

A genetic approach to solving disease.txt
"BruceCattanach"

In reply to Bruce and Judy Voran's question on the 'messiness' of cardiomyopathy inheritance:

Cardiomyopathy or CM, if I can reduce it as such, is a relatively new disease at the level of intense investigation - and I am talking about human genetics, rather than dog genetics. I think we can probably regard CM as a cluster of diseases, all with the same or similar outcomes. The term only means heart muscle disease; much could cause it. In humans a number of genes, perhaps nine, cause one or more kinds of inherited CM (there are environmental causes too). Mutations in any one of these genes alone can cause CM. Even dependent upon the nature of the exact mutation it may cause dilated CM (too little strength, contractibility) or hypertrophic CM (too much). All the genes seem to have effects upon calcium balance/absorption/utilisation of the heart muscle cells; they affect energy balance, affecting the capacity of the muscle to keep pulsating over and over throughout the lifetime of the individuals.

So, this is one minor complication. It means that there are different CMs in different populations/breeds/lines. So diagnostic procedures in Dobs may not have the same application in Boxers or Newfoundlands or Wolfhounds, even though the tools will be the same, ECG, Holter etc. And signs/symptoms vary. In the UK I suspect, although it has yet to be proven, that we have two slightly different CMs in our Boxers. One is like the form most commonly described in the US - often picked up by ECG/Holter and most commonly at later ages (6-8 years) with arrhythmias, progressing slowly and variably to clinical signs and maybe death. The other is an early onset severe form (mean age of onset 3-4 years with sometimes puppies being affected) with little if any warning and detected by the onset of the severe clinical signs or even sudden death. Lifespan has almost invariably been only a few months after onset of clinical signs.

The inheritance of CM in humans is easier to pinpoint than in inbred dogs. It almost invariably is that of a dominant. This fits with what knowledge there is on the abnormal proteins produced by the mutant CM genes. They interfere with the function of the normal proteins produced by the normal genes. So, the carrier is liable to be affected. The major problem that contributes to the 'messiness' is the poor penetrance of the gene. This means that probably a majority of carriers do not show signs of the disease. This varies with age too. Thus, few pups will show signs but signs are more likely to develop with aging. However, even in old age probably only some carriers express the disease while others go undetected. Despite seeming normal, these 'hidden' carriers still transmit the disease, so that a parent may develop the disease after numbers of its progeny have been diagnosed with the problem. A consequence is that one may harbour CM in one's kennels over several generations without knowing it, especially if one does not keep tabs on puppies sold (the majority usually). Thus, as a dominant, it only needs one parent to transmit the disease, and it can, 'like a recessive', travel through normal animals without signs. This is what I mean by 'messy'.

The 'messiness' is what one has to accept. One can forget about numbers of genes, at least until one thinks about mapping. Genes are mapped one at a time, and if one combined different families with different CM genes responsible for the disease in each, one would get nowhere. In our case, were one ever to take this route, I would be stressing within family data collection and not pooling until one might learn that the same gene is involved in each.

As you may gather, things are unsettled over here as yet with CM, but should
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be largely resolvable. We have just the one 'big' family and two other smaller and unrelated families of as yet little significance for the breed as a whole (these are the three that break down into two seemingly different types of CM). The majority of the breed is probably clear (with the odd worry). It is now open news on identities and the question is one of trying to offer affected kennels a way out without spreading the disease to the rest of the population. The alternative is total avoidance of the affected groups by those uninvolved (with-holding stud use etc) and maintaining a risk CM population in such isolation.

Anyway, these are some of my thoughts.

Bruce