Commonalities in late stages of inherited blinding diseases suggest targets for therapy

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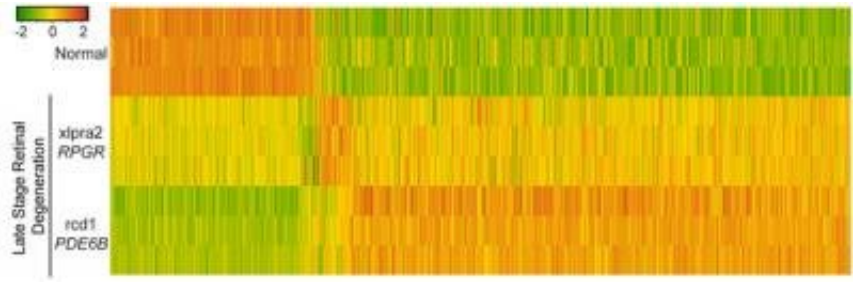

A heat map showing patterns of gene expression reveals similarities between two different forms of retinitis pigmentosa, a blinding disease. The commonalities involve innate immune pathways, and point to new strategies for treatment. Credit: University of Pennsylvania

Gene therapy holds promise for treating a variety of diseases, including some inherited blinding conditions. But for a gene therapy to be effective, one must know the precise gene responsible for a given individual's disorder and develop a tailored treatment. For diseases that may be caused by mutations in many different genes, developing individual gene therapy approaches can be prohibitively costly and time-intensive to pursue.

In a new study published in the journal *Scientific Reports*, a research team from the University of Pennsylvania School of Veterinary Medicine took a different approach, using canine models of vision-robbing disorders. Rather than looking at what distinguished two forms

of retinitis pigmentosa, or RP, a progressive blinding disease, they looked for what they had in common: specifically, what genes were expressed at the later stages of disease. Their findings, showing the involvement of common immunity-related pathways, point toward potential new strategies for treating the late stages of inherited blinding diseases.

"We were surprised to find so many similarities between these two diseases, but most striking was that some of these common signatures are shared with other conditions like diabetic retinopathy and age-related macular degeneration," said William A. Beltran, senior author on the study, an associate professor of ophthalmology in Penn Vet's Department of Clinical Sciences and Advanced Medicine and director of the Division of Experimental Retinal Therapies. "If we could perhaps modulate these pathways and prolong survival of photoreceptor cells, we might be able to delay any further degeneration even when intervening at these later stages of disease."

Beltran co-authored the work along with first author Raghavi Sudharsan, a research associate in his lab; Daniel P. Beiting, assistant professor; and Gustavo D. Aguirre, professor of medical genetics and ophthalmology.

Retinitis pigmentosa is a progressive form of blindness that affects approximately 1 in 4,000 people. Mutations in at least 60 genes are known to cause the disease, and many people are not diagnosed until after a a substantial proportion of photoreceptor cells, the eye's rods and cones, have already degenerated and died.

"One of the major limitations in developing a corrective gene therapy is that it will treat only a single disease," said Sudharsan. "We wanted to identify some potential therapeutic targets that are common not just to one but to multiple forms of retinitis pigmentosa at late-stage disease, when it is more likely to be clinically diagnosed in a patient population."

With that in mind, the Penn Vet team chose to examine two of their well-established canine models of RP, which recapitulate many features of the human diseases, each involving mutations in different genes. Their goal was to determine what molecular pathways were playing a role in cell death during the later stages of degeneration.

To do so, they examined two canine models of RP, rcd1 and xlpra2. Both involve rapidly progressing blindness. Analyzing retinas at a point when more than 50 percent of the photoreceptor cells had died, the team performed transcriptomic analysis to find out what genes were activated at this late stage compared to gene expression in the retinas of normal dogs.

Their results showed that both forms of RP had clear differences in gene expression compared to normal retinas. Using a software program to identify patterns in the genes that were activated, they found that several pathways stood out as being activated in both diseases, including the complement pathway, the inflammasome pathway and the Toll-like receptor signaling pathway. These three and others are components of innate immunity, the arm of the immune system that responds both to invading pathogens and to the body's own cells when they are damaged or dying, helping clear away debris.

Though the results make clear that innate immunity and inflammation are involved in the advanced stages of rcd1 and xlpra2, the researchers cannot be sure whether the molecular pathways at work are trying to clean up the mess caused by the degenerating photoreceptor cells, or whether they are part of the problem, a sort of hyperactive immunity causing damage in its own right.

"We see genes upregulated that are related to inflammation," Sudharsan said. "As to which are helpful and which are further exacerbating the degeneration, we can't answer at this stage; we need to study this

further."

An unexpected finding was that many of the innate immunity pathways that were active in the late stages of these inherited blinding diseases were the same as those that are associated with more common vision disorders including diabetic retinopathy and age-related macular degeneration, or AMD. Because there are already drugs in development for treating those diseases, these findings hint that these same compounds might also be able to address the degeneration occurring in RP.

In addition, the researchers noted, there are no large animal models for age-related macular degeneration that faithfully replicate features of the human condition. The gene expression similarities between this common condition and the current findings in late-stage RP suggest that the canine RP models could serve as stand-ins to evaluate the effectiveness of pharmaceutical interventions that target innate immunity pathways in AMD

Despite this new direction for identifying targets for pharmaceutical interventions against RP, the researchers underscore that gene therapy still has great potential and possible benefits, and they are actively pursuing efforts with this approach for several forms of RP. But therapies that target common molecular pathways active late in disease could be part of a multi-pronged treatment plan for people with these inherited conditions.

"It could be that a cocktail of therapies will eventually be used in these cases," Beltran said.

"These approaches," said Sudharsan, "may help sustain photoreceptor cells for the time period needed to develop a specific gene therapy."

More information: Raghavi Sudharsan et al, Involvement of Innate Immune System in Late Stages of Inherited Photoreceptor Degeneration, *Scientific Reports* (2017). DOI: 10.1038/s41598-017-18236-7