Craniomandibular Osteopathy (CMO)

Introduction

The Kennel Club (KC) recently received a request to publish results of DNA tests for CMO in Scottish Terriers. At present, the KC is hesitant to undertake this step due to the inconclusive diagnostic nature of the test.

Background

To date, most DNA tests have been for diseases where affectation or disease status (clear/affected) is entirely determined by the genotype, or pair of variants at a gene possessed by an individual. Thus, the genotype definitively describes whether or not an individual will develop the disease (table 1).

Genotype \ disease status	Disease	Healthy
Normal / Normal	0%	100%
Normal / Mutant	0%	100%
Mutant / Mutant	100%	0%

Table 1. The segregation of disease with a mutant gene variant. In this case the disease is described as 'recessive' since when an individual possesses a normal and mutant copy (a heterozygote), the disease status (phenotype) is the same as individuals with 2 normal copies of the gene, i.e. the normal copy is 'dominant' to the mutant copy. With a 'dominant' disease, 100% of heterozygotes will show disease and 0% will be healthy – the mutant variant is 'dominant' to the normal variant (the rest of the table remains the same).

It can be seen from table 1 that there is zero risk of developing the disease when an individual possesses either 2 'normal' copies of the gene (homozygous normal), or one normal and one mutant copy of the gene (heterozygous). By extension, 100% of heterozygous and homozygous normal individuals will be healthy. On the other hand, 100% of individuals homozygous for the mutant copy will develop the disease.

DNA tests are particularly useful in this case, as breeding from a pair of healthy heterozygote animals means that there is a 25% probability that an offspring will be a mutant homozygote and so affected by the disease (and so a probability that 25% of all offspring will be affected). DNA tests allow breeders to prospectively ascertain the genotypes of breeding animals and so avoid producing any puppies affected by the disease.

However, not all genes act in the manner described. For example, there is no single gene for body weight resulting in the binary categorisation 'light' or 'heavy'. In most cases we are dealing with variation and so, when it comes to disease, risk. This appears to be the case with CMO – the variant at the gene that is tested partially determines affectation. This is often described by geneticists as incomplete penetrance (in contrast the examples described in table 1 are completely penetrant).

Information on CMO mutation in 3 Scottish Terrier breeds
The following is taken from Optigen's website (bold highlights and annotations are added by me):
Recently, a single causal DNA mutation for CMO has been identified by researchers at the Institute of Genetics, Vetsuisse faculty, University of Bern, Switzerland, and the Department of Veterinary Biosciences and Research Programs Unit, Molecular Medicine, University of Helsinki and Folkhälsan Research Center, Finland.
The mutation is highly associated* with CMO in Cairn Terriers, Scottish Terriers, and West Highland White Terriers. In this study, about 85% of the CMO affected dogs had two copies of the mutation, 10% had a single copy of the mutation, and 5% of CMO diagnosed dogs did not carry the mutation. The development of the CMO disease is obviously dependent on the genetic status of a dog for the CMO mutation, but is also influenced by other unknown genetic and/or environmental factors. The mode of inheritance of the CMO mutation is best described as autosomal dominant with incomplete penetrance†, meaning that dogs of both sexes that are homozygous mutant (with two copies of the mutation) have a comparably higher risk to develop CMO. Dogs heterozygous for the mutation (one copy of the mutation) might also develop the disease, but some of the dogs carrying the CMO mutation will live without showing clinical signs.
* associated, not definitively predictive.
† meaning that the gene does not entirely determine disease status (as discussed above).

Therefore, while the test offered may well be useful, Optigen are explicit that it is not a definitive predictor of disease as so many other DNA tests are – and breeders should be aware of this.

The following information is from the research paper describing the mutation (http://journals.plos.org/plosgenetics/article…).
The study determined the genotypes for samples of 3 breeds of dog known to be affected by CMO; West Highland White Terrier, Scottish Terrier, and Cairn Terrier. Crucially, although the mutation at the gene identified was shown to be associated with CMO, there were CMO affected dogs that were homozygous normal (table 2). This indicates that either other genes are involved, or some environmental factor is involved, or both.
normal/normal normal/mutant mutant/mutant Total
Westie Terr 0 10 59 69
Scottish Terr 1 3 10 14
Cairn Terr 1 3 9 13

Table 2. Tally of genotypes of CMO affected dogs of three breeds. Note that for the Scottish and Cairn Terriers the researchers found that one of each breed was homozygous normal, despite being diagnosed with CMO.

Further validation was undertaken by testing population controls; dogs which had no history of CMO (although the researchers stress that variation in the severity of the condition and inability to retrospectively diagnose may complicate definitive categorisation). The results show that in the West Highland Terrier there were a considerable number of dogs that were homozygous for the CMO mutation but without any apparent clinical signs of the disease (table 3):
normal/normal normal/mutant mutant/mutant Total
Westie Terr 297 265 64 626

Scottish Terr 195 40 0 235
Cairn Terr 83 12 0 95

Table 3. Tally of genotypes of dogs of three breeds with no apparent clinical signs of the disease. Note that for the West Highland Terrier the researchers found a substantial number of dogs homozygous for the mutation but without apparent clinical signs of the disease.

Therefore, we may derive percentages of diseased/healthy dogs by genotype (as per table 1) for each breed:

	Percent affected		
	normal/normal	normal/mutant	mutant/mutant
Westie Terr	0%	3.6%	48.0%
Scottish Terr	0.5%	7.0%	100%
Cairn Terr	1.2%	20.0%	100%

Table 4. Percent of each genotype of each breed affected by CMO

From table 4 it can be deduced that i) in the West Highland Terrier this mutation is associated with CMO but that additional factors are implicated, and ii) in the Scottish and Cairn Terriers the two copies of the mutation do appear to result in CMO but also that CMO may occur in the absence of two copies of this mutation.
Finally, it should be noted that the study located the gene and determined the causal mutation reported to influence CMO using Swiss, Finnish and American dogs. It is possible that the mutation may well be more or less common in the UK population of these breeds, as may mutations at other genes with an influence on CMO.

Conclusions

It appears that the DNA test for CMO, while highly associated, is not definitive and that use of this test should be undertaken in full knowledge of this. The Kennel Club is increasingly aware of DNA tests for mutations associated with, rather than definitively predictive of, disease and understands the need to provide information and guidance to breeders. The reticence to publish results of such tests at present is not due to potential inaccuracy, but rather due to concerns that breeders and owners fully understand the nature of these tests – what they can, and cannot, deliver. Particularly the Kennel Club is concerned that such DNA tests may be used to exclude large numbers of dogs from the breeding pool, without sufficient justification, which may have an effect on genetic diversity of future generations and risk the emergence of novel genetic disease. However, it may well be that breeders who are fully aware that such tests provide an indicator of risk can implement such tests in their breeding strategies.