This is an article prepared by Nottingham University in September 2015 to summarise a recent journal paper they have published which modelled existing canine dilated cardiomyopathy (DCM) genetic datasets with the goal of helping determine a genetic interaction with DCM in Doberman Pinschers. The research requires further validation but a genetic relationship was determined which could be relevant to other breeds.

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A predictive model for canine dilated cardiomyopathy—a meta-analysis of Doberman Pinscher data

We would like to present the results from our recently published paper 'A predictive model for canine dilated cardiomyopathy—a meta-analysis of Doberman Pinscher data' https://peerj.com/articles/842/. Although this paper is based around Doberman Pinschers, a similar effect could be observed in different breeds and species for many disorders.

Dilated cardiomyopathy (DCM) is a prevalent and often fatal disease requiring clinical management in humans and dogs. DCM is the second most common cardiac disease in dogs and often leads to heart failure. There are many possible causes of DCM, but in humans there is often a genetic cause. Despite many studies into canine DCM very few, so far, have found a genetic association.

DNA contains the basic building blocks that make up an individual, but although the same basic parts are there, there is variation between individuals and different species. For example all houses have windows, but not all windows are the same, there is variation. A genetic locus is small part, for example the part with instructions for windows, of the DNA which makes up an individual. There can be multiple loci, or separate bits of instructions, contributing to a trait – in humans a trait might be eye colour or whether or not the heart functions in a specific way.

There have been two genetic loci with variants associated with DCM in Doberman Pinschers. In each of the studies that identified the associations, the locus differences do not explain all the cases of DCM. This may mean that other variations exist in different parts of DNA, or that by combining two or more differing genes, a different trait, disease or incidence is observed.

We thought that by looking at the effects of the previously identified DCM loci together, rather than individually, that this could explain more cases

of DCM than individual loci variations alone. In addition within DCM there are several different presentations of the disease, even within a single breed. Some individuals have relatively mild symptoms and live for many months or even years, whereas others unfortunately go into heart failure and die within a few days or weeks of diagnosis. By combining the effects of multiple loci this could explain some of this variation, if an individual has several DCM variants the disease is potentially worse than if they only have one 'disease causing' variant. For example if you have instructions that include a small gap in the window frame it will be a bit draughty so your house will be a bit cold and you will have to put more energy into heating it. While this is not good, a worse situation would be if you have instructions in different places that include a small gap in the window frame and big hole in the middle of the glass – your house will be very cold and you will need to put a lot more energy into heating it. The same is true for hearts, a small defect and the heart has to work a little bit harder, but will probably be OK for a while, larger or multiple defects and it has to work a lot harder so will probably go into heart failure quite quickly.

We tested the combined effects of the two loci that are associated with Doberman DCM in mathematical models which were designed to allow us to predict the effects of multiple loci on the development of DCM. We also included additional hypothetical loci to establish if combining the effects of different loci could improve the predictive nature of the model.

Individually each locus does not explain all cases of Doberman DCM, but when combined together they explain an increased number of DCM cases, but still not all cases. The best model, although it is still not perfect, was one including both known Doberman DCM loci and an additional as yet unidentified X chromosome-linked (females get two copies, males only get one) locus.

This work is all theoretical and needs validating by genotyping (determining the genetic code) a large number of Doberman Pinschers with and without DCM at the two known loci. The models show that there are still additional DCM loci to be discovered within the Doberman breed and that looking for an X linked locus may yield results.

If this work is validated it could lead to genetic screening of potential parents to minimise the chances of offspring developing DCM by either not breeding from individuals with any DCM loci, or by minimising the number and severity of DCM loci that are being combined in the offspring.

While this study focuses on Doberman DCM loci, it is plausible that similar effects are happening in other breeds and species.

Please feel free to visit the published paper by our group at
https://peerj.com/articles/842/

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