Team identifies a form of congenital night blindness in dogs

September 14 2015

People with congenital stationary night blindness, or CSNB, have normal vision during the day but find it difficult or impossible to distinguish objects in low light. This rare condition is present from birth and can seriously impact quality of life, especially in locations and conditions where artificial illumination is not available.

Working in collaboration with Japanese scientists, researchers at the University of Pennsylvania have for the first time found a form of CSNB in dogs. Their discovery and subsequent hunt for the genetic mutation responsible may one day allow for the development of gene therapy to correct the dysfunction in people as well as dogs.

They reported their findings in *PLOS ONE.*

The team included the Penn School of Veterinary Medicine's Gautami Das, a postdoctoral researcher; Keiko Miyadera, an assistant professor of ophthalmology; and Gustavo Aguirre, professor of medical genetics and ophthalmology. Their main collaborator was Mineo Kondo, a professor and chair of ophthalmology at Mie University Graduate School of Medicine in Tsu, Japan, from whom they found out about a unique population of beagles with night-vision problems.

The dogs had been bred by a Japanese pharmaceutical company and displayed behaviors characteristic of night blindness.

"In bright light they can walk around and navigate easily, but in darkness

they sort of freeze," Aguirre said. "It's really very dramatic."

The company enlisted the expertise of Kondo's team, which confirmed that the condition was CSNB by using physiological measures of the dogs' retinal function.

"They used a technique called electroretinography, which is what you would use as a diagnostic tool in human patients," Miyadera said. "You flash a light and you can detect the signals coming from the photoreceptors and other cells of the retina. Doing that with different light intensities and different dark and light adaptation situations helps you nail down the particular condition the dogs have."

All the affected dogs showed signs that were characteristic of CSNB, specifically a type known as Schubert-Bornschein complete CSNB, which is also seen in humans. In this condition, there is a malfunction in the process by which signals are transmitted between the retina's photoreceptor cells and bipolar cells.

The Japanese investigators first evaluated the dogs' pedigree to determine how the condition was inherited and found it was an autosomal recessive disease; in other words, a dog needs two copies of the mutated gene in order to be affected. This process also allowed the scientists to see which of the dogs was a carrier for the disease.

Kondo reached out to Aguirre's research group to delve deeper into the molecular underpinnings of the disease and to attempt to find a genetic cause.

Because the inheritance pattern they observed in the dogs is characteristic of several forms of human night blindness, the scientists examined genetic markers in both night-blind and carrier dogs to see if they had mutations in genes that also cause the disease in affected

humans. But their analysis failed to turn up any matches with the human conditions; still, this allowed them to rule out 11 candidate genes and two other functionally relevant genes.

Continuing the search for a responsible gene, the Penn Vet researchers also examined affected, carrier and normal dogs for expression patterns of genes involved in the function of cones, rods, photoreceptor synapses and several key elements responsible for communication between photoreceptor and the retinal ganglion cells. Again, they failed to turn up clear patterns to indicate which gene was responsible for the condition.

They did, however, find a distinct pattern between affected, carrier and normal individuals when they used protein markers that labeled the synaptic end of the photoreceptor cells. Affected individuals had reduced labeling compared to carrier individuals, which in turn had reduced labeling compared to the control dogs.

"We often find with a disease where we have a loss of function that, even without a loss of cells, proteins and receptors may redistribute to different locations," Aguirre said.

The gene responsible for these dogs' condition remains a mystery, but the researchers believe a genome-wide approach by means of whole-genome sequencing will narrow their hunt. The scientists are excited about this possibility, as the gene may represent a novel one not previously associated with CSNB, or a new manner in which the mutation can cause disease.

"It could be that the mutation is in a regulatory region of the unidentified gene, such as within an intron or the promoter," Das said.

Once they find it, they can begin development of a gene therapy approach to treating the condition, a strategy found successful by

Aguirre's group multiple times in dogs.

And this could find application in humans as well.

"The good news about this condition is that it is not progressive," Miyadera said. "You have all the cells there that you need to treat."

More information: *PLOS ONE*, dx.doi.org/10.1371/journal.pone.0137072

Provided by University of Pennsylvania