MedicalXpress

Man's best friend helps to solve puzzle of a genetic disorder

December 6 2010

(PhysOrg.com) -- Observations in purebred dogs led an international team of scientists from Duke University Medical Center and other institutions to make an important gene discovery in a devastating human genetic condition hallmarked by severe inflammation of the respiratory system, primary ciliary dyskinesia (PCD).

Primary cilia, which resemble microscopic "hairs" on the surface of a cell (although not related to hair), are complex structures that affect many aspects of health, including a regular, beating rhythm in the trachea's cells to move mucus to the throat, and also for proper motion and propulsion in sperm cells, essential for fertilization.

A team led by Professor Michel Georges at the University of Liège in Belgium recently examined Old English sheepdogs that suffered from chronic airway inflammation at birth. They then explored the possibility that the cause could be a ciliary abnormality and took electron micrographs of the tracheal cells of these dogs, which showed a unique structural defect in the cilia. Meanwhile, the purebred genetic makeup of the affected dogs enabled researchers to narrow the number of possible mutated genes from thousands to 151.

"Working together across two continents, we were able to see how the dogs, all tracing back to the same founder mother, had this particular defect on electron micrographs, and we mined databases to find likely proteins that play a role in ciliary function. Then we were able to identify the causative mutation in dogs and importantly, to identify loss-

of-function mutations in the same gene in humans and show that disruption of this protein disrupts normal airway function," said Nicholas Katsanis, Ph.D., co-senior author and Jean and George Brumley Jr., MD. Professor of Pediatrics, Professor of Cell Biology, and director of the Duke Center for Human Disease Modeling.

Meanwhile, the labs of Serge Anselm in France and Heymut Omran in Germany had been collecting and studying samples from patients with PCD for many years, but they also collected electron micrographs of cilia from the tracheas of these patients. The team found that as many as 40 percent of human PCD patients with the same ultrastructural ciliary defect had mutations in the same gene resulting in airway problems. "While we could go back to all humans with PCD and run expensive large-scale genome studies, it is better to inform our studies with what we know about cilia and ask which patients with the disease have electron micrographs similar to those of the dogs," Katsanis said.

Co-lead author Erica Davis, Ph.D. who did graduate studies at the University of Liège and is now faculty in the Duke Department of Pediatrics, said, "The fact that nearly half of patients with a particular ciliary signature have a chance of having this genetic condition highlights how animal biology can help to inform clinical practice, and at the same time, further inform biology about how cells build and maintain moving cilia."

Davis said that the work is only part of the puzzle, but each solution and new piece of information is important.

Asked how just knowing one genetic mutation in a rare genetic disease, without a cure yet, can help people, Katsanis gave an analogy: "In the medieval times of exorcisms, the first requirement was being able to identify the name of the demon," he said. "Knowing what you have is fundamental to human nature. In order to deal with a medical problem

emotionally, socially or medically, you have to be able to conceptualize what is happening in the body. People have an exceptional capacity to process even bad news if they know what they have to deal with. Our work is helping to pull back the veil of the unknown."

Katsanis is a world expert in the group of genetic disorders in which the primary cilium of cells is abnormal and leads to a host of problems. About one child in 1,000 live births will have a disease of the primary cilium (ciliopathy), an incidence that is in the range of Down's syndrome, said Katsanis.

The study has been published in *Nature Genetics* on Dec. 5, 2010.

Provided by Duke University