Researchers identify genes and cell types that may have causal role in primary open-angle glaucoma formation

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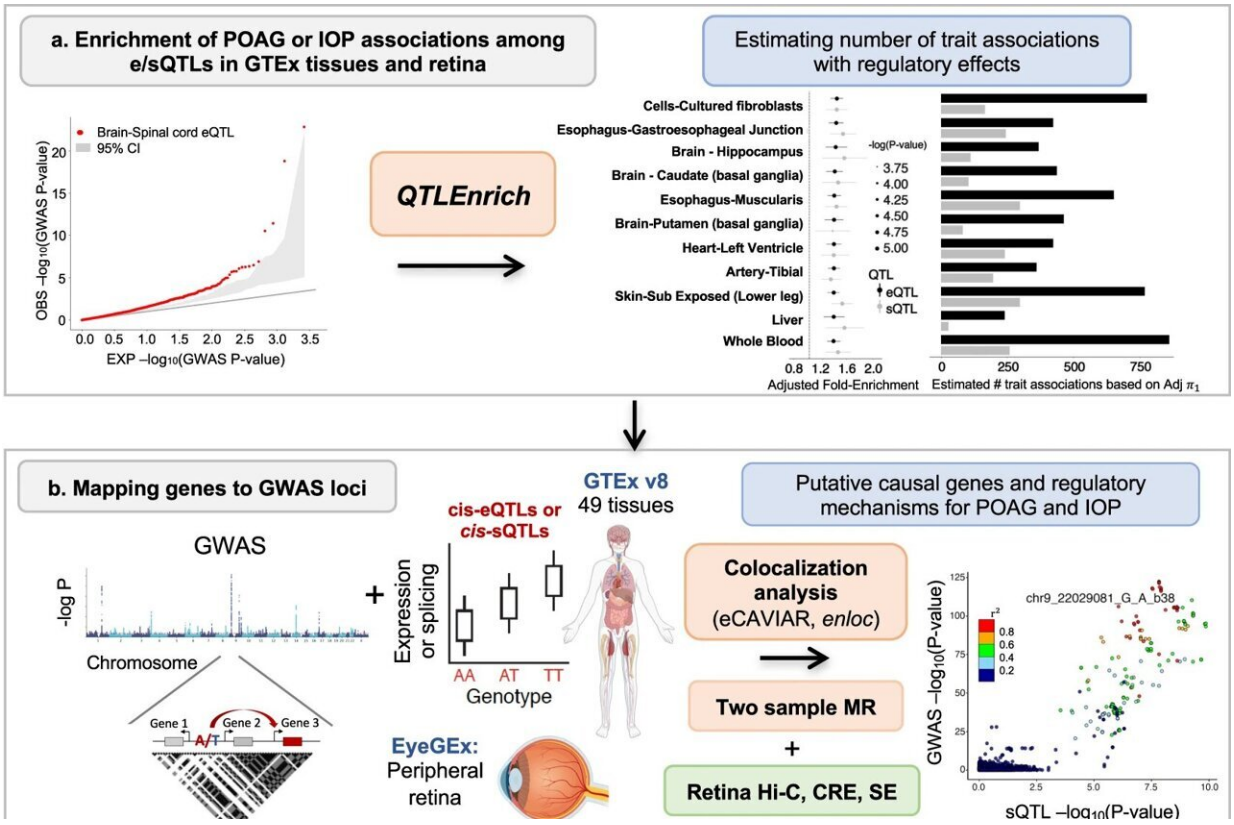

Analysis workflow from POAG and IOP GWAS to causal regulatory mechanisms, genes, pathways, and cell types. **a** POAG and IOP associations genome-wide (known and modest associations) were tested for enrichment among expression and splicing quantitative trait loci (e/sQTLs) in GTEx tissues and retina compared to permuted null sets of variants matched on confounding factors, using *QTLEnrich* (one-sided). In cases where enrichment was found, the

lower bound number of e/sQTLs in a given tissue, likely to be true trait associations, was estimated using an empirically derived, true positive rate ((π1)({\pi }_{1}) approach. **b** Putative causal genes were prioritized per known POAG and IOP genome-wide association study (GWAS) locus by applying two colocalization methods (eCAVIAR, *enloc*) to all e/sQTLs from 49 GTEx tissues and retina eQTLs that overlapped each locus, followed by two-sample Mendelian Randomization (MR). Overlap of the colocalizing GWAS loci and e/sQTLs with Hi-C (3D chromosome conformation capture), *cis*-regulatory element (CRE), and super-enhancer (SE) regions from the human retina was utilized to prioritize causal genes further. The human and eye images were created with BioRender.com. **c** All target genes of significantly colocalizing e/sQTLs (e/sGenes) or cell type-specific genes per trait were tested for enrichment in signaling and metabolic pathways (Reactome, KEGG), gene ontologies, and mouse phenotype ontologies using *GeneEnrich* (one-sided). The POAG cross-ancestry GWAS meta-analysis Manhattan plot was generated using QMplot (https://github.com/ShujiaHuang/qmplot). **d** Significantly colocalizing e/sGenes were tested for enrichment in specific cell types in single-nucleus RNA-seq data of glaucoma-relevant eye tissues, using ECLIPSER (one-sided). Cell type-specific genes were defined with cell type fold-change>1.3 and FDR