# What is the Canine Phenome Project?

The Canine Phenome Project is an effort to describe the dog as a species in all of its variability and to understand the factors, both genetic and non-genetic, that contribute to this variability. It is an open-ended attempt to describe and understand the basis for all of the characteristics (or phenotypes) of dogs in great detail. The emphasis will be on describing those characteristics that distinguish one breed from another and those characteristics that distinguish one individual from another within a breed. In this context we consider the canine phenome to consist of all aspects of the dog including size and anatomy, composition and metabolism, behavior and temperament, and health and disease susceptibility. In order to facilitate the discovery of associations between genotype and phenotype or environmental factor and phenotype, efforts will be made to define canine phenome descriptors in fundamental terms most likely to reflect the influence of one gene or a few genes or the influence of a single environmental factor. Of course a complete description of something as complex as the canine phenome is impossible in the foreseeable future. Nonetheless, substantial progress toward the ultimate goal is likely if the extensive expertise of the vast dog-owning, dog-breeding, dog-training, and dog-treating public can be mobilized to contribute their knowledge in an efficient and organized fashion.

# Why start the project now?

The Canine Phenome Project is intended to complement the recently completed Canine Genome Project. This genome project has produced a nearly complete DNA sequence for a female Boxer. The Boxer sequence has been posted on internet sites where it is freely available to scientists around the world and provides ready access to essentially all of the approximately 30,000 canine genes. By comparing the Boxer DNA sequence to sequences from random segments of DNA from other dogs, the scientists working on the Canine Genome Project have identified over two million sequence differences among different dogs. Some of these sites of alternative sequence (or polymorphic sites) may be directly responsible for the differences that comprise the canine phenome while other polymorphic sites can serve as markers to help identify those sites directly responsible for phenotypic differences. These markers should, in theory, be sufficient for the discovery of the genetic causes for most of the characteristics and diseases of dogs. Unfortunately, with today's technology, it is not logistically or financially feasible to make use of hundreds of thousands or millions of markers. Nonetheless, new technologies are under development and current technologies are capable of analyzing DNA samples with over a thousand markers simultaneously and inexpensively. In just a few years when these technologies improve, it should be possible to evaluate canine DNA samples with a large subset of the markers from the Canine Genome Project.

The Canine Genome Project is sponsored by NIH; and, as such, its expense is justified because investigations of canine diseases benefit mankind by providing insights into similar human diseases. Of course, these investigations should also prove beneficial to dogs in breeds with the target diseases. We have been considering what we can do to ensure that dogs and their owners benefit from the Canine Genome Project as widely and completely as is practical. Our solution is to initiate the Canine Phenome Project.

The goal of the Canine Phenome Project is to assemble a resource consisting of DNA samples from a wide variety of dogs with well characterized phenotypes and have it ready when the technology is ready. Computer correlations between this marker data and information about the characteristics of the individual dogs that supplied the DNA will lead to the identification of genes responsible canine diseases, temperaments, and other characteristics. Markers for

these genes could guide the selection of breeding stock to consistently produce new generations of dogs well suited for their roles in modern society.

# How will it work?

The Canine Phenome Project is in an early stage of development. We have begun with Basenjis and soon plan to add two additional breeds, Collies and Kerry Blue Terriers. Gradually, we will add additional breeds, a few at a time, while we build on aspects that work, correct mistakes, and fine-tune our strategy. Our first step was to construct this Canine Phenome Website which facilitates organized interactions with a network of motivated scientists, veterinarians, dog owners, dog breeders, and dog trainers with expertise about specific target dog breeds. With their help we are assembling breed-specific questionnaires to be filled out on-line by dog owners to describe specific phenotypic features and pedigree information about individual enrolled dogs. We store this information in a database and create a password-protected website page for each enrolled dog. The webpage can be accessed by the dog's owner for updating when additions are made to the questionnaire and whenever there are changes in the dog's phenotype or medical history. We also obtain blood samples for DNA from each enrolled dog. We will analyze this DNA, first at polymorphic sites associated with genes that are candidates for causing targeted heritable diseases, problem behaviors, and other phenotypes of importance. This approach has already proven successful in identifying the mutation responsible for a severe neurodegenerative disease of American Bulldogs and we instigated a program to eradicate the disease. Eventually, when genotyping technology improves, we will genotype the samples at numerous polymorphic sites throughout the genome and check for associations between the DNA test results and a wide variety of phenotypes. When we find associations, we will use this information to devise DNA tests to help breeders produce new generations of dogs with desired traits while avoiding genes responsible for unwanted phenotypes such as specific diseases or undesirable behaviors.

# What are the short-term benefits?

The password-accessible website pages for each enrolled dog will help dog owners maintain medical records (vaccination dates, symptoms and dates of illness, breeding records, etc). These records should promote the accurate diagnosis of diseases by making it convenient to describe and record disease episodes or other pertinent information (medications, appetite, etc) while still fresh in the owner's mind. With the owners permission (and password) the dog's medical history could be accessed by an available veterinarian in emergency situations or by a new veterinarian, should the dog's owner move or change veterinarian for other reasons.

We intend to perform at least one genotype assay on the DNA from each newly enrolled dog. This test will be done at no charge and will ensure and document that the DNA preparations from all enrolled dogs are of sufficient quality to be used in future scientific studies. With the Basenjis, we test for a mutation in a pyruvate kinase gene (PKLR) which causes a life-threatening, recessive form of hemolytic anemia.

Although large-scale DNA testing will be deferred until the technology for high throughput DNA analysis improves, we plan to conduct focused research on one or a few heritable diseases or traits of particular interested to each specific participating breed. For the most part, this research will focus on diseases or traits for which there are "suspect" (or candidate) genes. For Basenjis, we are studying Fanconi syndrome, a common kidney disease that can occur in adult Basenjis and that can be life-threatening if not aggressively managed. In some cases we may seek supplemental funds to study the phenotypes targeted for special emphasis. For the

Basenjis, we have applied for and received a small grant from the American Kennel Club/Canine Health Foundation to study Fanconi Syndrome. When possible, we will collaborate with other research groups that have special expertise and/or funding to investigate the targeted phenotypes.

# What will the long-term benefits be?

In the past decade technological advances have lead to spectacular accomplishments in molecular genetics and we expect this to continue for the foreseeable future. The quest to find the genetic risk factors for common and complex human medical problems such as idiopathic epilepsy, Alzheimer's disease, schizophrenia, autism, and type II diabetes has spurred the identification of over three million polymorphic sites in the human genome. There is now a high stakes race to develop microarray and microbead technologies to make use of a large subset of the these polymorphic sites and it is likely that within a few years it will be possible to analyze DNA samples using tens or hundreds of thousands of DNA markers simultaneously and inexpensively. Although this technology is being developed to analyze human DNA, it should work equally well for analyzing DNA from dogs. In the next few years when the technology is improved, it should possible to use many of the over two million polymorphic sites identified from the Canine Genome Project as markers to discover the genes influencing a wide variety of canine characteristics and behaviors. This, however, will only be possible if the fundamental phenotypic characteristics from a large number of dogs are described and recorded in a format that is compatible with computer tests designed to detect genotype/phenotype associations. Rather than waiting until the genotyping technology is perfected, we want to start collecting the phenotypic data by beginning the Canine Phenome Project now so that the required phenotypic information will already be available when the genotyping technology is ready. This should lead to the development of DNA markers to help dog breeders consistently produce litters that are free of heritable diseases and other undesired behaviors and characteristics.

# How can I participate?

We will soon be ready to add a few more breeds to the Canine Phenome Project. To do this, we will need support from Breed Clubs or associated Foundations. The current costs for two years of participation range from $5,000 for the smallest breeds to $30,000 for the most popular breeds. If you have questions or would more information contact Liz Hansen at HansenL@missouri.edu or 573-884-3712.