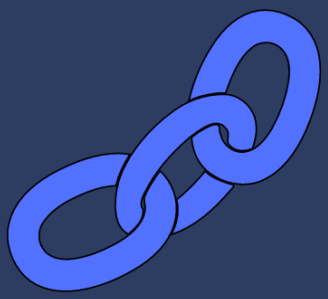
NUMBER 7 · JANUARY 2022

LEONBERGER HEALTH FOUNDATION INTERNATIONAL Newsletter

Another link in the chain. . .



Genome-Wide Analyses for Osteosarcoma in Leonberger Dogs Reveal the CDKN2A/B Gene Locus as a Major Risk Locus

The Universities of Minnesota & Bern recently published the discovery of a gene locus that influences an individual Leo's susceptibility to osteosarcoma.

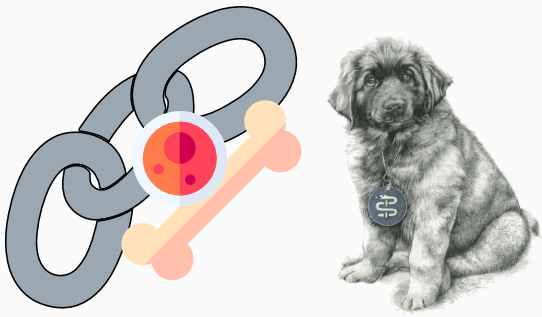
"Heritability was determined to be 20%. . . .indicating additional environment factors are having significant impact on the phenotypic variation in Osteosarcoma."

While not the whole answer, it is another link in the chain.

An announcement and summary of the study is found on the following page, along with information for finding the complete research paper.

Donate at www.lhfi.org

This issue:



Leonberger Genetics of Osteosarcoma Study (Dec. 2021)

This summary is provided by the Universities of Bern & Minnesota.

Background:

Osteosarcoma, the major form of bone cancer in dogs, is a significant life-limiting disease in Leonbergers. Yet, little to nothing is known of the genetic basis for this devastating disease.

The Universities of Minnesota, Bern and Uppsala, and the Broad Institute (USA), with support from the world-wide Leonberger community, conducted a long-term study to increase our knowledge of the geneticfactors that contribute to the development of osteosarcoma in Leonberger dogs.

Our worldwide health survey of almost 3000 Leonbergers, published in 2020, confirmed a high prevalence of cancer, particularly osteosarcoma and hemangiosarcoma in the breed.We are now very pleased to report that a manuscript describing our analyses and conclusions was published in the peer-reviewed journal Genes in mid-December 2021.

What we did?

We performed genomic analyses of osteosarcoma susceptibility in a large global cohort of Leonbergers consisting of 273 osteosarcoma cases with a median age of 8.1 years (range of 3.1-13.5)and 365 controlsolder than 8 years.

The analyses were based on hundreds of thousands of DNA markers known as SNPs. SNP markers are spread evenly across all the canine chromosomes and the precise location of each SNP along each chromosome is known. The presence of SNP combinations (termed genotypes) at each location gives information on the origin of that chromosomal segmentwithin the population.

What we found!

We calculated, for the first time, that the heritability of osteosarcoma in Leonbergers is approximately 20%. Several thousand SNPs across the genome accounted for this heritability, with each SNP contributing just a small fraction to the total (so called)heritability.

The genomic position most significantly associated with development of osteosarcoma was on chromosome 11, along with further suggestive regions on five other chromosomes.

There are multiple versions (known as haplotypes) of the short segment of chromosome 11 associated with the occurrence of osteosarcoma in the population. However, a haplotype containing the most significant SNPs was present at a significantly higher frequency in cases comparedto controls (approximately 1.5 times more frequent). The distribution of osteosarcoma cases carrying 0, 1 or 2 copiesof the associated haplotype (20%, 53%, 27%) was also significantly different than in the control dogs (38%, 48%, 14%), respectively.

This chromosome 11 segment contains the CDKN2A and CDKN2B genes and has been previously described in osteosarcoma-affected greyhounds, as well as in histiocytic sarcoma-affected Bernese mountain dogs, flat-coated retrievers and rottweilers.

Leonberger Genetics of Osteosarcoma Study
continued from Page 02.

What it means?

The heritability of osteosarcoma in Leonbergers is now accurately known and shown to be a moderately heritable complex polygenic disease. **This means that there are many contributing variants (mutations), genetics alone does not explain all of osteosarcoma susceptibility, and there is a considerable impact of (unknown) environmental variables.**

With so many variants (mutations) contributing, many different additive combinations of these variants are possible that, in turn, result in varying levels of susceptibility to the development of osteosarcoma in the population.

The chromosome 11 haplotype conferring the most significant association to osteosarcoma development is common in the breed. Although our findings confirm the crucial role of the CDKN2A/B locus in canine cancer predisposition, unfortunately we do not yet know the specific DNA mutation(s) that is/are responsible.

Further, although dogs carrying 1 or 2 copies of the susceptible haplotype are more likely to develop osteosarcoma, not all dogs that carry 1 or 2 copies of the susceptible haplotype will go on to develop osteosarcoma, and dogs not carrying any copies of this haplotype can still develop osteosarcoma.

This means that any predictive assay must account for many different genetic variants and would provide only an estimate of the likelihood that an individual dog with that set of variants would develop osteosarcoma. Given the high frequency of the chromosome 11 haplotype in the breed (>50%), and an uncertain predictive value at present, we do not plan to offer a genetic test for osteosarcoma at this time.

We also share our concern that any test aimed at reducing or eliminating a susceptible haplotype from the population could do major harm in the face of the breed's already limited genetic diversity.

It is important to remember that many selection criteria must already be considered in Leonberger breeding,(e.g., three known forms of polyneuropathy, leukoencephalomyelopathy with tests that enable breeders to safely retain carriers in their breeding programs).

Therefore, we strongly recommend giving priority to dogs free of signs of any disease. It is of the utmost importance when selecting breeding pairs that genetic diversity is considered. Maintaining the current level of genetic diversity will only be possible through informed selection decisions, especially by including more dogs in breeding programs, avoiding repeated matings and the use of popular sires, and minimizing co-ancestry among the selected parents.

This study was made possible by your willingness to complete health updates on your dogs. Also with the great help of the pedigree information at the Worldwide Independent Leonberger Database.

Visit LHFI.org for full research publication.

MODIANO/CHF STUDY: EARLY DETECTION OF OSTEOSARCOMA

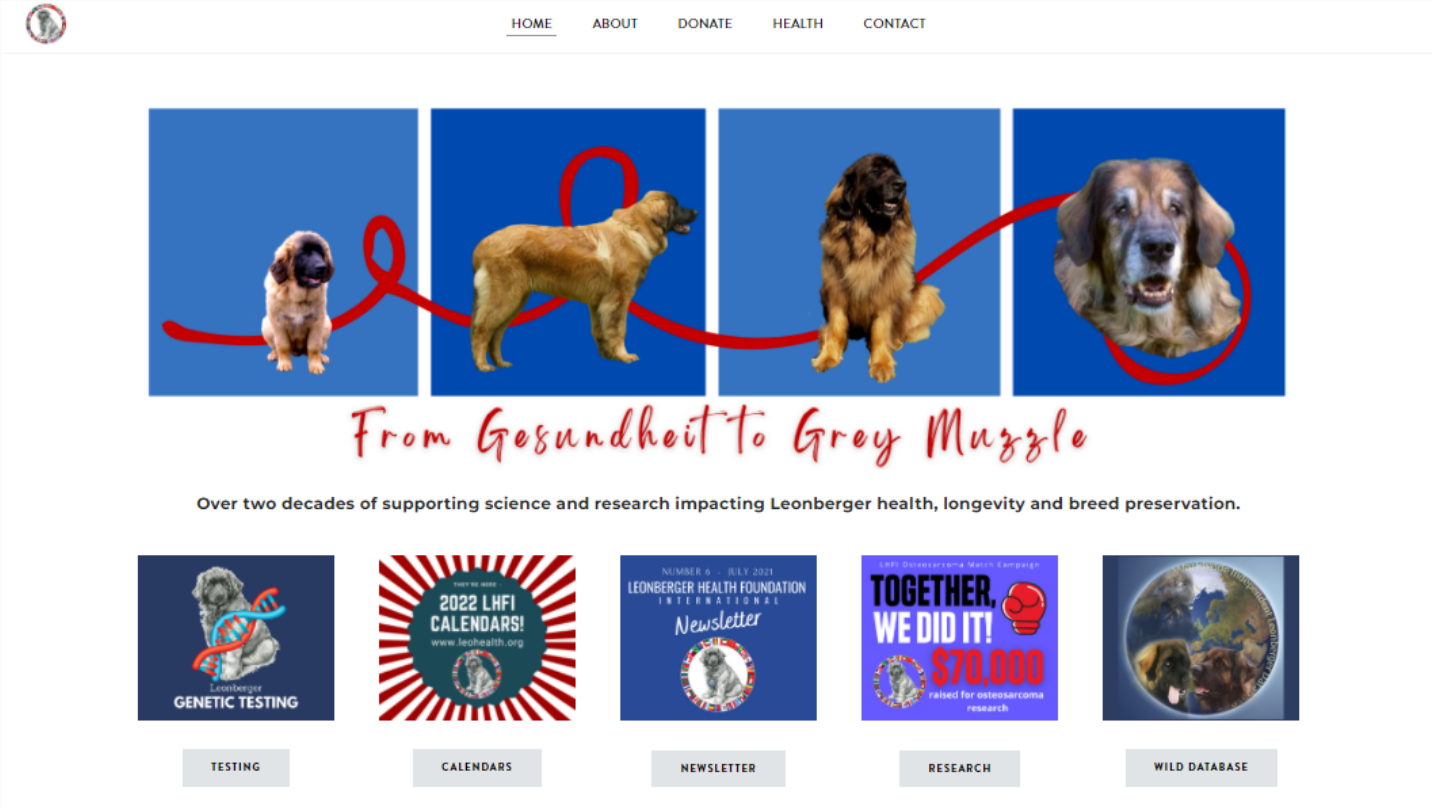
Update

After securing full financial support from the participating breeds, Dr. Modiano submitted the study proposal to the Canine Health Foundation in the Fall of 2021. The proposal is now undergoing the CHF's grant review process, a process that takes an average of 2-3 months. We will continue to provide updates as they are available.

SUPPORTED BY THE
LHFI OSTEOSARCOMA MATCH CAMPAIGN

VISIT OUR NEW WEBSITE!

WWW.LHFI.ORG



New Look, More Information

Our website doesn't just have a brand new look. We also added more information.

- General Health Information of the Leonberger
- Genetic Testing - Why, Where, and How
- Grey Muzzle Award Hall of Honor
- History of the LHFI
- Waltraut Zieher Award
- Meet our mascot, Gesundheit
- Links to Research Publications
- How you and your Leo can participate in research
- Our History of Research Funding
- Ways to Give

Don't Forget!

Ongoing LHFI studies

CURRENT STUDY

GLAUCOMA IN THE LEONBERGER

LHFI.ORG > HEALTH > RESEARCH > YOU AND YOUR LEO CAN PARTICIPATE

For more info on these studies, go to:
> LHFI.org
> Health
> Research
> Your & Your Leo Can Participate

* Leonberger Inherited Ventricular Arrythmia & Sudden Death Study
  University of Helsinki
  Email details to Julia Niskanen at julia.niskanen@helsinki.fi

* Overall Survey of Cardiac Health in the Leonberger
  University of Liverpool
  Email details to lhficardiac@gmail.com

* All submissions will be held in strict confidence and no details of individual dogs, their breeders or their owners will be published.

leohealth.org

THANKYOU

View a full list of supported projects on our website.
> LHFI.org
> Donate
> LHFI History of Research & Support

Since 2002, the LHFI has enabled Leo owners and lovers to raise almost 500,000 USD towards health related research!

This incredible total could not be possible without the support of a fantastic community. Your efforts have already made a genuine and positive impact on the health of our dogs.