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Key to Asthma Attacks May Lie in Mouse Genes, Promising Research Published by Academy of Sciences

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NEWS RELEASE

KEY TO ASTHMA ATTACKS MAY LIE IN MOUSE GENES, PROMISING RESEARCH PUBLISHED BY ACADEMY OF SCIENCES

DAYTON, Ohio — Something as simple as watching water flow may hold the key to understanding asthma attacks, and the route to finding out could be mapped on the mouse genome.

Carissa M. Krane, assistant professor of biology at the University of Dayton, works with mice to mimic the traits of clinical patients with asthma. "We can do the same battery of tests on mice and find that mice with induced asthma exhibit similar responses as do human asthma patients," she said. It's due to the similarities between the mouse and human genomes, where the relevant strings of genes are located in the same positions and have very similar functions in both humans and mice.

Krane is the lead author of "Aquaporin 5-deficient mouse lungs are hyperresponsive to cholinergic stimulation," to be published in the Nov. 20 issue of the *Proceedings of the National Academy of Sciences*. Her field is known as physiological genomics — using both physiology and genetics for research in the post-human genome sequencing era.

It's the movement of water through cells that lies at the base of Krane's research.

"Water is critically important in all living systems," she said. "The inside of our cells are separated from the fluid outside of our cells by a fatty membrane layer called a lipid bilayer, and water can't move through that layer very fast. Imagine a drop of water sitting on a pat of butter. However, our cells have evolved a mechanism that allows for water to move quickly through this lipid bilayer when we need it. That's what happens when we cry or when we salivate.

"Aquaporins are holes or channels in the cell membrane that allow movement of water through cells in a rapid fashion only when we need it and not when we don't. We are examining what happens to an organism when these channels malfunction."

Lack of regulation of the water in lung tissues is one cause of asthma.

Krane and her research colleagues showed for the first time that mice susceptible to

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induced asthma — not a chronic condition, but one caused by physical exertion or exposure to an environmental irritant — show a deficient gene that is linked to aquaporin regulation.

"We found that the tight bronchial constriction and slow relaxation that is characteristic of asthma happens in mice without a specific aquaporin — aquaporin 5. And aquaporin 5 is the main water channel in the lungs. So what is aquaporin 5 doing to mediate the fluid in the lungs that can be a part of the physical process of bronchial constriction? How does its absence affect normal lung function?"

Or, to race ahead of research, will it one day be possible to treat this defect in the 10.6 million Americans who suffer asthma attacks?

Maybe.

"The supposition that a genetic change in the aquaporin 5 gene is involved in asthma is supported by two independent methods, and that strengthens the argument. We have physiological and genetic confirmation, and that makes this a really good candidate for human asthma," Krane said.

The study grew out of Krane's post-doctoral work at the University of Cincinnati. She's continuing her investigation at UD, with the help of one graduate and five undergraduate students conducting research in her Sherman Hall lab. The next phase will include further study of aquaporin 5 and how it regulates the intensity and duration of bronchial constriction. They will also assess the genes of clinical patients with asthma to see if they too are missing functional aquaporin 5.

Krane's research has implications for more than asthma. "Aquaporins are involved in many fluid regulatory processes that can be affected by everyday pharmaceutical drugs. A lot of elderly people take drugs for hypertension or congestive heart failure that have side effects of a dry mouth and dry eyes. These are essential drugs for major problems, but they can compromise the quality of life. If we knew more about where to target drugs and how to target drugs so that aquaporin regulation wasn't compromised, we could maybe eliminate that side effect."

But as a scientist, her enthusiasm is tempered by experience.

"The asthma and genetics link is complex and difficult to study because there are probably a number of different things happening to contribute to the condition," Krane said. "Learning the physiological genomic implications to water channel function will allow us to develop better diagnosis and treatment for patients with asthma."

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