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Team finds a new structure in dogs' eye linked to blinding retinal diseases

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In humans, a tiny area in the center of the retina called the fovea is critically important to viewing fine details. Densely packed with cone photoreceptor cells, it is used while reading, driving and gazing at objects of interest. Some animals have a similar feature in their eyes, but researchers believed that among mammals the fovea was unique to primates—until now.

University of Pennsylvania vision scientists report that dogs, too, have an area of their retina that strongly resembles the human fovea. What's more, this retinal region is susceptible to genetic blinding diseases in dogs just as it is in humans.

"It's incredible that in 2014 we can still make an anatomical discovery in a species that we've been looking at for the past 20,000 years and that, in addition, this has high clinical relevance to humans," said William Beltran, an assistant professor of ophthalmology in Penn's School of Veterinary Medicine and co-lead author of the study with Artur Cideciyan, research professor of ophthalmology in Penn's Perelman School of Medicine.

"It is absolutely exhilarating to be able to investigate this very specialized and important part of canine central vision that has such unexpectedly strong resemblance to our own retina," Cideciyan added.

Additional coauthors included Penn Vet's Karina E. Guziewicz, Simone Iwabe, Erin M. Scott, Svetlana V. Savina, Gordon Ruthel and senior

author Gustavo D. Aguirre; Perelman's Malgorzata Swider, Lingli Zhang, Richard Zorger, Alexander Sumaroka and Samuel G. Jacobson; and the Penn School of Dental Medicine's Frank Stefano.

The paper was published in the journal *PLOS ONE*.

The word "fovea" comes from the Latin meaning "pit," owing to the fact that in humans and many other primates, the inner layers of the retina are thin in this area, while the outer layers are packed with cone photoreceptor cells. It is believed that this inner layer thinning allows the foveal cone cells privileged access to light.

It is known that dogs have what is called an area centralis, a region around the center of the retina with a relative increase in cone photoreceptor cell density. But dogs lack the pit formation that humans have, and, before this study, it was believed that the increase in cone photoreceptor cell density didn't come close to matching what is seen in primates. Prior to this study, the highest reported density in dogs was 29,000 cones per square millimeter compared to more than 100,000 cones per square millimeter seen in the human and macaque foveas.

It turns out that previous studies in dogs had missed a miniscule region of increased cell density. In this study, while examining the retina of a dog with a mutation that causes a disease akin to a form of X-linked retinal degeneration in humans, the Penn researchers noticed a thinning of the retinal layer that contains photoreceptor cells.

Zeroing in on this region, they examined retinas of normal dogs using advanced imaging techniques, including confocal scanning laser ophthalmoscopy, optical coherence tomography and two-photon microscopy. By enabling the scientists to visualize different layers of the retina, these techniques allowed them to identify a small area of peak cone density and then estimate cone numbers by counting the cells in this

unique area.

Based on their observations, the researchers found that cone densities reached more than 120,000 cells per square millimeter in a never-before-described fovea-like region of the area centralis—a density on par with that of primate foveas.

"There's no real landmark for this area like there is in humans," Aguirre said, "so to discover such a density was unexpected."

They also recognized that the "output side" of this cone-dense region corresponded with an area of dense retinal ganglion cells, which transmit signals to the brain.

Human patients with macular degeneration experience a loss of photoreceptor cells—the rods and cones that process light—at or near the fovea, resulting in a devastating loss of central vision.

To see whether the fovea-like region was similarly affected in dogs, the Penn researchers used the same techniques they had employed to study normal dogs to examine animals that had mutations in two genes (BEST1 and RPGR) that can lead to macular degeneration in humans.

In both cases, the onset of disease affected the fovea-like region in dogs in a very similar way to how the diseases present in humans—with central retinal lesions appearing earlier than lesions in the peripheral retina.

"Why the fovea is susceptible to early disease expression for certain hereditary disorders and why it is spared under other conditions is not known," Cideciyan said. "Our findings, which show the canine equivalent of a human genetic disease affecting an area of the retina that is of extreme importance to human vision, are very promising from the

human point of view. They could allow for translational research by allowing us to test treatments for human foveal and macular degenerative diseases in dogs."

In addition, the discovery offers insight into a rare human condition known as fovea plana, in which people have normal visual acuity but no "pit" in their fovea. In other words, their fovea resembles that of dogs, challenging the previously held assumption that lack of tissue and blood vessels overlaying the fovea is a prerequisite for the high resolution of vision.

The fact that dogs have a fovea-like area of dense photoreceptor cells may also indicate that dogs are seeing more acutely than once suspected.

"This gives us a structural basis to support the idea that dogs might have a higher visual acuity than has been measured so far," Beltran said. "It could even be the case that some breeds have an especially high density of cells and could be used as working dogs for particular tasks that require high-level sight function."

Looking ahead, the researchers may focus on this fovea-like area in studies of therapies for not only X-linked retinal degeneration and Best disease but also other sight-related problems affecting the macula and fovea.

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