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Study conclusively ties rare disease gene to Parkinson's

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An international team led by a National Institutes of Health researcher has found that carriers of a rare, genetic condition called Gaucher disease face a risk of developing Parkinson's disease more than five times greater than the general public. The findings were published today in the *New England Journal of Medicine*.

In previous studies, several genes have been linked to Parkinson's disease. However, researchers say their work conclusively shows that mutations in the gene responsible for Gaucher disease are among the most significant risk factors found to date for Parkinson's disease. The discovery was made by investigators from the National Human Genome Research Institute (NHGRI) and the National Institute on Aging (NIA), both parts of the National Institutes of Health, in collaboration with scientists from 16 research centers across four continents.

"This analysis illustrates how studying a rare but important disorder, like Gaucher disease, can provide powerful clues about more common disorders, such as Parkinson's disease," said NHGRI Scientific Director Eric Green, M.D., Ph.D. "Understanding the genetic basis of rare conditions can thus provide insights into normal cellular and biological processes, which in turn may lead to improved diagnostic and therapeutic strategies."

Parkinson's disease, a neurological condition that typically causes tremors and stiffness in movement, affects about 1 to 2 percent of people over the age of 60. The chance of developing Parkinson's disease

increases with age and involves a combination of environmental risk factors and genetic susceptibility.

Gaucher disease occurs when an individual inherits two defective copies of the GBA gene, which codes for an enzyme called glucocerebrosidase. This enzyme breaks down a fatty substance called glucocerebroside, which, when not properly disposed of, can harm the spleen, liver, lungs, bone marrow and, in some cases, the brain. The enzyme functions in a part of the cell called the lysosome, where cellular components are broken down, or metabolized, for recycling.

In the past, it was thought that people who carry just one altered GBA gene were unaffected. However, in recent years, research groups at NHGRI and elsewhere have completed small studies suggesting that carriers of GBA alterations may have an increased risk of developing Parkinson's disease.

"The opportunity was right to amass the data into one powerful study," said Ellen Sidransky, M.D., senior investigator in NHGRI's Medical Genetics Branch, who is the lead author of the study and coordinated the effort. "Our analyses of the accumulated data provide a convincing association between GBA alterations and Parkinson's disease."

The research team examined the frequency of GBA alterations in 5,691 patients with Parkinson's disease, including 780 Ashkenazi Jews, a population in which a particular type of Gaucher disease is more prevalent. Those data were matched against 4,898 unaffected volunteers, called controls, which included 387 Ashkenazi Jews.

At least one of the two common GBA alterations was found in 3.2 percent of Parkinson's patients and 0.6 percent of controls. Among the Ashkenazi subjects, 15.3 percent of those with Parkinson's disease carried a GBA alteration compared to 3.4 percent of Ashkenazi controls.

In addition to screening for the two common alterations, five of the research centers sequenced the entire GBA gene in 1,642 non-Ashkenazi patients with Parkinson's disease and 609 non-Ashkenazi controls. Using this more thorough method, they found many additional alterations associated with Parkinson's disease, and showed that 7 percent of patients carried an alteration, indicating that it is important to look beyond the two common alterations to gain a true picture of risk in the general population.

Besides significantly increasing the risk of Parkinson's disease, GBA alterations also appear to increase the likelihood of early disease onset. According to the new study, Parkinson's patients with GBA alterations developed symptoms an average of four years earlier than other Parkinson's patients.

Overall, the researchers found that the association between GBA and Parkinson's disease is not confined to any single ethnicity or to specific GBA mutations, though they did find that some gene alterations are seen more frequently in certain populations. Compared with the general population, in which GBA alterations occur in fewer than one out of 100 people, GBA alterations occur in at least one out of 16 people of Ashkenazi descent. However, many GBA mutation carriers as well as patients with Gaucher disease never develop Parkinson's disease, so this appears to be only one of several risk factors involved.

Further research is in progress to understand the full spectrum GBA alterations, their biological significance and their association with both Parkinson's and Gaucher disease. The researchers are also pursuing ways to provide more accurate guidance based on the findings for genetic counseling and for the development of new therapeutic strategies for these disorders.

More information: For information about Parkinson's disease, go to

www.genome.gov/10001217 , and for Gaucher disease, go to www.genome.gov/25521505 .

Source: NIH/National Human Genome Research Institute