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Study finds genetic variation that protects against Parkinson's disease

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An international team of researchers led by neuroscientists at Mayo Clinic in Florida has found a genetic variation they say protects against Parkinson's disease. The gene variants cut the risk of developing the disease by nearly 20 percent in many populations. The study, published in the online Aug. 31 issue of *Lancet Neurology*, also reports the discovery of different variants of the same gene, LRRK2 -- the most important Parkinson's risk gene found to date -- that double Parkinson's risk in Caucasians and Asians.

Parkinson's disease is a common movement disorder that affects 1 to 2 percent of people over age 65. The researchers say that although the relative influence of the variants in this study on risk is small, given the late-onset nature of Parkinson's, any variation that can delay the disease is important. In addition, the finding provides evidence that Parkinson's disease is influenced by multiple genetic risks that act together to cause disease.

"The idea that Parkinson's disease occurs mostly in a random sporadic fashion is changing," says lead investigator Owen Ross, Ph.D., a neuroscientist at Mayo Clinic Florida. "Our study, one of the largest to date in the study of the genetics of Parkinson's disease, shows that a single gene, LRRK2, harbors both rare and common variants that in turn alter the susceptibility to PD in diverse populations."

Researchers hope to use these and future genetic findings to predict who is at risk of Parkinson's and to develop novel targeted therapies, Dr. Ross

says.

The Genetic Epidemiology of Parkinson's Disease consortium that contributed to the three-year study included investigators from 23 sites representing 15 countries on five continents. The investigators contributed clinical samples on a total of 15,540 individuals (8,611 PD patients and 6,929 controls). The researchers in Mayo Clinic Florida, funded by The Michael J. Fox Foundation for Parkinson's Research and the Mayo Clinic Morris K. Udall Center of Excellence in Parkinson's disease Research, then quantified Parkinson's risk for each LRRK2 variant. Co- investigator Matthew Farrer, Ph.D., is a former Mayo Clinic neuroscientist now at the University of British Columbia in Vancouver.

"This is an important study that will help us learn more about how the same gene can both increase and reduce risk of late-onset, sporadic Parkinson's disease, the kind that affects most people," says co-author Zbigniew Wszolek, M.D., a Mayo Clinic neurologist who has helped build international collaborations at Mayo Clinic. "Our goal is to find out how we can intervene in this process to help prevent development of this disease."

In 2004, Mayo researchers led by Dr. Wszolek discovered that the little understood LRRK2 gene was responsible for causing a form of "familial" or inherited Parkinson's. "Through this study and subsequent follow-up investigation, we and others identified a LRRK2 variant (G2019S) which turned out to be the most common genetic cause of familial PD yet found. For example, it is found in more than 30 percent of Arab-Berber patients with the disease," he says. To date, seven such familial pathogenic LRRK2 variants have been discovered in different ethnic populations.

However, LRRK2 variation has also been found to increase the risk of sporadic late-onset Parkinson's, so in this study, researchers set out to

address every possible variant in the part of the LRRK2 gene that codes for protein production to determine which variants affect risk, and by how much. The researchers found that common and rare variants contributed to late-onset sporadic PD in both a risk or protective manner. Dr Ross adds that there remain many more PD risk genes to be found outside of LRRK2, and that together they contribute to a significantly higher likelihood of developing PD.

Major funding for the study also came from the National Institutes of Health, Mayo Foundation, and several international funding agencies.

Provided by Mayo Clinic