

Different mutations in single gene suggest Parkinson's is primarily an inherited genetic disorder

Two new international studies by researchers at the Mayo Clinic site in Florida are rounding out the notion that Parkinson's disease is largely caused by inherited genetic mutations that pass through scores of related generations over hundreds, if not thousands of years. These genetic influences, which can be small but additive, or large and causative, overturn common beliefs that the neurodegenerative disease mostly occurs in a random fashion or is due to undetermined environmental factors.

These latest studies bring the total of number of disease-related mutations in an as yet poorly understood gene, leucine-rich repeat kinase 2 (LRRK2), to seven, all of which are linked, either weakly or strongly, to typical, late onset development of Parkinson's disease in people around the world. One mutation (R1628P) doubles the risk of Parkinson's disease in ethnic Chinese, according to a study published on Wednesday, April 16, 2008 in the online edition of the *Annals of Neurology*. The second study, published April 15 in *Neurology*, demonstrates that another very rare mutation (R1441C), found in people on three continents, increases risk by more than 10-fold.

The R1628P was identified by the strong collaborative effort of researchers from Taiwan, Singapore, Japan, and the U.S. The research institutions included the National Taiwan University Hospital, led by Dr. Ruey-Meei Wu, Chang Gung Memorial Hospital led by Dr. Yih-Ru Wu, National Neuroscience Institute of Singapore led by Dr. Eng-King Tan and Juntendo University, led by Dr. Nobutaka Hattori. This group believes the R1628P mutation arose from a single individual in the Han Chinese population about 2,500 years ago and has since spread through generations of descendants, wherever they live. This is the second common LRRK2 mutation discovered in Asians – a mutation labeled G2385R believed to have originated 4,500 years ago was first reported in the journal 'Neurogenetics' in 2006 and subsequently confirmed by several groups. Lrrk2 G2385R and R1628P predispose over 100 million Chinese people to Parkinson's disease.

"The picture that is emerging of Parkinson's disease is one in which genetic risk factors, passed down through the population for hundreds or thousands of years, add up to substantial susceptibility within a single individual, and, with some possible environmental influences, can result in disease," says Mayo Clinic neuroscientist Owen A. Ross, Ph.D., first author on the *Annals of Neurology* study.

"These types of mutations are important because the goal of this research is to be able to screen people who are most at risk because of their genetic profiles, and design therapies that interfere with the disease process," Dr. Ross says.

The stronger R1441C mutation, also currently being reported, originated from several different "founders" and is now found in 20 families on three continents. It is relatively causative in nature, meaning the majority of people with the mutation are likely to develop the disease.

"Parkinson's disease is fascinating to study because we can now roughly trace when and where mutations occur, and how they travel through offspring and in populations," says Kristoffer Haugarvoll, M.D., a visiting scientist at Mayo Clinic and lead author on the *Neurology* study. "It also shows us that disease that appears to be the same in the majority of patients can originate from different genetic mutations – either

genes that increase risk substantially, or by several risk factors, genetic and environmental, that each have minor but additive effects.”

Same mutations in familial and sporadic forms of the disease

Only about 10 percent of patients diagnosed with Parkinson’s disease have a strong family history of the disease, and Mayo Clinic researchers in Florida have been part of a worldwide effort to discover whether common genes may explain the origin of the other 90 percent, the so-called “sporadic” form. In 2004, they were part of a team that discovered that the LRRK2 gene is linked to both familial and non-familial cases of the disease.

Since then, they have found LRRK2 mutations that can cause the same clinical manifestations of Parkinson’s disease in people with and without a family history – discoveries that “have caused a paradigm shift in the field,” says Dr. Ross. For example, a mutation labeled G2019S causes both familial and non-familial Parkinson’s disease in a high number of Berber Arabs and Ashkenazi Jews. “This shows that the effect of mutations in different areas of the Lrrk2 protein lead to the same disease, although it may not manifest in each generation and so did not appear to be familial,” he says.

In the latest study, Dr Ross and colleagues studied 1079 ethnic Han Chinese diagnosed with Parkinson’s disease, of which 44 reported a family history of the disease. These patients were compared with 907 ethnically matched Han Chinese who did not have Parkinson’s disease, and results showed the R1628P variant was approximately twice as frequent in Parkinson’s disease patients as in the control population. From this, the researchers estimated that for every 100 Chinese, 3 will have the gene variant. Further research then suggested that the R1628P carriers were related to a single common founder that dated from about 2,500 years ago.

The researchers then searched for evidence of the mutation in Japanese patients and controls – but did not find it. “The theory is that this mutation arose in China after the Japanese and Chinese segregated their populations, which explains why the G2385R mutation, which is 2,000 years older than R1628P, is found in both populations and is more common,” Dr. Ross says.

“Inheriting one or both of these mutations doesn’t mean that a person will develop Parkinson’s disease, but that an individual’s risk is increased,” he says. “The basis of population genetics is that disease is familial; people are so distantly related that they don’t know they may have inherited specific genes. While there may be an environmental component to development of the disease, none have been identified that have risks as large as those seen by the LRRK2 gene mutations.”

Generations that carry rare but critical mutations

In the Neurology study, Dr. Haugarvoll, who is from Norway, worked with researchers from a number of countries to collect genetic information from discrete populations of people representing three continents who had previously been found to be carriers of the R1441C mutation. “This was a completely collaborative effort,” he says. “Rare mutations affect relatively few patients, but if we join forces in a worldwide initiative, we have larger samples to look at, and that is the only way you can advance the science.”

The scientists identified 33 affected and 15 unaffected R1441C mutations from 20 families, including four patients with no family history of Parkinsonism. These patients all developed disease that mimicked the typical, late onset disease normally seen in non-familial, sporadic Parkinson’s disease, Haugarvoll says. The scientists believe the same disease-causing mutation has occurred independently on several occasions; however, most patients seem to originate from two different founders. One variant was found in Italian,

German, Spanish, and American patients. The second was discovered in patients from Belgium and from a single American family, located in Nebraska.

Dr. Haugarvoll says the region of R1441C appears to be “a hotspot for mutation events” because other mutations occur in this general area. What is most interesting, he says, is that “even though there are familial mutations in different locations of the gene, it produces the same effect, the same disease.”

“It seems like mutations are occurring in a few founders, and that these founders have a lot of offspring over generations that carry the mutation. Even in sporadic disease, then, familial genes are inherited but symptoms may skip some generations, making the disease appear sporadic” Dr. Haugarvoll says.

Source: Mayo Clinic

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