National Institute on Aging:
Understanding the Genetic Underpinnings of Parkinson's

NIA intramural scientists have successfully identified mutations of the LRRK2 gene that cause Parkinson's disease, first in five families in Spain and England and later in approximately 1 percent of sporadic PD and 5 percent of cases of PD with a positive family history in the United States and Canada, making it the most common genetic cause of PD identified to date. Ongoing work from NIA scientists is aimed at turning this genetic discovery into new avenues for treatment.

Lead Agency:
National Institute on Aging (NIA)/National Institutes of Health (NIH)

Agency Mission:

- Support and conduct genetic, biological, clinical, behavioral, social, and economic research related to the aging process, diseases and conditions associated with aging, and other special problems and needs of older Americans.
- Foster the development of research and clinician scientists in aging.
- Communicate information about aging and advances in research on aging to the scientific community, health care providers, and the public.

Principal Investigators

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General Description:

Understanding the Genetic Underpinnings of Parkinson's
In November 2004, NIA intramural scientists discovered mutations in a gene called *LRRK2* that cause Parkinson's disease (PD). The investigators studied four families with a history of PD who lived in the Basque region of Spain and one family with a similar disease in England. The *LRRK2* gene encodes dardarin, a protein named by the researchers from the Basque word dardara, which means tremor, a major symptom of PD. In addition, the group identified a *LRRK2* mutation, called G2019S, as a cause of disease

in PD families in the United States and Canada. This single mutation causes disease in approximately one percent of all PD and five percent of cases of PD with a positive family history, an estimated 10,000 Americans. In other populations, the same mutation accounts for 9-30 percent of PD based on clinical analysis. As such, *LRRK2* mutations are the most common genetic cause of PD identified to date, and they may represent an attractive target for developing new therapies for treating PD. NIA scientists have shown that the same mutations will trigger cell death in cultured neurons, and this can be limited by inactivating the protein. This suggests that a small, drug-like molecule might be developed to achieve the same goal. To develop this idea further, these investigators have started to explore the three dimensional structure of the protein so that drug-like compounds can be 'designed' in the future. This work is ongoing and is stimulating a great deal of interest in the field.

Excellence: What makes this project exceptional?

Researchers demonstrated that LRRK2 is the gene commonly mutated in people with Parkinson's disease (PD) and that these mutations result in toxic effects to neurons that can result in PD.

Significance: How is this research relevant to older persons, populations and/or an aging society?

Parkinson's disease (PD) is a neurological condition that typically causes tremor and/or stiffness in movement. The condition affects about 1 to 2 percent of people over the age of 60 years and the chance of developing PD increases as we age.

Effectiveness: What is the impact and/or application of this research to older persons?

The onset of Parkinson's disease (PD) most frequently occurs in older people. The long-term goal of NIH studies is to develop new ways to influence specific activity of LRRK2, which is a potential therapeutic target for PD.

Innovativeness: Why is this research exciting or newsworthy?

Further understanding the LRRK2 gene and mutations to that gene may enable us to identify molecules and pathways as targets for therapeutic and preventive interventions that could potentially benefit thousands of older Americans who have PD or are at risk.