Large, diverse genetic study of glaucoma implicates vascular and cancer-related genes

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An international genetic study using multiancestry biobanks has identified novel genetic locations associated with primary open-angle glaucoma (POAG), the most common type of glaucoma and the leading cause of irreversible blindness globally. The findings, published in *Cell Reports Medicine*, detail ancestry- and sex-specific genetic loci associated with POAG and implicate vascular and cancer-related genes in POAG

risk.

"Although there has been significant progress using genome-wide association studies (GWAS) to explore the genetic pathophysiology of glaucoma in humans, there is still a lack of understanding of the underlying pathogenic mechanisms and the genetic mechanisms that could explain the differences in prevalence, clinical presentation and outcomes for POAG across ethnicities and sex," said Jibril Hirbo, Ph.D., research assistant professor of Medicine in the Division of Genetic Medicine at Vanderbilt University Medical Center and the corresponding author of the new study.

More than 3 million Americans have glaucoma, according to the Centers for Disease Control and Prevention. Members of some racial and ethnic groups are at higher risk of developing the eye disease: It is six times more common among Black Americans compared to white individuals. Other risk factors for glaucoma include high pressure inside the eye, being older than 60, having a family history of the disease, and having diabetes or high blood pressure.

In a collaboration involving institutions around the world, the researchers performed a meta-analysis of data from 15 biobanks that are part of the Global Biobank Meta-analysis Initiative (GBMI), a network of biobanks from four continents representing more than 2.2 million individuals of diverse ancestries. BioVU, Vanderbilt's DNA biobank linked to de-identified electronic health records, is part of the GBMI network.

In the meta-analysis, they identified 62 genetic risk loci, six of which were novel. The researchers then merged their analysis with previously published multiancestry GWAS and used "sophisticated statistical methods to identify unique molecular actors across ancestries," Hirbo said.

"The combined dataset represents the largest and most diverse POAG study to date with almost 1.5 million individuals and 46,235 POAG cases," he added.

Overall, the study identified 17 novel genetic loci associated with POAG, five of which were specific to certain ancestries.

To identify functional roles of POAG-associated variants and tissues mediating genetic effects, the researchers used publicly available genotype-tissue expression data and performed gene enrichment studies.

These, along with transcriptome-side association studies, implicated vascular and cancer genes in POAG risk, the researchers noted. In particular, 20% of the associated genes were related to primary cilia, a structure on the surface of many vertebrate cells involved in cell proliferation and signaling.

"Investigating mechanisms that influence primary cilia functionality will contribute to understanding the role of this structure in the pathogenesis of glaucoma and point to new therapeutic targets and strategies," Hirbo said.

Although the analysis identified large ancestry- and sex-specific loci associated with POAG, Hirbo noted that the subjects represented by the GBMI biobanks are still predominantly of European ancestry. The investigators are seeking to broaden participants represented by international biobanks.

"Recruitment of cohorts that include ethnic minorities will improve knowledge transferability and health equity, not just for glaucoma research, but across disciplines," Hirbo said.

Co-author and ophthalmologist Karen Joos, MD, Ph.D., marveled at how

a simple conversation at an event in 2015 grew into a large international study of glaucoma.

"It has been rewarding being part of this endeavor ever since the initial exploratory brainstorming meeting at Vanderbilt and witnessing the project's amazing growth with Jibril's efforts into the global consortium of biobanks examining glaucoma," said Joos, Joseph N. and Barbara H. Ellis Family Professor of Ophthalmology and chief of the Glaucoma Service at the Vanderbilt Eye Institute.

"I expect it will continue to expand in discovery in the future as additional diverse biobanks are formed and join the consortium, and more samples are sequenced at all biobanks. A real global collaboration for one of the greatest worldwide blinding diseases is underway."

More information: Novel ancestry-specific primary open-angle glaucoma loci and shared biology with vascular mechanisms and cell proliferation, *Cell Reports Medicine* (2024). DOI: 10.1016/j.xcrm.2024.101430. www.cell.com/cell-reports-medi … 2666-3791(24)00053-3

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