

Parkinson's disease research

Update

It was international news when scientists in the DIR's Genetic Disease Research Branch found a gene that causes Parkinson's disease. Until that 1997 report, most experts believed the disease—which eventually strikes about one in a 100 people—was probably due to unknown factors in the environment. Now the discovery is helping scientists puzzle out the causes of a number of other serious brain diseases.

The causes of most cases of Parkinson's disease—whose symptoms include trembling of a limb, rigidity, a slow, shuffling walk, and stooped posture—are still a mystery. In the original report, the gene mutation was found in families of Italian and Greek origin, and subsequently a different mutation in the same gene has been linked to the disease in a German family.

The Parkinson's research was led by Dr. Mihael Polymeropoulos' and Dr. Robert Nussbaum's laboratories at NHGRI, in collaboration with researchers outside of NHGRI.

The normal gene produces a protein called alpha synuclein. The finding of an alteration in this protein not only hints at why Parkinson's develops, but suggests that it may be one of several forms of frightful degenerative diseases of the brain that all share a common mechanism.

Polymeropoulos' hypothesis is that in these diseases, the normal cellular apparatus for

protein breakdown goes awry, leading to an accumulation of debris in the brain that is eventually severely disabling and ultimately deadly. One of the other disorders is the extremely common affliction of aging: Alzheimer's disease. The others are rare but also well-known: Huntington's disease, Amyotrophic Lateral Sclerosis (ALS or Lou Gehrig's disease), and the so-called prion diseases, such as Creutzfeldt-Jakob, a human disease, and its livestock analog commonly called Mad Cow disease.

Brains of Parkinson's disease patients examined after death contain microscopic brain structures called Lewy bodies. Lewy bodies appear to be tombs for proteins the body has failed to recycle, including alpha synuclein.

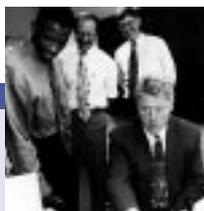
“Although the alpha synuclein mutations are a rare cause of Parkinson's, we have shown that in all Parkinson's—even in patients who don't have any alterations in the gene—alpha synuclein is a major constituent of the Lewy bodies. So finding the altered gene has identified a rare direct genetic way of recruiting alpha synuclein into Lewy bodies. But there must be many other ways that this can happen, genetic and non-genetic. Alpha synuclein may be a final common pathway for developing intracellular accumulations such as Lewy bodies,” note Polymeropoulos and Nussbaum.

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Parkinson's, Alzheimer's, and Huntington's that they may all be looking at the same process. In each disease, the inclusions that infest the brain are different from each other and accumulate in different regions, and the constituent proteins are different (beta amyloid in Alzheimer's and huntingtin in Huntington's disease). “But there may be a common theme being that cellular proteins fail to undergo normal repair and eventually degradation which is primarily conducted by the protein garbage grinders known as proteasomes.”

“Proteasomes are cellular subunits responsible for degrading the bulk of cellular proteins. These macromolecular machines act like garbage grinders inside the cell. They're cylinders; abnormal



August, 1995
President Clinton experiments with chromosome microdissection during a tour of NIH.

October, 1995
High-frequency alteration in the BRCA1 gene found in several discrete population groups, including Eastern Europeans and Ashkenazi Jews.



Dr. Mihael Polymeropoulos



Dr. Robert Nussbaum

proteins are fed into one end and out the other end come small peptide fragments. But in these diseases, something goes terribly wrong with the garbage-grinding process. Either the proteins are abnormal, perhaps folded abnormally, and they clog the proteasome, or perhaps components of the proteasomes themselves are dysfunctional," Polymeropoulos explains.

And how do Mad Cow and the other prion diseases fit into this grand unified theory of neurodegenerative disease? Prions are peculiar proteins that can persuade other proteins to fold abnormally, thus helping to gum up the works. The Parkinson's protein, abnormally folded alpha synuclein, apparently shares the prion protein's persuasive powers. It, too, is

believed to induce abnormal folding in other proteins, further challenging the brain's ability to dispose of rubbish and eventually overwhelming it.

NHGRI researchers were first to find a gene that causes Parkinson's disease and, recently, Dr. Polymeropoulos' team discovered a second PD gene. Researchers elsewhere have followed suit in the search for PD genes as well. One group has recently mapped another PD locus and cloned a gene for juvenile Parkinson's. ●

http://www.nhgri.nih.gov/DIR/LGDR/PARK/park_home.html

October, 1995

After four years, patients who had undergone gene therapy for treatment of adenosine deaminase deficiency still showed improved immune activity.

June, 1996

Anti-HIV genes successfully introduced into human lymphocytes.

June, 1996

Atm mouse model developed.