# New research provides genetic clue to Parkinson's disease

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Researchers at Rhode Island Hospital and The Warren Alpert Medical School of Brown University have discovered a gene that could hold the key to developing new treatments for Parkinson's disease – a progressive and often debilitating movement disorder that affects as many as one million Americans.

According to the findings of the study, published online in the *American Journal of Human Genetics*, mutations in the gene, known as GIGYF2, appear to be directly linked to the development of Parkinson's in people with a family history of the disease. The gene is one of only a handful linked to Parkinson's and one of just two genes known to be a common contributor to this degenerative disease, which has no known cause or cure.

Although less than a quarter of all cases of Parkinson's are familial, researchers believe genes like GIGYF2 can provide clues to the mechanisms behind Parkinson's and could point to new treatments for the more common and sporadic forms of the disease.

"These findings may ultimately help open the door to the development of new therapeutic – and possibly even preventive – strategies that target the underlying cause of Parkinson's disease, improving the quality of life of the many people worldwide who are affected by this devastating disorder," said senior author Robert J. Smith, M.D., director of the division of endocrinology and the Hallett Center for Diabetes and Endocrinology at Rhode Island Hospital and professor of medicine at

Alpert Medical School.

Their research also revealed an intriguing secondary finding — the possible association between Parkinson's and insulin and the related hormone known as insulin-like growth factor (IGF). This joins a small but growing body of research linking insulin and IGF to Parkinson's disease and other neurodegenerative disorders, such as Alzheimer's.

"A better understanding of the link between insulin or IGF and Parkinson's may lead us to new treatment strategies for Parkinson's and also new insights into the connection between diabetes and nervous system disorders," Smith said.

Parkinson's is one of the most common neurodegenerative disorders, second only to Alzheimer's, affecting between one and two percent of the population above age 60. The disease occurs when certain nerve cells in the part of the brain that controls muscle movement either die or become impaired. Normally, these cells produce a vital chemical known as dopamine, which allows smooth, coordinated function of the body's muscles and movement. When the dopamine-producing cells are damaged, the symptoms of Parkinson's appear – including tremors, slow movements, stiffness, and difficulty with balance or coordination.

Smith, an endocrinologist, and his team at Rhode Island Hospital and Brown typically focus on proteins important to the function of insulin and IGF. They initially identified GIGYF2 nearly five years ago because of its potential involvement in IGF and insulin signaling systems, but did not explore an association with Parkinson's at that time.

In the current study, they examined where GIGYF2 is located on the human genome in hopes of learning more about the gene's function, and discovered that it is right in the center of a chromosomal region linked to Parkinson's. Specifically, it appears GIGYF2 resides on PARK11 – a

region that was initially identified through a genetic analysis of families with Parkinson's disease.

Because of the potential links between Parkinson's, IGF and diabetes, Smith and his team decided to investigate the involvement of GIGYF2 in Parkinson's. Colleagues in Milan, Italy and Paris, France provided close to 250 DNA samples from patients who had Parkinson's and at least one first-degree relative (parent, child or sibling) with the disease. This included 123 Italian patients and 126 French patients. For comparison, they also studied DNA from more than 200 unrelated healthy controls from both countries.

Following gene sequencing and mutation analysis, the researchers identified seven different forms of GIGYF2 mutations occurring in 12 different people – approximately five percent of those in the study. Eight of these patients had at least one parent with Parkinson's, one had both parents affected, and three had one sibling affected. When available, relatives with Parkinson's were also sampled and the researchers found they carried the same mutation, which led to single amino acid substitutions in the protein encoded by the GIGYF2 gene. None of the mutations were observed in the healthy controls.

"Our data provides strong support for GIGYF2 as a PARK11 gene with a causal role in familial Parkinson's disease," said Smith. "The next step is to zero in on this gene to learn more about its involvement in triggering Parkinson's. It will also be important to evaluate additional and larger families with Parkinson's and these genetic mutations, as well as the frequency of GIGYF2 mutations in patients with the more common, idiopathic form of the disease."

Source: Lifespan