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Childhood asthma tied to combination of genes and wheezing illness

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About 90 percent of children with two copies of a common genetic variation and who wheezed when they caught a cold early in life went on to develop asthma by age 6, according to a study to be published March 28 by the *New England Journal of Medicine*.

These children, all from families with a history of asthma or allergies, were nearly four times as likely to develop the disease as those who lacked the genetic variation and did not wheeze. The effects of each—the genetic variation and wheezing illness caused by a human rhinovirus infection—are not merely additive but also interactive, the authors say.

The genetic marker studied, a variation on chromosome 17, is common. Half of the children in the study had one copy and 25 percent had two. Colds caused by human rhinoviruses also are extremely common, affecting almost all infants. But the combination of genetic risk plus the wheezing response to rhinovirus infection by children under age 3 was tightly linked to the development of asthma by age 6.

"We found that the interaction between this specific wheezing illness and a gene or genes on a region of chromosome 17 determines childhood asthma risk," said study author Carole Ober, PhD, Blum-Riese Professor of Human Genetics at the University of Chicago. "The combination of genetic predisposition and the child's response to this infection has a huge effect."

Wheezing caused by respiratory syncytial virus (RSV), a more serious but less common childhood infection, did not show this same interaction.

Several genome-wide association studies have linked asthma to genetic variation on a region of chromosome 17, referred to as 17q21. Although this variation applies primarily to early-onset asthma, it still "dwarfs every other asthma-related genetic risk factor," Ober said.

Exactly how the genes and viral infection interact to cause asthma is unclear. Two genes in the 17q21 region may play a role. One of them, known as ORMDL3, is the "most likely candidate," Ober said. The protein produced by ORMDL3 is found in the endoplasmic reticulum membrane, the same component of airway cells that rhinovirus uses to makes more copies of itself. Less is known about the function of the second gene, GSDMB.

The researchers studied two carefully monitored cohorts of children from families at high risk for asthma. All of the 200 children in the COAST cohort, based at the University of Wisconsin under the leadership of Robert Lemanske, MD, principal investigator of the project, had at least one parent with asthma, respiratory allergies, or both. They were followed from birth and evaluated for asthma at age 6. The 297 Danish children in the COPSAC cohort were born to mothers with asthma and evaluated for asthma at age 7.

The researchers first investigated the links between genes, wheezing with viral infection, and asthma in the COAST group, in which they found significant interactions. Less than 30 percent of children in this group who lacked the asthma-related genetic marker were subsequently diagnosed with the disease, compared to 40 percent of children with one at-risk allele and 50 percent with two. Children who had two copies of the asthma-related genetic variation also had far more HRV-related wheezing illnesses.

When the researchers combined both factors, the difference was striking. Only about 25 percent of children who had no wheezing illness from HRV developed asthma. About 40 percent of those who wheezed in the first three years of life but lacked the risk-related genes got asthma. That increased to nearly 60 percent for those with one copy of the asthma-related allele and to 90 percent for those with two copies.

Next they sought to replicate that finding in a similar group, but from a different continent. Although the overall asthma prevalence, based on slightly different criteria in the Danish cohort, was lower, the more-than-additive association between the at-risk genotype, wheezing illness in early life and asthma diagnosis persisted.

To see how exposure to HRV altered expression of genes associated with the 17q21 marker, the University of Chicago researchers recruited 100 normal adult volunteers, collected blood from them and exposed immune-system cells from the blood to HRV. The leading suspect, ORMDL3, had the most robust response, more than doubling its presence in exposed cells.

This result suggests that "higher expression of ORMDL3 may increase the efficiency of the infection or viral replication in respiratory epithelial cells," according to the study's first author, Minal Çalışkan, a graduate student in Ober's laboratory.

"This is the site where rhinovirus infection and replication occur," she explained. "Upregulation of this gene may lessen these cells' ability to repair the airway after an HRV infection, a feature associated with asthma. Our next project is to look more closely at this process in airway epithelial cells."

What can parents do to prevent early onset asthma? At this point, "nothing that we know of," Ober said. Parents can't prevent their

children from catching colds, but "perhaps they could work with their pediatricians to find proactive ways to prevent wheezing in young children with the asthma genotype."

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