Genetic variations may predispose people to Parkinson's disease following long-term pesticide exposure, study finds

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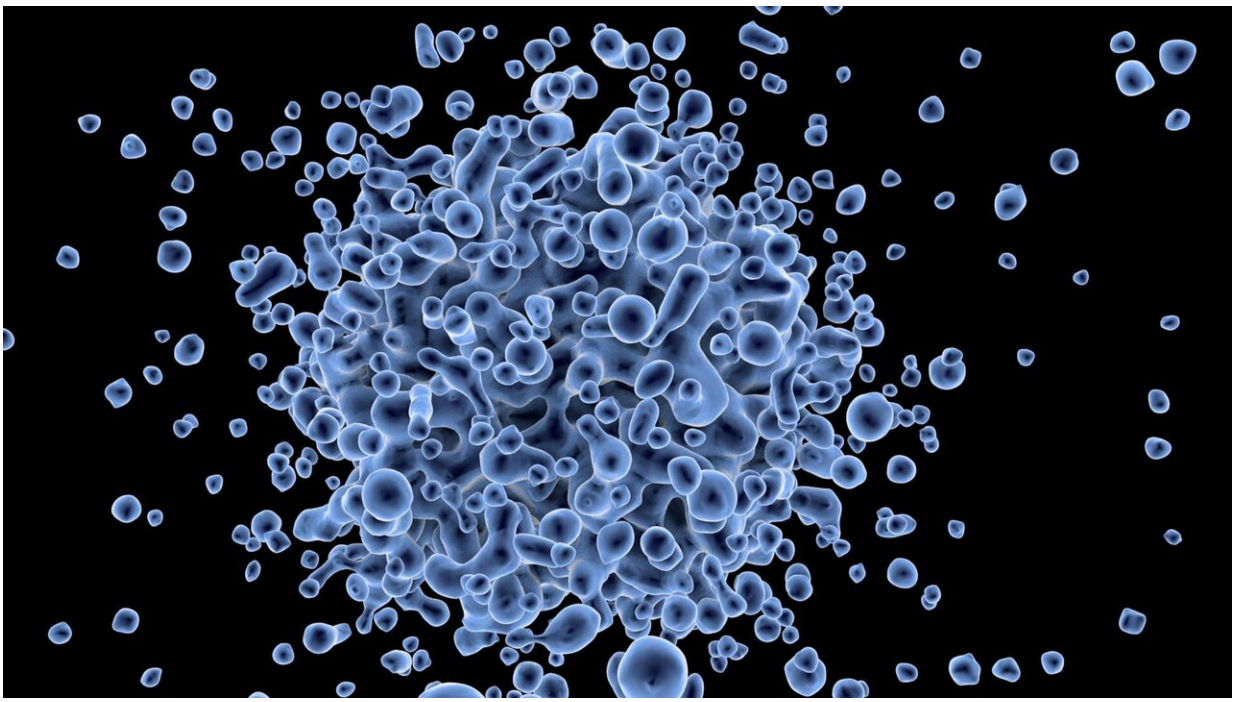

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A new UCLA Health study has found that certain genetic variants could help explain how long-term pesticide exposure could increase the risk of Parkinson's disease.

While decades of research have linked pesticide exposure and Parkinson's disease risk, researchers have sought to explain why some individuals with high exposure develop the disease while others do not.

One longstanding hypothesis has been that susceptibility to the disease is a combination of both environmental and genetic factors.

The new study, published in the journal *npj Parkinson's Disease,* used genetic data from nearly 800 Central Valley (California) residents with Parkinson's disease, many of whom had long-term exposure to 10 pesticides used on cotton crops for at least a decade prior to developing the disease, with some patients having been exposed as far back as 1974.

The researchers examined the study participants' genetic makeup for rare variants in genes associated with the function of lysosomes—cellular compartments that break down waste and debris, thought to be associated with the development of Parkinson's disease—and looked for enrichment of variants in patients with high exposure to pesticide use compared to a representative sample of the general population.

Researchers found that variants in these genes were enriched in patients with more severe Parkinson's disease who also had higher exposure to pesticides. These genetic variants also appeared to be deleterious to protein function suggesting that disruption of lysosomal activity may be underling the development of Parkinson's disease combined with pesticide exposure.

Dr. Brent Fogel, the study's corresponding author and professor of Neurology and Human Genetics, said that while the specific interactions between pesticides and the expression of these genetic variants requires further study, the results suggest that in someone with such variants, long-term exposure to the cotton pesticides could lead to the buildup of toxic

compounds, due to alterations of the cells' ability to break down damaged proteins and organelles—a process known as autophagy—and thus lead to Parkinson's disease.

Previous studies have shown that altered autophagy can result in a buildup of a protein called alpha synuclein, which is abundant in the brain and neurons. As the protein builds up, it forms clumps known as "Lewy" bodies that are a pathological hallmark of Parkinson's disease.

"The study supports the hypothesis that the genetic predisposition comes from minor changes in genes that are associated with lysosomal function," Fogel said. "On a day-to-day basis, these variants are not having much of an impact. But under the right stress, such as exposure to certain pesticides, they can fail, and that could, over time, lead to the development of Parkinson's disease. This is called a gene-environment interaction."

The findings build on decades of research by UCLA Health investigators Drs. Jeff Bronstein and Beate Ritz into the associations between pesticide exposure and Parkinson's disease risk in the Central Valley.

The study's co-lead author and assistant professor of Neurology at UCLA, Dr. Kimberly Paul, said that Parkinson's disease is the fastest growing neurodegenerative disease in the world. While an increase in the number of new patients is expected given the large aging population in the U.S., the rate of new Parkinson's disease patients is outpacing the rate that is expected from aging alone, Paul said.

Paul said the findings of the new study raise the question of whether there are other genetic variants that may be altering the susceptibility to Parkinson's disease among this population, including other biological pathways affected by different types of pesticides.

"These patients were susceptible somehow and if we can figure out why they were susceptible, maybe we can act on those pathways," Paul said.

"There are data for a lot of common disorders suggesting that environmental influences impact the development of these diseases, but we don't yet have a good way of measuring that impact or determining who is specifically at risk," Fogel said. "This is a step forward in that direction."

More information: Lysosomal Genes Contribute to Parkinson's Disease near Agriculture with High Intensity Pesticide Use, *npj Parkinson's Disease* (2024). DOI: 10.1038/s41531-024-00703-4. www.nature.com/articles/s41531-024-00703-4

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