

# The potential role of genetic and environmental interaction in autism spectrum disorder

14 July 2021



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Researchers at Johns Hopkins Bloomberg School of Public Health have shown in a brain organoid study that exposure to a common pesticide synergizes with a frequent autism-linked gene mutation.

The results represent one of the clearest pieces of evidence yet that genetic and environmental factors may be able to combine to disturb neurodevelopment. Researchers suspect that genetic and environmental factors might contribute to the increased prevalence of autism spectrum disorder, a developmental disorder characterized by cognitive function, social, and communication impairments.

The study's use of [brain organoids](#) also points the way towards quicker, less expensive, and more human-relevant experimentation in this field when compared to traditional animal studies.

The brain [organoid](#) model, developed by the

Bloomberg School researchers, consists of balls of cells that are differentiated from human stem cell cultures and mimic the developing human brain. The researchers found in the study that chlorpyrifos, a common pesticide alleged to contribute to developmental neurotoxicity and autism risk, dramatically reduces levels of the protein CHD8 in the organoids. CHD8 is a regulator of gene activity important in brain development. Mutations in its gene, which reduce CHD8 activity, are among the strongest of the 100-plus [genetic risk factors](#) for autism that have so far been identified.

The study, which appears online July 14 in *Environmental Health Perspectives*, is the first to show in a human model that an environmental risk factor can amplify the effect of genetic risk factor for autism.

"This is a step forward in showing an interplay between genetics and environment and its potential role for autism spectrum disorder," says study lead Lena Smirnova, Ph.D., a research associate in the Department of Environmental Health and Engineering at the Bloomberg School.

Clinically rare as recently as 40 years ago, autism spectrum disorder now occurs in roughly two percent of live births, according to the Centers for Disease Control and Prevention.

"The increase in autism diagnoses in recent decades is hard to explain—there couldn't have been a population-wide genetic change in such a short time, but we also haven't been able to find an environmental exposure that sufficiently accounts for it," says study co-author Thomas Hartung, MD, Ph.D., professor and Doerenkamp-Zbinden Chair in the Bloomberg School's Department of Environmental Health and Engineering. Hartung is

also director of the Center for Alternatives to Animal Testing at the Bloomberg School. "To me, the best explanation involves a combination of genetic and environment factors," says Hartung.

How environmental factors and genetic susceptibilities interact to increase risk for autism spectrum disorder remains mostly unknown, in part because these interactions have been difficult to study. Traditional experiments with laboratory animals are expensive and, especially for disorders involving the brain and cognition, of limited relevance to humans.

Advances in stem cell methods in the past decades have allowed researchers to use human skin cells that can be transformed first into stem cells and then into almost any cell type and studied in the lab. In recent years, scientists have expanded beyond simple lab-dish cell cultures to make cultures of three-dimensional organoids that better represent the complexity of human organs.

For their study, the researchers used brain organoids to model the effects of a CHD8 gene disruption combined with exposure to chlorpyrifos. A group led by co-author Herbert Lachman, MD, professor at Albert Einstein College of Medicine, engineered the cells that make up the organoids to lack one of the two normal copies of the CHD8 gene. This modeled a substantial, but less-than-total, weakening of the CHD8 gene's activity, similar to that seen in people who have CHD8 mutations and autism. The researchers then examined the additional effect of exposure to chlorpyrifos, which is still widely used on agricultural produce in the U.S. and abroad.

"High-dose, short-term experimental exposures do not reflect the real-life situation, but they give us a starting point to identify genetic variants that might make individuals more susceptible to toxicants," says Smirnova. "Now we can explore how other genes and potentially toxic substances interact."

The researchers found that the brain organoids with just one copy of the CHD8 gene had only two-thirds the normal level of CHD8 protein in their cells, but that chlorpyrifos exposure drove CHD8 levels much lower, turning a moderate scarcity into a severe

one. The exposure demonstrated clearly how an environmental factor can worsen the effect of a genetic one, likely worsening disease progression and symptoms.

As part of their study, the researchers compiled a list of molecules in blood, urine, and brain tissue that prior studies have shown to be different in autism spectrum patients. They found that levels of several of these apparent autism biomarkers were also significantly altered in the organoids by CHD8 deficiency or chlorpyrifos exposure, and moreso by both.

"In this sense, we showed that changes in these organoids reflect changes seen in autism patients," Smirnova says.

The findings, according to the researchers, pave the way for further studies of gene-environment interactions in disease using human-derived organoids.

"The use of three-dimensional, human-derived, brain-like models like the one in this study is a good way forward for studying the interplay of genetic and [environmental factors](#) in [autism](#) and other neurodevelopmental disorders," Hartung says.

**More information:** Sergio Modafferi et al, Gene–Environment Interactions in Developmental Neurotoxicity: a Case Study of Synergy between Chlorpyrifos and CHD8 Knockout in Human BrainSpheres, *Environmental Health Perspectives* (2021) [DOI: 10.1289/EHP8580](https://doi.org/10.1289/EHP8580)

Provided by Johns Hopkins University Bloomberg School of Public Health

APA citation: The potential role of genetic and environmental interaction in autism spectrum disorder (2021, July 14) retrieved 19 October 2021 from <https://medicalxpress.com/news/2021-07-potential-role-genetic-environmental-interaction.html>

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