

Genes Linked to Parkinson's Protection Identified by UA Researchers

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University of Alabama researchers have identified five genes within animal models displaying protective capabilities against a hallmark trait of Parkinson's disease.

The research, published this month in the *Proceedings of the National Academy of Sciences' Early Edition*, is a possible step toward identifying both new targets for drug treatment development and genetic factors that make some people more susceptible to the disease, the researchers said.

“We've found five genes so far that significantly protect dopamine neurons from dying within our animal models,” said Dr. Guy Caldwell, associate professor of biological sciences at UA and co-author of the research.

The UA researchers' efforts, Caldwell said, represent one of the largest functional analyses of genes ever reported for Parkinson's disease. Shusei Hamamichi, a UA doctoral student, is lead author of the research paper and led the University's effort, along with Renee Rivas and Adam Knight, two UA undergraduates; Songsong Cao, a former doctoral student; Dr. Kim Caldwell, assistant professor of biological sciences, and Guy Caldwell.

Hamamichi's role represents a “heroic effort,” Guy Caldwell said.

UA researchers used specific strains of tiny nematode worms as animal models for the research. These genetically engineered worms contain a

human protein, alpha-synuclein, within their cells. Scientists have learned that people with too many copies of the code for alpha-synuclein within their DNA will contract Parkinson's.

Extra copies of alpha-synuclein can lead to repeated protein misfolding and death of the dopamine producing neurons in the brain. In Parkinson's patients, the death of these neurons leads to rigid and tremoring limbs, difficulty in movement and impaired reflexes. More than 1 million Americans are estimated to have Parkinson's.

Utilizing bioinformatic databases – which contain an abundance of information related to various genes and their genetic associations – the UA researchers first mined the data, prioritizing 867 genes for testing.

Using a revolutionary technique known as RNA interference, or RNAi, Hamamichi removed, one at a time, the functions of each of the 867 genes from the tiny nematodes. This, Caldwell said, enabled the research team to investigate the impact the missing function would have on cellular processes.

“Of these approximate 900 genes, we narrowed it down to 20 top candidates that seemed to have the most significant affect on alpha-synuclein aggregation as the animals aged,” Caldwell said.

Importantly, secondary screening of the 20 genes has thus far revealed five that offer dopamine neurons protection from dying, Caldwell said. The gene identified as offering the most statistically significant protection is a subject of a Michael J. Fox Foundation Target Validation initiative. In that effort, the Caldwells, with foundation funding, are teaming with UAB's Dr. David Standaert for additional research in mammalian models.

“Even though our functional analysis was done in a worm, worms have

dopamine neurons, worms have many of the features in their cells that are shared with us,” said Guy Caldwell, a faculty member in UA’s College of Arts and Sciences. “There’s good reason to believe that things functionally discovered in worms will still have meaning in higher systems.”

More than 50 percent of all human hereditary diseases have been linked to genetic components also found in the worm, so it’s frequently used by scientists as a model on which to study human diseases. “The power of the animal is that we can screen through large numbers of genes very rapidly, and it’s inexpensive. While worms are wonderful, in order to identify a target for true therapeutic development, the best way is to go forward by validating in mammalian models of Parkinson’s,” Caldwell said.

Source: University of Alabama

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