# New twist in a blindness-causing disease gene found

September 21 2011

After more than three decades of research, University of Pennsylvania veterinarians and vision-research scientists, with associates at Cornell University, have identified a gene responsible for a blindness-inducing disease that afflicts dogs. In the process, the Penn scientists may have discovered clues about how retinal cells, and perhaps even neurons, can be regenerated.

The research was conducted by Gustavo D. Aguirre, William A. Beltran, Agnes I. Berta and Sem Genini of Penn's School of Veterinary Medicine, along with Kathleen Boesze-Battaglia of the Penn School of Dental Medicine. They collaborated with researchers from Cornell, the National Eye Institute and the Semmelweis University of Medicine, in Hungary.

Their study was published in the open access journal PLOS One.

At the University of Pennsylvania in the late 1960s, Aguirre was studying rod dysplasia, a genetic disease that causes blindness in a rare breed of dog known as the Norwegian Elkhound. After the blinding disorder in the original group of dogs was eliminated, Aguirre and his colleagues endeavored to find other dogs that suffered from the same condition, only to discover a similar but separate disease instead.

This disease, which they termed early retinal degeneration, or ERD, resulted in the same blindness but in a much shorter period of time; the afflicted dogs became completely blind within a year of birth, instead of

between two and four years.

Interested in gene therapies to cure blindness, Aguirre and his colleagues began narrowing down the list genes that could be responsible for ERD. As the relevant technologies improved, the researchers were able to work faster, but it was only recently that they discovered the culprit.

It was hiding in an unlikely place in the dog's genome.

"After developing the dog genetic map in the late '90s and then mapping the disease to a known region of the genome," Aguirre said, "we had a physical interval to look for this gene in, but we had to prioritize gene candidates by their location and what their function is. This gene was at the bottom of our list because it's normally only found in the brain and was not related to any known vision defect. But, lo and behold, it's actually a very important gene to the retina."

Identifying the gene is a first step to explaining a puzzling aspect of ERD: a "plateau" in its progression. The visual cells in the retina initially remain but then are lost and vision quickly fades. Microscopic analyses of retinas from afflicted dogs showed that, during this period, vision-related cells die at an accelerated rate but are just as quickly replaced; the cell death and compensatory formation of new ones is a new and totally unexpected finding in diseases of the retina. This work was done by Ágnes Berta, a medical doctor from Budapest who, as part of her Ph.D. studies, spent a year in the Aguirre lab through a Fulbright educational exchange program fellowship.

The researcher used an antibody-labeling system to identify how the photoreceptors were affected. The two types of these cells responsible for vision are rods, which are very sensitive to dim light, and cones, which distinguish color. Humans have short, medium and long cones, which correspond to the wavelengths of light they detect. Dogs and most

other mammalian species have only two cone types, one that is sensitive to short wavelengths and another that absorbs light in both the long and medium wavelength range.

"When Berta used an antibody label for the medium and long cones, it was very discreet, but when she used label for the short wave length sensitive cones a population of rods was also labeled," Aguirre said. "We saw that as the cell proliferates it goes back to a primordial, hybrid photoreceptor."

Though the exact function of the relevant gene has yet to be identified, it is likely involved in the control of the cell division cycle. Normally, photoreceptors cells in the retina stop dividing shortly after birth. These hybrid photoreceptors, however, continue to divide during ERD's plateau period.

Understanding what keeps those cells rejuvenating may hold the key for therapies that can hold off the onset of blindness, or even reverse it.

"These cells are abnormal," Aguirre said. "Normally, there is no good evidence of large amounts of new cells being created in the retina or the central nervous system. We can better understand the way that the photoreceptor cells divide by studying this disease and potentially manipulate the gene in such a way that you could get the division component without the abnormal component. If we could regrow our diseased retinal cells, it would be wonderful."

Provided by University of Pennsylvania