Discovery of mutated gene in dogs could help treat blindness

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Swedish vallhund. Credit: Marja-Liisa Lainepää

A Finnish-North American collaboration of scientists at Michigan State University and the University of Helsinki has found a MERTK gene defect responsible for a recently identified form of progressive retinal atrophy in Swedish vallhund dogs. This discovery opens the door to the

development of therapies for diseases that cause blindness both in dogs and humans. The research findings were published in the paper A Novel Canine Retinopathy Associated with MERTK in the journal *PLoS ONE* in December.

Inherited retinal diseases are among the leading causes of incurable blindness in humans as well as in dogs, where most of these conditions are classified as progressive retinal atrophy (PRA). Because of the similarities in ocular anatomy, canine models contribute significantly to the understanding of retinal disease mechanisms and the development of new therapies for human patients. The gene identified as a cause of PRA in the Swedish vallhund is associated with a form of human retinitis pigmentosa (RP), one of the most common incurable blindness worldwide.

This is the third paper published in *PLoS ONE* by the collaborating research teams of Dr. András Komáromy at Michigan State University, and Professor Hannes Lohi and Dr. Saija Ahonen at the University of Helsinki. The teams' three papers, each on Nordic dogs (Swedish Vallhund and Norwegian Elkhound) and each addressing blinding ocular diseases affecting both dogs and people, identified genes causing retinal disease and glaucoma, which may lead to gene therapies for dogs and humans.

"The work to characterize these diseases in two Nordic dog breeds drew from well-established international collaborations between clinicians, geneticists, and dog breeders. This type of longstanding, multi-disciplinary collaboration certainly strengthens a team's response to the challenges of unraveling complex problems and creating innovative solutions", explains professor Lohi. All three papers were also part of Dr Ahonen's PhD thesis published recently (helda.helsinki.fi/handle/10138/136144).

Ten years, seven countries, and three continents

The identification of MERTK gene as a cause of Swedish Vallhund PRA is the result of a decade-long project that first described the newly emerged disease in September 2014 in A Novel Form of Progressive Retinal Atrophy in Swedish Vallhund Dogs, PLoS ONE 9(9): e106610.

Beginning in the late 1990s, Swedish and Finnish eye panelists recognized the emergence of a new retinal disease in Swedish vallhund dogs. The retinal abnormalities were different from any known forms of canine inherited retinopathy.

In 2004, Komáromy, then at the University of Pennsylvania, received a telephone call from a breeder in Midwest about a new retinal disease. "I drove from Philadelphia to Michigan to examine the affected dogs, and began visiting dog shows and other venues around North America and Scandinavia to examine other Swedish vallhund dogs. It is wonderful to see that these trips helped us to later get this far to understand these conditions", tells Komaromy. The larger research project, which has led now to the identification of a responsible gene, became possible when Komáromy learned of the work of professor Lohi and Dr. Ahonen in the Department of Veterinary Biosciences and Research Programs Unit at the University of Helsinki, Finland, and the Folkhälsan Institute of Genetics.

Komáromy, the researchers from University of Helsinki, and collaborators from numerous institutions, took an investigative journey across three continents, examined 324 dogs in seven countries, described a new disease, and managed to identify a gene that causes the disease.

Future studies will include the search for the regulatory mutation and study of overexpression-related disease mechanisms with a possibility for a therapeutic option with MERTK inhibitors. Meanwhile, a genetic

marker test can be developed to revise breeding programs to reduce the frequency of this disease in the Swedish vallhund breed.

The teams' research on another, more common blinding disease in a Nordic dogs, is about the primary glaucoma in the Norwegian Elkhound. "This study helped us to developed a genetic test for the breed, and provides very important information to breeders to reduce frequency of detrimental disease in middle aged dogs", tells Dr. Ahonen. In November 2014 the team published their discovery in A Novel Missense Mutation in ADAMTS10 in Norwegian Elkhound Primary Glaucoma (*PLoS ONE* 9(11): e111941).

Glaucoma is a leading cause of irreversible blindness wordwide, affecting approximately66 million people. With support from the Glaucoma Research Foundation, Dr. Komáromy's laboratory at Michigan State University has recently begun the development of a new treatment for this form of glaucoma.

More information: A Novel Form of Progressive Retinal Atrophy in Swedish Vallhund Dogs, A Novel Missense Mutation in ADAMTS10 in Norwegian Elkhound Primary Glaucoma
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