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Indicators of Parkinson's disease risk found in unexpected places

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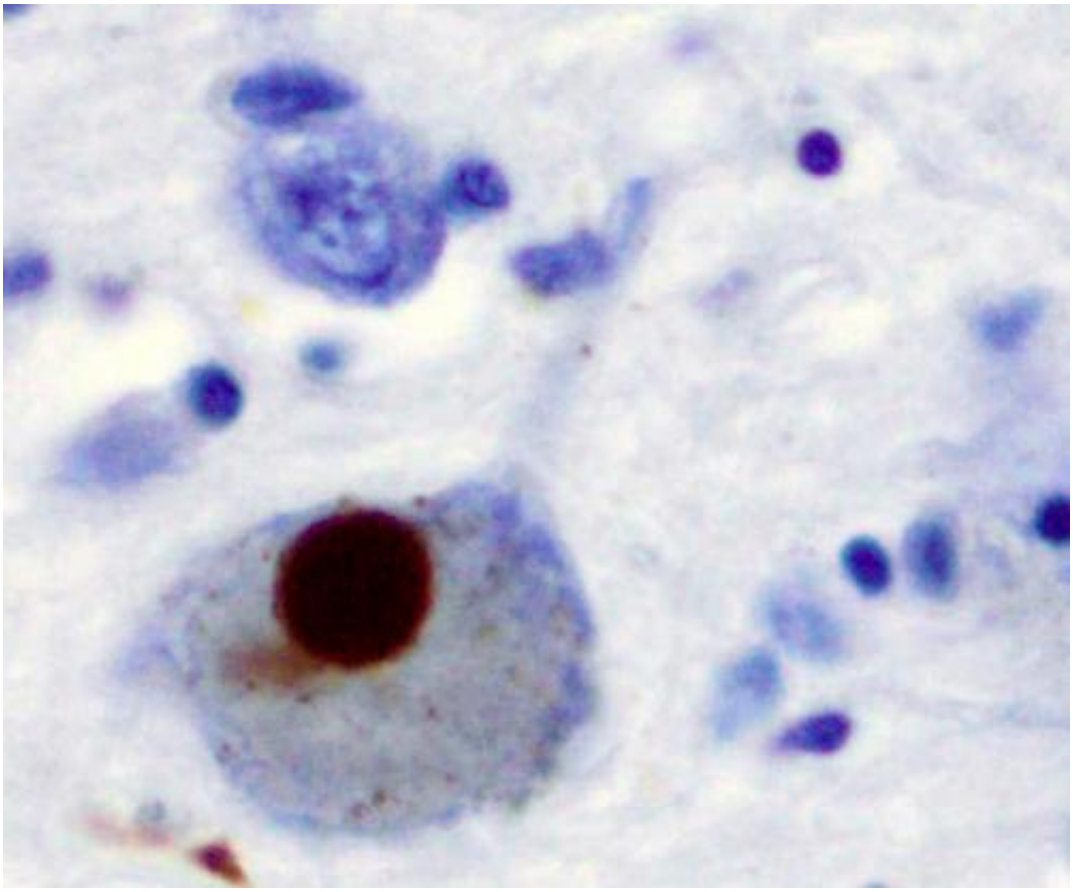

Immunohistochemistry for alpha-synuclein showing positive staining (brown) of an intraneural Lewy-body in the Substantia nigra in Parkinson's disease. Credit: Wikipedia

Clues that point toward new risk mechanisms for developing Parkinson's

disease are hiding in some unusual spots, according to a study published today in *Scientific Reports*.

Tiny changes in DNA that have been linked to Parkinson's, the second most common neurodegenerative disorder after Alzheimer's, were found not only in brain cells, where they were expected, but also in liver, fat, immune and developmental cells. These findings may one day contribute to the development of preventative interventions before the disease's effects become pronounced.

"When we looked at the data, we were quite surprised to see the variation in tissue types," said Gerry Coetzee, Ph.D., a professor at Van Andel Research Institute (VARI) and the study's corresponding author. "Ultimately, if we can more precisely define risk factors for Parkinson's, we can develop ways to mitigate them early on. We still have a long way to go but these findings are some of the first steps down that path."

A cumulative effect

Although these changes, called single-nucleotide polymorphisms (SNPs), are very small, an accumulation of enough SNPs can significantly heighten a person's risk for developing Parkinson's. It can be likened to dropping sand onto a scale—a single grain will have little effect, but if enough grains are added, the balance will tip.

The human genome contains about 80 million SNPs, many of them located in regions of the DNA that were once thought to be junk. Scientists now know that these areas, located outside of genes on the DNA, play critical roles in regulating gene expression and are a useful tool for matching a particular gene with its function or role in disease.

As such, investigating SNPs linked to Parkinson's offers a unique opportunity to answer one of the major questions in Parkinson's

research—what causes or contributes to the disease? While scientists know that five to 10 percent of Parkinson's cases are passed down genetically through families, they're still determining what's behind the majority of cases. The prevailing theory is a mix of genetic and environmental factors create a perfect storm, leading to the hallmark clumping of abnormal proteins that spread through the brain, killing cells that produce a chemical called dopamine that is vital for voluntary movement.

Different tissues, common link

Using information from the federally funded Roadmap Epigenomics Mapping Consortium as a guide, Coetzee, the team at VARI and collaborators at Cedars-Sinai in Los Angeles analyzed 21 of these risk areas, called loci, in 77 cell types. Of these, the team found 12 loci across several tissue types that were particularly enriched—or full of SNPS—indicating an increase in risk.

Intriguingly, only one locus was identified in the substantia nigra, the part of the brain where dopamine-producing neurons die. Other loci were found in liver, fat, immune and developmental cells. It is the first time this type of genome-wide analysis has been used to investigate Parkinson's disease.

Although much more work must be done to unravel exactly how these loci affect risk, there are interesting parallels between the team's findings and recent work done by others investigating Parkinson's. For example, three of the risk loci were found in immune cells, a promising finding as evidence suggests that Parkinson's may be linked to inflammation, the immune system's reaction to help fight off potential threats.

"Only a small percentage of Parkinson's cases are familial and have a

clear and well-defined genetic inheritance. The remaining cases develop the disease seemingly at random," said Patrik Brundin, M.D., Ph.D., director of VARI's Center for Neurodegenerative Science and one of the study's authors. "The emerging view is that Parkinson's is more of a syndrome—a defined set of clinical symptoms and some shared features of brain pathology—with a diverse set of underlying causes. One surprising finding in our study is that only one gene locus was clearly linked to the brain while others were associated with tissues throughout the body. This supports the emerging theory that Parkinson's is a disorder that can be caused by disruptions in cellular processes in many locations, not just one. Furthermore, for the disease to develop in one person there has to be an unfortunate combination of a genetic predisposition and, as yet undefined, environmental insults."

More information: Simon G. Coetzee et al. Enrichment of risk SNPs in regulatory regions implicate diverse tissues in Parkinson's disease etiology, *Scientific Reports* (2016). DOI: 10.1038/srep30509

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