The end for the genetic test in CU research

Article on the end of CU research in Bern

Dr. Ulrich Merschbrock

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On 22 February 2024, I received an extensive email from Prof. Leeb in Bern, in which he had to inform me that he was discontinuing research into a genetic test for cystinuria in Irish Terriers (IT) and Kromfohrländer (KF) due to the absolute lack of chance of success. Due to the lack of recognisable difference between a healthy and a diseased male dog, it is impossible for him to obtain meaningful results with the existing research approach. He would like to thank all his fellow researchers and the dog owners and breeding centres who have collaborated with him. He is not happy about this conclusion, but feels compelled to take this step due to the circumstances.
Even after my enormous efforts over the last two years, a new research approach, an attempt at a different classification of phenotypic traits, the acquisition of new test subjects and the reworking and categorisation of existing blood samples, unfortunately no new findings were obtained. In this last genome-wide association study (GWAS), almost 300 dogs were carefully phenotyped.

Five subgroups of both dog breeds were compared with each other, which were classified either as healthy or already affected as stone formers according to the **COLA values** (Prof Giger's suggestion) and my **PP test results**. When the genomes were evaluated, all the results of the 5 different subgroups of dogs were practically identical; there were no signals at all in the difference between "healthy" and "diseased" males and thus for a defective genome site. The research group then asked itself whether this phenotypic differentiation approach was correct at all.

What is astonishing and also interesting for future evaluation is the fact that neither the results of the **COLA test** nor the PP test give any indication of a genetic defect. In my opinion, it is therefore presumptuous to label a male dog as possibly suffering from CU solely on the basis of the urine amino acid test. That's why I developed the **PP test**, which, when used correctly, gives an absolutely reliable result in the case of positive crystal formation. In my investigations, only 30 per cent of the 27 male dogs tested showed cystine crystals after high protein feeding with simultaneous testing of urine amino acid values and urine sediment analysis with a high COLA value. Neither I nor any other scientist I consulted can provide an explanation for this actually incorrect physiological situation.

Prof Leeb suggests the following possible explanations for the absence of signals in the GWAS:

1. perhaps all IT and KF are genetically predisposed to cystinuria. Then there is no relevant genetic variation within these breeds and therefore we cannot find anything in a GWAS within these breeds.

2. perhaps the genetics behind this cystinuria are very complex with several genes that play a role and which may also interact in different combinations in different dogs. This could perhaps be solved with (significantly) larger cohorts, but then we are talking about thousands of dogs that we will never be able to phenotype and sample.

Therefore, in his opinion, he sees no hope for a "simple" genetic test that could help breeding and recommends selection based on phenotypic criteria as the only way out. As a former practising vet, I am not in a position to judge. As a former veterinary surgeon, I am also unable to judge whether the rather negative assessments from Bern are correct and whether positive results can be achieved with a different approach, a different research laboratory and testing methods.

As Bern now sees no point in continuing to work on this problem area and no further financial resources or personnel are available, the project will unfortunately be discontinued after 10 years of research. Prof Leeb offers to hand over the blood samples and test results to a suitable interested party for further possible research development after consultation and declaration of handover. *Prof Leeb will be happy to provide information at any time*. As far as I know at the moment, a discussion is to be held this week with a foreign laboratory owner. You will be kept up to date with all the latest developments here.

At the annual meeting of German Irish Terrier breeders, I will be available to answer questions with further and more detailed information. Here too, a further strategy for the treatment and therapy of the CU problem in Irish Terriers will certainly be discussed. I'm sorry that I can't report any more positive news. When I started this project 6 1/2 years ago, I had no idea what a complex subject the cystinuria disease in Irish Terriers is, a subject on which several professors have now cut their teeth. But as a practitioner, I think that existing problems should be solved or tackled sensibly. And with this motto we will make progress.

I would like to thank all the people who have supported me in my work and who have made their dogs available for this research project. I am also very convinced that, despite this setback, we have been able to gain valuable insights for the health of our Irish Terriers and that we will end up with an acceptable result.

Heinsberg, 27.02.2024 Dr. Ulrich Merschbrock