

## **A Success Story! A Model for Identifying the Genetic Bases for Inherited Traits in Dog Breeds**

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Due to the nature of selective mating within dog breeds, certain traits with underlying genetic bases tend to become concentrated within a breed. These traits can be desirable, such as a certain coat color or body form, or undesirable, such as glaucoma or seizures. The most reliable way of selecting for or against any of these traits in a breeding program is to perform matings based on knowledge of the genotype that is associated with a particular phenotype. Genotype refers to the specific form of a gene or genes. Phenotype refers to any observable trait of an individual, such as tail length or the occurrence of an inherited disease. If one can establish which gene controls a particular trait and how variations in the structure of the gene (the genotype) affect that trait (the phenotype), then by determining the genotypes of individual dogs one can plan matings to generate dogs with desired phenotypes.

As an example of how this approach can be adopted practically by a breed club, let me describe work we have been doing with the Tibetan Terrier Club of America to eradicate an inherited disease called neuronal ceroid-lipofuscinosis (NCL). This disease is an autosomal recessively inherited neurodegenerative disorder with symptoms that usually start to appear at 5 to 7 years of age. Affected dogs exhibit visual impairment, loss of coordination, behavioral changes, and often seizures. Death usually occurs before the age of 10. The disease is an example of a undesired phenotype, and to eradicate it we need to be able to identify the underlying genotype. That is, out of the tens of thousands of genes in a dog, we must identify which gene contains a defect that leads to NCL. To accomplish this, we need to be able to associate a particular collection of DNA samples (for genotype analyses) and reliable disease phenotype information from a large pedigree or a number of pedigrees from within the breed. It is critical that we be able to distinguish affected from unaffected dogs within the collection. Any dogs for which the disease phenotype is equivocal cannot be used to help identify the disease mutation.

Once the DNA samples and phenotype information have been collected from a sufficient number of related dogs, the search for the gene defect (mutation) responsible for the disease can begin. There are two strategies

that can be adopted to find the disease mutation depending on how much information is available about the disease at the start of the search. If similar diseases occur in other dog breeds or in other species and the mutations responsible for these diseases are known, one can adopt the candidate gene approach. In this approach, one analyses a candidate gene from affected and healthy animals from the same family to see if there are different forms of the gene in affected and unaffected dogs. If a difference is identified, each animal in the pedigree is examined to determine which form of the gene it carries. If all of the affected dogs in the family have two copies of one form of the gene and all of the unaffected dogs have either only one copy or no copies of this form, then we have either identified the gene defect responsible for the disease, or at least a genetic marker for the disease. By analyzing which forms of the marker a dog carries, we can mate only those dogs that would not produce affected offspring. If there are no known candidate genes for the disease, one must look for the disease gene by mapping it to a precise location in the dog genome (the entire collection of dog genes). The genes of dogs (and most other species) are organized in a precise order on a number of separate chromosomes, much as books in a library are organized on shelves. By determining where a disease causing mutation is located within a genome, we can eventually identify what that mutation is. To map the location of a disease gene, we need to analyze DNA from a large number of related dogs whose phenotypes relative to the disease of interest are known. We analyze many individual locations in the DNA across the genome for each dog. At each location the DNA can have a number of different forms or sequences. We examine the form of the DNA at each of hundreds of locations for each dog in a pedigree. What we are looking for is a location at which every affected dog is identical and none of the unaffected dogs have this same form at this location. Such a location will be close to the gene that carries the disease mutation. Once such a location is found, the form of the DNA at this location (the genotype) can be determined and used to select dogs for breeding that do not have the form associated with the disease. If necessary, further studies can be done to find the precise mutation responsible for the disease.

The above approach can be used to identify DNA markers associated with any simply inherited trait. To successfully apply this approach for directed matings within a breed the following needs to be done: (1) DNA from as many members of a pedigree in which the trait of interest occurs needs to be collected and preserved; and (2) the DNA samples need to be accompanied by accurate phenotype information relative to the trait of interest. With

these tools in hand, a geneticist can identify genetic (DNA) markers that can be used to select for or against that trait. Any breed club that has an interest in using this approach should set up a mechanism for collecting DNA, pedigree, and phenotype information in a coordinated manner. The phenotype information should include all traits that might be of interest, since the same genotype information can be used to find DNA markers for multiple traits.