

# UCSF transgenic mouse mimics Parkinson's earliest symptoms

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UCSF researchers have created the first transgenic mouse to display the earliest signs of Parkinson's disease using the genetic mutation that is known to accompany human forms of the disease.

The mouse model, which expresses the same mutant proteins as human Parkinson's patients, also displays early signs of constipation and other gastrointestinal problems that are a common harbinger of the disease in humans.

As a result, researchers say, these animals could serve as a means of investigating therapies for reversing the neurological dysfunction of the disease at its earliest stages.

The findings are featured as the cover story in the May 1, 2010 issue of the journal, *Human Molecular Genetics* and are available [online](#).

Researchers have long suspected that the neurological component of Parkinson's, which causes tremors and stiffness among other symptoms, is actually a late-stage effect of a larger, systemic problem, according to UCSF geneticist Robert L. Nussbaum, MD, who was senior author on the paper.

"This new model validates that theory by mimicking what we know to be the genetic pathway leading to Parkinson's, while also displaying the earliest symptoms that occur in humans," said Nussbaum, who is the Holly Smith Distinguished Professor in Medicine and chief of the UCSF

Division of Medical Genetics. "This will give us an important tool in identifying an early intervention for this devastating disease."

[Parkinson's disease](#) is the second most common neurodegenerative disease after Alzheimer's, affecting 1.5 percent of adults over 55 years of age, and is typically characterized by motor disorders such as tremors, rigidity and postural instability.

Several non-motor abnormalities also frequently accompany Parkinson's, including depression, [sleep disorders](#) and gastrointestinal dysfunction, the researchers explained. Gastrointestinal dysfunction is a particularly common symptom, seen in 80 to 90 percent of patients, and often precedes the motor-control symptoms by 10 to 15 years.

The UCSF [mouse model](#) is the first to display the full gastrointestinal symptoms as well, and is consistent with the progression of the disease in humans.

Nussbaum, in collaboration with former colleague Mihael Polymeropoulos, MD, had previously identified the first Mendelian-inherited form of Parkinson's, which involves a mutation in the gene that produces alpha-synuclein proteins. Since then, he has been studying the rare, inherited forms of the disease to better understand the pathways and processes that may be involved in the more common, sporadic forms, and to create mouse models of the disease that can help in developing therapies.

The current model, based on that research, is significant in having the same genetic mutation that causes alpha-synuclein to misfold in an inherited form of Parkinson's, causing the proteins to stick together to form insoluble fibrils in the nerve cells. Those clumps, known as Lewy bodies, are often associated with Parkinson's, as well as with some other forms of dementia and multiple system atrophy.

Previous mouse models of the disease had relied on an over-expression of alpha-synuclein caused by a combination of human and mouse genes, according to the paper. The UCSF team created two new lines that only express the human form of the protein, with each line expressing one of two mutant forms that occur in human Parkinson's patients, according to lead author Yien-Ming Kuo, PhD, in the UCSF Institute for Human Genetics.

In these lines, gastrointestinal dysfunction could be seen at three months of age, reached its highest severity at six months and persisted until 18 months, which follows the human course of the disease in sporadic Parkinson's, according to the paper. That dysfunction occurred before there was any evidence of loss of smell and also before any evidence arose of pathological changes in the brain stem.

"This suggests that, at least in mice with the human proteins, these gastrointestinal symptoms are an intrinsic defect caused by the mutant protein, rather than being caused by abnormalities in brain function," Kuo said. "That knowledge could eventually help us test for the disease long before it starts to cause neurodegenerative problems and prevent them from occurring."

Provided by University of California - San Francisco

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