Gene variant increases risk of asthma

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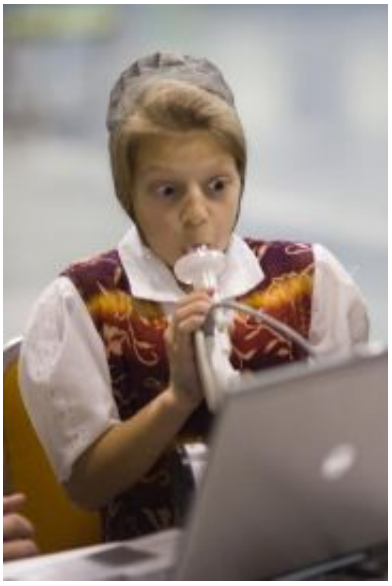

Testing lung function in a Hutterite community. Credit: Jason Smith for the University of Chicago Medical Center

A tiny variation in a gene known as CHI3L1 increases susceptibility to asthma, bronchial hyperresponsiveness and decline in lung function, researchers report early online in the *New England Journal of Medicine*. (The printed version will appear in the April 17 issue). The gene variant causes increased blood levels of YKL-40, a biomarker for asthma. A slightly different version of the genetic variation lowers YKL-40 levels and protects against asthma.

Although the original discovery came from a study of a genetically

isolated population, the Hutterites of South Dakota, the researchers were able to confirm the same connections between the CHI3L1 variations, YKL-40 levels and asthma susceptibility in three genetically diverse Caucasian populations from Chicago; Madison, Wisconsin; and Freiberg, Germany.

This gene, "may have important implications in the early identification of, susceptibility to, and prevention and treatment of asthma," said Elizabeth G. Nabel, M.D., director, the National Heart, Lung, and Blood Institute.

"This is exciting because it connects asthma susceptibility to a whole new pathway at the protein and the genetic levels," said study author Carole Ober, professor of human genetics at the University of Chicago Medical Center. "There is a good deal more we need to find out about this connection, but now we know where to look."

"This is also the most significant genetic discovery based on our years of gathering data on asthma in the Hutterites," Ober added. "This is a group with enormous potential to advance our understanding of the genetic underpinnings of disease. We now have a remarkable collection of data, which we expect will lead us to many more insights."

Ober and colleagues at the University of Chicago had long been searching for genetic factors that could influence the risk of common diseases, such as asthma. To simplify this quest, they have focused since 1994 on the Hutterites, a genetically isolated U.S. religious community descended from about 90 people. The Hutterites came to the United States in 1874 and settled in small communal farming colonies in what is now South Dakota. Today Hutterite communities are present in the Dakotas, Minnesota, Montana, Washington and Canada.

They provide an ideal community for genetic studies because they are all

members of a large pedigree that is known back to the 1700's and they live communally, sharing resources and maintaining a traditional lifestyle. "They eat the same food, live off the same allowance and have the same education," said Ober, who has been working with them since 1979. They have similar, but not identical genomes. "So the genes that make a difference are easier to detect."

In 1996 and 1997, Ober's team gathered clinical data about asthma from more than 700 members of the Hutterite communities, and stored blood samples that were recently used to measureYKL-40 levels. About 11 percent of Hutterites had asthma and another 12 percent had bronchial hyperresponsiveness.

The genetic studies took on a sharper focus in 2007, when a team led by Geoffrey Chupp of Yale University showed that, on average, patients with asthma had higher levels of the protein YKL-40 in their blood than people without asthma, and that those with more severe asthma had even higher levels.

YKL-40, a natural suspect as a cause of asthma, belongs to a family of enzymes called chitinases. These enzymes are part of the innate immune system's response to chitin, a common biologic polymer found especially in insects – including dust mites and cockroaches, which have been associated with asthma – as well as in certain disease-causing organisms, including fungi and parasitic worms. The chitinases help break down chitin. They also trigger inflammation, which is a central component of asthma.

Working with Chupp's laboratory, Ober found that mean YKL-40 levels were also increased among Hutterites with asthma or hyperresponsive airways. Ober's group also showed that these elevated YKL-40 levels were handed down from generation to generation, indicating that differences between individuals were due nearly entirely to genetic

differences.

So they began looking for variations in the CHI3L1 gene on chromosome 1 that codes for YKL-40,. They found one very slight genetic difference between those with asthma and those without. Hutterites with asthma were more likely to have a small but consistent variation in one part of the gene, called a promoter, which regulates when the gene is expressed.

That variation changes one DNA base pair, out of the 3 billion in the human genome, at a location in the CHI3L1gene known as -131C/G. Those with asthma were more likely to have a cytosine (C), rather than guanine (G) at this location.

Those inheriting two copies of a C at -131 had higher YKL-40 levels and an asthma prevalence of 0.20. Those with CG had intermediate YKL-40 levels and an asthma prevalence of 0.12. Those with GG had the lowest YKL-40 levels and a prevalence of only 0.08, less than half that of the CC allele.

To see if these results could be generalized from the genetically isolated Hutterite population to a more diverse group, the researchers tested the same variations in the CHI3L1 gene in 178 Caucasian children enrolled in prospective birth cohort, known as COAST, a collaboration led by Robert Lemanske of the University of Wisconsin at Madison.

They also looked for correlations between asthma and SNP -131C/G in two clinical samples, one from the Children's University Hospital in Freiberg, Germany (344 children with asthma and 28, and 94 without), and one from the asthma clinics at the University of Chicago Medical Center (99 children and adults with asthma and 197 without).

In the two clinical samples, those with the CC configuration at position

131 were more likely to have asthma, with CG intermediate and GG the lowest risk of the disease. In the COAST cohort, many subject were still too young to have developed asthma, but the genetic patterns was closely associated with YKL-40 levels, and this association was already present at birth.

The authors suspect that the change from C to G at this site reduces expression of the gene, resulting in lower levels of YKL-40 and protection from asthma.

Although variation in CHI3L1 appears to be one of the most significant genetic triggers yet discovered for susceptibility to asthma, it is far from the sole cause of the disease, the researcher caution. In the Hutterites, it explains 9.4 percent of the variance in YKL-40 levels, suggesting that additional genetic variants also influence these levels. Finding those variations "could identify additional genes," they add, "with significant impact on asthma risk and lung function."

"This evolutionarily ancient pathway involving the innate immune system plays a surprisingly important role in asthma pathogenesis," said Ober, "and a single genetic variant in the CHI3L1 gene may account for most of this risk."

This could have a significant impact on drug development, she added. "For some people, if you block YKL-40 you might dramatically reduce the severity of the disease. Knowing the genotype at SNP -131C might identify those who most likely to benefit from such a treatment."

Asthma is a chronic, treatable disease that causes narrowing of the airways, making breathing difficult at times. More than 22 million people in the United States have asthma, including 6.5 million children under age 18, according to the Centers for Disease Control and Prevention (CDC). The disease generates annual health care costs

estimated at $14 billion.

Source: University of Chicago