The CMO DNA Test

Shades of Gray

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DNA tests are routinely used to detect mutations present in dogs for various inherited diseases, and they are an important tool for dog breeders. For instance, by using a test that identifies the mutation in the gene responsible for vWD, Scottie breeders can identify animals that are Affected (2 copies of the mutation), Carrier (one copy) and Clear (no copies) so that they can make informed decisions for their breeding programs.

Today several companies are competing for our business. Some of these tests, like the vWD test, have direct significance for our breed, whereas others, such as Degenerative Myelopathy (DM) and Progressive Retinal Atrophy (PRA), identify the mutations associated with diseases not commonly seen in Scotties and therefore have more significance in other breeds.

Craniomandibular Osteopathy (CMO) is of significance in our breed, and the current commercially available DNA test is of value to other breeds as well (Westies, Cairns and others). However, this test is not a simple "black or white" kind of test. Instead, it is "correlated" to the inheritance for the disease and NOT PREDICTIVE, a fact that causes some confusion in the interpretation of the results. These "shades of gray" are rooted in the very genetics of the CMO mutation.

In 1998, with help from the AKC Canine Health Foundation, the STCA HTF joined forces with the Cairn and Westie National Clubs to fund research with Dr. Patrick Venta at Michigan State University to develop a DNA based diagnostic test for CMO. It was believed from earlier research by Dr. George Padgett that the mode of inheritance for CMO was autosomal recessive. The research carried out by Dr. Venta over a 2-year period held great expectations for the three Clubs but ultimately did not yield predictive results.

Then, in March of 2013, Dr. Venta announced the following to the STCA:

The laboratories of Dr. Hannes Lohi (Finland) and Dr. Cord Drögemüller (Switzerland) recently identified the causative gene and mutation [for CMO], thus permitting the development of a DNA-based test to determine carrier status of terriers for this mutation.

Drs. Drögemüller and Lohi identified a mutation in the SLC37A2 gene associated with painful and proliferative jaw bone development, the symptoms that we see on the radiographs of affected puppies. Today, Dr. Venta remains convinced that there are other mutations in a different part of the gene (or perhaps in another gene altogether), all of which need to align perfectly for the disease to be expressed. Further complicating this story is that CMO might be tied to other things happening in the dog's early life, such as rapid bone development or some nutritional element as yet unidentified (Personal conversation, July 2019).

Dr. Venta went on to conclude that the data produced by the European labs suggested that the mode of inheritance for CMO was more complicated that we thought. We now know that CMO has an autosomal dominant mode of inheritance with incomplete penetrance. What exactly does this mean? And what are the implications for our breeding programs?

Remember that genes code for proteins which can be critical for the normal, cellular functioning of many processes in the body. There are always two copies of a gene, and a mutation in one or both of the copies can cause the gene to produce defective protein or may turn off that gene entirely. And there can be multiple mutations in the gene affecting the formation of the complete protein. In a Simple Autosomal Recessive mode of inheritance (think vWD), the single mutation must be present in both copies of the gene to produce the disease. If just one copy of the gene pair carries the mutation, the dog will not exhibit the disease but will pass it on to its offspring 50% of the time. If the mutation is present in both copies of the gene, then the disease will be expressed and a copy of the mutation will be passed on to 100% of the offspring of this individual.

On the other hand, Drs. Drögemüller and Lohi found that about 85% of the CMO affected dogs had two copies of the mutation, 10% of affected dogs had a single copy of the mutation, and 5% of CMO affected dogs did not carry the mutation at all! They determined that expression of the CMO disease is obviously dependent on the genetic status of a dog for the CMO mutation but is also influenced by other, as yet unknown, genetic and/or environmental factors, a concept known as "incomplete penetrance".

These extra factors may or may not be directly causative or they may just be linked to the gene, "along for the ride" so to speak. They may suppress or accelerate the function of the protein coded for by the gene, thus exerting a strong or weak influence on expression of the disease. The disease may be easily recognized and diagnosed, or it may be so mild as to not even be noticed by the dog's owner. These extra factors may be different between individuals within a breed and among the affected breeds. What is interesting to note is that after a puppy is diagnosed clinically with the disease, the expression of CMO disappears within a few weeks or months, usually in response to anti-inflammatory therapy. This signifies that the genes responsible for bone development and remodeling must be involved, and they work in a compensatory capacity somehow with genes regulating growth rate.

What is clear is that the expression of CMO is complicated, and it involves several genetic players! To quote Dr. Venta: ***It's a weird disease.***

Dominant with incomplete penetrance leads to "shades of gray" in interpretation of the CMO test. How then can we interpret the results and use them in our breeding programs?

1. **CMO-0** is the result you hope to get: No copies of the mutation present. Even though there is a very small chance (5%) that the disease will still be expressed, the odds are good in the Scottie breed that you are safe with this result. **Plan: Breed CMO-0 dogs to each other and there will (probably) be no CMO.**

2. **CMO-2** is the result you don't want to get: Two copies of the mutation present. 85% of the affected dogs had this result. Even if the disease is not expressed, or is so mild as to be missed by the owner, genetically speaking, this individual will pass the mutation on to 100% of its offspring. **Plan: Do not breed. Or breed only excellent, irreplaceable CMO-2 dogs to CMO-0 dogs and keep only the tested CMO-1 puppies for the future.**

3. **CMO-1** is the result that may be the most confusing: One copy of the mutation is detected. This individual carries the mutation, **and** there is a 10% chance that he is also affected. The disease may be so mild as to not even recognize the symptoms. However, this individual will pass the mutation to its offspring 50% of the time. **Plan: Breed CMO-1 to a CMO-0 dog and 50% of the puppies will be CMO-1, the other 50% CMO-0. Or breed CMO-1 to CMO-1 and you will get CMO-1 (50%) and CMO-2 (25%) puppies.** Just remember that the CMO-1 puppies may be affected, so hypothetically, this litter could have 75% affected pups.

Don't throw the baby out with the bathwater! Use the DNA test to your advantage by retaining the best individuals and breeding away from the carrier and affected states. Test the offspring. Meanwhile, the STCA Health Trust is looking into the commercial tests currently on the market and evaluating them for how they are conducted in the lab. We hope to determine if some testing methods are more accurate in predicting the disease than others. When we have useful information to share, we will report our findings. So, stay tuned!

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