A genetic mutation found to cause chronic lung disease in indigenous children

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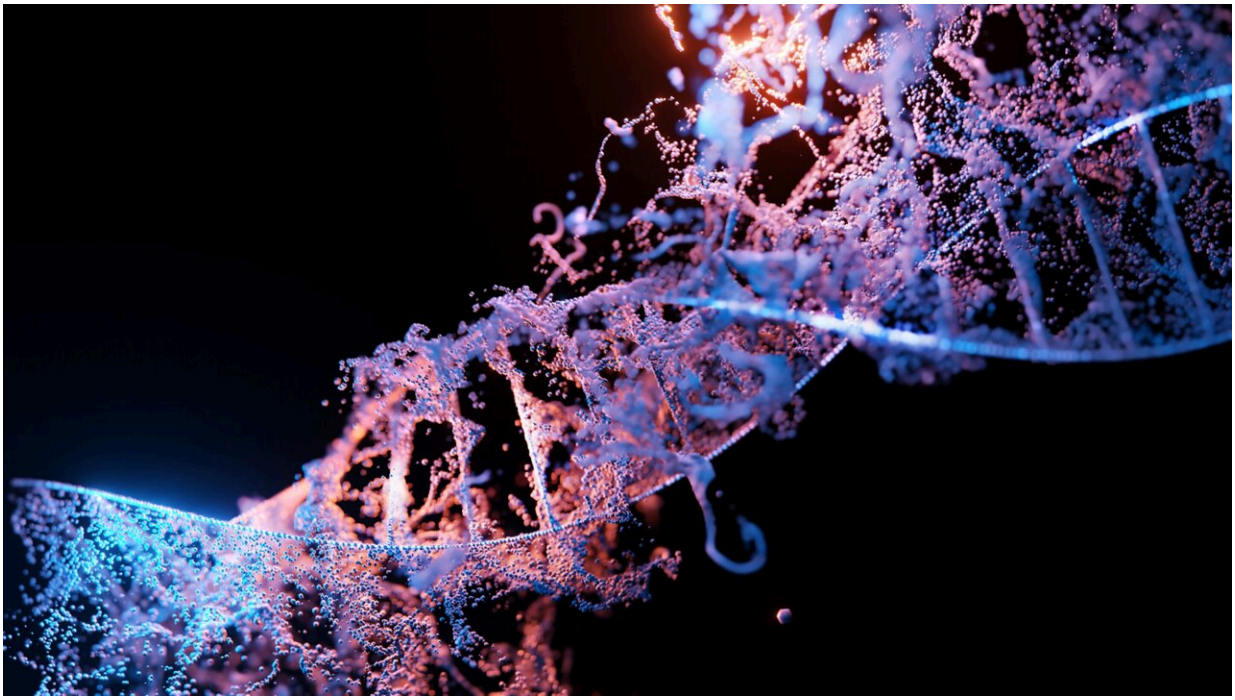

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Overcrowded housing, high rates of tobacco exposure, poor vaccination uptake and damage after severe respiratory infection in infancy: these are some of the reasons that are sometimes suggested to explain why indigenous children suffer more severe lung infections than other children in North America—with no conclusive proof.

According to a team of scientists led by Dr. Adam Shapiro at the Research Institute of the McGill University Health Center (RI-MUHC), one of the explanations could lie in one specific genetic mutation known to cause a rare disease called primary ciliary dyskinesia (PCD). Working with other physicians and scientists in Canada and the United States, Dr. Shapiro found four cases of this disease in unrelated indigenous North American children caused by identical mutations in the gene DNAL1. This discovery is the subject of an article published recently in the *Journal of Pediatrics*.

"When we found First Nations children with primary ciliary dyskinesia caused by mutations in an extremely rare gene, we knew there would be other cases, so we kept looking. The fact that we found four cases among dispersed indigenous populations suggests that PCD may be much more common in the First Nations than we ever thought," says Dr. Shapiro, investigator in the Child Health and Human Development Program at the RI-MUHC and pediatric respirologist at the Montreal Children's Hospital of the MUHC. "This should encourage other physicians across North America to test for PCD in indigenous children with chronic lung disease."

Primary ciliary dyskinesia is a rare genetic disease of the cilia—microscopic hair-like structures that sweep the airways, ears and sinuses to keep them free from inhaled particles and bacteria that cause infection. Symptoms generally present shortly after birth or in early childhood. They include chronic wet cough and nasal congestion, recurring pneumonia and middle ear infections. In many cases, PCD is also associated with bronchiectasis—a chronic condition characterized by permanent damages to the airways, which is 30-40 times more common in certain indigenous populations than in affluent western societies. Children with PCD often require hospitalization.

"People with PCD cannot effectively get mucus out of their lungs, which

leads to many bronchial infections. But because PCD symptoms look like a number of other common lung diseases, the disease often goes unnoticed," explains Dr. Shapiro, who has worked with the Genetic Disorders of Mucociliary Clearance Consortium for many years pioneering the diagnostic criteria for PCD.

The importance of early diagnosis

When the disease is diagnosed early, a treatment can be offered to help slow down its progression. Unfortunately, diagnosing PCD is challenging, because it requires a series of tests to rule out more common diagnoses, as well as specialized tests to find faulty genes linked to the disease.

"So far, we have found variants in more than 50 different genes that cause PCD, and that is why finding identical mutations in one specific gene, among geographically distant Canadian First Nations and Native American populations, is so significant," adds Dr. Shapiro. "Our finding means further PCD genetic testing and population analyses could detect larger numbers of indigenous PCD patients, who would benefit from early disease recognition and timely treatment initiation. It also means respiratory conditions in indigenous children should not be blamed on socioeconomic exposures or on damage from past respiratory infections unless extensive testing (including PCD genetics) has been performed."

The authors of the study emphasize that PCD should be suspected and investigated in indigenous patients with key PCD clinical features starting in early infancy and/or with bronchiectasis. In health centers lacking specific PCD expertise, diagnosis testing could be pursued using commercial genetic testing.

Patient-oriented research

Actively engaged in new gene discoveries for PCD, Dr. Shapiro holds a clinic that provides state-of-the-art diagnostic testing, with phenotype and genotype testing. He also participates in numerous pharmaceutical trials for novel therapeutic agents to treat PCD and other respiratory diseases.

"Here at the MUHC, we have diagnosed one of the largest PCD patient populations in the world. We have developed a specialized expertise and have acquired one of the only machines in Canada that can perform a non-invasive test to measure a special gas coming out the nose called nasal nitric oxide, which is very low in PCD patients," says Dr. Shapiro, who is also an associate professor in the Department of Pediatrics at McGill University. "What we do is real patient-oriented research: research that is part of the clinical care."

More information: Karolina Poplawska et al, Deletions in DNAL1 Cause Primary Ciliary Dyskinesia Across North American Indigenous Populations, *The Journal of Pediatrics* (2023). DOI: 10.1016/j.jpeds.2023.01.023

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