Genetic discovery could help prevent irreversible blindness in people with glaucoma

July 3 2023

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International research led by QIMR Berghofer has found hundreds of new genes linked to a person's risk of developing glaucoma, including key genetic targets that could, for the first time, pave the way for treatments that prevent the retinal damage that causes blindness.

The findings, from the largest-ever global genetic study of the degenerative eye disease, have been published in *Nature Genetics*.

The research significantly advances our understanding of the genetics of glaucoma, building on a previous 2021 study to identify another 185 previously unknown genes linked to glaucoma risk, bringing the total number to 312 genes.

Glaucoma is the leading cause of irreversible blindness globally affecting more than 75 million people around the world, including 300,000 Australians. The disease causes pressure from fluid in the eye to build up causing damage to the retina and the optic nerve.

Around 50% of all glaucoma cases aren't diagnosed until permanent optic nerve damage has already occurred, so early diagnosis and treatment is vital.

Lead researcher and internationally-recognized genetic epidemiologist Professor Stuart MacGregor who heads QIMR Berghofer's Statistical Genetics Laboratory, said the discoveries could rapidly accelerate a new approach to treatment.

"Glaucoma robs your sight by stealth. You lose your peripheral vision first, and then one eye often covers for the loss of sight in the other. You don't realize what's happening until you've already suffered permanent damage and loss of vision," Prof Stuart MacGregor said.

"Existing treatments focus only on lowering eye pressure. The dream has always been to find a way to make the retina itself stronger so it can withstand the build-up of pressure and prevent the damage that causes permanent blindness.

"Our findings are really exciting because for the first time we've

discovered the set of genes that could be targeted to induce this 'neuro-protection' in the retinal cells.

"We've also identified existing drugs that could be used on those genetic targets. This could rapidly advance effective treatment to finally prevent retina and optic nerve damage."

Repurposing drugs has many benefits including faster translation of research findings into treatments for patients because the drugs have already been proven safe in humans.

Lead author Associate Professor Puya Gharahkhani from QIMR Berghofer said the findings are also helping to develop a genetic test to predict a person's risk of developing glaucoma.

"Glaucoma is one of the most strongly genetic of all human diseases. We can use our genetic discoveries to identify those who are at higher risk.

"If we can find people before the disease develops, we can prevent blindness in those people," A/Professor Gharahkhani said.

The researchers are hoping to collect more data to increase the accuracy of their genetic prediction tool and find even more genes linked to glaucoma risk.

More than 5,000 Australians have already volunteered to take part in the QIMR Berghofer Genetics of Glaucoma study, but the researchers are appealing for more participants.

"We're urging Australians who have a personal or family history of the disease to sign up to the QIMR Berghofer Genetics of Glaucoma study. We particularly encourage people aged 50 to 65 who don't have glaucoma currently but who have a close relative (parent, sibling) with

the disease to sign up.

"We want to prevent glaucoma from robbing people of the ability to drive and read and recognize their loved ones, but we need your help to do this," Professor MacGregor said.

The goal is to be able to offer the genetic test to everyone in the community in the near future. To find out more information about the study visit www.qimrberghofer.edu.au/genetics-of-glaucoma/

Previous genetic studies of glaucoma have focused on people of European ancestry, however, glaucoma rates are highest in people of African and Asian ancestry. This research combined data from across the globe on an unprecedented scale.

"The global nature of our data allowed us to identify a large number of glaucoma risk genes, and to also discover that most of those genes are actually shared across different ethnic ancestry groups.

"This means that genetic tests for glaucoma are likely to work well across a wide range of ancestries," A/Professor Gharahkhani said.

The research involved collaboration with the International Glaucoma Genetics Consortium (IGGC), which aims to increase knowledge of the genes that influence glaucoma by bringing together global data sets from genome-wide association studies.

The research also found, for the first time, links between glaucoma risk and diabetes and immune diseases such as multiple sclerosis.

"Some of our drug discovery work suggests that certain existing treatments for other diseases, such as the diabetes drug Metformin, may have potential for use in glaucoma," Professor MacGregor said.

More information: Xikun Han et al, Large-scale multitrait genome-wide association analyses identify hundreds of glaucoma risk loci, *Nature Genetics* (2023). DOI: 10.1038/s41588-023-01428-5