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UNIVERSITEIT GENT

INVITATION PUBLIC DEFENSE

DNA, a guide to improve our pets' health -
A researcher's role in refining genetic testing for dogs and cats

Evy Beckers

8 March 2023

PROMOTORS

Prof. dr. Luc Peelman
Faculty of Veterinary Medicine, UGent

Prof. dr. Bart Broeckx
Faculty of Veterinary Medicine, UGent

Dr. Sofie Bhatti
Faculty of Veterinary Medicine, UGent

Curriculum Vitae

Evy Beckers was born on the 25th of December 1991 in Vilvoorde. In 2009, she started her veterinary training at Ghent University where she graduated in 2015. For her master's thesis, she participated in genetic research estimating variant allele frequencies of genetic diseases in Belgian dog breeds at the Laboratory for Animal Genetics.

After her graduation, Evy continued as an assistant in the same laboratory, where she conducted genetic research on dogs and cats to obtain her Ph.D. She also contributed to the lab's services by providing genetic advice to veterinarians, breeders and owners. Evy is the author and co-author of multiple scientific publications in international peer-reviewed journals and presented her findings at multiple international conferences. She also took several transferable skills seminars and specialist courses and fulfilled the Ghent University Doctoral Training Program.

Evy currently works at the Center for Animal Breeding and Genetics at the KU Leuven as project manager of Breeding Healthy Pets, a project in collaboration with the Flemish government. There, she continues her work to improve the genetic health of dogs and cats in Flanders.

Where?

The defense will take place on March 8th, 2023 at 16.00h

Auditorium Hoogbouw (Entrance 23, 3rd floor)

Faculty of Veterinary Medicine
Ghent University, Campus Merelbeke
Salisburylaan 133, Merelbeke

How to attend?

The public defense is accessible to everyone without registration.

If you would like to attend the reception after the defense, please register before March 1st, by email to evy.beckers@ugent.be

Members of the Jury

Prof. dr. Hans Nauwynck
Chairman of the Jury
Faculty of Veterinary Medicine, UGent

Dr. Catherine André
Institute of Genetics & Development of Rennes, Rennes University

Dr. Paul Mandigers
Faculty of Veterinary Medicine, Utrecht University

Prof. dr. Ward De Spiegelaere
Faculty of Veterinary Medicine, UGent

Prof. dr. Pascale Smets
Faculty of Veterinary Medicine, UGent

Prof. dr. Dominique Paepe
Faculty of Veterinary Medicine, UGent

Summary

Dogs and cats are the most popular pets in the world. Both species have coexisted for thousands of years and over time, humans have created breeds through stringent artificial selection. This selection has led to a wide range of physical differences, most notably in the dog. Moreover, the domestication process and breed creation have caused several population bottlenecks, reducing the population size. Unfortunately, these population bottlenecks gave rise to an increase in genetic diseases and a decrease in genetic diversity in both species. How our pets' genetic health can be improved through DNA tests is being studied in this thesis. Different ways in which researchers can contribute to this health improvement are highlighted in Chapter 1.

The first step is the identification of disease-causing variants, which can be achieved through several techniques, and this is also the aim of the first two studies. The first genetic disease studied is one in the cat. Feline X-linked muscular dystrophy is a monogenic muscular disorder (Chapter 3). Immunohistochemical staining of an affected cat's muscle was negative for the dystrophin protein, which is encoded by the *DMD* gene. The entire dystrophin mRNA was sequenced and this revealed a nonsense variant in exon 11. The variant was confirmed at a genomic level and abundant proof was gathered to identify the variant as pathogenic. This study is a good example of a candidate gene study.

Chapter 4 is a study on idiopathic epilepsy in the Dutch partridge dog, a complex disorder that is probably caused by different variants and influenced by environmental factors. Few studies have been able to identify risk loci for idiopathic epilepsy, let alone causal variants. Here, a genome-wide association study including 16 cases and 43 controls identified a new risk locus on chromosome 12. Furthermore, whole exome sequencing was performed on one family (a case, both unaffected parents, and an unaffected sibling), which revealed a likely pathogenic variant in the *CCDC85A* gene, for which homozygous variant dogs showed an increased risk of developing the disease. Even though a risk locus and a likely pathogenic variant were found, more research is needed before they are employed in breeding strategies, to not unnecessarily endanger the genetic diversity of the breed.

The identification of disease-causing variants is a crucial first step in which genetic research can help improve the health of pets. However, the availability of a DNA test does not necessarily mean the test is relevant to the breed or the population. While some variants are widely spread between breeds, others are isolated within one breed or even within one population. Therefore, it is important to perform population studies to estimate variant allele frequencies. The Belgian dog population of 17 breeds was screened for 36 disease-causing variants (Chapter 5). The study identified which variants have a high enough frequency to warrant routine DNA testing in breeding programs. It also demonstrated the effectiveness of employing DNA tests in breeding schemes and stresses the importance of well-informed partner choices instead of excluding animals from breeding, to avoid a decrease in genetic diversity.

A different kind of population study is performed in Chapter 6. Multidrug sensitivity is a genetic disorder that only becomes phenotypically visible after the administration of certain drugs. Affected dogs are extremely sensitive to these risk drugs and display severe side effects. Since veterinarians regularly administer drugs, multidrug sensitivity is especially important in veterinary practice. However, a recent study in Belgium and the Netherlands showed that most veterinarians never request a DNA test. The study in Chapter 6 aimed to estimate the risk of veterinarians not genotyping for the variant by estimating the frequency in a clinical population. Only one of the 286 dogs (a known at-risk breed) was a carrier, which demonstrates a seemingly low risk. However, multidrug sensitivity still occurs in Belgian at-risk breeds. Therefore, the current recommendation of routinely genotyping at-risk breeds before treatment is advised.

In the final chapter (Chapter 7), the results of the four studies are discussed in light of their impact on pet health. The potential of dogs and cats as model species for human genetic disease is advocated. Since dogs and cats can be affected by/carriers of more than one genetic disease, some attention is provided to looking at the individual as a whole. In light of this, the potential role of screening panels and second-generation sequencing is discussed and future perspectives are given.