# Immune gene variant magnifies Parkinson's risk from insecticide exposure

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Exposure to pyrethroids may interact with genetics via the immune system to increase Parkinson's risk. Pyrethroids are found in the majority of commercial household insecticides. Although they are neurotoxic for insects, exposure to them is generally considered safe for humans by federal authorities. Credit: Thinkstock.

Genetic variation and exposure to pesticides both appear to affect risk for Parkinson's disease. A new study has found a connection between these two risk factors, in a way that highlights a role for immune

responses in progression of the disease.

The results are published in the inaugural issue of *NPJ Parkinson's Disease*.

The findings implicate a type of pesticide called pyrethroids, which are found in the majority of commercial household insecticides, and are being used more in agriculture as other insecticides are being phased out. Although pyrethroids are neurotoxic for insects, exposure to them is generally considered safe for humans by federal authorities.

The study is the first making the connection between pyrethroid exposure and genetic risk for Parkinson's, and thus needs follow-up investigation, says co-senior author Malu Tansey, PhD, associate professor of physiology at Emory University School of Medicine.

The genetic variation the team probed, which has been previously tied to Parkinson's in larger genome-wide association studies, was in a non-coding region of a MHC II (major histocompatibility complex class II) gene, part of a group of genes that regulate the immune system.

"We did not expect to find a specific association with pyrethroids," Tansey says. "It was known that acute exposure to pyrethroids could lead to immune dysfunction, and that the molecules they act on can be found in immune cells; now we need to know more about how longer-term exposure affects the immune system in a way that increases risk for Parkinson's."

"There is already ample evidence that brain inflammation or an overactive immune system can drive the progression of Parkinson's. What we think may be happening here is that environmental exposures may be altering some people's immune responses, in a way that promotes chronic inflammation in the brain."

For this study, Emory investigators led by Tansey and Jeremy Boss, PhD, chair of microbiology and immunology, teamed up with Stewart Factor, DO, head of Emory's Comprehensive Parkinson's Disease Center, and public health researchers from UCLA led by Beate Ritz, MD, PhD. The first author of the paper is MD/PhD student George T. Kannarkat.

The UCLA researchers used a California state geographical database covering 30 years of pesticide use in agriculture. They defined exposure based on proximity (someone's work and home addresses), but did not measure levels of pesticides in the body. Pyrethroids are thought to decay relatively quickly, especially in sunlight, with half-lives in soil of days to weeks.

In a group of 962 people from California's Central Valley, a common MHC II variant combined with above-average exposure to pyrethroid pesticides to increase the risk of Parkinson's disease. The riskiest form of the gene (where an individual is carrying two risk alleles) was found in 21 percent of Parkinson's patients and 16 percent of controls.

In this group, genes or pyrethroid exposure by themselves did not significantly increase Parkinson's risk, but together, they did. People with more-than-average exposure to pyrethroids and carrying the riskiest form of the MHC II gene had 2.48 times more risk for Parkinson's than less-exposed people with the least risky gene form. Exposure to other types of pesticides such as organophosphates or paraquat did not heighten risk in the same way.

Larger genetic studies (some including Factor and his patients) have previously identified variations in MHC II genes as having connections to Parkinson's. Puzzlingly, the same genetic variants affect Parkinson's risk differently in Caucasian/European and Chinese populations. MHC II genes are highly variable between individual humans; that's why they

play a big role in organ transplant matching.

Other experiments showed that the genetic variant connected to Parkinson's is connected with immune cell function. In a group of 81 Parkinson's patients and control participants from Emory of European ancestry the immune cells from people who had the higher-risk MHC II gene variant studied in California displayed more MHC molecules on their surfaces, the researchers found.

MHC molecules are central to the process of "antigen presentation," a driver for T cells to become activated and have the rest of the immune system get involved. Heightened expression of MHC II was present in resting cells from both Parkinson's patients and healthy controls; but greater responsiveness to immune challenges were observed in Parkinson's patients with the higher risk genotype.

The authors conclude: "Our data suggest that cellular biomarkers (like MHC II activation) may prove more useful than soluble molecules in plasma and cerebrospinal fluid to identify individuals at risk for disease or for patient recruitment into neuroprotective trials testing immunomodulatory drugs."

**More information:** "Common genetic variant association with altered HLA expression, synergy with pyrethroid exposure, and risk for Parkinson's disease: an observational and case–control study." *NPJ Parkinson's Disease* 1, Article number: 15002 (2015) DOI: 10.1038/npjparkd.2015.2

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