DOG DISEASE RESEARCH
at the Broad Institute

IT HAS BEEN ANOTHER GREAT YEAR WITHIN THE DOG DISEASE RESEARCH GROUP (DDRG). THANK YOU FOR YOUR CONTINUED SUPPORT!

Without the help of dog owners like you and our funding collaborators we would not be making the strides in understanding dog disease genetics that we are. The generous donations of biological samples, and the responses we continue to receive to our requests for health updates have been essential to our success. Your support makes it possible to apply the very latest genetic research tools to the study of a wide variety of diseases, cancers, and behaviors that affect different breeds. (See our webpage www.dogDNA.org for descriptions of all of our dog disease research projects). With your help, we have now collected over 15,000 samples from over 150 different breeds to support these studies!

We would like to share an update on what your donations have helped us achieve, and where we are heading in the future.

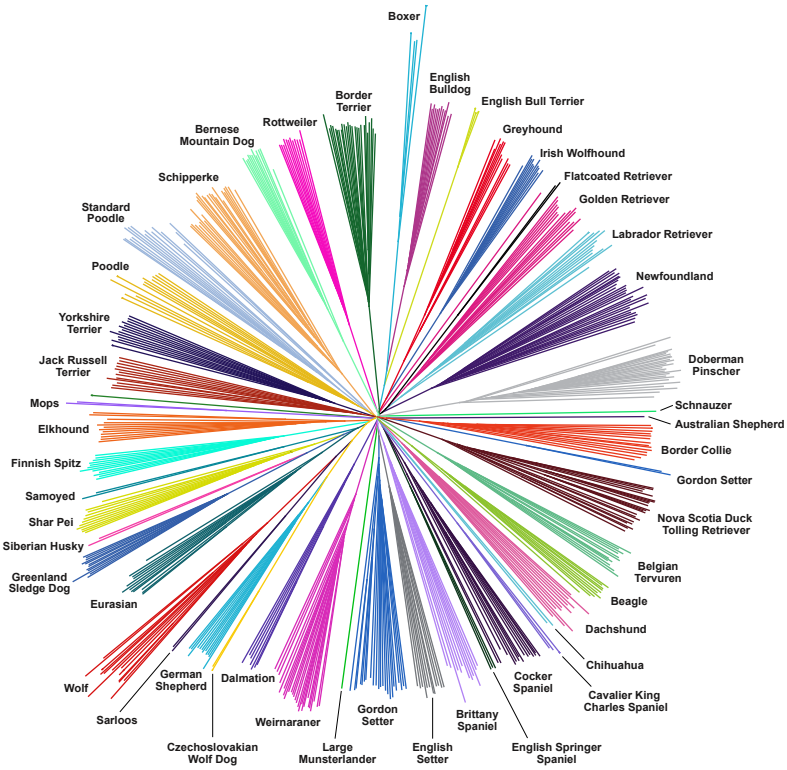
OUR LATEST RESEARCH...

Within the past year, researchers working in the Dog Disease Research Group at the Broad Institute of MIT and Harvard, Uppsala University in Sweden and the Swedish University of Agricultural Sciences have published more than 20 important new scientific papers. By publishing our work, we are making the latest available research known to the larger scientific community. Our goal is to expand awareness of these findings so that others can build on them and advance the study of genetic disease in dogs.

This year, we published several papers specifically related to new genetic tools and resources that will assist in learning more about the dog genome. Here are a few examples:

LARGEST GENE MAPPING ARRAY:
A new tool to help locate disease-associated genetic mutations

The diversity seen in dog breeds seems limitless. But the genes explaining the traits possessed by various breeds are not. To learn more about the genetic differences between dog breeds, researchers within the Dog Disease Research Group undertook a detailed study to map them.



Neighbor-joining tree constructed from raw genetic distances representing relationships between samples.
Image credit: Matt Webster

> “ FINDING THESE DIFFFERENCES ALLOWS US TO PINPOINT THE GENES CAUSING DISEASE.”

In a paper published in October 2011, working in collaboration with the LUPA Consortium, the DDRG discussed the creation of the largest SNP array ever developed for the dog genome. A SNP array (or single nucleotide polymorphism) is a tool that allows researchers to find regions in the genome that differ between two groups of dogs – for example, dogs with bone cancer and dogs without bone cancer. Finding these differences allows us to pinpoint the genes causing disease. This new SNP array allows any researcher working in the field of dog genetics to carefully survey more than 170,000 specific sites on the genome for regions related to diseases of interest or particular dog traits. This new tool contains the largest SNP panel produced for studying dog genetics.

Specifically, the team designed a SNP array including 170,000 single nucleotide polymorphisms (SNPs). SNPs are a variation in the DNA sequence that occur when a single molecule within a genome varies from the sequence found in other members of the same species. In much of our earlier work we have described the use of SNP arrays to sift through the dog genome to find information related to a variety of conditions, traits, behaviors, and disorders. For example, in March 2011 the DDRG published a paper describing a study including 50,000 dog genome SNPs that led to the link between a particular gene called HSA2 and Periodic Fever Syndrome in the Shar-Pei breed.

Identification of genomic regions associated with phenotypic variation between dog breeds using selection mapping. Vaysse A, Ratnakumar A, Derrien T, Axelsson E, Rosengren Pielberg G, Sigurdsson S, Fall T, Seppälä EH, Hansen MS, Lawley CT, Karlsson EK; LUPA Consortium, Bannasch D, Vilà C, Lohi H, Galibert F, Fredholm M, Häggström J, Hedhammar A, André C, Lindblad-Toh K, Hitte C, Webster MT.PLoS Genet. 2011 Oct;7(10):e1002316. Epub 2011 Oct 13.

FILLING IN THE GENOME GAPS

Research points to missing PRDM9 Gene

The full sequence of the dog genome is approximately 98% complete. Among mammals, only those of humans and mice are better understood. But researchers have not fully known what is found in the gaps or holes of that missing 2% of the dog genome because these regions are difficult to sequence with accuracy. A paper published by DDRG researchers in January 2012 reports that these gaps likely contain large amounts of guanine (G) and cytosine (C), two of the four nucleotides that compose DNA molecules, in genetically active regions called promoters. Researchers have known that DNA sequences that carrying long stretches of repeated G and C nucleotides indicate a gene-rich region. Further, the team determined that these GC-rich areas are a result of the absence in dogs of a gene known as PRDM9.

Much of the genetic shuffling that naturally takes place in mammals, including humans, occurs in locations where PRDM9 is active. This reshuffling of genetic information, called recombination, leads to the development of traits not possessed by either parent. In dogs, reshuffling happens in the promoter sites making them more and more GC-rich. These findings leads the DDRG researchers to speculate that some of the genetic changes that cause diseases or lead to new traits in dogs may reside in these GC-rich areas where gene function is altered because PRDM9 is not present. This information is useful when trying to find mutations that affect when and where proteins are made.

Death of PRDM9 coincides with stabilization of the recombination landscape in the dog genome.Axelsson E, Webster MT, Ratnakumar A; LUPA Consortium, Ponting CP, Lindblad-Toh K. Genome Res. 2012 Jan;22(1):51-63. Epub 2011 Oct 17. Erratum in: Genome Res. 2012 Apr;22(4):810.

PAPERS IN THE PIPELINE...

The Dog Disease Research Group is always working on new genetic science with the goal of improving the health of dogs and humans alike. As we develop important new genetic tools, like the 170,000-SNP gene array, we use them to learn more about genetic causes of dog diseases. In the next few months, we expect to publish several new important papers related to cancers and inflammatory diseases in dogs. These include some of the most common dog cancers - osteosarcoma, lymphoma, hemangiosarcoma and mast cell tumors.

IN OTHER NEWS...

Dr. Linblad-Toh Photo by Max Brovwers

Royal acknowledgement

Professor Kerstin Lindblad-Toh, who leads the DDRG group at the Broad Institute and at Uppsala University in Sweden, was elected to the Royal Swedish Academy of Sciences in January 2012. Her inclusion into the Academy recognizes her work as a world-renowned researcher in comparative genomics and in the field of dog disease mapping. Today, under her leadership the Dog Disease Research Group is investigating the genetic links to 20 different diseases in dogs, ranging from cancer, immune disease to behavioral disorders.

Dr. Lindblad-Toh is the Scientific Director of Vertebrate Genome Biology at the Broad Institute. She is also a professor in comparative genomics at Uppsala University and the Director of Science for Life Laboratory Uppsala, a strategic research center modeled on the Broad. An author on over 120 papers, Dr. Lindblad-Toh has received several scholarships and awards from the Svenska Institutet Scholarship for Research Abroad and the Swedish Medical Research Council and the prestigious European Young Investigator Award (EURYI), the Fernström Prize and the Théreus Prize. This year she also received the prestigious European Research Council Young Investigator Award for her work on canine cancer and immunological disease.

The DDRG is honored that Professor Lindblad-Toh and her work involving an extensive network of collaborators in the United States, Sweden and around the world has achieved this recognition.

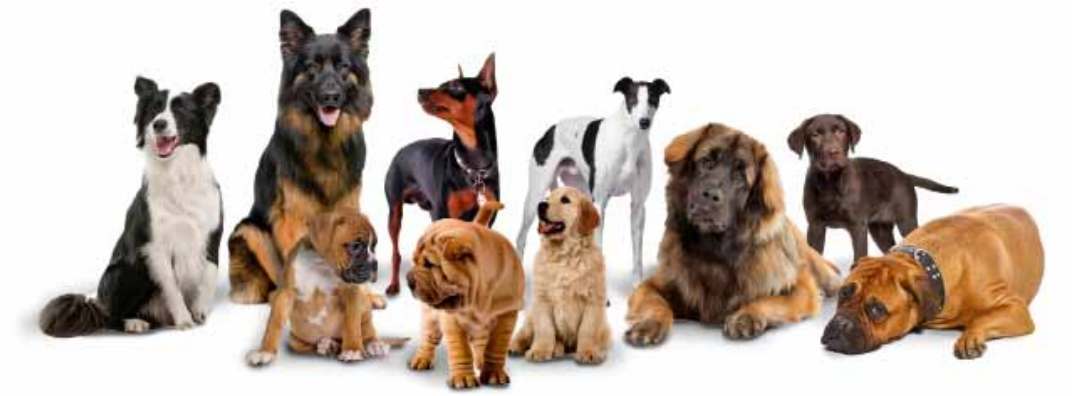
NEW GIFT TO SUPPORT STUDY OF OSTEOSARCOMA IN IRISH WOLFHOUNDS

The DDRG is delighted that the Irish Wolfhound Foundation (IWF), together with the Irish Wolfhound Club of America (IWCA) and regional clubs devoted to the breed, have made a gift of $42,160 to the Broad Institute to support research on genetic risk factors for early onset osteosarcoma in Irish Wolfhounds. This one year project will be part of an ongoing effort at the Broad to identify the primary risk factors for this cancer in Irish Wolfhounds.

The project is the first step toward developing specific genetic markers that can be used for identification of wolfhounds likely to develop osteosarcoma. It will also aid in understanding the modes of transmission of risk factors and will provide insights that could help improve clinical treatment for this disease, which affects so many Irish Wolfhounds.

“We are delighted to be teaming with the IWCA and other regional clubs to fund this research study under Dr Lindblad-Toh and her excellent team,” said Douglas Marx, President of the Irish Wolfhound Foundation. “The gift is a great example of what can be accomplished when so many clubs and supporters of the breed come together. We hope to continue working toward a better understanding of the susceptibilities for this devastating disease and means to reduce its incidence and impact.”

Broad associated researcher, Dr. Noriko Tonomura and Adria Karlsson draw a blood sample from a thoughful donor at the 2012 IWANE Specialty Show



HELP PUT A LEASH ON DISEASE

DNA samples are still needed

Several disease studies are in motion, and our collection of biological samples continues. To learn more about our current need for biological samples from select breeds diagnosed with the diseases being researched, and from older, healthy dogs of the same breeds please visit **broadinstitute.org/dogresearch**

To help support the work of our researchers with a financial contribution, please visit broadinstitute.org/contribute

ABOUT THE DOG DISEASE RESEARCH PROGRAM AT THE BROAD INSTITUTE

In 2005, scientists sequenced the full dog genome from a boxer named Tasha. That work helped lay the foundation for a variety of studies into the genetic basis of disease — research that depends on help from dogs as well as their human companions. Dogs and humans get many of the same diseases, including cancer and diabetes. Studying DNA from both healthy and sick dogs can help researchers gain insights into diseases that affect both species.

Our dog disease researchers use canine DNA to study diseases because - thanks to the genetic diversity among breeds - the disease genes are easier to find. To find disease genes for complex diseases in humans, thousands of people and millions of genomic markers (SNPs) are needed. In dogs, twenty thousand markers and a few hundred dogs can suffice to find genes for complex diseases.

With the help of people and their canine companions, we hope to continue identifying risk factors in many more diseases in a step toward better understanding the overall health risks for dogs and humans alike.

ETHICAL STATEMENT

The Broad Institute's Canine Disease Mapping group performs disease research under a conservative ethical model so that no harm should come to the dogs. Dogs enrolled in our studies are pet dogs, participating after owner consent, only in ways that do no harm.

We do not induce cancer or other diseases in dogs, nor do we ever keep any animals in the laboratory.

For more information on Dog Disease Research at the Broad Institute: Visit our website at broadinstitute.org/dogresearch or send an email to dog-info@broadinstitute.org

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