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## Reviewer Comments

The authors would like to thanks the reviewers for their time, effort and comments. We have addressed all of your suggestions.

Yours faithfully,

Catrin Rutland

### Reviewer 1 (Anonymous)

#### Basic reporting

The authors describe an attempt to develop a predictive model for DCM in Doberman Pinschers that includes different combinations of genetic risk factors. In my opinion there are not enough reliable data available that would allow the development of any meaningful models for DCM in dogs. The current work may have been based on correct theoretical assumptions and with the appropriate methodology, but I don't see the use of the results in either a breeding program or a future research effort to finally identify the elusive genetic risk factors. Also, with no word the authors mention that Dobermans have different phases, constituting in VPCs only, or echo changes , or a combination of both.

* We have added a few sentences into the introduction, thank you for the suggestion.

#### Experimental design

I think that the GWAS leading to the identification of the PDK4 variant was not properly executed and consequently I doubt the predictive potential of the PDK4 variant.

* The authors could not find any published evidence for this. The GWAS which identified the *PDK4* variant in North American Dobermans, was published in a peer reviewed journal. Although subsequent studies failed to find an association in European Dobermans, this likely reflects that the two studies used different, separate populations.

The authors claim that an additional X-chromosomal locus better explains the available data. I have to admit my limited knowledge and experience in modeling. However, to me it did not become clear how the authors could discriminate between an additional X-chromosomal genetic risk locus and a sex-specific expression of disease (e.g. males have an earlier onset and more severe progression of disease than females). How would that be possible without pedigree data, which the authors did not have?

* We are grateful for the comments. Our model tested both a sex effect and X-linked effects. The 50% more- susceptible model accounts for sex specific expression, and does not predict the observed data as effectively.

Also, the cited study by Wess et al showed that the prevalence is the same in male and female dogs, only the disease progression is different: males develop in the disease earlier echocardiographic changes and were therefore easier to identify in older studies, which did not use 24-hour-ECGs. Female dogs have longer only arrhythmias.

* We have shown that the model incorporating an additional X linked DCM locus predicts similar proportions of male and female dogs developing DCM, fitting with the above comment.

#### Validity of the findings

see above

#### Comments for the author

see above

### Reviewer 2 (Anonymous)

#### Basic reporting

Much of the methods are not well explained; for example, the odds ratios that are central to the analyses are undefined.

* We have now defined these better, thank you for your suggestions on improving our communication.

#### Experimental design

It needs additional explanation - while I'm sure this makes sense to people who do these kinds of studies, others will not be able to follow the meager explanations.

* We appreciate this suggestion and have therefore added further explanations

#### Validity of the findings

I'm not qualified to opine on this.

#### Comments for the author

2014:11:3093:0:1:REVIEW

Abstract

The authors indicate that dilated cardiomyopathy (DCM) is the second-most common cardiac disease in dogs. What is the basis for this statement? I suspect that mitral valve disease is most common, but is DCM more common than tricuspid valve disease or congestive heart failure of valvular origin?

* This was an oversight to be included in the abstract but not the introduction and has now been rectified with associated reference

When the authors write: “suggest a genetic basis for the known sex-disparity” is that not a tautologous statement, because sex itself has a genetic basis?

* Thank you. This was indeed an unnecessary repetition. This is no longer included as it is not a critical part of the paper

Materials and Methods

The authors write: “Odds ratios of each genotype for each model were obtained by testing each genotype against the other two combined. Odds ratios for each allele were also obtained. The significance of these odds ratios were assessed using χ2 tests. It is expected that the models will show similar odds ratio patterns and significance levels to those of the reported data.” This is an inadequate description of the statistical methods. What is the outcome? Presumably the predictor is the genotype? What is the explicit interpretation of the odds ratio? Were these crude or adjusted? What does “similar odds ratio patterns” mean when they are simply numbers reflecting associations? It is likewise unclear what “significance levels to those of the report data” means.

* The authors have now amended this section and hopefully this has improved the materials and methods
* The odds ratio methodology is now explained in detail

Results

Line 138 states: “each model was optimised to minimise the χ2 test statistic.” Apart from the fact that it is unclear what this even means, it is a method that should be explained in the Materials and Methods section of the manuscript, and not introduced in the Results section

* The authors have now explained this more clearly in the methods section and adjusted in the results