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Moving towards gene therapies for retinal atrophies

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Researchers at Michigan State University (MSU) provide the first phenotypic evidence a mutated gene causes one form of progressive retinal atrophy in papillon dogs. Progressive retinal atrophy is analogous to one of the leading cause of inherited blindness in humans and the findings may lead to new treatments for blindness in humans.

Professor Simon Petersen-Jones, Myers-Dunlap Endowed Chair in Canine Health, and PhD candidate Paige Winkler at MSU College of Veterinary Medicine's Comparative Ophthalmology Lab, in collaboration with Dr Kari Ekenstedt, Assistant Professor of Animals Genetics at University of Wisconsin-River Falls, first identified the mutated gene in papillon dogs in June 2011. The team subsequently developed and licensed to OptiGen the first screening test for the gene.

Progressive retinal atrophy (PRA) is the canine equivalent of retinitis pigmentosa (RP) in humans. PRA and RP are marked by the early loss of rod photoreceptors, which are responsible for night vision. Loss of day vision usually occurs later in the disease. The team focused their research on PRA in papillon dogs and found that the CNGB1 subunit of the rod photoreceptor channel had a mutation in the PRA-affected dogs resulting in an early onset loss of rod function as would be anticipated by the gene mutation. The mutation of the CNGB1 gene identified by the researchers is considered to be responsible for about 70 percent of papillon PRA.

The research team's findings were published on August 19, 2013,

following two years of investigation and verification.

"Whenever you see a genetic change, you have to be sure that it's causing disease," says Petersen-Jones. "Although this change looked convincing of being disease-causing, we wanted to confirm that the mutation definitely caused that disease."

The mutation causes a lack of normal CNGB1 protein that is necessary for healthy functioning of rod photoreceptors. The researchers verified that the normal protein was not being produced in the retinas of affected dogs.

Using electroretinography, the team measured the electrical responses of the photoreceptors to light stimulus to assess retinal function in the affected dogs. The dogs lost function as expected from the lack of protein, and had markedly reduced or absent rod-mediated responses from an early age.

"We now have the evidence in animals that this gene mutation causes the disease," says Petersen-Jones. "We can show that that there's no rod response from a very early age—this is what you'd anticipate from the lack of normal protein."

The team's discoveries are leading the way and opening doors for research around the world. The genetic mutation identified by Petersen-Jones' team was subsequently independently identified by a team in Finland.

"The next step is to initiate gene therapy trials," says Winkler. "We expect to begin these in the coming year. We will also continue to detail the progression of the disease."

Because of the similarities of this retinal dystrophy in humans and dogs,

developments of therapies for dogs may provide an important foundation for preclinical assessment of therapies for human patients. Dogs with retinal dystrophies are valuable models of human retinal disease, and in numerous cases have proven invaluable to developing treatments for human blindness and for advancing investigations in human patients.

More information: Winkler PA, Ekenstedt KJ, Occelli LM, Frattaroli AV, Bartoe JT, et al. *PLoS ONE*, August 19, 2013.

Provided by Michigan State University