Identified Genetic Interaction Offers Possible New Target for Glaucoma Therapy

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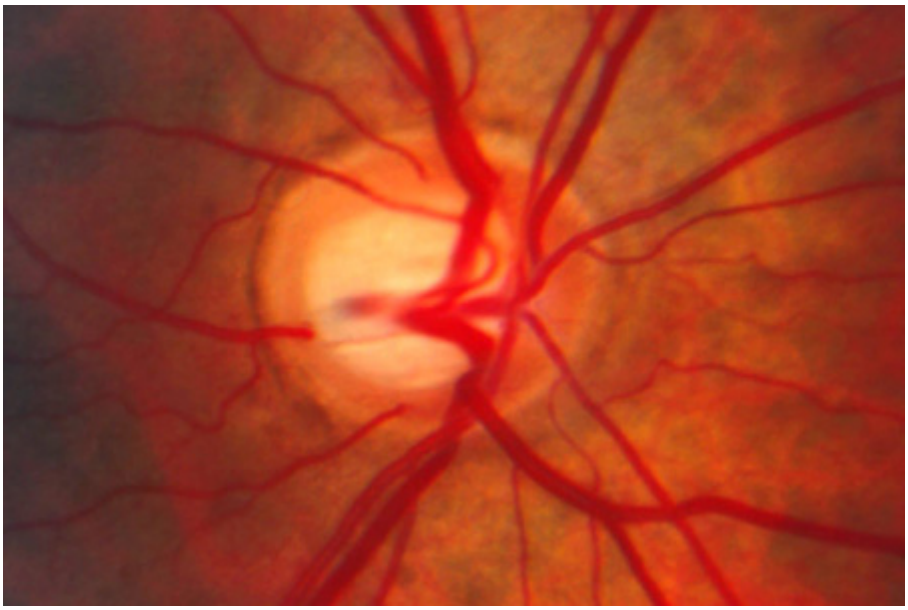
Scientists at the University of California, San Diego School of Medicine have elucidated a genetic interaction that may prove key to the development and progression of glaucoma, a blinding neurodegenerative disease that affects tens of millions of people worldwide and is a leading cause of irreversible blindness.

The findings, published in the September 10 online issue of *Molecular Cell*, suggest a new therapeutic target for treating the eye disease.



Optic nerve head of patient with glaucoma.

Primary open-angle glaucoma (POAG) is the most common form of glaucoma, affecting more than 3 million Americans, primarily after the age of 50. Pressure inside the eye (known as intraocular pressure) and age are the leading risk factors for POAG, resulting in progressive degeneration of retinal ganglion cells, optic nerve damage and eventual vision loss.

Genetics also plays a role. Recent genome-wide association studies have identified two genes – *SIX1-SIX6* and *p16INK4a* – as strongly associated with POAG. *SIX6* is required for proper eye development. *P16INK4a* irreversibly arrests cell growth, a phenomenon called senescence.

In their new paper, principal investigator Kang Zhang, MD, PhD, professor of ophthalmology and chief of Ophthalmic Genetics at Shiley Eye Institute at UC San Diego Health, and colleagues

report that some variants of *SIX6* boost expression of *p16INK4a*, which in turn accelerates senescence and death of retinal ganglion cells.

"We also show that high intraocular pressure in glaucoma increases expression of *p16INK4a*, making it a key integrator of inherent genetic and environmental risk factors that can result in glaucoma," said Zhang.

The findings suggest that inhibiting *p16INK4a* could offer a new therapeutic approach for glaucoma, which is currently treated by drugs that lower intraocular pressure. "Although lowering intraocular pressure can slow worsening of the disease, it does not stop it and prevent further cell death or possible blindness," said co-author Robert N. Weinreb, MD, Distinguished Professor of Ophthalmology and director of the Shiley Eye Institute.

The authors note that earlier studies in mouse models have shown that selective elimination of *p16INK4a*-positive senescent cells can prevent or delay age-related tissue deterioration.

According to the UC San Diego team, the next step is to conduct preclinical studies to assess the efficacy and safety of antisense oligonucleotides – strands of synthesized DNA or RNA that can prevent transfer of genetic information – which might inhibit *p16INK4a* expression and prevent worsening of glaucoma. "If they are effective, we may contemplate a human clinical trial in the future," Zhang said.

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