How an emerging disease in dogs is shedding light on cystic fibrosis

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A canine gallbladder disease that involves the accumulation of abnormal mucus similar to that seen in human cystic fibrosis (CF) patients is caused by improper expression of the gene associated with CF in

humans. The finding could have implications for human CF patients as well as for animal models of CF.

The paper is published in the *American Journal of Physiology-Gastrointestinal and Liver Physiology*.

The disease, gallbladder mucocele formation, is caused by the slow accumulation of thick, dehydrated mucus that interferes with normal gallbladder function and eventually leads to obstruction and rupture. Mucocele formation is seen primarily in purebred dogs—in the U.S. it's most common in Shetland sheepdogs, whereas in the U.K. border terriers are most impacted.

"We really only started seeing this disease about 20 years ago in a handful of breeds," says Jody Gookin, professor of small animal internal medicine at North Carolina State University and corresponding author of the research. "What captured my attention was how similar these gallbladders looked to those in animal models of CF."

The thick immobile mucus associated with CF in humans stems from a defect in a gene called CFTR, which is responsible for depositing channels in epithelial cells that then secrete chloride and water. These channels lubricate the cell surface, keeping mucus moist and moveable. In CF, the absence of these lubricating channels means that the mucus dehydrates and clogs lungs and intestines. But in human patients, gallbladders don't fill up with dehydrated mucus.

"There are no recorded instances of naturally occurring CF in any non-human species," Gookin says. But when researchers study CF in animal models by knocking out the CFTR gene, those animals often develop the same gallbladder pathology that we see in dogs with mucocele formation. "That led us to wonder whether dogs with mucoceles had a mutation in CFTR—but they didn't. What they did have was a failure of

CFTR to function."

Gookin performed whole genome sequencing on blood collected from eight Shetland sheepdogs with gallbladder mucocele formation and compared the location and frequency of variants in the CFTR gene to 115 dogs from 12 breeds at high risk for mucocele formation and 2,519 dogs from 340 breeds considered low risk for mucocele formation. There were no significant differences between the groups. Additionally, the dogs with mucocele formation did not have mutations in CFTR in locations where humans with CF do.

"What that means is that somehow these dogs are acquiring a dysfunction of the CFTR channel that is not based on a defect in the gene," Gookin says.

"It could be due to the influence of other genes and environmental factors that influence CFTR function. Our next steps will be looking at the entire genome of these dogs to see if there are other mutations that could be a factor—if there's something else in their genome that makes them susceptible to developing this disease.

"The most eye-opening piece for me is the idea that it is possible to develop a CF-like disease that isn't caused by a mutation in the CFTR gene. Identifying the underlying cause of CFTR dysfunction in dogs with mucocele formation has important implications for people where similar factors might contribute to CF-like diseases—or reveal new treatment targets for CF."

Research techs Jenny Holmes and Stephen Stauffer; veterinary student Nicole Torres-Machado; former veterinary student Bryanna Meredith; postdoctoral scholar Michael Vandewege; radiologist Gabriela Seiler; small animal surgeon Kyle Matthews; and Dean of the College of Veterinary Medicine Kathryn Meurs are NC State co-authors. Steven

Friedenberg of the University of Minnesota St. Paul and Lane Clark of the University of Missouri, Columbia, also contributed to the work.

More information: Jody L. Gookin et al, Acquired dysfunction of CFTR underlies cystic fibrosis-like disease of the canine gallbladder, *American Journal of Physiology-Gastrointestinal and Liver Physiology* (2024). DOI: 10.1152/ajpgi.00145.2024