Research shows genetic variants are more common in people with Parkinson's disease than previously thought

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Investigators in the Parkinson's Foundation-backed PD GENEration study—which reached its goal of 15,000 participants ahead of schedule this spring—found that 13% of participants have a genetic form of Parkinson's disease (PD), which is a significant observation compared to

long-standing estimates. Results from the first 3.5 years of the study, which examined a broad North American cohort, were published in the peer-reviewed journal *Brain*.

PD GENEration, which tests for clinically-relevant Parkinson's-related genes, has been offered by the Parkinson's Foundation since 2019 to any person with a confirmed PD diagnosis. The study is the first of its kind to return results at scale via live genetic counseling in English or Spanish.

This enables participants and physicians to make more informed decisions about their care, including enrollment in gene-specific clinical trials.

Additional key findings from the PD GENEration study include:

- 7.7% of participants carried a GBA1 genetic mutation, 2.1% of participants carried a PRKN genetic mutation, and 2.4% of participants carried a LRRK2 genetic mutation. All participants were informed about their genetic status through the genetic counseling component of the program.
- The positivity rate for a genetic variant is significantly higher for individuals with high risk. Those with early-onset PD, high-risk ancestry (such as Ashkenazi Jewish, Spanish Basque, or North African Berber), or a first-degree relative affected with the disease had an 18% positivity rate. The positivity rate for individuals without one of those risk factors was nearly 10%.
- Many of these participants may qualify for precision medicine trials, showing the feasibility and importance of broadly offering genetic testing.

"We did not anticipate the high positivity rate for genetic mutations, specifically the nearly 10% having a positive result even without any known genetic risk factors," said Roy Alcalay, MD, MS, Tel Aviv

Medical Center, Israel, and the Department of Neurology, Columbia University Irving Medical Center, and lead principal investigator for PD GENEration.

"Further, the speed at which participants enrolled in PD GENEration is a testament to the interest of people with PD to obtain data on their genetic status. Taken together, the positivity rate and the high interest in getting genotyped will hopefully translate to increased participation in observational studies and clinical trials toward therapies targeting these genes, simplifying precision medicine clinical trials in PD."

"PD GENEration stands at the forefront of precision medicine and the potential for tailored treatments. In large part, this is because the Parkinson's Foundation has recognized the importance of including genetic counseling in a research study that discloses genetic results," said Lola Cook, MS, CGC, Department of Medical and Molecular Genetics at Indiana University, who is first author of the *Brain* article and one of six genetic counselors involved in the study to date.

"As we've seen from the study's enrollment numbers and survey results, there is a strong interest among people with PD to push the research effort forward. This includes understanding the disease's genetics, generally and individually. It's the idea that we are all doing our part to move toward improved treatments and a cure."

PD GENEration is continuing into its next phase with support from the Global Parkinson's Genetics Program (GP2), a program of the Aligning Science Across Parkinson's (ASAP) initiative. The study focuses on those who have been historically underrepresented in research. Such enhanced wide-scale recruitment is reaching a larger and more diverse community in the United States, Canada and Latin America.

The Parkinson's Foundation aims to enroll an additional 8,000

participants, including 2,400 in Latin America, during the next phase of the study.

"PD GENEration is designed to be inclusive and accessible to all populations, with the goal of improving clinical outcomes for everyone. We are proud that the data we have collected through PD GENEration reflects the largest and most diverse North American cohort ever tested—and even though we reached our initial recruitment goal of 15,000 this spring, bigger things are on the horizon," said James Beck, Ph.D., senior vice president and chief scientific officer of the Parkinson's Foundation.

"Our partnership with ASAP and GP2 allows us to reach significantly more people, further increasing the diversity of participants. Being able to understand the genetics that people with PD have in common across different populations could reveal biological secrets of the disease, with the potential to lead to new treatments."

More information: Lola Cook et al, Parkinson's Disease Variant Detection and Disclosure: PD GENEration, a North American Study, *Brain* (2024). DOI: 10.1093/brain/awae142

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