

Heritable Risk for Lymphoma and Hemangiosarcoma in Golden Retrievers New Discovery Identifies Shared Genetic Risk Factors

In June 2010, The Golden Retriever Foundation and Morris Animal Foundation entered into a partnership to jointly fund a major three-year, \$1 million canine cancer initiative titled *Discovery and Characterization of Heritable and Somatic Cancer Mutations in Golden Retrievers*, or the MADGiC Project (Making Advanced Discoveries in Golden Cancers). The study was led by premier canine cancer researchers Jaime Modiano, VMD, PhD, at the University of Minnesota; Matthew Breen, PhD, at North Carolina State University; and Kerstin Lindblad-Toh, PhD, at the Broad Institute of MIT and Harvard, and Uppsala University, Sweden. They worked together to investigate mutations that are involved in risk and progression of the two most common cancers affecting Golden Retrievers, hemangiosarcoma and lymphoma. Although focused on Goldens, this research benefits all dog owners because these cancers affect every breed and cause the deaths of tens of thousands of dogs each year.

This research benefits humans too, because the genes involved in cancer are sometimes the same in dogs as in people, but the mutations can be more difficult to discover in people. Therefore, identifying these genes also advances scientists' understanding of common human cancers such as lymphoma, and rare angiosarcomas.

Some groundbreaking findings from this study appear in a recent paper in *PLoS Genetics*, "*Genome-wide Association Study Identifies Shared Risk Loci Common to Two Malignancies in Golden Retrievers*"

(<http://journals.plos.org/plosgenetics/article?id=10.1371/journal.pgen.1004922>) From work performed in Dr Lindblad-Toh's lab, the investigators report that they have identified two loci that together contribute approximately 20% of the risk of developing hemangiosarcoma and lymphoma in Goldens. These two "loci" can be thought of as a location on a chromosome (in this case, both loci are on chromosome 5) at which DNA sequences that elevate risk can be found. So if all of the DNA sequences that create the "map" for building a dog could be compared to the map of the US, then identifying "loci" would be similar to narrowing the locations down to specific neighborhoods.

After identifying these loci, the scientists searched the "neighborhoods" for specific protein-coding genes that could be the cause of the increased cancer risk. No genes that produce abnormal proteins were found, but instead the elevated risk appears to come from groups of tightly-linked DNA sequences called "haplotypes" that regulate the expression of protein-coding genes. It was found that these risk haplotypes regulate genes involved in immune response, and this may be the reason that risk for both hemangiosarcoma and lymphoma is elevated in dogs that carry them. Conclusions from the paper suggest that

"the interaction between the immune system and malignant cells plays a common role" in the development of both of these cancers.

"It was unexpected and remarkable to discover that two rather different cancers, B-cell lymphoma and hemangiosarcoma, are linked to the same inherited risk factors," the study authors state. "We find the existence of at least four disease-associated haplotypes in the two nearby chromosome 5 regions intriguing, and speculate that there may be genes in the region affecting traits for which dogs are bred in this population."

The research team of Modiano, Breen, and Lindblad-Toh was awarded another three year grant in 2013, this time in a partnership between the Golden Retriever Foundation and the AKC Canine Health Foundation. The investigators are continuing to validate the newly discovered haplotypes that predispose some Golden Retrievers to cancer so that breeders may soon be able to reduce cancer risk through testing for these risk haplotypes. And while these known inherited risk haplotypes convey a significant percentage (~20%) of the risk of hemangiosarcoma and lymphoma, it is likely that there are additional genetic risk factors too. (And of course, environmental and sporadic factors also play a role in the development of cancer.)

In addition to informing breeding decisions, these discoveries could also lead to DNA tests that may be useful for diagnosis and possibly even to guide treatment choices in the future. The scientists are also continuing to investigate mutations that occur in the tumors themselves (somatic mutations) and are profiling the susceptibility of specific tumor types to various chemotherapy compounds, which may lead to improved therapy options.

We express our grateful appreciation to the dedicated Golden owners who supported this research by donating samples when their beloved dogs were diagnosed, as well as those who contributed to Golden Retriever Foundation fund raising campaigns.

There is still more to do, and owners of Golden Retrievers diagnosed with lymphoma or hemangiosarcoma can support this important research by donating a tumor sample (www.modianolab.org or www.breenlab.org) or a blood sample (www.dogdna.org)

To contribute to a fund (Zeke Fund) that supports this ongoing research, please visit the Golden Retriever Foundation website at www.goldenretrieverfoundation.org

By Rhonda Hovan
GRCA Research Facilitator
rhondahovan@aol.com