NEUROBIOLOGY

Gene Discovery Offers Tentative Clues to Parkinson's

Neurobiologists long ago identified the defect underlying the tremors, halting movements, and other cruel symptoms of Parkinson's disease: the gradual die-off of a set of brain neurons that make the neurotransmitter dopamine. But what causes those neurons to degenerate is still a mystery. Now, scientists may have taken a big step toward answering that question.

On page 2045, researchers from the National Human Genome Research Institute (NHGRI) in Bethesda, Maryland, the Robert Wood Johnson Medical School in Piscataway, New Jersey, and colleagues in Italy and Greece report pinpointing the gene that, when defective, causes a hereditary form of Parkinson's in a large Italian family. The gene, which encodes a brain protein of unknown function called α-synuclein, will probably account for only a few percent of all Parkinson's cases. But if researchers can pin down how the mutated α-synuclein exerts its effects, they may learn just what kills off the crucial dopamine-producing neurons in the much larger number of patients with nonhereditary Parkinson's.

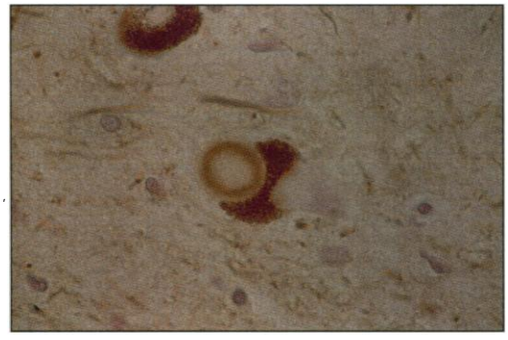
Other researchers hail the finding. "It is a marvelous piece of work—of great importance," says C. Warren Olanow, a neurologist at Mount Sinai School of Medicine in New York City. "This is a major clue as to what might be going on." Demetrius Maraganore, a neurologist at the Mayo Clinic in Rochester, Minnesota, agrees: "It's the first major breakthrough in the understanding of the disease in 30 years."

Ultimately, a better understanding of what causes the neurodegeneration of Parkinson's may lead to better therapies. Although current treatments with drugs that replace the missing dopamine control the symptoms for a time, they become useless as the patients' brains deteriorate. But learning what causes the deterioration might make it possible to design drugs to prevent it.

The current work is an outgrowth of a discovery made late last year. For many years, most evidence suggested that an environmental factor, not heredity, is responsible for Parkinson's. Last November, however, the NHGRI, Robert Wood Johnson, and Italian teams reported that the disease afflicting the Italian family, which develops at an unusually early age, showed strong genetic linkage to a region on chromosome 4 (*Science*, 15 November 1996, p. 1085).

By analyzing blood samples from more family members, the researchers were able to locate additional chromosomal markers that seemed to be inherited along with the disease. The additional markers allowed the group to narrow the suspect region to about 6 million base pairs of DNA. That stretch of DNA contained a promising gene: the α-synuclein gene, which had previously been mapped to that area. "All along, we knew that synuclein was a good candidate," says NHGRI geneticist Mihael Polymeropoulos, because other researchers had shown that the protein is expressed in the brain areas that deteriorate in Parkinson's.

Sure enough, when the researchers sequenced the gene in the Italian family, they found that the affected members had a mutation not present in unaffected members. The group found the same mutation in three of five Greek families with strong histories of the disease. But it did not appear in any of the nearly 100 controls from southern Italy or in 52 Italian patients with sporadic Parkinson's disease.



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Body of evidence. Lewy bodies (stained tan, in center) are characteristic of Parkinson's disease.

The link to α-synuclein does not provide any easy answers to what causes Parkinson's, but it does offer some tantalizing clues. Proteins must fold up into a three-dimensional structure to function, and the researchers suggest that the mutation causes α-synuclein to misfold. It might then produce abnormal deposits in the brain, much as the accumulation of a protein called β amyloid in neurotoxic deposits may contribute to nerve degeneration in Alzheimer's disease. Just as the brains of Alzheimer's patients are riddled with these plaques, Parkinson's brains are studded with inclusions called Lewy bodies.

Polymeropoulos notes that the α-synuclein mutation, which replaces the amino acid alanine with a threonine, has the potential to cause the protein to misfold. Although the exact conformation of α-synuclein is not known, alanine is commonly found in a coiled structure, called an α helix, while threonine is common in a more rigid and insoluble structure called a β sheet—the same kind of formation that is suspect in the formation of Alzheimer's plaques. The next step, Polymeropoulos says, is to find out if the Lewy bodies actually contain α-synuclein.

The possibility that α-synuclein misfolding leads to Parkinson's is very much an unproven hypothesis, however, and it does not jibe with a current leading theory of what causes the disease. Evidence has been building that oxidative stress—the buildup of cell-damaging compounds called free radicals—may be behind the neuron loss. "It's not apparent how to link the two theories," says John Trojanowski, a pathologist at the University of Pennsylvania Medical Center in Philadelphia who has studied both Alzheimer's disease and Lewy bodies.

Deepening the mystery of how the mutation causes disease are the versions of α-synuclein found in the rat and mouse. These proteins already have a threonine where the normal human protein has an alanine, yet the threonine causes no apparent problems in the animals. The rodents' short lifespan may be one explanation for the paradox, the authors suggest: The animals may simply die before they can develop the disease. The researchers also raise the possibility that the mutation in humans may disrupt—or encourage—the interaction of α-synuclein with another protein not present in rodents. Finally, Polymeropoulos notes that the mutation in the Italian family is dominant—only one of the two gene copies is mutated—and the normal and mutant forms of the protein may have to interact to cause problems.

To try to figure out just what the α-synuclein mutation does, researchers would like to transfer the mutant gene into mice to see whether they can re-create Parkinson's in the animals. The natural threonine in the mouse suggests that the transgenic animals might not get sick, Polymeropoulos concedes. The researchers hope they might succeed by mimicking the genetic endowment of the Italian and Greek patients: knocking out both copies of the mouse gene and then substituting one normal human gene and one with the threonine substitution.

But even if researchers can pin down how the α-synuclein gene mutation leads to Parkinson's in the Italian family, they won't completely solve the riddle of the disease. "Parkinson's disease is going to be a 100-piece puzzle," Polymeropoulos says. "α-Synuclein may be a central piece of the puzzle and will hopefully give us a picture of what it will look like when it is done. But we should be prepared for another 99 pieces."

–Gretchen Vogel