# Gene variants that protect against glaucoma identified, opening therapeutic possibilities

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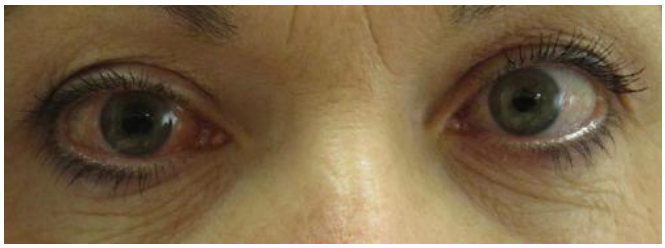

Acute angle closure glaucoma of the right eye (intraocular pressure was 42 in the right eye). Credit: James Heilman, MD/Wikipedia

An international research collaboration led by researchers from the University of Helsinki and Stanford University has identified rare changes in a gene called ANGPTL7 that lower intraocular pressure and significantly reduce the risk of glaucoma. The results open important new therapeutic possibilities.

Glaucoma is an eye disease affecting almost 80 million people and is the second leading cause of blindness worldwide. Glaucoma results in progressive damage to the optic nerve head, which leads to a corresponding visual field loss and when severe, blindness. The pressure within the eye (intraocular pressure) is the only modifiable risk factor for glaucoma.

Glaucoma has a clear genetic component and tens of common genetic variants affecting intraocular pressure and/or glaucoma risk have been identified. The clinical impact of these results has, however, thus far been negligible.

In this study, published in the journal *PLOS Genetics*, researchers searched for less common genetic variants which might lower intraocular pressure and protect from glaucoma, and focused on those with a clear effect on the function of the corresponding protein product. Such variants have particularly high therapeutic potential—since they would highlight a specific gene and a genetic modification that protects from disease.

The results of the study are based on two big European cohorts with large-scale genome and health information data available. Altogether more than 514,000 individuals from the UK Biobank and the Finnish FinnGen studies were examined. Both cohorts include thousands of individuals with a glaucoma diagnosis. Furthermore, over 120,000 UK Biobank participants have participated in the intraocular pressure measurement tests.

Both study cohorts provided independent, complementary and convincing evidence for the role of the ANGPTL7 gene in glaucoma. UK Biobank participants carried several rare genetic changes that were shown to reduce intraocular pressure, while FinnGen study provided very strong evidence of another variant specific to the Finnish population which significantly decreased glaucoma risk.

"The variant we identified is more than 50 times more common in the Finnish population than elsewhere in the world. In fact, more than 8% of Finns carry it and have a substantially reduced risk of glaucoma. This again demonstrates how the population history of the Finns makes it much easier to identify clinically important genetic variants," said Professor Mark Daly from the Institute for Molecular Medicine Finland (FIMM), University of Helsinki who co-led the study.

"With clinic-based recruitment focused on several areas including ophthalmology, and with more than 30% of the participants being above age 70, FinnGen is particularly well-powered for aging-associated endpoints."

"We often think of the body as a machine whereby taking a single bolt out of that machine and

something could go wrong. In this study that hypothetical bolt made the 'machine' work even better by protecting human individuals from glaucoma. Our results highlight the benefits of multi-cohort analysis for the discovery of rare protein-altering variants in common diseases, and ANGPTL7 provides the best therapeutic hypothesis out there for glaucoma," said Manuel Rivas, assistant professor of biomedical data science, Stanford University's School of Medicine, who co-led the study.

Importantly, cohorts such as FinnGen and UK Biobank make it possible for the researchers to assess whether the identified protective variants increase the risk of some other condition.

"Using the comprehensive health information in the two population cohorts, we assessed the potential impacts of rare genetic variants in ANGPTL7 on a spectrum of human disorders. We did not find any severe medical consequences that would be of obvious concern in developing a therapeutic to mimic the effect of these alleles," said Yosuke Tanigawa, doctoral student, Stanford University's School of Medicine and the first author of the study.

Better understanding of the genetic and pathological mechanism behind intraocular pressure can open up new ways of preventing or treating glaucoma. In this case, the genetic findings support inhibition or lowering the amount of ANGPTL7 as a potentially safe and effective therapeutic strategy for glaucoma.

"Our results position angiopoietin-like 7 as an appealing and safe target for glaucoma therapies. If a drug can be developed that mimics the protective effect of these mutations, intraocular pressure in at-risk individuals could be lowered," said Mark Daly.

**More information:** *PLOS Genetics* (2020). DOI: 10.1371/journal.pgen.1008682

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