

EXAMINING THE GENETIC ARCHITECTURE OF GLAUCOMA



The discovery of new genetic markers has significant implications for predictive screening and disease prevention.

WITH STUART MACGREGOR, PHD



Previous genome-wide association studies have identified more than 100 loci for primary open-angle glaucoma, but much of glaucoma heritability has yet to be explained. In a recent investigation,¹ researchers conducted a large-scale multitrait genome-wide association study in participants of European ancestry, combining primary open-angle glaucoma and its two associated traits (total sample size > 600,000) to substantially improve genetic discovery power (263 loci).

According to the study, the investigators “further increased [their] power by employing a multi-ancestry approach,” which increased the number of independent risk loci to 312, with the vast majority replicating in a large independent cohort from 23andMe (total sample size > 2.8 million; 296 loci replicated at $P < .05$, 240 after Bonferroni correction).

Lead study author Stuart MacGregor, PhD, shed light on the questions steering this work and other ongoing investigations and commented on the significance of these findings.

GT: What was/were the fundamental question(s) steering this investigation?

Stuart MacGregor, PhD: Glaucoma is a leading cause of blindness, but diagnosis frequently comes after irreversible damage has occurred. We sought to understand what caused differences in who is and is not affected.

As glaucoma is one of the most strongly genetic human diseases, we examined the genetic architecture of the disease. By identifying the specific genes underlying risk, we hope to gain insight into who is at highest risk and to develop more effective treatments.

GT: This investigation identified 312 loci, dramatically expanding the knowledge of glaucoma genetics. What were the keys to this outcome?

Dr. MacGregor: In 2021, the International Glaucoma Genetics Consortium conducted a case-control genome-wide association study; this work identified 127 risk loci for glaucoma, but it was clear that this only accounted for a minority of the overall genetic contributions to glaucoma.

In our recent investigation,¹ we expanded on the 2021 study by

adding very large-scale glaucoma risk factor data to the previous case-control cohorts. We showed that, by including information on more than 600,000 individuals with genome-wide genetic data, we could identify more than 300 genetic loci that influence glaucoma risk. We validated the vast majority of the novel loci in an independent cohort.

GT: What is known about these 312 loci, and how could this understanding impact future investigations and/or treatment efforts?

Dr. MacGregor: Leveraging multi-omics datasets, we identified many potential druggable genes, including neuroprotection targets likely to act via the optic nerve, a key advance for glaucoma because existing drugs target only IOP.

In our study, we identified lists of drugs that, based on genetic evidence, show excellent promise for repurposing. Repurposing drugs in this way is likely to rapidly accelerate work seeking to find drugs that prevent retinal damage from progressing in glaucoma.

“In recent years, we have been building an increasingly complete picture of the genetic architecture of the disease. It has become apparent that a very large number of genes underpin glaucoma risk. Our new paper leverages very large glaucoma cohorts, together with data on glaucoma risk factors, to almost triple the number of genes for the disease.”

Using genetic evidence to enable more efficient drug discovery has been shown to be effective for a range of diseases, and it is exciting to be able to do this for dozens of new drug targets for glaucoma, focusing on protecting the optic nerve from damage.

GT: What question(s) are still on your mind related to this work?

Dr. MacGregor: In recent years, we have been building an increasingly complete picture of the genetic architecture of the disease. It has become apparent that a very large number of genes underpin glaucoma risk. Our new paper leverages very

large glaucoma cohorts, together with data on glaucoma risk factors, to almost triple the number of genes for the disease.

Glaucoma is typically treatable with eye drops or surgery, but, if left untreated, the damage is irreversible. Therefore, the discovery of these new genetic markers has significant implications for predictive screening and the prevention of glaucoma. In ongoing work, we are using the set of newly discovered genes to improve risk prediction for glaucoma.

We think effective genetics-based prediction will be extremely important because there are typically no warning

signs of glaucoma, with more than 50% of cases not diagnosed until irreversible optic nerve damage has occurred. ■

1. Han X, Gharahkhani P, Hamel AR, et al; 23andMe Research Team; International Glaucoma Genetics Consortium; MacGregor S. Large-scale multitrait genome-wide association analyses identify hundreds of glaucoma risk loci. *Nat Genet.* 2023;55(7):1116-1125.

STUART MACGREGOR, PHD

- Group Leader and Principal Research Fellow at QIMR Berghofer Medical Research Institute, Brisbane, Australia
- Honorary Professor, University of Queensland, Brisbane, Australia
- stuart.macgregor@qimrberghofer.edu.au
- Financial disclosure: Founder and stockholder (Seonix Pty Ltd)