Norwich Terriers, 05-20
Title: Genetic testing: what it doesn't tell us

Direct-to-consumer marketing of genetic testing is a booming business, for both humans and dogs. The number of DNA tests promoted to detect health risks in dogs is increasing, but when the information is not clearly understood it may be used improperly with unintended consequences. Genetic information is often difficult to understand. In human medicine, genetic counselors help interpret the results of DNA tests, but most veterinarians are not trained to do this.

DNA testing is being promoted directly to dog owners to identify genetic mutations that cause disease. Mutations are permanent changes in the nucleotide sequence of a gene. These variant forms can alter the function of the gene, and if they exist in the germ cells may pass on to offspring. Mutations are not necessarily bad. Through evolution, mutations can produce desirable traits. The majority have little or no consequences. Mutations are problematic when they contribute to disease. In some instances, a single variant may have a large influence on disease risk, or the contribution of a mutation may be small. With a complex disease, many variants may contribute to disease risk, and in different ways. Even with highly prevalent disease, it's often complicated. For instance, in type 2 diabetes in humans—a well-studied disease—variants in 28 genes have been identified but it's not yet known how exactly they cause diabetes, or how non-genetic factors contribute to the disease.

Responsible breeders want to avoid breeding dogs that are likely to pass on disease-causing mutations to their puppies. So, the idea that a simple cheek-swab test can guide breeding decisions is attractive. Researching this column, I found a kit available for purchase online to test for a panel of 175 genetic conditions for less than $200. Another company sells breed specific tests, and two are specifically listed for Norwich terriers. One is for Upper Airway Syndrome in the Norwich Terrier, and is based on a variant in the ADAMTS3 gene, reported by a European collaborative group to be a risk marker.

Although the reference for this study is not provided on the company's website, it was published last year and prompted discussion amongst breeders of Norwich terriers in the U.S. and confusion about what the results actually mean. At the request of the NTCA, Dr. Bryden Stanley (lead investigator on our NTCA multi-site clinical study, CHF# 02232-MOU) provided her interpretation: "We think this variant appears to be a 'risk allele' that is associated with more severe airway disease, rather than a causative gene mutation. The gene does not appear to be an obvious candidate for upper airway disease, as the NTs affected with severe upper airway issues do not have any other systemic lymphedema

issues." This is important to understand. Association does not mean causation. Genes that are associated with a particular disease, may not cause it. Characterizing a disease and understanding the pathogenesis is a critical step.

Like many DNA tests, the results of the ADAMTS3 test tell whether a dog is "clear", carries one copy, or 2 copies of the genetic variant. So, what does this mean? What is an owner or breeder to do with this information? At this stage, we don't know. As Dr. Stanley noted, "It seems most likely that the ADAMTS3 missense variant in Norwich Terriers is a modifying factor that was shown in the study to be statistically associated with more severe manifestations of the condition and that the main gene mutation(s) underlying the condition remains to be discovered." Modifiers include other genetic factors, in addition to an identified genetic change, that in combination determine the risk of disease, along with other factors such as environmental and lifestyle factors.

Owners want to know the likelihood (risk) that their dog will have a disease. Breeders want to know whether breeding a particular dog will pass a disease causing mutation to a future generation. Typically, DNA test results indicate that the dog has a genetic predisposition to developing the disease, but it does not tell the risk of disease. Some dogs with a predisposing genetic variation will never get the disease while others will, even within the same family. It is conceivable that a breeding program that avoids breeding from dogs with the ADAMTS3 variant will over time reduce the severity of the upper airway changes. However, the European study found that the variant was present at a high frequency within the breed. Eliminating Norwich Terriers from the breeding pool based on the presence of this variant runs the risk of narrowing the genetic variability within the breed and perhaps selecting for animals that may have another deleterious trait.

Another limitation (and caution) with genetic testing is the mistaken belief that an owner might have when their dog is "clear" from a condition. This can happen if a test is based on one known mutation when, in fact, multiple mutations may be associated with the condition. For example, a commercially available genetic test has been available for some time to determine coat color dilution (D locus). Preliminary evidence of a causal mutation in the melanophilin (MLPH) gene was published by Drögemüller et al. in 2008. Owners testing for this mutation alone may be led to believe that their dog is "clear". Subsequently, Bauer et al. (2018) and Graham (2019) published discovery of additional mutations in MLPH, and those mutations do not account for all dilute colors.

Owners and breeders are eager for genetic tests to guide decisions, but DNA testing for dogs is in early stages. Before you purchase online DNA tests, it's important to understand the limitations and what genetic testing doesn't tell us.

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