



## University of New Hampshire NH Veterinary Diagnostic Laboratory

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### Respiratory Syndrome of Unknown Etiology in Dogs 2022-3 in New England: Diagnostic Investigation

Introduction: The NHVDL and the Hubbard Center for Genome Studies (HCGS) at UNH have preliminary findings in the diagnostic investigation regarding the recent atypical respiratory syndrome in dogs. We believe that we have identified a potential candidate etiologic agent in this syndrome.

Clinically the cases present similarly to kennel cough, and seem to be refractory to standard medical treatment, as well as often being negative on syndromic canine respiratory disease PCR testing. Cases commonly have a long course of illness, with some progression to pneumonia. There have been anecdotal reports of mortalities, however submissions of carcasses or excised lung tissue have been minimal, as have respiratory culture submissions.

Molecular and analytic work began at the NHVDL and HCGS in early December, 2022, with an initial pilot of seven clinical samples and one non-clinical control. This early work did not reveal any RNA or DNA virus of concern, and no primary fungal or bacterial respiratory pathogens were identified. After these initial work, continued sequencing, bioinformatic analyses, and sample collection was continued.

Findings: We recently concluded sequencing on an additional group of animals bringing the total to 31 dogs with the shared clinical syndrome. With deeper sequencing, paired with rigorous bioinformatic analysis and literature review, 21 of 31 samples were found to have segments of DNA that are predicted to belong to a likely non-culturable bacterium that is most similar to a pathogen reported in association with respiratory disease in people in 2021 ([pubmed.ncbi.nlm.nih.gov/34040152](https://pubmed.ncbi.nlm.nih.gov/34040152)). The bacteria from the human report, tentatively named IOLA KY405, has a minute and AT-rich genome, and is phylogenetically quite distinct from most well-characterized bacteria in people (and dogs). These types of bacteria have been minimally studied and are not well characterized. Based on what we do know it is probable that they are amongst myriad non-culturable or difficultly cultured bacteria that inhabit respiratory tracts in many species, with most being non-pathogenic commensals or even possibly symbionts. It is likely that the bacteria we may have identified in this syndrome and the IOLA KY405 in people are each host-adapted bacteria with long histories of colonizing their dog and human hosts, respectively. Then at some point an evolutionary event (spontaneous mutation, gene acquisition from mobile genetic element, etc.) lead to development of potential pathogenicity due to acquisition of a virulence-associate gene / trait. There is no evidence to indicate a zoonotic potential in these cases, but as is often the case with emergent animal diseases, there is no evidence to dismiss this possibility completely.

The genome of IOLA KY405 is even smaller than *Mycoplasma* spp. and similarly to *Mycoplasma* it does not encode proteins to make a cell wall. This means that this bacteria is unlikely to be sensitive to  $\beta$  lactam antibiotics, and could respond to empiric treatments as indicated by the 2017 International Society for Companion Animal Infectious Diseases (<https://www.iscaid.org/guidelines>) Antimicrobial use Guidelines for Treatment of Respiratory Tract Disease in Dogs and Cats. During the study period we have had one canine respiratory *Rhodococcus (Prescottella) sp.* isolate outside of the study set, so it would likely be prudent to submit a culture in all cases of respiratory disease prior or concurrent to initiating any therapy. In terms of preventative medicine the likelihood is that public health awareness and limiting dog-to-dog contact is the best and realistically only way to prevent spread as development of a vaccine would be years of work and investment.

Context: It is important to note that this is a preliminary finding, and under normal circumstances of a study we would not release these findings. The technology and methods used by the HCGS include cutting edge metagenomic sequencing, and multiple bioinformatic pipelines that are uncommonly utilized in veterinary medicine. Additionally this is an uncommonly studied group of bacteria. There are

multiple experiments that need to be run in order to clarify correlation vs. causation, and this gives reason for pause in releasing the findings. However, the syndrome is ongoing and there may be an opportunity to benefit animal health as we continue to validate these initial findings. There is a chance that this preliminary data is disproven with further study, but at this point it does appear that the bacteria we have identified is a potential causative agent.

Next steps: Additional work is ongoing with the previously received samples to perform additional, deeper sequencing on some specimens, as well as performing PCR for higher sensitivity and more rapid investigation. We are examining temporal controls from our biobank and additional samples from colleagues at distant institutions. We are in need of more samples from our region, so if you have a dog that has respiratory disease that fits the syndrome, please contact us. For antemortem analysis, we are utilizing samples collected as you are already doing for respiratory testing, both for culture and PCR. Please collect samples as soon as you can in the course of disease, as some syndromic testing can be negative when testing is performed after a longer course of illness. If you have a mortality associated with the syndrome, we have a strong desire to receive paired formalin fixed and frozen fresh lung from these cases. The study protocols are not validated diagnostic tests, and as such reports or results for any individual submission will not be released. Findings from the whole group will be shared as part of future communications and in any scientific outputs. Please do not send a swab or tissue without contacting us first. In addition to ensuring we are ready for the sample and still in need of it, a sample from an animal that is not part of this atypical pneumonia syndrome could add “noise” to the data which could slow progress to confirming the initial results.

**Thank you** to the clinicians and clinics that supported the work with donations and to the clinics and clinicians that have provided samples and metadata.

Please email [david.needle@unh.edu](mailto:david.needle@unh.edu) with any questions or to arrange submissions, etc.

*Reference for antimicrobial usage in respiratory disease in dogs* Lappin MR, Blondeau J, Boothe D, et al. *Antimicrobial use Guidelines for Treatment of Respiratory Tract Disease in Dogs and Cats: Antimicrobial Guidelines Working Group of the International Society for Companion Animal Infectious Diseases. J Vet Intern Med.* 2017;31(2):279-294. doi:10.1111/jvim.14627