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ARTICLE

Glaucoma Drug Target Prioritisation Informs Disease-specific Therapeutic Potentials of Targeting *SMAD4*

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Abstract

Genome-wide association studies (GWAS) identify genetic associations for glaucoma, particularly its subtype, open-angle glaucoma (OAG). Translating these disease-genetic associations into therapeutic targets and potential drugs, however, remains a challenge. We propose to address this post-GWAS challenge with the priority index solution to glaucoma (PIG), which leverages genetic and network evidence for drug target prioritisation. PIG not only recovers clinical proof-of-concept targets for OAG but also supports integrated analysis for pathway crosstalk identification. The latter further enables crosstalk-based therapeutic discovery: removal analysis to identify key nodes with the crosstalk; drug repurposing analysis to identify candidate drugs; and construction of a prioritisation map across diseases to reveal disease-specific targeting potential for OAG. These multifaceted functionalities provide therapeutic insights into targeting the FoxO signaling pathway, which includes tumor suppressor genes, including the disease-specific critical gene *SMAD4*. Collectively, our post-GWAS solution establishes a foundation for discovering potential drug targets. PIG guides the future exploration of therapeutic possibilities, such as repurposing drugs like arsenic trioxide and employing mRNA therapeutics delivered via lipid nanoparticles, to advance translational medicine strategies for glaucoma—the second leading cause of irreversible blindness, particularly for patients also with pancreatic disease.

Keywords Glaucoma · Genetic targets · Drug repurposing · Computational translational medicine

Abbreviations

CDF	Cumulative distribution function
GWAS	Genome-wide association study
IOP	Intraocular pressure
LD	Linkage disequilibrium
OAG	Open-angle glaucoma
PCHi-C	Promoter capture Hi-C
QTL	Quantitative trait loci
RGCs	Retinal ganglion cells
RWR	Random walk with restart
VCDR	Vertical cup-to-disc ratio

Introduction

Glaucoma, the second leading cause of irreversible blindness globally (Bourne et al. 2021), is characterised by chronic and progressive manifestations, including optic disc cupping, apoptosis of retinal ganglion cells (RGCs), and vision loss (Jayaram et al. 2023). The primary risk factor is the pathological increase in intraocular pressure (IOP) due to abnormal aqueous humor circulation (Wang et al. 2022). A large vertical cup-to-disc ratio (VCDR) and elevated IOP are recognised as fundamental endophenotypes for glaucoma (Charlesworth et al. 2010). Glaucoma has diverse phenotypic classifications, with primary glaucoma being the most common, which is further divided into primary open-angle glaucoma (OAG) and primary angle-closure glaucoma based on the anterior chamber angle status. Globally, over 90% of glaucoma cases remain undiagnosed in low- and middle-income countries, and about half are undetected in high-income countries (Jayaram et al. 2023). The worldwide prevalence is estimated to affect approximately 95 million individuals, with 65 million having primary

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OAG (predominantly in Africa) and 30 million having primary angle-closure glaucoma (highest incidence in Asia) (Charlesworth et al. 2010; Wang et al. 2022; Jayaram et al. 2023). Due to the lack of early symptoms and limited screening, the actual number of affected patients may exceed current detection rates (Soh et al. 2021), and is expected to rise as more countries gradually transition into ageing societies.

Glaucoma exhibits an intricate pathogenesis. Several pathophysiological theories and factors elucidate the biological mechanisms underlying glaucoma, namely: (i) biomechanical factors, where increased IOP compresses the optic nerve head; (ii) vascular factors, involving insufficient vascular supply to the optic nerve; and (iii) oxidative stress factors, with free radicals generated during metabolic processes damaging the trabecular meshwork and optic nerve (Wang et al. 2022; Jayaram et al. 2023; Wang and Wang 2023). Among these mechanisms, reducing IOP stands out as the sole effective method for treating and managing glaucoma. On average, a 20%–40% decrease in IOP can halve the rate of visual loss. Consequently, current treatment strategies focus on lowering IOP. Topical pressure-lowering medications comprise six major types: prostaglandin analogues (considered the first-line treatment), α-agonists, β-adrenergic blockers, carbonic anhydrase inhibitors, cholinergic agonists, and Rho kinase inhibitors (Weinreb et al. 2014). These drugs either decrease aqueous humor production or enhance its drainage. If these medications are ineffective, laser therapies (such as laser trabeculoplasty) can be employed to effectively and safely reduce IOP, although their effectiveness may diminish over time. If laser therapies fail to lower IOP to a safe range, incisional surgeries (such as trabeculectomy and glaucoma drainage device surgery) should be considered to establish a drainage outlet for the aqueous humor. However, these surgeries are highly invasive and carry a substantial risk of complications (Kwon et al. 2009; Charlesworth et al. 2010; Quigley 2011; Stein et al. 2021; Jayaram et al. 2023). While reducing IOP effectively halts the progression of glaucoma, it does not reverse the damage to RGCs. Hence, developing neuroprotective strategies independent of IOP is an essential therapeutic direction. Despite experiments investigating the prevention of RGC apoptosis using calcium channel blockers, antioxidant agents, and neurotrophic factors, no drug directly targeting neurodegeneration has currently received approval (Shalaby et al. 2022; Tribble et al. 2023; Boccaccini et al. 2023).

Glaucoma is a highly heritable eye disease, with a heritability estimate nearing 0.7 in the U.S. population (Wang et al. 2017). First-degree relatives have a nearly tenfold higher risk than the general population (Wolfs et al. 1998). The heritability for primary OAG ranges from 0.17 to 0.81 in twin and family studies (Asefa et al. 2019), and a family study with electronic medical records estimated it to be 0.93 (95% confidence interval = [0.52, 1]) (Polubriaginof et al. 2018). Understanding the genetic foundation holds significant importance in unraveling the genetic susceptibility of glaucoma. Genome-wide association study (GWAS) have revealed glaucoma loci and associated genes (Wiggs and Pasquale 2017; Wang et al. 2022; Gao et al. 2022). Initially, GWAS conducted in Japan, Europe, and Australia identified pathogenic genes for primary OAG (Thorleifsson et al. 2010; Burdon et al. 2011; Wiggs et al. 2012; Osman et al. 2012). More common variants contributing to glaucoma have been discovered with expanding research efforts (Chen et al. 2014; Gharahkhani et al. 2014; Bailey et al. 2016; Shiga et al. 2018; Choquet et al. 2018; Craig et al. 2020; Xue et al. 2022). Moreover, polymorphisms in the gene *TP53*—known for its high mutation frequency in cancer—have been reported to be associated with an increased risk of primary OAG and primary angle-closure glaucoma across various ethnic groups, including Chinese (Lin et al. 2002), Spanish (Blanco-Marchite et al. 2011), and North Indian populations (Gupta et al. 2018). In 2021, a multi-ethnic meta-analysis revealed 127 loci (including 44 novel ones), explaining 9.4% of the heritability and exhibiting consistent effects across populations from Europe, Asia, and Africa (Gharahkhani et al. 2021). Recognising the strong genetic correlation between the endophenotypes IOP and VCDR and primary OAG (Hysi et al. 2014; Choquet et al. 2017; Khawaja et al. 2018; MacGregor et al. 2018; Han et al. 2021), a 2023 study employed multi-trait GWAS to identify 312 glaucoma loci (Han et al. 2023).

Despite advancements, genetic insights obtained from GWAS have yet to be fully leveraged for drug target discovery due to three factors. The first factor is the limited explanation of heritability. The largest-scale European primary OAG GWAS explains only 14.1% of heritability (Han et al. 2023), indicating that a significant portion of the genetic architecture remains unexplained. Utilising multi-trait and multi-ethnic analyses based on IOP and VCDR may help identify additional loci. The second factor is the complex genetic architecture. Only 2–4% of primary OAG cases are Mendelian glaucoma due to single-gene mutations, such as myocilin (*MYOC*), optineurin (*OPTN*), and TANK binding kinase 1 (*TBK1*). Myocilin is responsible for regulating IOP, and patients carrying mutations in *MYOC* often exhibit very high IOP. In contrast, carriers of mutations in the genes *OPTN* and *TBK1* tend to have normal IOP (Wang et al. 2022; Jayaram et al. 2023). The remaining 95% of cases are complex glaucoma, where multiple common SNPs with small effect sizes collectively contribute to higher disease risk (Jayaram et al. 2023). However, not all individuals with a higher genetic risk will develop glaucoma, as environmental factors also play a role. In other words, common SNPs identified through GWAS may facilitate the screening of high-risk populations and elucidate pathogenic mechanisms, but they may not represent optimal therapeutic targets. The

third factor is an inherent challenge in linking risk loci with effector genes. Glaucoma risk loci are primarily situated in the non-coding genome, and their interactions with effector genes may extend over long distances and are often specific to particular cell types/states, thus necessitating the identification of missing regulatory effects across diverse cell states (Connally et al. 2022; Fang 2024).

Considering the above-mentioned facts/challenges and building on our previous success (Fang et al. 2019, 2020; Plenge 2019; Fang and Knight 2022), we introduce the Priority Index for Glaucoma (PIG) for OAG drug target prioritisation (Fig. 1). We demonstrate its efficacy in successfully identifying known therapeutics and its potential for computational translational medicine approaches to develop innovative strategies for treating this second leading cause of irreversible blindness.

Materials and Methods

OAG GWAS Summary-level Data

Using the Experimental Factor Ontology term 'EFO:0004190', which describes the phenotype 'open-angle glaucoma' from the NHGRI-EBI GWAS Catalog (Sollis et al. 2023), summary-level data on OAG were obtained from GWAS performed on European populations (Thorleifsson et al. 2010; Wiggs et al. 2012; Gharahkhani et al. 2014, 2021; Bailey et al. 2016; Choquet et al. 2018; Han et al. 2023).

OAG GWAS Lead SNPs and Their Linkage Disequilibrium (LD) SNPs

From the GWAS Catalog, we extracted GWAS lead SNPs (p-value $< 5 \times 10^{-8}$) and identified their additional LD SNPs ($R^2 \geq 0.8$) based on European population data. SNP scoring accounts for disease genetic associations: GWAS-detected p-values, the significance threshold, and R^2 values.

OAG Core Genes Identified with Genetic Evidence

Based on the lead and LD SNPs identified above, we identified core genes with genetic evidence, including genomic proximity, quantitative trait loci (QTL), and promoter capture Hi-C (PCHi-C). The scoring for core genes considers genomic proximity, genetic associations with gene expression or protein abundance for each QTL dataset, and the strength (CHiCAGO scores) of gene promoters that physically interact with genomic regions harbouring SNPs in each PCHi-C dataset. For details on how to score core genes, please refer to our recent publication (Zhang et al. 2024).

OAG Peripheral Genes Identified with Network Evidence

Using core genes as seed nodes, the random walk with the restart (RWR) algorithm was used to identify non-seed peripheral genes through network evidence by exploiting knowledge of protein–protein interactions from the STRING database (Szklarczyk et al. 2023). In essence,

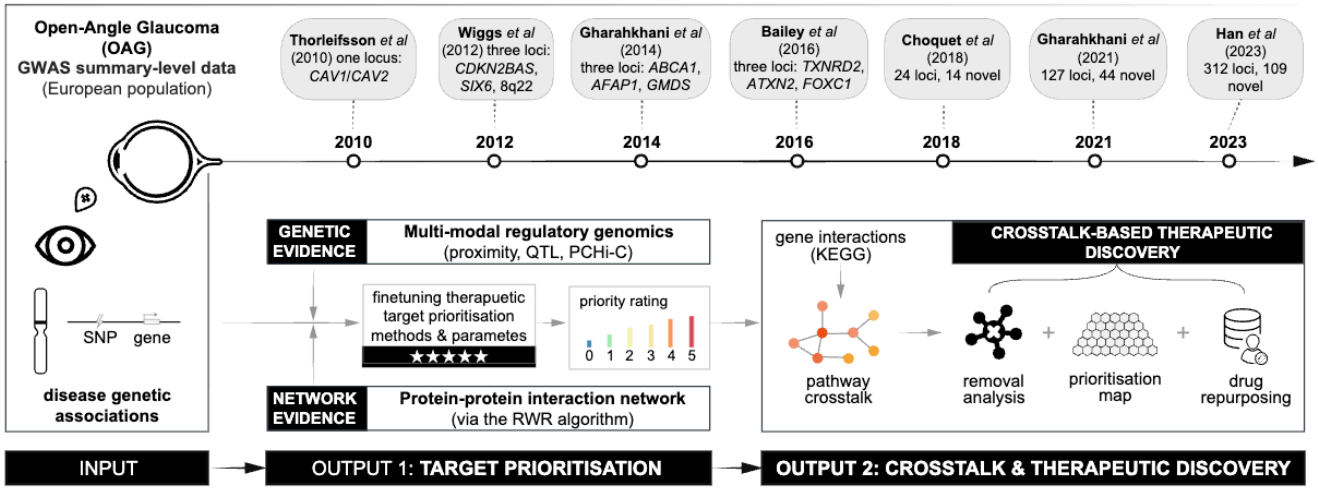

Fig. 1 Schematic overview of the Priority Index solution to glaucoma (PIG). The input consists of European open-angle glaucoma (OAG) GWAS summary-level data (shown in the timeline). The target prioritisation (OUTPUT 1) integrates genetic evidence (utilising multimodal regulatory genomic datasets such as QTL and PCHi-C) along with network evidence, leveraging protein–protein interactions via the random walk with restart (RWR) algorithm. Target genes are ranked based on a priority rating (ranging from 0 to 5). Crosstalk-based therapeutic discovery (OUTPUT 2) involves identifying crosstalk from pathway-derived gene interactions and target prioritisation, followed by removal analysis, drug repurposing, and construction of the prioritisation map. Abbreviations include PCHi-C (promoter capture Hi-C), QTL (quantitative trait loci), and SNP (single nucleotide polymorphism)

RWR calculated affinity scores that represent the collective influence of the starting seed nodes collectively exerted across the network. Please refer to our recent publication (Bao et al. 2024), which explains how to calculate affinity scores using RWR.

OAG Clinical Proof-of-Concept Targets

Information on existing drugs, their development phases, target genes, mechanisms of action, drug efficacy, and disease indications was obtained from the ChEMBL database (Zdrazil et al. 2024). For OAG, its clinical proof-of-concept targets were defined as therapeutic genes targeted by drugs that had reached phase II clinical trails or beyond.

OAG Target Prioritisations and Their Performance Evaluation

We evaluated performance by calculating the area under the curve (AUC) for the recovery of OAG clinical proof-of-concept targets. Three prioritisation methods were evaluated for combining predictors, including *Fisher's*, *logistic*, and *order statistic* combined methods; for details, see our previous publications (Fang et al. 2019; Bao et al. 2023a; Zhang et al. 2024). Briefly, for each predictor, affinity scores were first converted into *p*-like values through the empirical cumulative distribution function (eCDF). For each gene, these converted *p*-values were then combined across predictors using one of the combined methods. Finally, the combined *p*-value was rescaled into a priority rating on a 0–5 scale.

OAG Pathway Crosstalk Identification and Crosstalk-Based Analyses for Therapeutic Discovery

Using a heuristic solution for solving the prize-collecting Steiner tree problem, pathway crosstalk was identified from KEGG pathway-derived gene interactions (Kanehisa et al. 2023) and OAG target prioritisation results from this study. Notably, the prize-collecting Steiner tree problem is known to be NP-hard, presenting significant computational difficulties. Our previously reported heuristic solution was designed to reduce the computational burden while still providing accurate results for identifying pathway crosstalk (Fang and Gough 2014a; Bao et al. 2023b; Wang et al. 2024). Crosstalk-based removal analysis evaluated the effects of nodes (single-node removal or combinatorial removal) on crosstalk, while crosstalk-based drug repurposing analysis relied on information extracted from ChEMBL (Zdrazil et al. 2024). For details on crosstalk-based removal and repurposing analyses, please refer to our publication (Zhang et al. 2024).

The supraHex package (Fang and Gough 2014b) was used to build a cross-disease prioritisation map for open-angle glaucoma crosstalk genes. Using a self-organising learning algorithm (Tan et al. 2019), a ladder-shaped map was trained using input data, namely a prioritisation matrix containing priority ratings across seven diseases. These diseases included OAG (this study) and six immune-mediated diseases: ankylosing spondylitis, Crohn's disease, juvenile idiopathic arthritis, psoriasis, rheumatoid arthritis, and ulcerative colitis (Fang and Knight 2022). The trained map was used to identify target gene clusters. Enrichment analysis for target clusters was based on a one-sided Fisher's exact test to identify enrichments regarding: (i) approved drug targets from ChEMBL (Zdrazil et al. 2024); (ii) Gene Ontology Cellular Component annotations from the NCBI (Carbon et al. 2021); and (iii) hallmark gene sets from MSigDB (Liberzon et al. 2015).

Results

PIG Prioritisation Rationale and Parameter Optimisation

The biological rationale underlying PIG is the omnigenic model for complex traits (Boyle et al. 2017; Fang et al. 2020), which considers target candidates that include core genes identified through genetic evidence and peripheral genes identified through network evidence. This genetics-led and network-driven target prioritisation generalises our previous Priority Index (Pi) approach by converting disease genetic findings (i.e., OAG GWAS summary-level data) into prioritised targets and repurposed drugs through bioinformatics and statistical analyses in PIG.

Target prioritisation involves two types of evidence: genetic evidence from proximity, QTL, and PCHi-C, along with network evidence derived from protein–protein interactions via the RWR algorithm. Prioritisation of target genes can be achieved using different target prioritisation methods (see Materials and Methods). Accordingly, we simultaneously explored the RWR restart probability parameter and the target prioritisation methods. By evaluating three combined meta-analysis-like methods (based on *Fisher's*, *logistic*, and *order statistics*) to recover clinical proof-of-concept targets in OAG, we found that the *order statistics* method exhibited competitive performance at an optimal restart probability of 0.7 (Fig. 2). This integrative prioritisation provides a framework for identifying OAG therapeutic targets.

PIG Supporting Drug Target Prioritisation and Pathway Crosstalk Identification

Applying PIG to OAG GWAS summary-level data generated prioritisation for ~ 14,500 genes, ranked by their priority ratings (see OUTPUT 1 of Fig. 1; Table S1). One notable

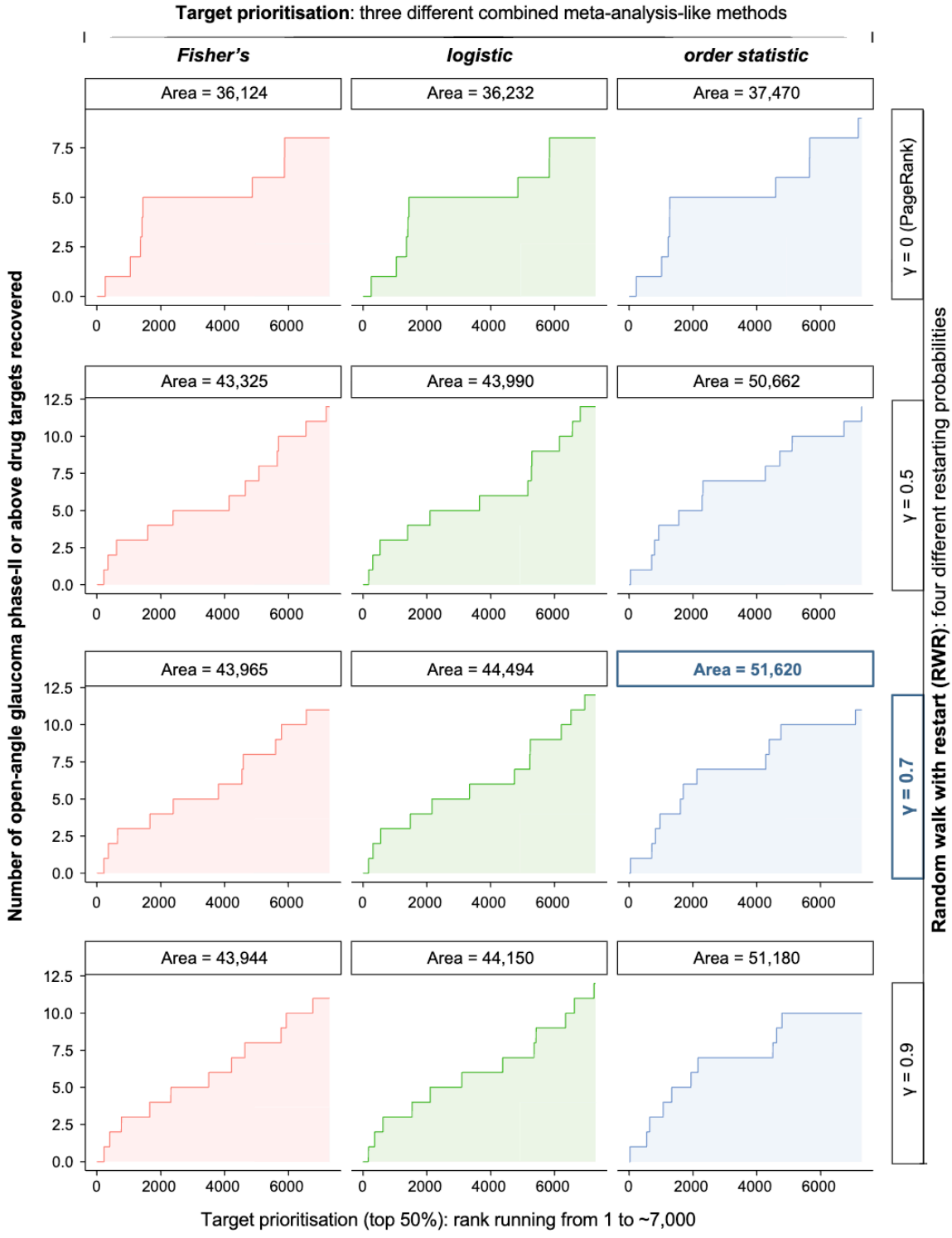

Fig. 2 Recovering pre-existing phase II or higher drug targets for open-angle glaucoma using different prioritisation methods and parameters. The performance is quantified by the area under the curve (color-coded), assessing the ability to recover pre-existing phase II or higher drug targets for open-angle glaucoma. Three different combined meta-analysis-like methods are denoted across columns, while four different RWR restart probabilities are illustrated across rows. Notably, RWR with a restart probability of 0 is equivalent to PageRank. Comparisons highlight the best performance: using the combined meta-analysis-like method based on *order statistics* at the optimised restart probability ($\gamma = 0.7$)

feature of PIG is its ability to identify genes mediating pathway crosstalk (see OUTPUT 2 of Fig. 1). The identified pathway crosstalk (i.e., a 58-gene network) comprised exclusively of highly prioritised genes (p-value = 3.03×10^{-73}; Fig. 3a and Table S2). Among these 58 crosstalk genes, several have confirmed associations with the pathogenesis or treatment of glaucoma. For instance, *RHOA* (ranked 67th), a member of the Rho subfamily of GTPases, is involved in cell apoptosis and proliferation mechanisms in various diseases, including glaucoma. Currently, RhoA kinase inhibitors like netarsudil and ripasudil have been approved for glaucoma treatment, targeting trabecular meshwork cells and enhancing the drainage of the aqueous humor to lower IOP (Hoy 2018; Singh et al. 2020). Other relevant genes that receive high ratings include *ROCK1* and *ROCK2*, downstream effectors of RhoA, along with *RAC1* and CDC42, components of the Rho/ROCK signaling pathway that exhibit differential expression in experimental glaucoma animal models (Brockhaus et al. 2020; Zhang et al. 2020). Furthermore, we found that 12 crosstalk genes are involved in the inhibition of unrestrained cell division, known as tumor suppressor genes (Suehnholz et al. 2024): *CREBBP*, *EP300*, *FOXO1*, *MAP3K1*, *NCOR1*, *NFKBIA*, *PIK3R1*, *PTEN*, *SMAD2*, *SMAD3*, *SMAD4*, and *TP53* (odds ratio = 11.6; 95% confidence interval = [5.52, 22.4]; p-value = 5.6×10^{-9} based on one-sided Fisher's exact test; Fig. 3b).

Next, we sought to provide a holistic representation of the crosstalk at the pathway level (Fig. 3c). The pathways enriched in crosstalk genes predominantly included the FoxO, MAPK, PI3K/AKT, and mTOR signaling pathways. Notably, member genes such as *FOXO1* and *FOXO3* in the FoxO signaling pathway were observed to exhibit reduced expression in the trabecular meshwork of primary OAG patients, indicating mitochondrial dysfunction and enhanced oxidative stress (Yaman et al. 2020). Studies employing drugs like nipradilol and timolol for the activation of FOXO3a have shown that this activation enhances antioxidant activities in the trabecular meshwork, suggesting a novel approach to glaucoma treatment by targeting the FoxO signaling pathway (Miyamoto et al. 2009). Interestingly, nine out of 12 tumor suppressor genes are involved in the FoxO signaling pathway: *CREBBP*, *EP300*, *FOXO1*,

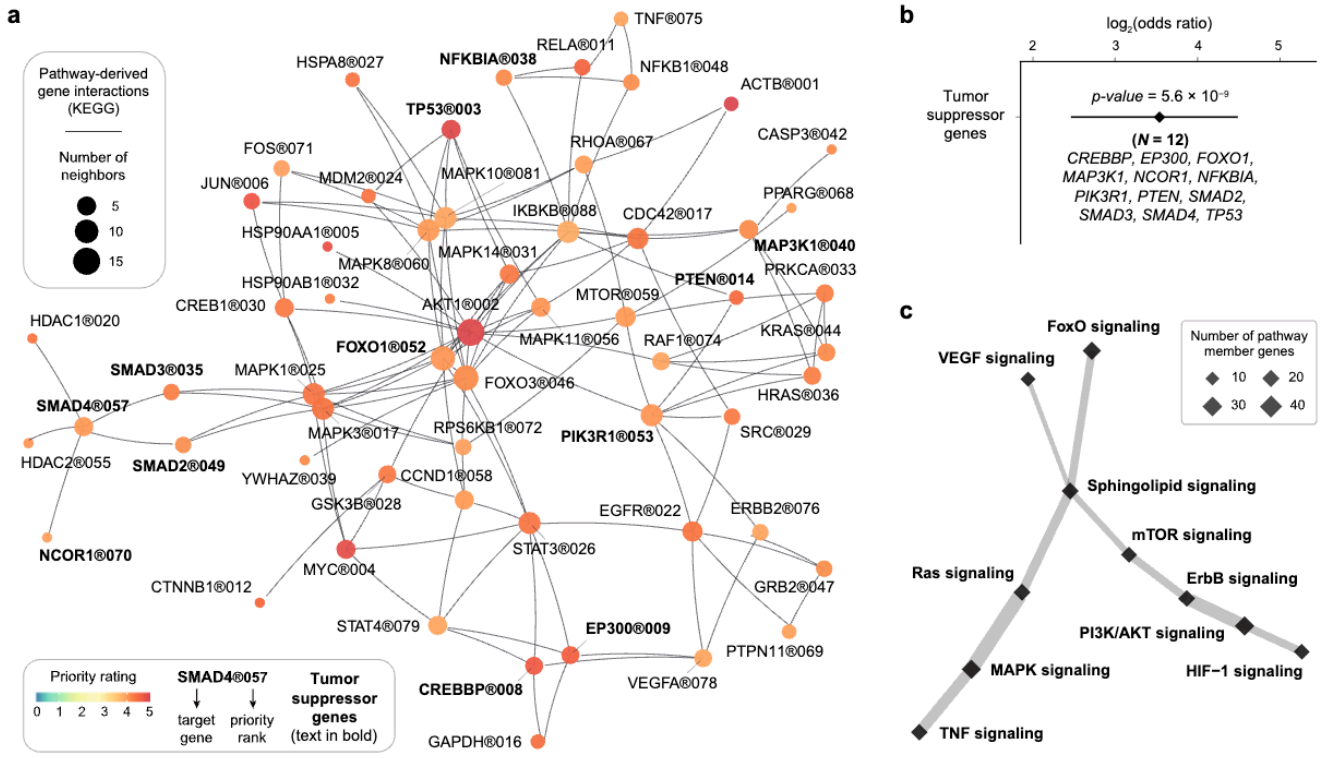

Fig. 3 Pathway crosstalk for open-angle glaucoma. This crosstalk was identified from KEGG pathway-derived gene interactions, but was constrained by information from open-angle glaucoma target prioritisation. The identified crosstalk contains highly prioritised and interconnected genes. **a** Gene-centric representation of the crosstalk. Nodes are color-coded by their priority rating and labelled as 'target gene @ priority rank'. **b** Forest plot of tumor suppressor gene enrichments. Tumor suppressor genes were obtained from OncoKB, with each entry supported by two or more primary sources. Enrichment analysis was performed using a one-sided Fisher's exact test, reporting the significance level (p-value), odds ratio, and 95% confidence interval. **c** Pathway-centric crosstalk illustration. This illustration shows nodes sized according to the number of pathway genes, and edges whose thickness is proportional to the number of genes shared between two pathways

PIK3R1, *PTEN*, *SMAD2*, *SMAD3*, *SMAD4*, and *TP53*. Furthermore, MAPK, PI3K/AKT, and mTOR signaling pathways are implicated in the mechanisms of RGC apoptosis and autophagy. Inhibition of RGC apoptosis was related to the activation of the PI3K/AKT signaling pathway (Nie et al. 2018), while the autophagy of RGCs was regulated via the AKT/mTOR signaling pathway (Li et al. 2018). Our crosstalk-based findings highlight the importance of targeting oxidative stress and anti-apoptotic pathways in glaucoma treatment.

PIG Supporting Crosstalk-based Analyses for Therapeutic Discovery

We explored targetable opportunities through removal analysis, assessing the impact of node removal on crosstalk (Fig. 4). Removing the gene *IKBKB* yielded a maximum of 8.6% node disconnection, followed by the gene *SMAD4*. The gene *IKBKB* encodes a crucial kinase implicated in the abnormal activation of the NF-κB signaling pathway, a factor involved in various disorders, including inflammation. In OPTN-mutation-associated amyotrophic lateral sclerosis (a neurodegenerative disease), *IKBKB* may be involved in ubiquitination and phosphorylation to regulate NF-κB activation, indicating its potential role in the treatment of glaucoma (Zhu et al. 2007; Nakazawa et al. 2016), and thus serving as a promising pharmacological target. Further removing *SMAD4* (i.e., *IKBKB* + *SMAD4*) increased the disconnection fraction to 15.5%, and removing *PIK3CA*, *MAPK1*, and *MAPK3* reached a maximum of 22.4%. Collectively, our removal analysis provides evidence for the potential treatment of OAG by targeting key crosstalk nodes (i.e., *IKBKB*, *MAPK1*, *MAPK3*, and *SMAD4*) of the crosstalk.

Next, we explored drug repurposing opportunities by identifying approved drugs (for diseases other than OAG) with target genes in the crosstalk pathway genes. We found 13 genes already targeted by approved drugs in other diseases (odds ratio = 8.52; 95% confidence interval = [4.18, 16.2]; p-value = 4.6×10^{-8} based on a one-sided Fisher's exact test; Fig. 5a and 5b; Table S3). Amongst them, 7 genes (*EGFR, ERBB2, KRAS, MAPK11, RAF1, TNF,* and *VEGFA*) played integral roles in the MAPK signaling pathway. Regarding disease indications, we observed that the approved drug target *VEGFA* is used to treat various macular disorders (Fig. 5c), aligning with the current use of anti-VEGF therapy in age-related macular degeneration and neovascular glaucoma, underscoring the potential for therapeutic targeting. Furthermore, *GSK3B* is already targeted for treating neuropsychiatric disorders (Fig. 5d), offering the potential for IOP regulation or neuroprotective targeting in neurodegenerative diseases (Wang et al. 2008, 2023; Pattabiraman et al. 2023). Remarkably, another approved drug target, *TNF*, is used to treat several immune-mediated diseases (Fig. 5e), raising interest in exploring the relationship between glaucoma and immune-mediated diseases.

Finally, we constructed a cross-disease prioritisation map via a supra-hexagonal map (Fang and Gough 2014b) for cross-disease comparisons based on OAG crosstalk genes as well as our previously reported prioritisation profiles in immune diseases (Fang and Knight 2022). Immune diseases considered here were restricted to those listed in Fig. 5e, including ankylosing spondylitis (AS), Crohn's disease (CRO), juvenile idiopathic arthritis (JIA), psoriasis (PSO), rheumatoid arthritis (RA), and ulcerative colitis (UC) (Fig. 6a and Table S4). We identified three target clusters (C1–C3; Fig. 6b). Genes in C3 were highly rated in all diseases analysed, while genes in C1 were highly rated only in OAG (for example, the disease-specific gene *SMAD4*). We characterised target genes in these clusters using Gene Ontology Cellular Component terms and MSigDB hallmark gene sets (Fig. 6c). Most of the genes in C3 were involved in immune system signaling pathways. In addition to *SMAD4*, genes in C1 were mostly functionally relevant to the PI3K/AKT/mTOR signaling pathway (*GSK3B*, *MAPK10*, and *SMAD2*), the transcriptional repressor complex (*FOXO3*, *MDM2*, and *NCOR1*), and the glutamatergic synapse (*ACTB*, *GSK3B*, and *YWHAZ*). In summary, genes highly prioritised only in OAG highlight the disease-specific potential of targeting the glutamatergic synapse for neuroprotection, in addition to *SMAD4*. As a pivotal tumor suppressor, *SMAD4* mediates the canonical TGF-β signaling cascade, regulating cell processes such as proliferation, apoptosis, and oxidative stress responses involved in glaucoma-related RGC degeneration. Since *SMAD4* has extensive interactions in the crosstalk network, targeting it or its downstream effectors may offer dual benefits in mitigating both IOP elevation and neurodegeneration and thus should be further explored in preclinical models.

Discussion

In our efforts to enhance therapeutic target prediction and validation, we have introduced the PIG solution for glaucoma translational medicine research. PIG enables the transition from target prioritisation to drug repurposing and guides the decision-making on preclinical and clinical validation. It successfully recovers known glaucoma drug target genes associated with the Rho/ROCK signaling pathway and identifies targetable pathways such as the FoxO signaling pathway, which is critical to the pathogenesis of glaucoma.

PIG detects crosstalk between pathways and offers downstream analyses like removal analysis and drug repurposing based on crosstalk genes, providing insights into glaucoma treatment. Removal analysis computationally evaluates the

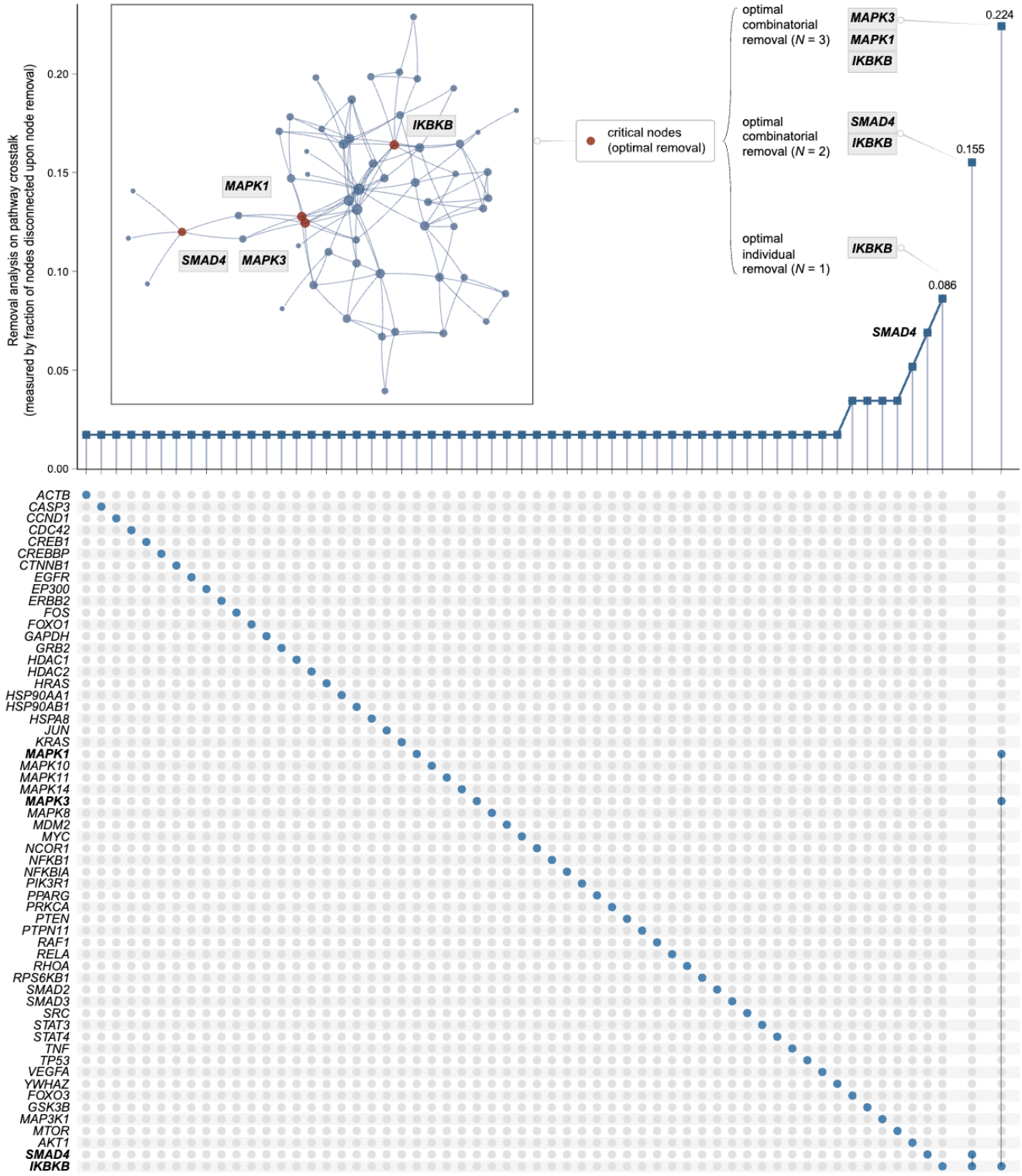

Fig. 4 Removal analysis based on pathway crosstalk for open-angle glaucoma. The fraction of disconnected nodes on the y-axis is plotted against node removal, either individually or in combination (indicated below the x-axis). Inserted on the top-left is the crosstalk with the same layout as Fig. 3a, but labelled only for key nodes or genes under optimal removal conditions

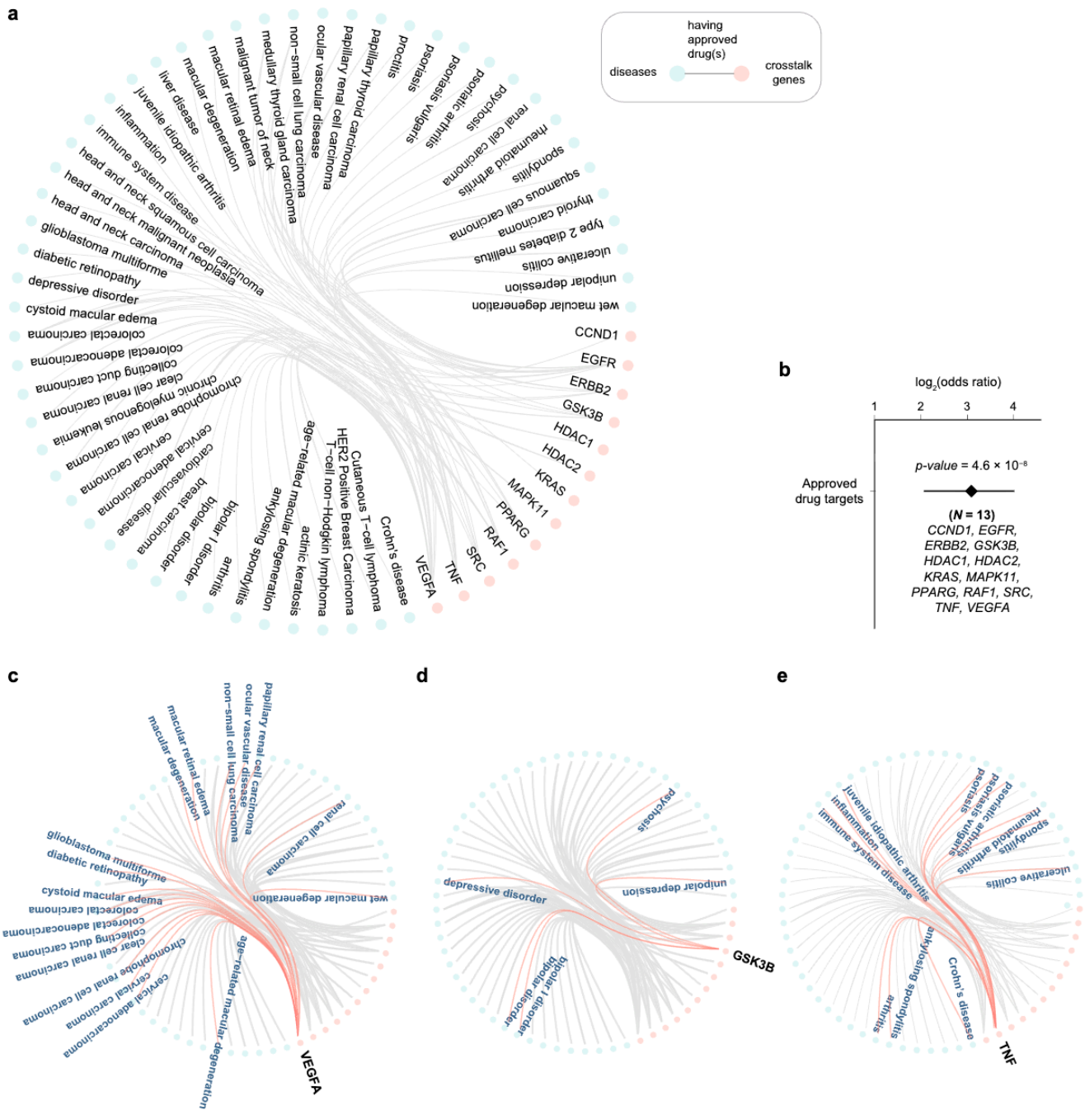

Fig. 5 Crosstalk-based drug repurposing using crosstalk genes identified in open-angle glaucoma. **a** Hierarchical edge bundling for targets and drugs. Crosstalk genes (in pink) already targeted by approved drugs in other diseases (in cyan) are linked by edges (in grey). **b** Forest plot of approved drug target enrichments. Approved drug targets were sourced from ChEMBL. Enrichment analysis was performed using a one-sided Fisher's exact test, reporting the significance level (*p*-value), odds ratio, and 95% confidence interval. **c–e** The same illustration as in **a**, but highlighting edges (in red) involving specific target genes, including *VEGFA* (**c**), *GSK3B* (**d**), and *TNF* (**e**)

effects of targeting genes, either individually or in combination, and shows the potential of repurposing MAPK inhibitors for treating OAG. Crucially, PIG identifies tumor suppressor genes such as *TP53* and *SMAD4* that maintain genomic stability; loss of their disease-suppressing functions promotes disease, and arsenic trioxide targeting *TP53* (Song et al. 2023, 2024) may restore its normal function. *SMAD4*, as a disease-specific critical gene in the FoxO signaling pathway, is of great therapeutic relevance in glaucoma. Structural biology techniques like cryo-electron microscopy or X-ray crystallography (Liu et al. 2020) can clarify how *SMAD4* mutations or dysregulated post-translational

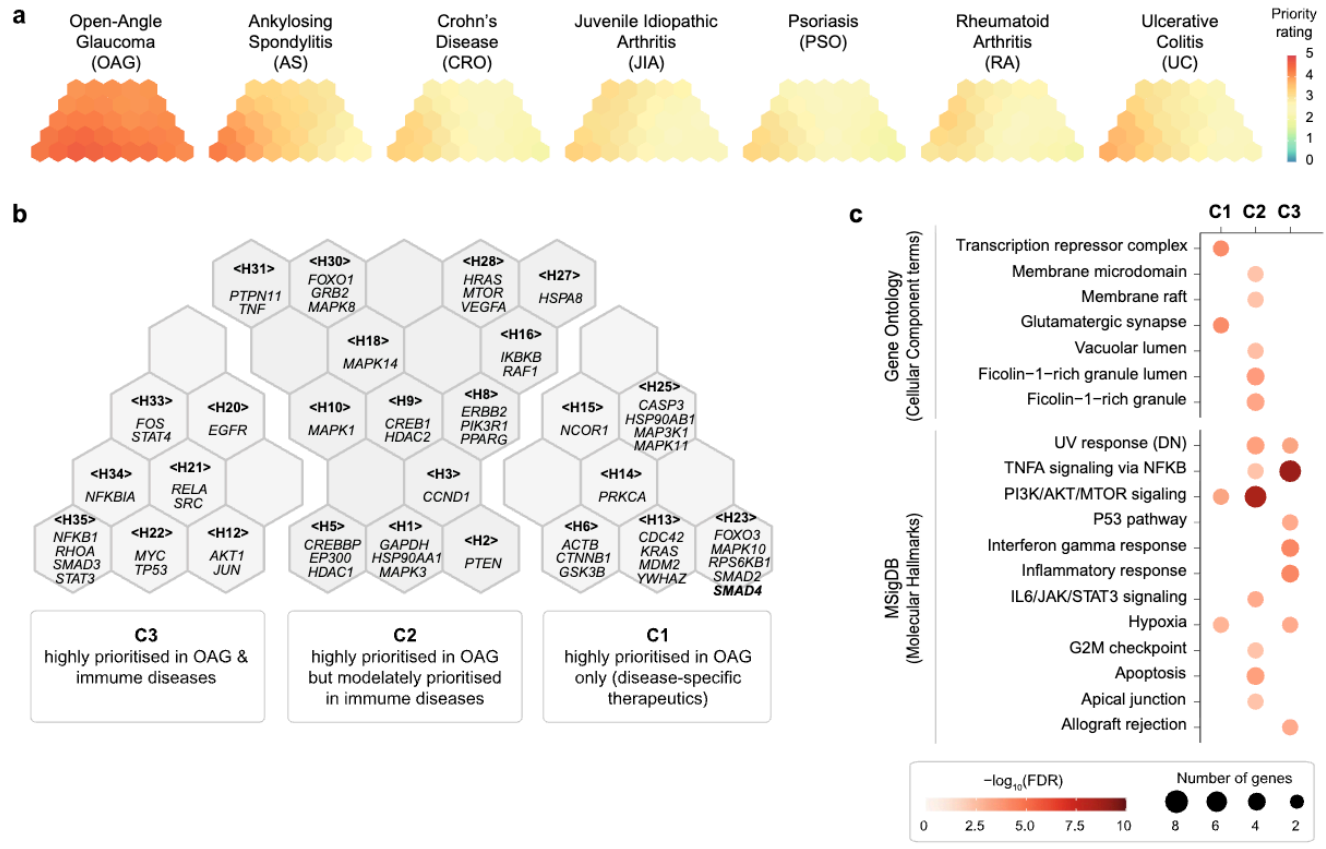

Fig. 6 Crosstalk-based cross-disease prioritisation map between open-angle glaucoma and immune-mediated diseases. Focusing on crosstalk genes in open-angle glaucoma, the map with a ladder-like 2D topology was trained and self-organised according to their prioritisations in open-angle glaucoma and six immune-mediated diseases. **a** Disease-specific illustration of target gene prioritisation. **b** Architecture of the prioritisation map, consisting of 35 hexagons (H1–H35) with genes listed within each hexagon (if any). Notably, the prioritisation map is divided into three clusters (C1–C3) as indicated. **c** Dot plot showing Gene Ontology Cellular Component and MSigDB hallmark gene set enrichments for clusters C1–C3

modifications alter its interaction with *SMAD2*, *SMAD3*, or co-repressors, potentially disrupting pathway crosstalk with MAPK and PI3K/AKT signaling pathways. Elucidating the atomic architecture of *SMAD4* and its complexes may reveal key sites for structure-based drug design to identify small molecules that stabilise functional conformations or restore disrupted interactions. Virtual screening of compound libraries against binding pockets, along with molecular dynamics simulations and thermal stability experiments, can prioritise small-molecule stabilisers to rescue pathway fidelity. Integrating *SMAD4* structural data with functional assays can clarify its role in IOP-independent neuroprotection. In addition to the use of arsenic trioxide or other small-molecule stabilisers, two other treatment strategies are viable: (i) gene repair therapy using CRISPR-Cas9 gene-editing technologies (Li et al. 2023); and (ii) protein replacement therapy, which uses lipid nanoparticles to locally deliver therapeutic mRNA encoding normal proteins (Paunovska et al. 2022). Notably, glaucoma often involves chronic inflammation of the optic nerve, manifested by immune cell activation and inflammatory factor release that damage the retina and optic nerve. Therefore, protein replacement therapy can also deliver anti-inflammatory factors or immunomodulatory factors (such as TGF-β) to reduce local inflammation and slow nerve damage.

However, PIG has limitations. One limitation lies in the impact of demographic distribution on its clinical utility. The genetic data primarily come from the European population due to available GWAS summary data, which limits generalisability to other populations such as Africa or Asia. A recent study on primary OAG in Africa showed that the incidence rate of this condition is notably higher in African populations (Verma et al. 2024). This finding reveals substantial differences in genetic architecture and glaucoma susceptibility between European and African populations, thereby highlighting the need for targeted investigations to identify population-specific drug targets. Likewise, the genetic correlation between European and African and Asian populations can reach 0.73 and 0.78, respectively. This suggests that targets identified from European population data

could potentially serve as a valuable reference for other populations as well. Furthermore, curating false targets (and definitively validated true targets as well) will be of utmost importance for evaluating both sensitivity and specificity. This will lead to the development of better combination methods in the future. Regarding techniques such as PCHi-C for mapping non-coding variants to genes, these methods have limited resolution. These techniques detect interactions between broad genomic regions, making it challenging to pinpoint specific nucleotide changes driving regulation. To address this, future improvements could integrate high-resolution methods such as HiChIP or CRISPR-based perturbation screens to refine regulatory element identification, thereby enhancing precision for therapeutic targeting. Another limitation is the lack of cell-type-specific pathway interaction analysis. The current crosstalk network approach does not account for pathway dynamics in RGCs, which are central to glaucoma pathology. This oversight risks misprioritising genes that are not functionally relevant to RGCs. Future iterations of PIG should incorporate single-cell omics data or cell-type-specific interaction networks (e.g., neurodegeneration-related pathways in RGCs) to improve mechanistic relevance.

Bias in genetic loci identification may impact clinical utility, including: (i) overlooking important genetic variants prevalent in African and Asian populations, potentially missing therapeutic targets; (ii) therapeutic targets identified by PIG may not work for non-European populations since the effects of genetic variants may differ across populations; and (iii) drugs repurposed based on European data may exhibit varied efficacy across different demographic groups. Addressing demographic disparities in the future includes: (i) expanding GWAS to include African, Asian, and other underrepresented populations to identify population-specific genetic variants and therapeutic targets, thereby enabling more effective treatments; (ii) validating prioritised targets across different populations to ensure their relevance and to highlight the need for population-specific interventions; and (iii) combining genetic data from multiple ethnic groups to improve the robustness and accuracy of identified targets (i.e., enabling more effective cross-population therapeutic strategies), enhancing the overall clinical utility of PIG.

The methodological framework of PIG also warrants refinement. While the RWR algorithm effectively integrates network evidence by capturing local and global structures, its reliance on the generic STRING protein–protein interaction network raises concerns about glaucoma-specific mechanistic relevance. For example, neurodegeneration-related signaling pathways critical to RGC survival may be underrepresented in STRING. Future work should incorporate RGC-specific interaction data, such as synaptic maintenance or axonal transport pathways, to better reflect disease mechanisms.

Additionally, alternative algorithms such as PageRank (that is, RWR with a restarting probability of 0; see Fig. 2) or heat diffusion kernels could be tested to assess their utility in capturing target influence or spreading pathway-specific signals. The self-organising learning algorithm (supraHex) remains advantageous for handling high-dimensional data and uncovering complex relationships between crosstalk genes, but alternative traditional algorithms based on hierarchical clustering or consensus clustering could enhance the robustness and applicability of the PIG results.

In summary, the demographic distribution of data used in PIG may impact its clinical utility. Including diverse populations, validating targets across populations, and integrating multi-ethnic datasets (particularly addressing the underrepresentation of non-European populations) will help fully realise the potential of PIG in global glaucoma treatment and prevention efforts. Concurrently, advancing cell-type-specific pathway analyses, refining regulatory element resolution, and integrating disease-relevant interaction networks will strengthen the biological validity of prioritised targets. These improvements will ensure that PIG evolves into a versatile platform for translating genetic insights into precision therapies for glaucoma.

Conclusions

Our PIG solution, tailored for glaucoma, provides a platform for translating disease genetic associations into therapeutic targets and drugs, thus guiding laboratory and clinical validation. Beyond the scope of PIG and glaucoma, computational translational medicine complements laboratory medicine (Ning and Wang 2024), emerging as an indispensable strategy for disease phenomics (Ying 2023) and effectively bridging the gap between disease genetic findings and their therapeutic applications. We expect improvements in the accuracy and scope of identified crosstalk genes and their repurposed drugs, especially by incorporating artificial intelligence–driven multi-modal foundation models, such as the BioMap foundational model ‘xTrimo’ (Han et al. 2024), which integrates multi-omics data into a unified framework for holistic biological modeling, and by leveraging causal network analysis platforms such as QIAGEN Ingenuity Pathway Analysis (Krämer et al. 2014). These approaches can be applied to genomic data from glaucoma (Liu et al. 2013) and other eye disorders (Lu et al. 2023). Such expansions will contribute to the development of more effective treatments for pancreatic-disease patients with hereditary eye diseases.

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Availability of Data and Materials All relevant data are within the paper and its supplementary files.

Declarations

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