National Primate Research Center, Emory University report.

The results, published online in the journal *Brain, Behavior and Immunity*, strengthen the case that transgenic Huntington's disease monkeys could be used to evaluate emerging treatments (such as this) before launching human clinical trials.

"Identifying emotional and immune symptoms in the HD monkeys, along with previous studies demonstrating their cognitive deficits and fine motor problems, suggest the HD monkey model embodies the full array of symptoms similar to human patients with the disease," says Yerkes research associate Jessica Raper, PhD, lead author of the paper.

In humans, Huntington's is an inherited disease caused by a gene encoding a toxic protein, called mutant huntingtin, which causes brain cells to die. Symptoms commonly emerge in adulthood and include uncontrolled movements, balance problems, mood swings and cognitive decline. Humans with Huntington's disease often display emotional dysregulation (anxiety/irritability) and immune system changes years before the onset of overt motor symptoms.

In a nonhuman primate model geneticist Anthony Chan DVM, PhD, and

his colleagues at Yerkes developed, rhesus macaques carry a gene encoding a fragment of mutant human huntingtin. These monkeys begin to display dystonia and fine motor impairment at two and three years of age, respectively. A multiyear study of the monkeys was published in 2015 in *PLOS One*.

In the *Brain, Behavior and Immunity* paper, Raper, Chan and colleagues describe their investigation of emotional and immune symptoms in two transgenic Huntington's disease monkeys, which were five years old.

The team exposed the monkeys to an acute stressor of an unfamiliar human's presence. The task is designed to detect the animals' ability to shift their behavior based on the level of threat present, Raper explains. No threat is the animal alone in the room, mild threat is the human in the room avoiding eye contact, and high threat is the human making direct eye contact with the animal.

Huntington's monkeys displayed "species typical" hostility during the high threat condition, yet displayed increased hostile behaviors during no threat and mild threat conditions compared to controls. This behavioral profile is akin to increased irritability. Huntington's patients often display irritability prior to motor symptoms, and irritability is rated among the top 10 symptoms that interfere with daily functioning among patients and caregivers, according to a survey published in *PLOS Currents* (2011).

"Before our work in rhesus monkeys, it has not been possible to detect or observe some of these symptoms in other HD animal models, especially emotional dysregulation," says senior author Chan, associate professor of human genetics at Yerkes National Primate Research Center and Emory University School of Medicine. "This will strengthen preclinical investigations of treatments in the HD monkeys."

Huntington's monkeys also show levels of inflammatory markers (cytokines and inflammatory pathway genes) in their blood that is greater than in controls. Hyperactivity of the innate immune system has been identified as a potential therapeutic target for HD.

The authors note this paper examines only two Huntington's monkeys, and that these experiments were not able to establish whether the emotional and immune changes appear before motor symptoms, as is the case in humans with Huntington's disease.

"Future studies will follow the emotional behavior development from infancy to adulthood in a new generation of HD monkeys to confirm whether increased anxiety and irritability is the result of brain or motor behavior changes," the authors write.

More information: Jessica Raper et al, Increased irritability, anxiety, and immune reactivity in transgenic Huntington's disease monkeys, *Brain, Behavior, and Immunity* (2016). DOI: 10.1016/j.bbi.2016.07.004

Anthony W. S. Chan et al. Progressive Cognitive Deficit, Motor Impairment and Striatal Pathology in a Transgenic Huntington Disease Monkey Model from Infancy to Adulthood, *PLOS ONE* (2015). DOI: 10.1371/journal.pone.0122335

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