Mutations in LRRK2 – what do they mean and how can we learn more?

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Leucine-rich repeat kinase 2 (LRRK2), also known as dardarin, is an enzyme that in humans is produced by the *LRRK2* gene. Changes in the DNA sequence of *LRRK2* have been found to cause Parkinson Disease (PD) in some people. *LRRK2* mutations are most commonly found among those having an onset of disease over the age of 50, unlike the other known genetic causes of PD which are primarily associated with an earlier onset of PD. Individuals with a *LRRK2* mutation have a very typical PD presentation. Therefore, there are no particularly unusual features that would suggest a person's PD is caused by a *LRRK2* mutation.

Seven different DNA sequence changes in the *LRRK2* gene have been reported to cause PD. Among Caucasian populations, the most common causative DNA sequence change, also called a mutation, is at amino acid 2019 and changes a glycine to a serine (called G2019S). The frequency of this mutation changes dramatically in different populations. In Northern Africa, as many as 40% of individuals with PD have this particular *LRRK2* mutation. Among individuals of Ashkenazi Jewish descent, the frequency of the G2019S mutation among PD patients may be as high as 25%. In other ethnic groups, the frequency of *LRRK2* mutations in PD patients is lower, about 1-2% in the general PD population and 5% among those who have a family history of PD in other relatives. In contrast, among Asian populations, there are very few G2019S mutations and instead, a mutation resulting in a change in the amino acid at position 2385, from a glycine to an arginine, is the most common *LRRK2* mutation (G2385A).

There are several clinical and genetic challenges that have not yet been overcome when considering *LRRK2* testing in a preclinical setting. Perhaps the most important consideration is that more than half the individuals who inherit one of the 7 reported causative *LRRK2* mutations do not develop PD. This is termed reduced penetrance. Because of this relatively high rate of reduced penetrance, use of *LRRK2* DNA testing as a way to identify those at increased risk of PD has not become widely used.

The Michael J. Fox Foundation has recently funded a new international initiative to better understand *LRRK2* PD. The study is being coordinated by researchers at

Indiana University. As part of this initiative, individuals who have been found to have a *LRRK2* mutation will be invited to participate in a research study. Their family members will also be invited to participate. The goal of the study is to include individuals with a *LRRK2* mutation who do and do not have clinical features of PD. Within North America, a network of research sites has been formed. These sites will evaluate people from families who have a *LRRK2* mutation. Research participants will be asked to complete an in-person study visit where they will undergo a neurological evaluation, complete several questionnaires covering very early features of PD and provide blood and urine samples.

If someone in your family has had *LRRK2* testing and was found to have a *LRRK2* mutation, you may be eligible to participate in this study. For more information, please visit the study website at http://progeni.iu.edu/ or call 1-888-830-6299.