Disturbed retinal gene function underlying canine blindness

March 10 2020, by Helsingin Yliopisto

Miniature Schnauzers suffer from progressive retinal atrophy (PRA), which results in complete loss of vision for the dog. Credit: Pixabay

A canine study carried out at the University of Helsinki has described a gene variant in the regulatory region of the retina resulting in the abnormal function of retinal genes and, eventually, in the loss of vision in dogs. The study can benefit the diagnostics and treatment of retinitis

pigmentosa, a disease suffered by two million human beings globally.

"For now, changes in the regulatory regions of genes as causes of disease are relatively poorly known. In fact, our recently published study offers, in addition to diagnostics, a valuable model for understanding the biology of the retina and associated diseases," says Professor Hannes Lohi, who headed the study.

Since the 1990s, attempts to identify the genetic cause of retinal atrophy in miniature Schnauzers have been made all over the world. The breed suffers from progressive retinal atrophy (PRA), which results in complete loss of vision for the dog. Lohi's group identified a number of dogs with the same pedigree in the process of losing their vision, an indication of hereditary disease.

"We started compiling research data by comparing eye examination statements, quickly suspecting that more than one form of the disease occurred in the breed. This was an observation central to the progress of the project," says Maria Kaukonen, DVM, the principal author of the article and postdoctoral researcher at the University of Helsinki.

Based on their symptoms, the researchers divided the dogs into two groups, after which subsequent gene analyses demonstrated that the diseases were also different on the basis of the underlying genes. Dogs in group 1 lost their vision by the age of five, while the age of vision loss among group 2 varied more, in addition to which male dogs were overrepresented among the sick dogs.

In addition to regular eye examinations, the study was supplemented by optical coherence tomography (OCT), a technique not previously used in veterinary medicine in Finland. The imaging revealed the complete destruction of photoreceptors, or cells that respond to light stimuli, in the dogs suffering from the type 1 atrophy.

Disease caused by a peculiar gene defect of the regulatory region

"For the longest time, looking for the gene defect felt like looking for a needle in a haystack. We finally made a breakthrough after finding out that some of the healthy dogs have an almost identical locus of chromosome 15, only missing the mutation causing blindness. This implies that the mutation is a recent development," Kaukonen explains.

"The mutation we identified in the regulatory region results in hyperactivity in at least two retina genes previously associated with blindness. This is an interesting and uncommon find, as well as one of the first regulatory region mutations linked to retinal atrophy. Most likely, there are many more similar mutations, but they remain underrepresented in the literature due to the challenge of identifying them," Lohi speculates.

Rectifying previous research findings

"An American study published last year identified the same chromosomal locus as did our analysis, but the PPT1 gene in their proposal is actually associated with a very different disease of the nervous system, leaving us unconvinced. Nevertheless, a commercial gene test was developed on the basis of these ambiguous findings, which has caused a great deal of confusion among dog owners and breeders. The gene variant identified by us has now been tested for in over 1,600 dogs, with the results matching the disease perfectly. Now, we will be able to design a reliable gene test for the breed to support breeding and diagnostics," Lohi enthuses.

The study was part of Kaukonen's recently approved doctoral thesis, which investigated the genetic causes of canine hereditary ocular

diseases, and also part of a bigger research effort by Professor Lohi's research group looking into the heredity of ocular diseases. This was also the first study to utilise findings generated by the international DoGA research project headed by Professor Lohi, aimed at expanding the understanding of the canine genome. The DoGA project also employs researchers from the Karolinska Institutet in Stockholm, Sweden.

More information: Maria Kaukonen et al, A putative silencer variant in a spontaneous canine model of retinitis pigmentosa, *PLOS Genetics* (2020). DOI: 10.1371/journal.pgen.1008659

Provided by University of Helsinki