"THE CANINE GENOME: WHAT BREEDERS NEED TO KNOW"

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Synopsis – Dr. Margaret (Peggy) Wallace, University of Florida

As discussed earlier by Dr. Hannah, the dog genome is known to vary at sites called polymorphisms or markers, as is the case with animals. These are thought to be generally quite neutral, but are very useful in mapping the dog genome because most animals will be heterozygous at the markers (they have a different version on each allele, maternal and paternal). This "informativeness" appears to be true across the 20 or so breeds tested thus far, and so marker-based genetics should be applicable to most breeds despite some inbreeding. But in addition to markers, animals can have DNA alterations that are not neutral - they affect the gene they are within or near. If the altered gene results in a deleterious condition (such as a disease), the changes are usually rather rare and are called mutations. Depending upon the mechanism of how the gene alteration causes the illness, the disease may appear inherited in one of several known fashions. Such conditions are called single-gene traits, or Mendelian traits. The most common modes of inheritance for single gene traits are autosomal dominant and autosomal recessive. Both of these are unrelated to gender (not sex-linked). In the dominant case, just having one of the two genes mutated is sufficient to induce disease and the chance of transmitting the disease mutation to offspring is 50% for each pup. In the recessive case, having one copy does not cause disease, but such individuals are heterozygous for the mutation and are called carriers. When two carriers are mated, each offspring has a 25% chance of having inherited both mutant alleles and being affected. If a dog affected with an autosomal recessive condition is mated to a carrier, each resulting pup has a 50% chance of developing the condition because the affected parent can only pass on a mutant allele. Likewise, probabilities can be calculated for various other situations, which often come up in dealing with specific breeds with complex inbreeding. For X-linked recessive traits, females (having two X-chromosomes) can be carriers, and those male pups (who have just one X) receiving the mutated X will be affected. Females with both alleles mutant will also be affected. X-linked dominant traits exist as well, but are rare.

There are a number of real-life variables that affect determination of mode of inheritance or diagnosis. One is the issue of penetrance – whether or not every individual who has the disease-causing genotype will show the disease (the phenotype). Some single-gene disorders have reduced penetrance, which can confound an effort to determine mode of inheritance or decide whether a dog is fit to be bred. Also, some conditions have a later age of onset, in which case dogs may be well into adulthood before the condition is obvious, also affecting breeding plans. Also, especially for dominant conditions, new mutations can arise in the sperm or egg, or shortly after fertilization, causing an affected pup even when parents are unaffected. In addition to Mendelian traits, some conditions result from combined interactions of multiple genes and the

environment. These are called complex, or multifactorial traits, and the incidence is higher among first-degree relatives than the population as a whole, because of some genetic predisposition. These traits don't usually show classic single-gene modes of inheritance, unless the pedigree is particularly inbred at that point. There may be several genes that contribute strong susceptibilities.

Like the human situation, researchers are interested in finding and cloning the genes that cause dog-genetic disease or contribute susceptibilities. Because of the recent advent of mapping the dog genome (finding polymorphic markers at certain distances across all the chromosomes), the ability to find these genes has been enhanced. The basis for these linkage studies is genotyping the markers in a set of related dogs (some affected, some unaffected), and testing for co-segregation of certain marker alleles with the disease. Tightly linked markers represent a flag for the general location of the disease gene, and various methods can then be used to more closely analyze that region and find the gene itself. A related method for autosomal recessive traits is homozygosity mapping. In this method, you genotype at least several affected dogs thought to carry the same recessive allele due to inbreeding, and when you find a marker that is homozygous (or nearly so) you analyze that region further as a possible linked region.

Either method should lead you to the general location of a gene that causes the condition of interest. Both methods rely heavily on obtaining DNA samples from affected dogs and their relatives, which is dependent upon participation by breeders and owners (even long distance). Without the dog DNA samples, such genes cannot be found. Once an interesting genetic region has been found, a very useful application is available even before the disease gene itself is found. Close markers can be used to determine with a high probability whether any dog in that immediate pedigree (or more distantly related dogs in some cases) carries the disease-causing mutation. It is not a perfect test because it is a linked marker and there is a slight chance of recombination, but it is nonetheless very useful for identifying carriers. This is a key for breeders to ensure mating that will prevent the production of affected (or possibly even carrier) dogs.

An alternative method to linkage for finding disease genes is a "fishing" approach, in which known disease genes in other species with the same conditions (such as human or mouse), or obvious candidate genes (due to their known functions) are tested for mutations in the dogs. This method depends partly on luck, but may pay off more quickly than linkage and subsequent cloning.

Ultimately it is important to identify the disease genes themselves and the mutations, to develop perfect DNA tests and to possibly identify better ways to treat the condition. For conditions in which the illness frequently arises due to a new mutation frequently, even responsible breeding will never eliminate the condition, and so it would be useful for the veterinarian to have a cure available.

Study of such conditions and corresponding genes also leads to improved understanding of our general biology of that system, which benefits man and animals alike. And in fact, the dog may provide a paradigm for many human illnesses, because some disease genes may be more easily found in the inbred animal situation. Once found in the dog, the human equivalent of that gene

can be screened in people with similar conditions. Thus, genetic research in dogs can benefit people, and vice versa. It is likely that many of the most common canine conditions will have susceptibility/causative genes found within the next 5-20 years. So it will be beneficial for breeders and organizations to support continued genetic research and the development of labs to administer these tests.

We should also encourage the establishment of databases or websites that keep current information about canine genetic test as they become available, so that breeders can make knowledgeable choices. Veterinarians will likely become more sophisticated in understanding the genetic issues and helping breeders make decisions about or interpreting tests, as well.