Researchers find a common genetic risk factor for Parkinson's disease in Asians

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Researchers at Mayo Clinic in Jacksonville, Fla. and the National Taiwan University Hospital in Taipei, Taiwan have discovered what to date appears to be the most common genetic risk factor for Parkinson's disease worldwide. They believe the majority of people carrying this genetic mutation descend from a common ancestor about 4800 years ago. Their study was published Jan. 9 in the online edition of *Parkinsonism and Related Disorders*.

Researchers found that ethnic Chinese individuals carrying a mutation they identified in the LRRK2 gene are over two times more likely to develop the disease than non-carriers. Given the population of China and the number of ethnic Chinese worldwide, this mutation may predispose more people to developing Parkinson's disease than any other genetic factor. However, researchers say not everyone with the mutation develops the disease, and in those that do, other genetic and environmental factors are probably in play.

Mayo Clinic neuroscientist Matthew Farrer, Ph.D., lead author on the study, says this discovery is a small part of the ongoing genetic revolution in medicine. "Seemingly sporadic Parkinson's disease may be a familial disorder, and we're finding that the genetic risk factors for Parkinson's disease are population specific," he says.

In 2004 Mayo Clinic researchers were part of a team that discovered the LRRK2 gene and its role in Parkinson's disease. This group and others went on to find a number of mutations in LRRK2, a gene that codes for a poorly understood protein, leucine-rich repeat kinase 2. One of the mutations, G2019S, has been shown to cause Parkinson's disease in people with and without a family history of the disease. G2019S is an especially common cause of Parkinson's disease in Berber Arabs and Ashkenazi Jews.

However, in contrast to the G2019S mutation, which is considered a disease causing mutation because it is rarely found in healthy, elderly people without Parkinson's disease, the newly researched G2385R mutation, the subject of this study, does not always lead to disease. It is found in approximately 4 percent of the ethnic Chinese population without Parkinson's disease, which is why researchers consider it a risk factor rather than a causal mutation.

The G2385R mutation was first discovered in 2004 by Mayo and Taiwanese researchers in a family of ethnic Chinese decent. One of the study authors, Ruey-Meei Wu, M.D., Ph.D., and her group in Taiwan, went on to find the G2385R mutation in just over 22 percent of familial Parkinson¡¦s disease cases. "The findings that the frequency of LRRK2 G2385R is observed at 8 percent within ethnic Chinese patients, 4 percent in control subjects and 22 percent in familial patients strongly suggests the G2385R variant is an important genetic risk factor in the ethnic Chinese population," Dr. Wu says.

Due to these findings, Wu says it will be important to look at subtle signs of disease in asymptomatic carriers for clues about the mutation's penetrance, meaning the extent to which symptoms associated with disease will occur. "We can also evaluate the effect of neuroprotection in these carriers in a long-term follow up study," Wu says. "Epidemiology studies looking for other environmental risk factors and their interaction with genetic risk factors will provide clues to prevent the occurrence of this chronic and disabling disease in the future."

Other research groups also have found the G2385R mutation is at a higher frequency in Asian patients with Parkinson's disease, than in matched control subjects. These types of case and control genetic studies provide a powerful tool for researchers to find disease genes and risk factors in homogeneous or isolated populations where there has been little immigration.

Interestingly, the present paper's authors found evidence to suggest G2385R carriers share a common ancestor. They performed a genetic analysis looking at the inheritance pattern of a specific DNA sequence along chromosome 12 that includes the LRRK2 gene.

Examining known genetic markers, which are short stretches of repeated DNA subject to variation in the number of times they repeat, their analysis showed a unique pattern of these DNA sequence markers is almost always passed from generation to generation along with the G2385R variant.

Researchers used genetic theory to estimate the level of variation at these genetic markers between carriers and healthy non-carriers, and used that data along with the genetic distance the markers are away from the LRRK2 gene to estimate how many generations have been passing on this unique stretch of DNA. Their analysis concluded that the G2385R mutation arose approximately 4,800 years ago, corresponding with the rise of Chinese civilization and the reign of Yellow Emperor Huang Di, credited with inventing traditional Chinese medicine.

This mutation does not appear to play a role in Parkinson's disease within other racial groups. Studies to date have failed to find the mutation in Caucasian populations. Farrer says therapeutic interventions focused on LRRK2 will be very important to develop given the global population affected by all the LRRK2 mutations.

Another study author, Mayo Clinic neuroscientist Owen A. Ross, Ph.D., says although the group's findings point toward one of the most important genetic risk factor for Parkinson's disease, he agrees with Wu that there is still much to understand about which carriers will develop the disease and at what age their symptoms begin. "There are going to be other significant disease modifiers," he says. "The age of onset for disease is variable in G2385R carriers and for LRRK2-parkinsonism in general. Not only may there be environmental factors, but also other genetic factors acting on this genomic background which determines disease presentation."

As the G2385R mutation dates so far back and is now so prevalent; researchers have an opportunity to assess thousands of carriers and treat them as members of one distantly related family in order to find other genetic and environmental factors that act with G2385R to trigger Parkinson's disease.

Source: Mayo Clinic, Jacksonville