Largest study on the LRRK2 variant leads to discoveries about health, ancestry, and history

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Findings from 23andMe research on Parkinson's disease published in Brain

- The LRRK2 variant is strongly associated with symptoms of Parkinson's disease (PD) that are different from non-variant carriers with the disease
- The study revealed novel findings of genetic "hotspots" in people from Mexico, Cuba, Puerto Rico, and Brazil, where the founder variant has sprung up in other communities
- 23andMe has the largest LRRK2 G2019S research cohort, and launched the Parkinson's Impact Project (PIP) in 2018 to better understand which carriers are at greater risk of developing Parkinson's disease

SUNNYVALE, Calif., May 29, 2024 (GLOBE NEWSWIRE) -- 23andMe Holding Co. (Nasdaq: ME) (23andMe), a leading genetic health and biopharmaceutical company, with support from The Michael J. Fox Foundation for Parkinson's Research, conducted the world's largest study on LRRK2 G2019S and uncovered new insights into the variant. 23andMe launched the Parkinson's Impact Project (PIP) in 2018 to better understand which LRRK2 G2019S carriers' are at greatest risk of developing Parkinson's disease. The 3.5-year longitudinal study included 1,286 genotyped LRRK2 G2019S carriers and 109,154 non-carriers. Findings from the study, published today in the June 2024 issue of *Brain*, illustrate how DNA weaves together health, ancestry, and history.

The LRRK2 G2019S variant

Only 10 percent of Parkinson's disease cases have a known genetic cause; the remaining 90 percent have idiopathic Parkinson's disease, where the cause is unknown. Of the 10 percent of PD cases known to be related to a high risk variant, only 5 percent have the Leucine Rich Repeat Kinase 2 Glycine to Serine variant, also known as LRRK2 G2019S. Yet, the LRRK2 G2019S variant is the most common pathogenic variant linked to Parkinson's disease. 23andMe's study showed that people with the G2019S variant are seven times more likely to develop Parkinson's than people without the variant. Yet, not everyone with this LRRK2 variant will develop Parkinson's disease.

LRRK2-associated Parkinson's compared to Parkinson's without the variant

Parkinson's disease is associated with the degeneration of nerves in the brain and body, which produces different symptoms according to the pattern of nerve death.

People who develop Parkinson's disease who have the LRRK2 G2019S variant have milder symptoms than those with Parkinson's who do not have the LRRK2 variant. LRRK2-associated Parkinson's tend to have a slower progression of the disease. The data also suggests that in LRRK2 Parkinson's disease, the areas outside the motor control regions are spared from the neurodegenerative process. Conversely, Parkinson's carriers without the variant report significantly higher rates of cognitive decline, memory deficits, hyposmia (decreased sense of smell), and REM sleep behavior disorder (RBD) symptoms, which occur at lower rates in Parkinson's disease patients who have the LRRK2 variant.

Acting out dreams (RBD) and poor sense of smell are common symptoms that can be an early warning sign of neurodegeneration in the brain. These symptoms may indicate the onset of idiopathic Parkinson's disease, sometimes decades before the typical motor symptoms like tremor become obvious. However, people with LRRK2-associated Parkinson's are less likely to experience RBD and loss of smell.

"Because people with the LRRK2 G2019S variant are less likely to have sleep and smell abnormalities, the scientific and medical communities might be underestimating the risk of Parkinson's disease in LRRK2 carriers," said Lucy Norcliffe-Kaufmann, Ph.D., Principal Scientist, Parkinson's Disease Research at 23andMe. "Existing criteria may lack sensitivity for early detection among LRRK2 carriers. If we are only looking for smell and sleep problems, which don't appear as often in the early stages of LRRK2-PD, we may be miscalculating a person's risk, because for some reason those areas of the brain are more resistant to neurodegeneration"

LRRK2 variant unifies different populations

The LRRK2 G2019S genetic variant originally emerged from North Africa and passed through the early Jewish settlers in that part of the world. Scientists have long been aware of high rates of the LRRK2 variant in North African and Ashkenazi Jewish populations.

However, novel ancestry findings from 23andMe's study revealed hotspots in people from Mexico, Cuba, Puerto Rico and Brazil where the carrier rate of the LRRK2 G2019S variant was much higher than expected. The new Latin Caribbean connection historically points to migration of the Jewish population from Iberia to the Americas, after fleeing the Inquisitions. The movement of populations throughout the Mediterranean Basin brought with it the LRRK2 G2019S variant. Once the variant became established in the Jewish community, it spread to other regions of the world. In particular, it appears to have been brought to the Latin Caribbean during transatlantic voyages in the late 15th century, and there it created new founder populations. "By understanding the genetic ancestry of LRRK2 carriers, we can build community among these people," said Dr. Norcliffe-Kaufmann.

23andMe's ongoing Parkinson's research

23andMe's Parkinson's Impact Project (PIP) has helped scientists better understand the progression of Parkinson's disease as well as how LRRK2 Parkinson's differs from idiopathic Parkinson's. Launched in 2018 to understand LRRK2 G2019S carriers' experience with Parkinson's disease, the 3.5-year longitudinal prospective observational study included more than 110K consented research participants (with nearly 1,300 genotyped LRRK2 G2019S carriers and more than 109K non-carriers). Ancestry composition from more than 11K additional consented research participants in

23andMe's database who have the LRRK2 G2019S variant was also included. 23andMe's cohort that participated in the LRRK2 study is three times bigger than any other study published.

The study participants took surveys every six months for 3.5 years. Sixty-six percent of participants completed at least one follow-up, and 42 percent of individuals with Parkinson's had at least two years of follow-up. Scientists at 23andMe built anatomic models of brain degeneration from survey answers, looked at polygenic risk scores (PRS), and evaluated genetic ancestry.

This study is one of many aspects of 23andMe's long-standing commitment to studying Parkinson's disease. 23andMe researchers have studied the genetic underpinnings of Parkinson's since 2009. These studies have also identified almost 100 new genetic variants associated with Parkinson's. It allows 23andMe scientists and collaborators to explore what role these variants play in the progression of Parkinson's disease.

The Michael J. Fox Foundation, the world's largest nonprofit funder of Parkinson's research, funded the postdoctoral program. Through the program, Matthew Kmiecik, Ph.D., a postdoctoral fellow at 23andMe, collaborated with a group of internal scientists to dive deeply into the analysis of the PIP study data. "The Michael J. Fox Foundation postdoctoral fellowship has enabled me to not only grow as a scientist, but also advance our understanding of LRRK2 Parkinson's disease," said Dr. Kmiecik.

The resulting study just published in *Brain* is 23andMe's first paper to utilize a longitudinal prospective data collection. Read the study here.

About 23andMe

23andMe is a genetics-led consumer healthcare and biopharmaceutical company empowering a healthier future. For more information, please visit www.23andMe.com.

Forward-Looking Statements

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