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New 'mouse models' give insight to gene mutation that is potential cause of Parkinson's disease

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Using new one-of-a-kind "mouse models" that promise to have a significant impact on future Parkinson's disease research, Mount Sinai School of Medicine researchers are among the first to discover how mutations in a gene called LRRK2 may cause inherited (or "familial") Parkinson's disease, the most common form of the disease. The study, published in *The Journal of Neuroscience,* is the first in vivo evidence that LRRK2 regulates dopamine transmission and controls motor performance, and that the mutation of LRRK2 eliminates the normal function of LRRK2, leading to Parkinson's disease.

Even though it was clear that LRRK2 played a role in causing Parkinson's, scientists had not been able to fully pursue the discovery of the gene mutation due to lack of a suitable animal model with abnormal forms of the gene. By using the new mouse model, Zhenyu Yue, PhD, Associate Professor of Neurology and Neuroscience, and his colleagues at Mount Sinai School of Medicine demonstrated that these mice capture a key feature of Parkinson's disease—age-dependent reduction of neurotransmitter dopamine—which is believed to cause motor function deficits in humans such as tremors, rigidity, and involuntary movement over time.

"While the mice are not at the stage where they experience the typical symptoms of Parkinson's, like tremors or reduced movement, we are able to study the potential root cause of the disease in these mice," said

Dr. Yue. "Importantly, as we have developed assays that allow us to measure the enzymatic activity of LRRK2 in the brain, the mouse models provide valuable tools in the preclinical development of drug compounds that target aberrant LRRK2 activity. This research may translate to non-familial Parkinson's disease as well."

In the study, Dr. Yue developed two mouse models with the normal or mutant LRRK2 using an advanced form of genetic engineering called bacterial artificial chromosome genetics (BAC). BAC gives scientists more control over where and when a foreign gene is expressed in the target animal. Dr. Yue and his team genetically engineered a fragment of genomic DNA containing a human Parkinson's disease mutation of LRRK2 and injected it into the mice.

How LRRK2 functions is unknown, but Dr. Yue and his team showed that the mutant LRRK2 produces too much so-called kinase activity in the brain. They are now pursuing the question whether the increased kinase activity accounts for the reduced dopamine levels, subsequently leading to neurodegeneration.

"Not having a mouse model has been a significant barrier to bringing the LRRK2 breakthrough from bench to bedside," said Dr. Yue. "The new model likely replicates the earliest stage of Parkinson's disease, giving us the opportunity to understand the biochemical and molecular events that cause the disease."

Provided by The Mount Sinai Hospital