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Dogs may provide an excellent model for understanding human complex diseases

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In the new Swedish-Finnish study, published in *Nature Genetics*, the researchers identified five loci that predispose to an SLE-related disease in Nova Scotia duck tolling retrievers. The study indicates that the homogeneity of strong genetic risk factors within dog breeds make dogs an excellent model in which to identify pathways involved in human complex diseases. The results of the study also open the door for further studies of specific T-cell activation pathways in human populations.

The unique canine breed structure makes dogs an excellent model for studying genetic diseases. Incidences of specific diseases are elevated in different breeds, indicating that a few genetic risk factors might have accumulated through drift or selective breeding. In the new Swedish-Finnish study with 81 affected dogs and 57 controls from the Nova Scotia duck tolling retriever breed the researchers identified five loci associated with a canine systemic lupus erythematosus (SLE) -related disease complex. Fine mapping with twice as many dogs validated these loci.

"Our results indicate that the homogeneity of strong genetic risk factors within dog breeds allows multigenic disorders to be mapped with fewer than 100 cases and 100 controls, making dogs an excellent model in which to identify pathways involved in human complex diseases", says Professor Hannes Lohi, University of Helsinki and Folkhälsan Research Center, Finland.

Nova Scotia duck tolling retrievers (NSDTRs) are strongly predis¬posed

to many immune-mediated diseases, including a systemic lupus erythematosus (SLE) -related disease complex comprising an immune-mediated rheumatic disease (IMRD) and steroid-responsive meningitis-arteritis (SRMA). The NSDTR breed was developed in the Yarmouth region of Nova Scotia in the early 1800s as a hunting and retrieving dog. The breed descended from a very small population of dogs that survived two devastating outbreaks of canine distemper virus in 1908 and 1912. One hypothesis for the abnormally high rates of autoimmune diseases in modern NSDTRs world-wide is that dogs with particularly strong or reactive immune systems were much more likely to survive these outbreaks.

Pedigree analysis of the SLE disease complex in NSDTRs has indicated that it involves multi-genetic inherit¬ance, like most autoimmune diseases in humans. The IMRD disease complex involves chronic musculoskeletal signs with a clinical picture indicative of immune-mediated non-erosive polyarthritis. Many of the clinical features of the canine IMRD complex are similar to those of human SLE.

"In this study, we have identified five loci that predispose to an SLE-related disease in NSDTRs. The study highlights the strength of disease mapping in dogs, where a canine breed may carry a few disease loci, each with a strong effect, that together are sufficient to predispose to a complex disease", Professor Lohi states. Some types of genetic risk factor will be more easily traced in dogs than in humans, and the dog studies might be a valuable complement to human study for identifying new genes and pathways that are important in disease pathogenesis.

"Although we plan to identify and characterize the functions of the canine mutations, this study opens the door for further studies of specific T-cell activation pathways in human populations. In the more long term, the development of clinical treatment regimens based on a dog's particular risk genotype might be possible. For instance, the effect

of calcineurin inhibitors could be studied in dogs as a comple¬ment or alternative to traditional corticosteroid therapy. Such studies might also lead to better treatment options for human rheumatic diseases and SLE", Lohi says.

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