Whole-genome sequencing study of over 450,000 individuals identifies rare variants and genes associated with glaucoma

---

Abstract Number: 1287 - B0530

Xiaoyi Raymond Gao[*1,2], Marion Chiariglione*[1]
[1]Ophthalmology, The Ohio State University, Columbus, Ohio, United States; [2]Biomedical Informatics, The Ohio State University, Columbus, Ohio, United States

Disclosures: Xiaoyi Raymond Gao: Code N (No Commercial Relationship) | Marion Chiariglione: Code N (No Commercial Relationship)

Purpose
Glaucoma is a leading cause of irreversible blindness worldwide, with primary open-angle glaucoma (POAG) being the most common form. While previous genome-wide association studies have identified more than 200 genomic loci associated with POAG, primarily through array-based genotyping and imputation, the role of rare variants remains poorly understood. Our study aims to address this gap by conducting the largest whole-genome sequencing (WGS) study of glaucoma to date.

Methods
We analyzed WGS data from 452,807 UK Biobank participants, comprising 15,386 POAG cases and 437,421 controls. Using REGENIE, we performed both single-variant and gene-based association analyses, adjusting for age, sex, and the first 10 principal components of genetic ancestry. To validate our findings, we examined the identified genes in the FinnGen dataset, which includes over 200,000 individuals of Finnish ancestry.

Results
We confirmed associations with known glaucoma genes, including *OPTN*, *MYOC*, and *FKBP9*, and identified more than 40 novel genes for glaucoma, such as *FMO4*, *PTEN*, *SEPTIN9,* and *DND1P1*. These novel genes also demonstrated significant associations within the FinnGen cohort, reinforcing their potential importance in glaucoma pathogenesis.

Conclusions
Our findings underscore the value of WGS for uncovering rare variants and novel genes implicated in glaucoma. By expanding the genetic architecture of this complex disease, our work paves the way for

future research into disease mechanisms, risk prediction, and ultimately, the development of more targeted preventive and therapeutic strategies.