Discovery of novel glaucoma loci using AI-derived optic nerve integrity estimates

Asma M. Aman, Eslam Zaher, Samantha Sze-Yee Lee, Santiago Diaz-Torres, Fred Roosta,
Stuart MacGregor, Maciej Trzaskowski, David A. Mackey, Puya Gharahkhani

Background: The Bruch's membrane opening-minimum rim width (BMO-MRW) and peripapillary retinal nerve fibre layer thickness (pRNFLT) are 3D retinal thickness measurements obtained from optical coherence tomography scans. They serve as clinical biomarkers for glaucoma diagnosis. GWAS has been conducted on datasets with the relevant OCT data, but their small sample sizes have limited discovery. Our goal is to demonstrate that AI-derived thickness from 2D fundus images can act as a proxy for the 3D measures in two large biobanks (UK Biobank and Canadian Longitudinal Study of Ageing, CLSA), enabling the discovery of novel risk loci to better understand the underlying biology of glaucoma.

Methods: We trained deep learning models on 6,500 labelled fundus images and applied them to the UK Biobank and CLSA to predict BMO-MRW and pRNFLT. GWASs were then conducted in each dataset, and the results were meta-analysed across datasets. We compared the SNP effect sizes of AI-based GWAS meta-analysis with those derived from actual thickness meta-analysis; subsequently, we joined them to enhance the power. The mtCOJO method was used to condition the phenotypes on vertical cup-to-disc ratio (VCDR) and intraocular pressure (IOP) in order to identify variants specific to BMO-MRW and pRNFLT, given that previously reported glaucoma loci are associated with IOP and VCDR.

Results: The R-squared for the BMO-MRW and pRNFLT models in the test set were 0.63 and 0.47, respectively. Also, the correlations of effect sizes for the independent genome-wide significant SNPs were strong for both phenotypes (0.83 and 0.62, respectively). We identified 126 genome-wide significant loci for BMO-MRW, of which 14 remained significant after adjusting for VCDR, demonstrating VCDR-independent effects. Also, we found 29 loci for pRNFLT, which we then conditioned on IOP and VCDR. Adding the adjusted pRNFLT to a previous glaucoma MTAG uncovered two previously unreported glaucoma genome-wide significant loci: rs12234378 (near *AGMO*), and rs10052843 (near *ABLIM3*).

Conclusion: We leveraged deep learning models to derive 3D retinal structural estimates from 2D fundus images, substantially increasing the available sample size for variant discovery. We also found the first evidence of glaucoma loci independent of IOP and VCDR. Further analyses are required to assess their therapeutic potential.