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Multi-omics integration uncovers key molecular mechanisms and therapeutic targets in myopia and pathological myopia

Jingwen Hui [a,b], Xuehao Cui [c,d,e,*], Quanhong Han [a,b,**]

[a] Tianjin Eye Hospital, No.4 Gansu Road, Heping District, Tianjin, China
[b] Tianjin Key Lab of Ophthalmology and Visual Science, Tianjin, China
[c] MRC Mitochondrial Biology Unit, Department of Clinical Neurosciences, University of Cambridge, Cambridge CB2 0XY, UK
[d] John van Geest Centre for Brain Repair, University of Cambridge, Cambridge CB2 0PY, UK
[e] Cambridge Eye Unit, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge CB2 0QQ, UK

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ABSTRACT

Purpose: Myopia, particularly pathological myopia (PM), poses a significant global health burden due to its increasing prevalence and associated vision-threatening complications. Despite extensive genetic research, the molecular mechanisms underlying myopia progression remain unclear. This study aims to identify key causal proteins and metabolic pathways in myopia and PM and explore potential therapeutic targets.

Methods: We employed a multi-omics framework integrating Mendelian Randomization (MR), colocalization analysis, protein-protein interaction (PPI) networks, metabolic pathway enrichment, and molecular docking to investigate the molecular mechanisms of myopia and PM. We analyzed five proteome-wide pQTL datasets, two whole-blood eQTL datasets, and a metabolic GWAS to identify causal proteins, genes, and metabolites. Small-molecule docking and molecular dynamics (MD) simulations were performed to assess potential drug-target interactions.

Results: We identified PDGFRA, LRRTM2, and PCOLCE as key regulators of myopia and PM. PDGFRA was associated with extracellular matrix (ECM) remodeling and fibroblast activation, LRRTM2 with retinal neurotransmission and dopamine signaling, and PCOLCE with collagen stability and scleral biomechanics. Functional enrichment analysis highlighted immune signaling, lipid metabolism, and oxidative stress pathways as contributors to myopia pathogenesis. Molecular docking and MD simulations identified 1,3-Propanediol, Cis-9-Octadecenoic Acid, and 17-Beta-Estradiol as potential therapeutic compounds that may stabilize ECM, enhance neurotransmission, and reinforce scleral integrity.

Conclusions: Our multi-omics framework prioritizes PDGFRA, LRRTM2, and PCOLCE as candidates linked to ECM remodeling, neurotransmission, and scleral biomechanics in myopia and PM. Integrating MR with colocalization, PPI, and pathway analyses yields mechanistic hypotheses and testable targets. Docking/MD findings are exploratory and will require experimental validation before any therapeutic inference.

1. Introduction

Myopia, particularly pathological myopia (PM), is a significant global health concern due to its rising prevalence and the risk of irreversible vision-threatening complications such as myopic maculopathy, retinal detachment, and glaucoma.[1–3] In East Asia, up to 80–90 % of young adults are affected, with high myopia cases also increasing.[4] Defined as a spherical equivalent of −6.00 D or worse, high myopia is associated with progressive axial elongation and structural changes in the sclera, choroid, and retina, contributing to PM development.[5,6] The underlying mechanisms involve excessive axial growth driven by biomechanical weakening of the scleral extracellular matrix (ECM), altered choroidal blood flow regulation, and dysregulated retinal signaling pathways.[7] Epidemiological projections estimate that nearly 50 % of the global population will be myopic by 2050, with approximately 10 % progressing to high myopia, emphasizing the urgent need for effective preventive and therapeutic interventions beyond optical corrections such as spectacles and contact lenses.[8,9]

* Corresponding author at: MRC Mitochondrial Biology Unit, Department of Clinical Neurosciences, University of Cambridge, Cambridge CB2 0XY, UK.
** Corresponding author at: Tianjin Eye Hospital, No.4 Gansu Road, Heping District, Tianjin, China.
E-mail addresses: xc350@cam.ac.uk (X. Cui), 5020200063@nankai.edu.cn (Q. Han).

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The etiology of myopia is multifactorial, shaped by both genetic predisposition and environmental influences such as prolonged near work and insufficient outdoor light exposure.[10,11] Genome-wide association studies (GWAS) have identified over 400 genetic loci associated with refractive errors, underscoring the substantial heritability of myopia.[12,13] However, despite these discoveries, the precise molecular mechanisms linking genetic variants to myopia pathogenesis remain poorly understood.[14] Myopia progression involves dysregulated ECM remodeling, abnormal scleral fibroblast activity, and disruptions in retinal neurotransmitter signaling, particularly those involving dopamine and retinoic acid pathways.[15] Emerging evidence suggests that protein dysregulation is pivotal in these processes, making proteins ideal candidates for therapeutic intervention.[16] Proteins directly affect genetic variations, translating genetic risk into phenotypic alterations at the tissue level. Yet, most prior studies have focused solely on genetic loci without systematically integrating functionally relevant protein changes.

To bridge this gap, we employed Mendelian Randomization (MR).[17] This robust analytical framework leverages genetic variants as instrumental variables to infer causal relationships between specific exposures and disease outcomes.[18] Unlike traditional epidemiological studies, MR mitigates biases from confounding variables and reverse causation, providing robust evidence for causal associations.[19] By integrating protein quantitative trait loci (pQTL) and expression quantitative trait loci (eQTL) data, we aimed to uncover proteins and genes that directly influence myopia and PM, thereby identifying potential therapeutic targets.

A key strength of our study is the simultaneous investigation of myopia and PM, allowing for a more comprehensive understanding of their molecular mechanisms. Unlike previous studies focusing on single genetic loci or limited datasets, we employed a multi-omics approach by integrating five large proteome-wide pQTL datasets and two whole-blood eQTL datasets. This high-resolution assessment of causal relationships between protein expression, gene regulation, and myopia risk enables us to move beyond simple genetic associations and toward mechanistic insights into disease progression. Furthermore, we incorporated protein-protein interaction (PPI) analysis, metabolic pathway enrichment, and small-molecule drug screening to systematically identify and prioritize therapeutic targets with clinical relevance.[20] These findings provide a molecular framework for myopia pathogenesis, highlighting candidate proteins that may serve as viable pharmacological targets and paving the way for precision medicine strategies to mitigate myopia progression and its associated complications.

2. Methods and materials

2.1. Study design

This study employed a comprehensive multi-omics framework to identify and prioritize therapeutic targets for myopia and PM by integrating proteomic, transcriptomic, and metabolomic data with genetic association studies (Fig. 1, Table S2). The approach involved a four-step analytical pipeline: (1) data acquisition from large-scale GWAS, including pQTL, eQTL, and metabolomic GWAS datasets; (2) causal inference using MR to identify proteins, genes, and metabolites associated with myopia and PM; (3) functional validation through colocalization analysis, PPI analysis, metabolic pathway enrichment, and small-molecule docking, and (4) MD simulations to evaluate the stability and feasibility of drug-target interactions. The study adhered to strict statistical frameworks to ensure robustness and reproducibility, applying

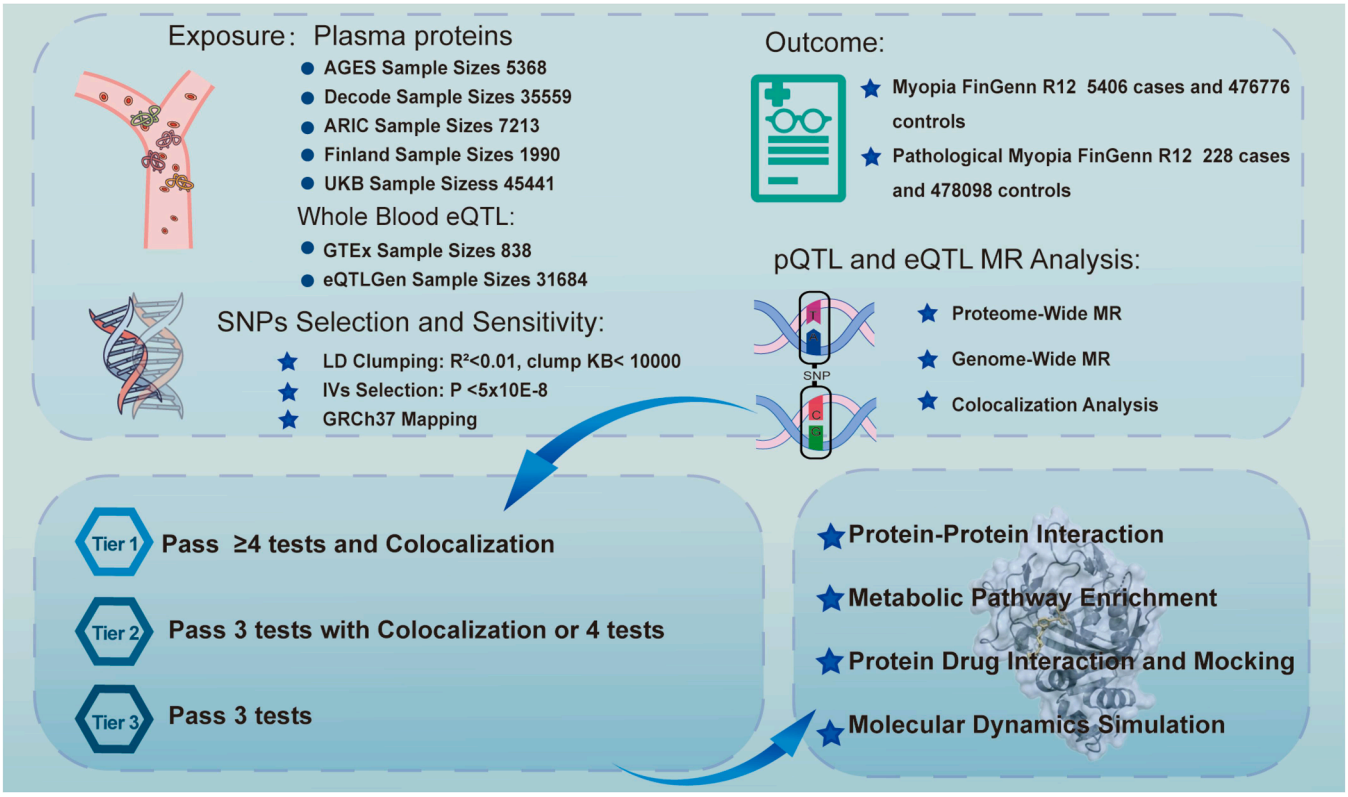

Fig. 1. Overview of the study design and analytical framework, This schematic outlines the study workflow, including data sources, genetic instrument selection, Mendelian randomization (MR) analysis, and downstream functional validation. Plasma protein levels were used as exposures, with genetic instruments derived from multiple cohorts. Myopia and pathological myopia were the outcomes, with genome-wide and proteome-wide MR analyses conducted using protein quantitative trait loci (pQTL) and expression quantitative trait loci (eQTL). Significant associations were further assessed via colocalization, pathway enrichment, protein-protein interactions, and molecular dynamics simulations.

multiple MR models and sensitivity analyses to mitigate potential biases and confounding effects. We selected five large pQTL resources to maximize cross-platform replication and reduce the chance that results are driven by a single cohort or assay platform. This strategy increases robustness by confirming protein instruments across different study designs, sample sizes, and measurement technologies. These resources provide complementary coverage across proteins, transcripts, and metabolites, enabling a more comprehensive and biologically grounded framework for causal inference in myopia and PM.

2.2. Data sources

We obtained summary statistics from multiple large-scale GWAS to investigate the genetic determinants of myopia and pathological myopia (PM). GWAS data were sourced from the FinnGen database, which includes 5406 myopia cases and 476,776 controls, as well as 228 PM cases and 478,098 controls. FinnGen integrates genetic data from Finnish biobanks with national health registry records, offering a well-defined case-control framework within a large population-based cohort. For this study, myopia and PM outcomes were derived exclusively from FinnGen R12 summary statistics. In FinnGen, PM is defined using clinical diagnostic codes mapped from national registries; posterior scleral staphyloma and ATN grading were not available at the summary-statistics level and therefore could not be applied. We acknowledge this as a limitation and regard the PM findings as hypothesis-generating, to be replicated in future datasets with harmonized, imaging-based definitions.

Proteome-wide pQTL data were obtained from five independent cohorts. The AGES Study is a longitudinal population-based study investigating aging and chronic diseases, offering valuable insights into protein expression variations with aging.[21] The Decode Icelandic cohort leverages a founder population structure, making it particularly powerful for identifying genetic determinants of protein levels in the bloodstream.[22] The Atherosclerosis Risk in Communities (ARIC) Study is a long-term epidemiological cohort investigating cardiovascular disease risk factors, with extensive proteomic profiling available.[23] The FinnGen study integrates biobank and registry-based data to enhance statistical power in identifying pQTL associations.[24] The UK Biobank (UKB) is a large-scale prospective cohort with deep genetic and health-related phenotyping.[25] It is a key resource for studying proteomic variation across diverse traits and diseases.

eQTL data were obtained from the GTEx (Genotype-Tissue Expression) Project and the eQTLGen Consortium. GTEx provides tissue-specific eQTL associations across multiple organs, allowing the exploration of gene expression regulation in relevant tissues.[26] The eQTLGen Consortium aggregates blood-based eQTL associations from various cohorts, increasing statistical power for detecting genetic effects on gene expression.[27] For this study, we combined summary statistics from these two eQTL datasets to create a harmonized dataset, which was then used for subsequent MR analyses. This integration allowed us to enhance statistical power and improve the accuracy of our causal inference regarding the role of gene expression in myopia risk.

Metabolomics GWAS data were sourced from a large-scale metabolic profiling study that measured 1400 metabolites across various biochemical classes, including amino acids, lipids, carbohydrates, and oxidative stress markers.[28] These datasets provide a comprehensive view of systemic metabolic perturbations and their potential impact on myopia development. Including metabolomic data allowed us to explore causal relationships between metabolic traits and myopia risk, further supporting our multi-omics approach to target discovery.

2.3. MR analysis

MR was conducted to infer causal relationships between genetically determined exposures and myopia risk by leveraging single nucleotide polymorphisms (SNPs) as instrumental variables (IVs). Separate MR analyses were performed for proteomic, transcriptomic, and metabolomic datasets using a structured approach involving instrumental variable selection, causal inference modeling, and sensitivity testing. IVs were selected from pQTL and eQTL datasets based on genome-wide significance ($P < 5 \times 10^{-8}$) and linkage disequilibrium (LD) clumping ($R^2 < 0.01$, clumping window = 10,000 kb) to ensure their independence. Cis-pQTL and cis-eQTL variants within 1 Mb of the corresponding gene were prioritized to reduce pleiotropy. Only IVs with an F-statistic greater than 10 were retained to avoid weak instrument bias. The primary analysis used inverse-variance weighted (IVW) regression via the TwoSampleMR and MR-Base packages in R, assuming all SNPs were valid instruments.[29] To account for potential violations of IV assumptions, additional MR methods were applied, including MR-Egger regression, which tests horizontal pleiotropy by assessing the interception term. For exposures instrumented by < 3 independent SNPs, MR-Egger intercepts are not estimable (reported as NA). The model-based estimator was also implemented to identify causal effects in heterogeneity by grouping instruments with similar effect estimates. Sensitivity analyses were performed to validate further MR results, including Cochran's Q test to evaluate heterogeneity among IVs. MR-PRESSO was employed to detect and correct horizontal pleiotropy by removing SNP outliers that contributed to bias. Additionally, Steiger filtering was applied to ensure correct causal directionality by verifying that IVs explained more variance in the exposure than in the outcome. By integrating these robust statistical approaches, we ensured high-confidence causal inferences, contributing to identifying putative therapeutic targets for myopia. Because proteomic platforms, quantification pipelines, ancestry mix, and sample sizes differ across AGES, deCODE, ARIC, FinnGen, and UKB pQTL resources, we performed separate two-sample MR analyses for each pQTL dataset against the same FinnGen outcomes, followed by cross-cohort replication via intersection. We avoided meta-analyzing heterogeneous pQTL summary statistics to reduce platform-dependent biases. In this study, proteome-wide MR was primarily used as an exploratory discovery step across multiple independent pQTL resources. For this reason, we initially reported nominal P values ($P < 0.05$) without direct FDR adjustment in the primary MR scans.[30–32] Instead, we prioritized robustness by requiring replication across cohorts and then validating candidates through independent eQTL-MR analyses and colocalization tests. This tiered strategy was intended to minimize false positives while still allowing discovery of novel targets in an exploratory context.

2.4. Colocalization analysis

Colocalization analysis used the Coloc package in R to determine whether a shared genetic variant influenced gene/protein expression and myopia risk. This analysis assessed whether GWAS loci associated with myopia overlapped with expression or protein quantitative trait loci by testing five mutually exclusive hypotheses: (H0) no association with either trait, (H1) association with trait one only, (H2) association with trait two only, (H3) two distinct causal variants, and (H4) a shared causal variant influencing both traits.[33] The posterior probability of H4 (PPH4) greater than 0.8 was considered strong evidence of colocalization, while PPH4 between 0.5 and 0.8 indicated weak colocalization evidence. Sensitivity analysis was conducted by varying prior probabilities for expected effect sizes to assess the robustness of colocalization results. Analyses were conducted within a $\pm$ 500 kb window centered on the lead SNP at each locus. Default prior probabilities were used ($p_1 = 1 \times 10^{-4}$, $p_2 = 1 \times 10^{-4}$, $p_{12} = 1 \times 10^{-5}$), and sensitivity analyses were performed by varying priors across one order of magnitude to assess robustness. Additionally, eCAVIAR, a Bayesian fine-mapping method, was employed to evaluate the likelihood of multiple SNPs jointly influencing both traits, thereby improving resolution in cases where multiple linked variants contributed to causal effects. By integrating colocalization with MR results, we identified high-confidence candidate genes and proteins with strong genetic support for their involvement in

myopia pathophysiology.

2.5. Protein prioritization strategy

Proteins identified through MR and colocalization analyses were classified into three tiers. Proteins were prioritized by cross-cohort replication rather than pooled meta-analysis: Tiering was based on the number of pQTL datasets with nominal MR support, colocalization probability, and concordant eQTL-MR signals. Tier 1 proteins were defined as those showing robust genetic evidence, either through significant associations in at least four independent pQTL or eQTL MR datasets with strong colocalization support (PP.H4 $>$ 0.8), or through significant associations in at least five independent datasets with moderate colocalization support (0.5 $\leq$ PP.H4 $\leq$ 0.8). This definition ensures that Tier 1 candidates combine broad replication across multiple cohorts with supportive colocalization evidence, thereby prioritizing proteins with the highest likelihood of true causal involvement. Tier 2 proteins were significantly associated in three pQTL or eQTL datasets with colocalization support or those with significant associations in at least four datasets. Tier 3 proteins had significant associations in at least three datasets but lacked strong support for collocation. This hierarchical classification ensured a systematic approach to prioritizing proteins for functional validation and drug discovery efforts in myopia and PM research.

2.6. PPI analysis

Using the STRING database, a PPI network was constructed to investigate functional interactions among identified proteins. High-confidence interactions (interaction score $>$ 0.7) were selected to identify key biological pathways and molecular complexes involved in myopia pathogenesis. By integrating PPI analysis with MR and colocalization findings, we identified core regulatory networks involved in myopia progression and provided mechanistic insights into the molecular underpinnings of disease susceptibility.

2.7. Metabolomics pathway enrichment analysis

Pathway enrichment analysis was performed using the clusterProfiler package in R, leveraging the Kyoto Encyclopedia of Genes and Genomes (KEGG) and Human Metabolome Database (HMDB) to identify metabolic pathways significantly associated with myopia risk. Over-representation analysis was conducted to determine whether specific pathways were disproportionately affected by metabolites identified in MR. Pathway impact scores were calculated based on the number of enriched metabolites, their statistical significance, and connectivity within KEGG networks. Statistical significance was determined using a hypergeometric test with Benjamini–Hochberg FDR correction across pathways; pathways with FDR $<$ 0.05 were considered significant and at 0.05 $\leq$FDR$<$ 0.20 as exploratory. This integrative approach helped refine target prioritization and provided insights into the metabolic mechanisms underlying myopia and PM development.

2.8. Small-molecule docking and molecular dynamics simulation

To explore potential therapeutic targets, molecular docking studies were conducted on three proteins strongly associated with myopia and PM. Small-molecule ligands were obtained from the PubChem database (http://pubchem.ncbi.nlm.nih.gov/), where their 2D structures were retrieved and then converted into 3D structures using ChemOffice software. The resulting 3D structures were saved in mol2 format for subsequent molecular docking studies. Protein targets were selected based on their relevance to myopia pathogenesis from the RCSB PDB database (http://www.rcsb.org/), prioritizing high-resolution crystal structures to serve as molecular receptors. Structural optimization was performed using PyMOL, including removing water molecules, phosphate groups, and other non-essential elements before saving the protein structure in PDB format. Molecular docking was carried out using AutoDock Vina 1.5.6 to explore the interactions between proteins and small-molecule ligands. Both protein and ligand structures were preprocessed using AutoDock Tools, where proteins were hydrogenated and stripped of water molecules, while ligands underwent hydrogenation and torsional force determination. Docking grid box coordinates were set based on the binding pocket, and docking results were evaluated based on binding energy scores. Vina runs used grid boxes encompassing the binding pocket with margins of $\geq$ 5 Å in each dimension, exhaustiveness = 8–12, and $\geq$ 20 independent runs per ligand. Pocket definition followed co-crystallized ligands or conserved cavities identified by receptor mapping. The lowest energy docking conformation was selected for further molecular dynamics simulations. PyMOL and Discovery Studio 2019 were used for 2D and 3D visualization of the interactions between the test compounds and key protein residues. Binding energy values were used to assess interaction strength, where binding energy less than −5.0 kcal/mol indicated good binding activity and values below −7.0 kcal/mol suggested strong binding affinity. Lower binding energy values implied stronger interactions, higher affinity, and excellent conformational stability of the protein-ligand complex. MD simulations were performed using GROMACS 2023 for a total simulation time of 100 ns to evaluate the stability of the protein-ligand complex. The CHARMM 36 force field was applied for proteins, while ligand topology parameters were generated using the GAFF2 force field. The system was enclosed in a periodic boundary box, and water molecules were added using the TIP3P water model to solve the system. The Particle Mesh Ewald (PME) method was used for long-range electrostatic interactions, while the Verlet algorithm was applied for short-range interactions. The system underwent 100,000 steps of NVT (constant volume and temperature) and NPT (continuous pressure and temperature) equilibrium simulations, with a coupling constant of 0.1 ps over a 100 ps period. Van der Waals and Coulombic interactions were calculated with a cutoff of 1.0 nm. The final 100 ns MD simulation was performed under constant temperature (300 K) and pressure (1 bar) to assess the conformational dynamics of the protein-ligand complex.

3. Results

3.1. Proteome-wide MR analysis identified proteins for myopia and PM

Using the Wald ratio method or IVW method, we identified a significant causal relationship between myopia and 144 proteins in the AGES proteomic GWAS (Figure S1A), 93 proteins in the Decode (Figure S1B), 81 proteins in the ARIC (Figure S1C), 147 proteins in the Finland (Figure S1D), and 111 proteins in the UKB (Figure S1E), with $p < 0.05$. Subsequently, we performed an intersection analysis of the MR results across the five proteomic datasets. We identified 19 proteins (LAG3, PDIA5, FCER2, SPARCL1, PDGFRA, C1QTNF5, CTSF, CHI3L2, LRRTM2, ERBB3, CALB2, CA13, TRIM3, TCN2, SAT2, EFEMP1, PSME2, GFRA2) that showed significant causal associations with myopia in at least three proteomic MR results (Fig. 5C). Among them, NID1, PDIA5, FCER2, PDGFRA, LRRTM2, ERBB3, CA13, TRIM3, and PSME2 exhibited a positive causal relationship with myopia, suggesting that these proteins may be causally associated with an increased risk of myopia. In contrast, other proteins showed a negative causal relationship with myopia, indicating a potential role in reducing the risk of myopia development. PDGFRA, CTSF, and CA13 consistently exhibited a significant causal relationship with myopia in four proteomic datasets. Additionally, the MR-PRESSO analysis showed insufficient evidence for horizontal pleiotropy in the associations between these 19 circulating proteins and myopia risk (global test P value $>$ 0.05; Tables S3, S5, S7, S9, S11). We also assessed heterogeneity, and no significant heterogeneity was detected in MR-Egger or IVW analyses (Q_pval $>$ 0.05; Tables S4, S6, S8, S10, S12).

We also conducted proteomic MR analysis in PM, identifying 98 significant proteins in the AGES dataset (Figure S2A), 67 significant proteins in the Decode (Figure S2B), 61 significant proteins in the ARIC (Figure S2C), 466 significant proteins in the Finland (Figure S2D), and 87 significant proteins in the UKB (Figure S2E) with PM. Further analysis revealed 13 proteins (ADH4, TNFSF14, DLK2, SPOCK3, PCOLCE, C1QTNF3, NPPB, RBP1, LRP11, SCIN, DARS1, BOLA3, RBP7) that were significantly associated with PM in at least three proteomic MR analyses (Fig. 5D). DLK2, SPOCK3, PCOLCE, C1QTNF3, NPPB, RBP1, LRP11, and BOLA3 were found to have a positive causal association with PM, indicating that these proteins may contribute to an increased susceptibility to PM. In contrast, the remaining proteins exhibited a negative causal relationship, suggesting a potential protective effect against PM development. Among them, PCOLCE, NPPB, and RBP1 exhibited significant causal relationships with PM in four proteomic datasets. Additionally, MR-PRESSO analysis indicated no significant evidence for horizontal pleiotropy between these 13 circulating proteins and PM risk (Tables S13, S15, S17, S19, S21). We also assessed heterogeneity, and no significant heterogeneity was detected in MR-Egger or IVW analyses (Tables S14, S16, S18, S20, S22).

3.2. Colocalization analysis in myopia and PM

We performed a genetic colocalization analysis to reduce potential confounding effects caused by LD. In myopia, we selected potential causal proteins identified in multiple proteomic MR analyses for colocalization analysis (Fig. 2A). We found that under PP4 $>$ 80 %, three proteins [PDGFRA (Fig. 2D), LRRTM2 (Fig. 2C), and CHI3L2 (Fig. 2E)] exhibited strong genetic colocalization evidence with myopia. Additionally, under PP4 $>$ 50 %, CTSF (Fig. 2B) showed weaker genetic colocalization evidence with myopia. In PM (Fig. 3A), we found that RBP1 (Fig. 3C), and SCIN (Fig. 3D) exhibited significant genetic colocalization evidence, while PCOLCE (Fig. 3B) showed weaker genetic colocalization evidence. These findings suggest that the variations in the levels of these proteins and the risks of myopia and PM may be driven by shared causal genetic variants.

3.3. Genome-wide MR and enrichment analysis

We analyzed MR using merged eQTL data to investigate causal associations for myopia and PM. We identified 530 genes that showed significant causal associations with myopia. After Benjamini-Hochberg (BH), 204 genes remained significantly associated with myopia at FDR $<$ 0.05 (Fig. 4A, Table S32). The MR-PRESSO analysis showed no evidence of horizontal pleiotropy or significant heterogeneity in the associations between these significant genes and myopia risk. We identified 456 significant genes associated with PM, and 140 genes remained significantly associated with PM in FDR $<$ 0.05 (Fig. 4B, Table S33).

Subsequently, our functional enrichment analysis revealed that myopia-associated proteins are primarily involved in immune response activation, ECM interactions, and lipid metabolism, suggesting a role for inflammation and metabolic dysregulation in myopia development (Figs. 4C, 4D). Key pathways include interleukin-12 production, leukocyte-mediated immunity, ECM-receptor interactions, and PI3K-Akt signaling, indicating that immune signaling and structural remodeling contribute to ocular changes in myopia. Additionally, the enrichment of cholesterol metabolism and lipid-atherosclerosis pathways suggest lipid homeostasis may play a role in disease progression.

In contrast, PM-associated genes exhibit stronger immune system activation, ECM remodeling, and metabolic dysfunction, pointing toward a more severe inflammatory and degenerative process (Figs. 4E, 4F). The significant involvement of ECM-receptor interactions, focal adhesion, and TNF signaling pathways suggests that structural instability and chronic inflammation may drive scleral and retinal degeneration in PM. Furthermore, pathologic myopia shows more substantial enrichment in oxidative stress and metabolic pathways, such as glutathione metabolism, lipid metabolism, and PI3K-Akt signaling, implicating metabolic imbalances in pathogenesis. Our findings suggest that immune dysregulation, ECM remodeling, and metabolic disturbances are central to both myopia and PM, with the latter exhibiting more severe immune and structural changes. These insights highlight immune and ECM-targeted interventions as potential therapeutic strategies for managing myopia and its progression to PM.

3.4. Protein prioritization based on MR and colocalization analysis

We classified 14 proteins associated with myopia (Table 1) and 13 with PM (Table 2) based on five proteome-wide MR analyses, a genome-wide MR analysis, and a colocalization analysis. Three proteins (PDGFRA, CHI3L2, and CTSF) were assigned to Tier 1 for myopia-associated proteins, demonstrating robust evidence. Four proteins (LRRTM2, CA13, FCER2, and ERBB3) were categorized as Tier 2, with moderate MR evidence. The remaining seven proteins, including NID1, TRIM3, CALB2, SAT2, C1QTNF5, TCN2, and GFRA2, were placed in Tier 3, exhibiting weaker but significant MR signals. RBP1 and PCOLCE were the most strongly associated with PM-associated proteins and classified as Tier 1, indicating robust support. SCIN, NPPB, and TNFSF14 were categorized into Tier 2, with significant but slightly weaker. The remaining proteins, BOLA3, ADH4, DLK2, RBP7, C1QTNF3, LRP11, and SPOCK3, were placed in Tier 3, showing moderate MR evidence but limited colocalization support.

3.5. PPI for candidate protein targets

We identified key proteins interacting with the targets of currently available myopia- and PM-related proteins (Figs. 5A, 5B). Using the STRING database, we identified several known and reliable interactions, including the role of PDGFRA in interacting with multiple proteins, which may play a crucial role in the pathogenesis of myopia. Additionally, PCOLCE was found to have potential therapeutic significance in treating PM.

3.6. Metabolomics pathway enrichment analysis

We identified 49 metabolites that exhibited significant causal associations with myopia (Tables S23, S24, S25) and 39 metabolites that showed significant causal associations with PM (Tables S26, S27, S28). Subsequently, we performed enrichment analysis on these metabolites and categorized them using KEGG and HMDB pathway analyses. In KEGG pathway analysis (Figure S3A, Table S30), the most significantly enriched metabolic pathways associated with myopia included caffeine metabolism, starch and sucrose metabolism, fructose and mannose metabolism, galactose metabolism, lysine degradation, cysteine and methionine metabolism, amino sugar and nucleotide sugar metabolism, and primary bile acid biosynthesis. Among these, caffeine metabolism showed the most substantial enrichment, suggesting a potential role of caffeine-related metabolic pathways in myopia. In HMDB pathway analysis (Figure S3B), the top significantly enriched pathways included spermidine and spermine biosynthesis, caffeine metabolism, starch and sucrose metabolism, fructose and mannose degradation, amino sugar metabolism, galactose metabolism, methionine metabolism, and bile acid biosynthesis. The involvement of polyamine metabolism (spermidine and spermine biosynthesis) and caffeine metabolism further supports the hypothesis that certain dietary and metabolic factors may affect myopia development.

For PM, KEGG pathway analysis (Figure S3C, Table S31) identified butanoate metabolism, glycerolipid metabolism, pantothenate and CoA biosynthesis, beta-alanine metabolism, propanoate metabolism, arginine and proline metabolism, glycerophospholipid metabolism, pyrimidine metabolism, and valine, leucine, and isoleucine degradation as the most significantly enriched pathways. Notably, butanoate metabolism and glycerolipid metabolism were highly enriched, suggesting a

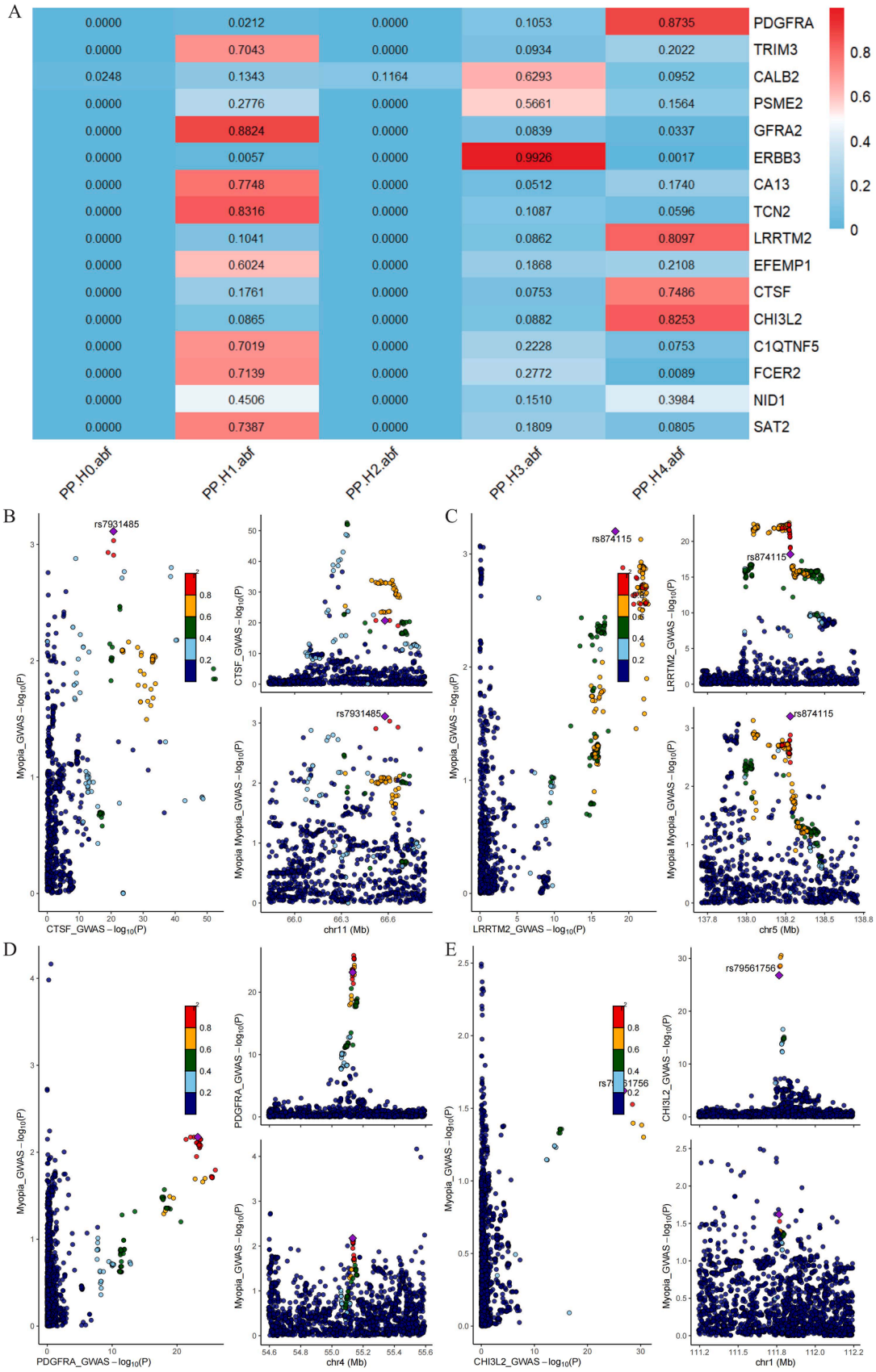

Fig. 2. Colocalization results for proteins associated with myopia, (A) Heatmap representing the colocalization probabilities (PP.H4) for significant protein-trait associations, with higher values (red) indicating stronger evidence of shared genetic signals. (B-E) LocusZoom plots for selected proteins (CTSF, LRRTM2, PDGFRA, CHI3L2), showing the association signals from myopia GWAS and the respective protein QTLs. The color scale represents a linkage disequilibrium (LD) with the lead SNP.

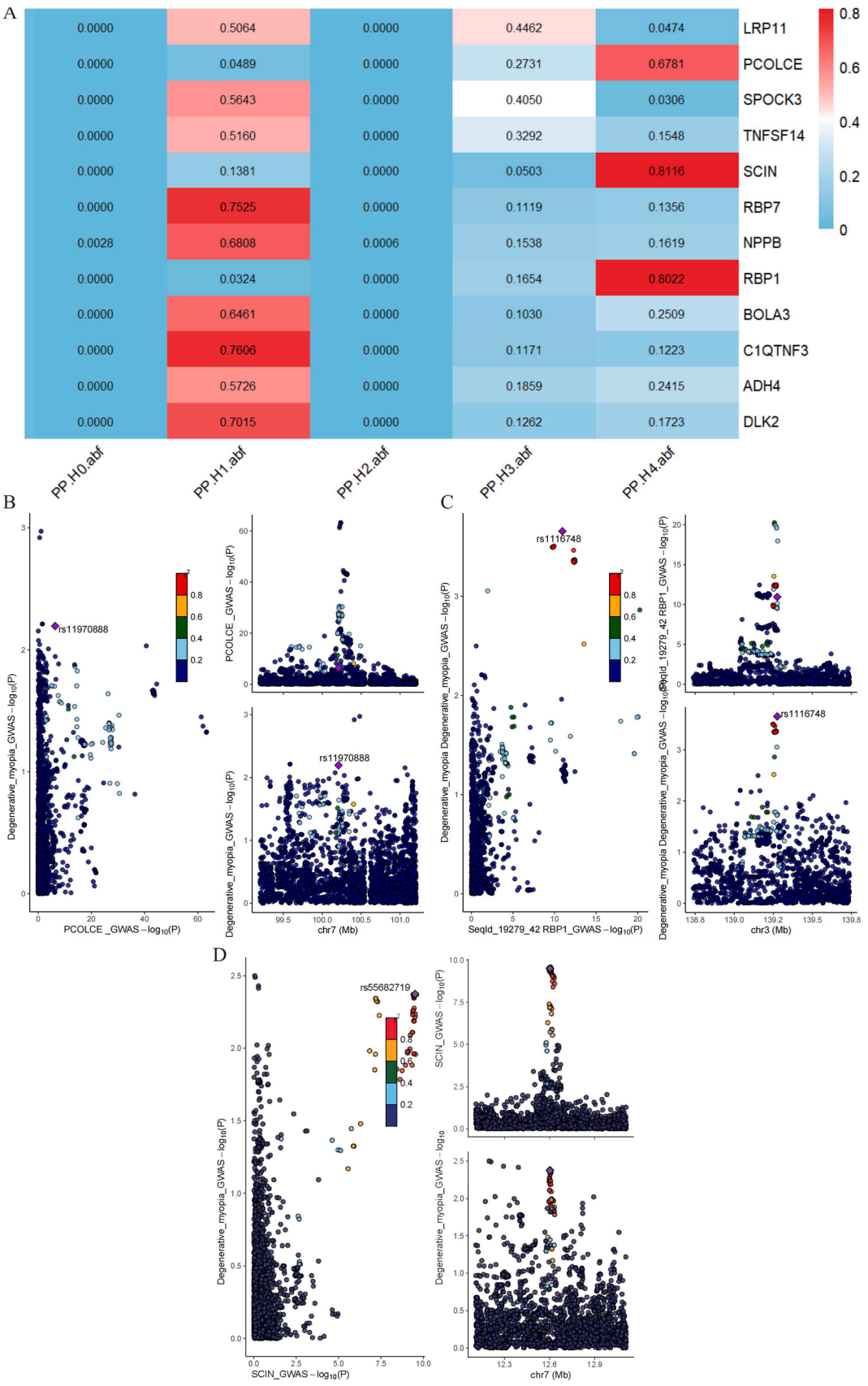

Fig. 3. Colocalization results for proteins associated with pathological myopia, (A) Heatmap of colocalization probabilities for proteins identified in pathological myopia. (B-D) Selected proteins (PCOLCE, RBP1, SCIN) showing the association signals from PM GWAS and the respective protein QTLs. The color scale represents a linkage disequilibrium (LD) with the lead SNP.

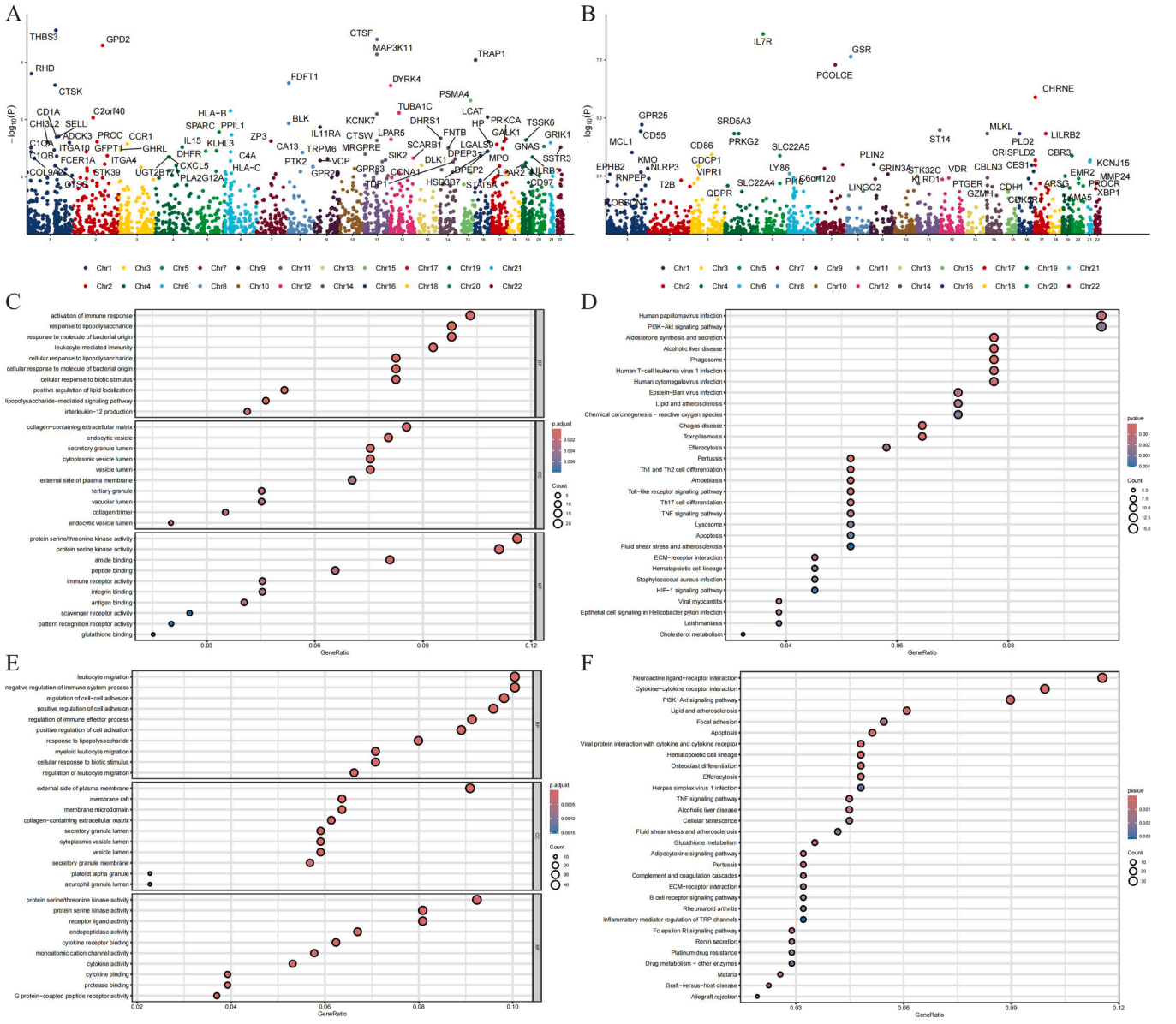

Fig. 4. Genome-wide Mendelian randomization (MR) results, (A-B) Manhattan plots of MR analysis results for myopia and PM traits, highlighting significant protein-trait associations. (C, E) Gene ontology and (D, F) KEGG pathway enrichment analyses for the identified proteins, showing biological processes and pathways significantly enriched among myopia and PM.

Table 1
Prioritization of myopia-associated proteins based on proteome-wide MR, eQTL MR, and colocalization analyses.

Protein/Gene	Proteome-Wide MR Analysis					eQTL MR	Colocalization PPH4 > 0.5 weak PPH4 > 0.8 strong	Category
	AGES *P*	Decode *P*	ARIC *P*	Finland *P*	UKB *P*	Druggable *P*		
PDGFRA	**0.0245**	0.488	**0.0160**	**0.0186**	**0.0192**	NA	**0.874**	Tier 1
CHI3L2	**0.0414**	**0.0499**	**0.0499**	0.752	NA	**1.53E-05**	**0.825**	Tier 1
CTSF	**0.0319**	0.153	**0.0143**	**0.0391**	**0.0143**	**6.28E-11**	**0.749**	Tier 1
LRRTM2	NA	**0.00227**	**0.00277**	**0.0244**	NA	NA	**0.810**	Tier 2
CA13	0.0560	**0.0114**	**0.0274**	**0.0495**	**0.0272**	**5.29E-05**	0.174	Tier 2
FCER2	**0.0171**	**0.0318**	0.0597	**0.0441**	0.351	**0.0220**	0.00890	Tier 2
ERBB3	NA	**0.00883**	**0.00883**	**0.0150**	0.4958	**0.00510**	0.00168	Tier 2
NID1	**0.00266**	0.113	NA	**0.0288**	**0.00656**	0.183	0.398	Tier 3
TRIM3	NA	**0.0144**	**0.0145**	**0.0138**	NA	NA	0.202	Tier 3
CALB2	NA	**0.00902**	**0.0239**	NA	**0.0146**	NA	0.0952	Tier 3
SAT2	0.902	**0.0323**	0.240	**0.0176**	**0.00265**	NA	0.0805	Tier 3
C1QTNF5	**0.0289**	**0.00598**	NA	0.112	**0.0340**	NA	0.0753	Tier 3
TCN2	0.992	**0.0180**	**0.0338**	0.0626	**0.0233**	0.265	0.0596	Tier 3
GFRA2	0.147	0.626	**0.0477**	**0.0181**	**0.0392**	NA	0.0337	Tier 3

Table 2
Prioritization of PM-associated proteins based on proteome-wide MR, eQTL MR, and colocalization analyses.

Protein/Gene	Proteome-Wide MR Analysis					eQTL MR	Colocalization PPH4 > 0.5 weak PPH4 > 0.8 strong	Category
	AGES *P*	Decode *P*	ARIC *P*	Finland *P*	UKB *P*	Druggable *P*		
RBP1	0.987	**0.00137**	**0.00137**	**0.00024**	**0.00137**	0.190	**0.802**	Tier 1
PCOLCE	**0.0472**	**0.0472**	**0.00226**	**0.0347**	**0.0474**	**6.51E-11**	**0.678**	Tier 1
SCIN	0.89262	**0.00646**	**0.00426**	**0.00062**	NA	NA	**0.812**	Tier 2
NPPB	**0.0487**	0.06105	**0.044**	**0.044**	**0.0295**	NA	0.162	Tier 2
TNFSF14	**0.0291**	**0.0365**	NA	**0.0234**	0.696	**0.0074**	0.155	Tier 2
BOLA3	NA	**0.00825**	**0.0231**	**0.0381**	NA	0.429	0.251	Tier 3
ADH4	**0.0179**	0.08715	**0.0179**	0.283	**0.0162**	NA	0.242	Tier 3
DLK2	**0.0417**	**0.0375**	**0.0284**	NA	NA	NA	0.172	Tier 3
RBP7	0.67962	NA	**0.03005**	**0.0149**	**0.0134**	NA	0.1366	Tier 3
C1QTNF3	**0.0484**	**0.0484**	**0.0483**	0.43078	NA	NA	0.122	Tier 3
LRP11	**0.00763**	**0.00244**	0.122	**0.0231**	0.0926	NA	0.0474	Tier 3
SPOCK3	**0.0439**	**0.0434**	NA	**0.0487**	NA	NA	0.0306	Tier 3

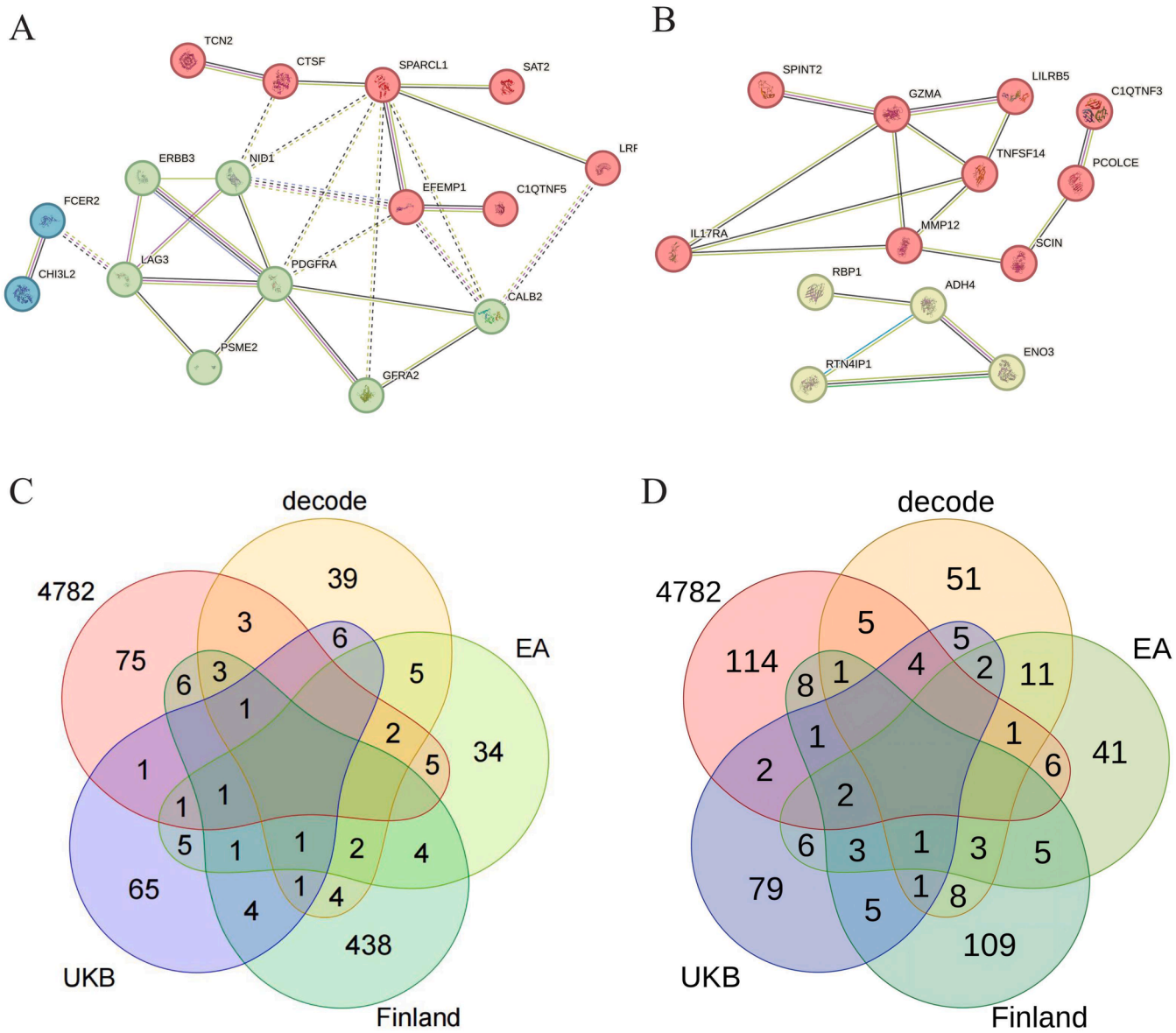

Fig. 5. Protein-protein interaction (PPI) networks and cross-cohort validation, (A-B) PPI networks for proteins associated with myopia and PM, illustrating key interacting partners and functional modules. (C-D) Venn diagrams showing the overlap of significant protein-trait associations across different pQTL datasets in myopia and PM.

potential role of lipid metabolism in PM pathogenesis. In HMDB pathway analysis (Figure S3D), the top significantly enriched pathways

included de novo triacylglycerol biosynthesis, glycerol phosphate shuttle, cardiolipin biosynthesis, ketone body metabolism, butyrate metabolism, mitochondrial electron transport chain, glycerolipid metabolism, phospholipid biosynthesis, and androgen and estrogen metabolism. These findings highlight the potential involvement of energy metabolism, mitochondrial function, and lipid metabolism in PM. Overall, our findings suggest that carbohydrate metabolism (starch, sucrose, fructose, and mannose metabolism), polyamine metabolism, and caffeine metabolism are significantly associated with myopia, while lipid metabolism, mitochondrial function, and ketone body metabolism appear to be crucial for PM.

3.7. Small-molecule docking and molecular dynamics simulation

We performed molecular docking to predict the potential binding sites of PDGFRA, LRRTM2, and PCOLCE, the most promising therapeutic target proteins for myopia and PM identified in the previous analyses. Subsequently, we calculated the binding energies between the predicted drug candidates and the protein complexes encoded by the target genes. The results showed that three drug candidates for each protein could successfully bind to their target proteins through hydrogen bonds and electrostatic interactions, occupying the binding pocket (Figure S4A∼I).

Next, we conducted MD simulations to evaluate the binding stability of these drug molecules with the three proteins. Root means square deviation (RMSD) is an essential indicator of the stability of protein-ligand complexes. As shown in Fig. 6A, the LRRTM2-D-mannitol, PDGFRA-propanediol, LRRTM2-cis-oleic acid, PCOLCE-17-β-estradiol, and LRRTM2-cis-9-octadecenoic acid complexes reached equilibrium after 98 ns, with RMSD fluctuations around 3.8 Å, 3.5 Å, 2.1 Å, 2.5 Å, and 2.8 Å, respectively. The PDGFRA-benzopyrene, PCOLCE-(7*E*)-9-hydroxymegastigma-4,7-dien-3-on-9-O-β-D-glucopyranoside_qt, PCOLCE-aldosterone, and PDGFRA-hexadecanoic acid complexes reached equilibrium at 40 ns, 75 ns, 40 ns, and 40 ns, respectively, with RMSD values fluctuating around 3.5 Å, 4.0 Å, 2.6 Å, and 3.0 Å, indicating that these small molecules bind stably to PDGFRA, LRRTM2, and PCOLCE. Further analyses of the radius of gyration (Rg) and solvent-accessible surface area (SASA) revealed that all complex systems exhibited stable structural compactness during the simulations (Figs. 6B, 6C). Hydrogen bond interactions are crucial in ligand-protein binding (Fig. 6D). During the simulations, LRRTM2-D-mannitol formed 0–9 hydrogen bonds (average of 4), PDGFRA-propanediol formed 0–4 hydrogen bonds (average of 2), and PCOLCE-17-β-estradiol formed 0–8 hydrogen bonds (average of 4). Other complexes also maintained 1–3 stable hydrogen bonds, suggesting predicted interactions between these small molecules and the target proteins. Root means square fluctuation (RMSF) analysis reflected the flexibility of protein residues (Fig. 6E). The RMSF values of all complex systems were generally low (mostly below 3 Å), indicating that the protein backbone remained stable, and the binding regions exhibited rigid structures. In summary, D-mannitol, propanediol, cis-oleic acid, 17-β-estradiol, cis-9-octadecenoic acid, benzopyrene, (7*E*)-9-hydroxymegastigma-4,7-dien-3-on-9-O-β-D-glucopyranoside_qt, aldosterone, and hexadecanoic acid formed stable

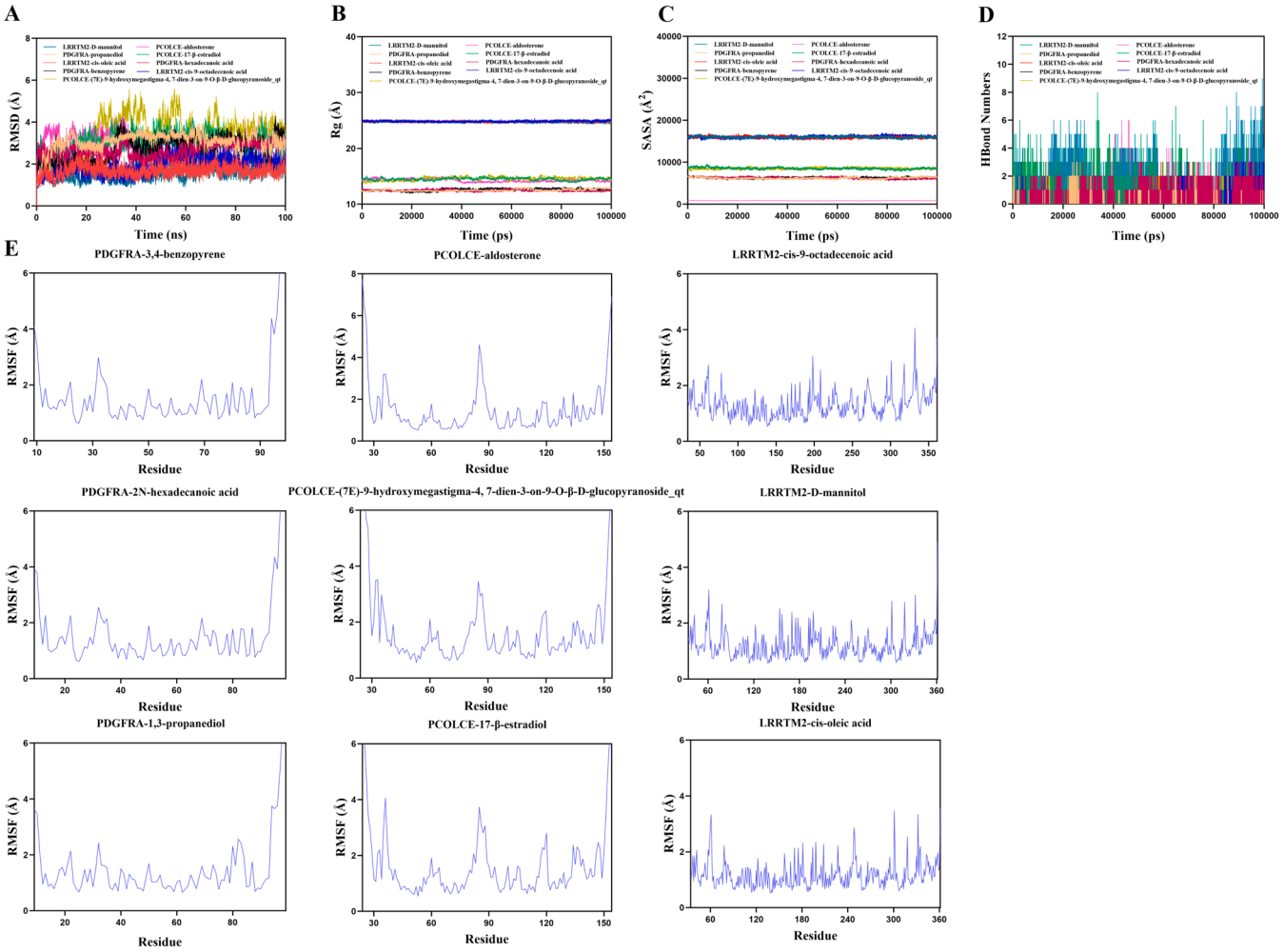

Fig. 6. Molecular dynamics simulations of selected protein variants, Time series plots of root mean square deviation (RMSD), radius of gyration (Rg), and hydrogen bond analysis for proteins carrying the identified genetic variants, indicating the structural stability and dynamic behavior of the mutant versus wild-type proteins.

interactions with PDGFRA, LRRTM2, and PCOLCE, demonstrating strong hydrogen bonding interactions and high binding stability. Although benzopyrene exhibited stable binding in docking and MD simulations, it is a well-recognized environmental toxicant and carcinogen.[34] On this basis, we excluded benzopyrene from consideration as a viable therapeutic candidate, and we focused subsequent interpretation on clinically relevant and low-toxicity compounds. Collectively, the docking and 100-ns MD simulations indicate predicted protein–ligand interactions with stable poses in silico. These results are hypothesis-generating and serve to prioritize targets and chemotypes for subsequent experimental validation, rather than establishing therapeutic efficacy.

4. Discussion

4.1. Principal findings

This study systematically explored the causal role of circulating proteins in myopia and PM using a multi-omics framework integrating MR, colocalization analysis, PPI networks, and metabolic pathway enrichment analysis. Among the identified proteins, PDGFRA, LRRTM2, and PCOLCE emerged as the most robust candidates with significant causal relationships and mechanistic relevance in ECM remodeling, synaptic plasticity, and metabolic regulation. These proteins were further validated through molecular docking and MD simulations, revealing stable interactions with bioactive small molecules and highlighting their potential as therapeutic targets. Our findings support the hypothesis that ECM remodeling, neurotransmission, and metabolic dysregulation play critical roles in myopia and PM progression. PDGFRA is involved in scleral fibroblast activation and ECM turnover, LRRTM2 modulates retinal neurotransmission, and PCOLCE regulates collagen processing and scleral integrity. Below, we discuss in detail how these proteins contribute to myopia pathogenesis.

Using complementary genetic and systems-level analyses, this study highlights PDGFRA, LRRTM2, and PCOLCE as candidates for further investigation in myopia and pathological myopia. In addition to these three proteins, our metabolite enrichment analysis also pointed to potential mechanisms underlying myopia. The enrichment of “caffeine metabolism” suggests potential links between adenosinergic signaling and ocular growth control, possibly via interactions with retinal dopaminergic pathways, choroidal perfusion, or light-dependent neuromodulation. Given the widespread dietary exposure and known pharmacology of adenosine receptor antagonists, these findings warrant targeted follow-up using exposure-informed MR and controlled experiments in retinal/ scleral models. Until such validation is available, the caffeine pathway signal should be interpreted as hypothesis-generating.

4.2. PDGFRA and ECM remodeling in myopia

PDGFRA is a key regulator of fibroblast proliferation,[35] ECM remodeling, and angiogenesis, and it is central to ocular growth control and scleral biomechanics.[36] In our MR analysis, increased PDGFRA levels were associated with a higher risk of myopia, suggesting that PDGFRA may play a role in excessive ECM degradation and axial elongation. PDGFRA is widely expressed in scleral fibroblasts and choroidal vascular endothelial cells, where it regulates collagen homeostasis and fibroblast-mediated ECM synthesis.[37] The sclera, primarily composed of type I collagen, proteoglycans, and glycosaminoglycans, undergoes continuous remodeling to adapt to visual demands.[38] In myopic eyes, excessive fibroblast activation leads to increased matrix metalloproteinase (MMP) activity, reducing collagen density and weakening scleral rigidity, thus promoting axial elongation.[39]

Another important aspect of PDGFRA-mediated signaling in myopia involves its crosstalk with TGF-β and PI3K-Akt signaling pathways.[40] TGF-β is a known modulator of ocular growth and ECM remodeling, and it is dysregulated in experimental myopia models.[41] PDGFRA activation induces PI3K-Akt signaling, which enhances fibroblast proliferation, ECM turnover, and collagen degradation, reinforcing myopia-related scleral changes.[42] The functional enrichment analysis in our study confirmed that PI3K-Akt signaling is significantly associated with myopia-related proteins, further supporting the role of PDGFRA-driven ECM remodeling in axial elongation.

Moreover, PDGFRA has been implicated in choroidal hypoxia and angiogenesis, which are emerging mechanisms in myopia development.[43] The choroid supplies oxygen and nutrients to the outer retina and sclera, and studies have shown that choroidal thinning and hypoxia contribute to scleral remodeling in myopic eyes. PDGFRA is essential for vascular endothelial cell proliferation, and its dysregulation could lead to compensatory angiogenesis, further exacerbating scleral ECM remodeling and axial elongation.[44]

Our molecular docking and MD simulations identified 1,3-Propanediol and 2n-Hexadecanoic Acid as promising small-molecule inhibitors of PDGFRA. 1,3-Propanediol, an antioxidant and anti-inflammatory agent, may help mitigate oxidative stress-induced ECM degradation, reducing collagen breakdown in the sclera.[45] Since oxidative stress promotes fibroblast-to-myofibroblast differentiation linked to scleral thinning, 1,3-Propanediol may preserve the scleral structure and limit progressive elongation.[46] 2n-Hexadecanoic Acid has been associated with lipid metabolism, an emerging factor in ECM stability.[47] Our metabolic enrichment analysis identified lipid biosynthesis pathways as significantly involved in myopia, suggesting lipid homeostasis plays a role in scleral remodeling. 2n-Hexadecanoic Acid may regulate fibroblast metabolism and ECM composition, helping stabilize scleral biomechanics and preventing excessive elongation. These findings suggest that PDGFRA-targeting compounds, such as 1,3-Propanediol and 2n-Hexadecanoic Acid, could help stabilize ECM homeostasis and slow myopia progression.

4.3. LRRTM2 and synaptic plasticity in myopia development

LRRTM2 plays a crucial role in synaptic organization, neurotransmission, and retinal signal processing, suggesting a strong link between neuronal activity and ocular growth regulation.[48,49] Our results indicate that increased LRRTM2 expression is associated with a higher risk of myopia, implying a potential role of LRRTM2 in promoting abnormal axial elongation. One of the significant pathways linking LRRTM2 to myopia is its role in retinal dopaminergic signaling. Dopamine is a well-established inhibitor of ocular elongation, and studies have shown that reduced dopamine release in myopic eyes leads to excessive axial growth.[50] LRRTM2 regulates glutamatergic synapse formation, essential for maintaining the balance between ON- and OFF-pathway activity in the retina.[48] Disruptions in retinal ON-OFF pathway signaling have been linked to myopia, with excessive ON-pathway activation promoting elongation.[51] Our findings suggest that increased LRRTM2 expression may destabilize the delicate balance of glutamatergic synapses, potentially leading to reduced dopaminergic output and impaired ocular growth control.

Additionally, LRRTM2 is involved in neuronal activity-dependent ocular growth regulation.[52] Studies have shown that light exposure increases dopamine release, inhibiting axial elongation.[53] However, excessive LRRTM2 expression may disrupt synaptic plasticity in response to visual stimuli, leading to altered neurotransmitter release and increased susceptibility to myopia.[49] Our study’s functional enrichment of myopia-associated proteins in neuroactive ligand-receptor interactions further supports the hypothesis that abnormal synaptic signaling contributes to myopia pathogenesis, possibly through LRRTM2-mediated synaptic modifications.

Another potential mechanism linking LRRTM2 to myopia involves its interactions with lipid metabolism and oxidative stress pathways.[54] Recent studies have highlighted that retinal lipid metabolism influences neurotransmission and photoreceptor function.[55] Our metabolic pathway analysis revealed enrichment of glycerophospholipid

metabolism and mitochondrial electron transport chain pathways in myopia, suggesting that LRRTM2 may contribute to oxidative stress responses and synaptic dysfunction through lipid dysregulation. The disruption of lipid homeostasis at the synapse could impair neurotransmission, exacerbating myopia progression.

Our molecular docking analysis identified Cis-9-Octadecenoic Acid as a strong LRRTM2-binding compound with potential therapeutic effects in myopia.[56] This neuroactive lipid may counteract the pro-myopic effects of LRRTM2 by stabilizing glutamatergic synapses, restoring neurotransmitter balance, and enhancing dopaminergic signaling, thereby preventing excessive ocular elongation. Additionally, our metabolic pathway analysis revealed enrichment of glycerophospholipid metabolism in myopia, supporting the idea that lipid signaling impacts neurotransmission and ocular growth control. By modulating lipid interactions at the synapse, Cis-9-Octadecenoic Acid may help normalize synaptic function, reduce ON-pathway overactivation, and restore dopamine-mediated inhibition of axial elongation, highlighting its potential as a novel therapeutic agent for myopia management.

4.4. PCOLCE and scleral biomechanics in myopia

PCOLCE is a major regulator of collagen processing and scleral biomechanical stability, which are critical factors in PM progression.[57] Our findings suggest that higher PCOLCE expression is associated with an increased risk of PM, indicating a role for PCOLCE in scleral collagen remodeling and biomechanical weakening. PCOLCE enhances the activity of procollagen C-proteinase, facilitating the maturation of type I collagen fibrils.[58] Increased collagen degradation and reduced fibril crosslinking in myopia lead to scleral thinning and biomechanical instability, promoting further axial elongation.[59] PCOLCE may mediate these effects by modulating collagen fibril organization and ECM stiffness, contributing to the progressive weakening of the sclera observed in high myopia and PM.

Furthermore, PCOLCE interacts with TGF-β and MMP signaling, key regulators of scleral remodeling in myopia.[60] TGF-β induced ECM degradation is a well-known feature of experimental myopia models.[61] Additionally, the KEGG enrichment results identified ECM-receptor interaction as a significant pathway associated with myopia, supporting the role of PCOLCE in ECM remodeling.

Our molecular docking analysis identified 17-Beta-Estradiol as a strong PCOLCE-binding compound, suggesting its potential to reinforce scleral collagen structure.[62] Estrogen is known to regulate ECM homeostasis, fibroblast function, and collagen crosslinking, which are crucial for scleral stability.[63] Additionally, PCOLCE interacts with TGF-β signaling, a major regulator of scleral fibroblast activity. Dysregulation of TGF-β signaling has been linked to myopia, particularly in ECM degradation.[64] By modulating TGF-β mediated collagen processing, 17-Beta-Estradiol may enhance scleral tensile properties and limit axial elongation in PM.

4.5. Future directions: drug development and delivery strategies

Further studies are needed to validate the efficacy of these small molecules in experimental models. Future research should focus on in vitro studies in scleral fibroblast and retinal neuronal cultures to assess their effects on ECM metabolism, neurotransmitter signaling, and collagen cross-linking. In addition, in vivo studies in animal models will be essential for evaluating pharmacokinetics, bioavailability, and therapeutic potential. Developing effective drug delivery methods is another important consideration. Topical eye drops may be viable for LRRTM2-targeting compounds that modulate neurotransmission. However, scleral-targeted therapies such as intravitreal injections or sustained-release implants may be more effective for ECM-stabilizing compounds like PDGFRA and PCOLCE inhibitors. Encapsulation in nanoparticle-based drug delivery systems could improve ocular penetration and provide sustained therapeutic effects, making it a promising approach for long-term myopia and PM treatment.

4.6. Study strengths and limitations

This study systematically integrates MR, colocalization analysis, PPI networks, metabolic pathway enrichment, and molecular docking simulations to explore the molecular mechanisms underlying myopia and PM. A significant strength is using genetic instruments from large-scale GWAS, minimizing confounding and reverse causation. Combining multi-omics data with functional enrichment and drug-target interaction analyses strengthens the biological relevance of the identified proteins PDGFRA, LRRTM2, and PCOLCE, highlighting their roles in ECM remodeling, neurotransmission, and scleral collagen stability. Furthermore, molecular docking and MD simulations validate potential therapeutic candidates, providing a translational perspective for future drug development.

5. Study limitations

5.1. Ocular tissue specificity

Our instruments were predominantly derived from whole-blood pQTL/eQTL resources, whereas the primary disease tissues for myopia/PM include sclera, retina, and choroid. This discordance can dilute tissue-relevant signals. Future analyses should integrate retina/sclera RNA-seq-based eQTLs or ocular proteomics, perform tissue-weighted MR, and validate colocalization within ocular LD intervals. Single-cell expression and chromatin-accessibility maps from ocular tissues will further refine target assignment to disease-relevant cell types.

5.2. Population ancestry and generalizability

Most exposure and outcome summary statistics leveraged in this study were derived from cohorts enriched for European ancestry due to data availability and sample size. This may attenuate transferability of effect estimates to high-prevalence regions such as East Asia, where LD structure, allele frequencies, and gene–environment interplay differ. To mitigate over-interpretation, we treat cross-ancestry extrapolation as hypothesis-generating and outline the following priorities for future work: (i) replicate proteome-wide and transcriptome-wide MR and colocalization in East Asian cohorts; (ii) implement trans-ethnic colocalization/fine-mapping to reduce LD-driven conflation; and (iii) compare instrument strength and causal effect sizes across ancestries using harmonized phenotypes. These steps are essential before any clinical translation across populations.

5.3. Adult derived pQTL instruments and extrapolation to childhood myopia

Our pQTL instruments were mainly obtained from adult and older cohorts. MR estimates the effect of lifelong genetic liability on myopia and PM risk, and in principle does not depend on the age at measurement. However, if target proteins show age or tissue specific regulation, cross age effect sizes may be weakened, which limits extrapolation to childhood myopia. To reduce this uncertainty, we prioritized cis pQTL instruments and applied colocalization, and we interpret the findings as hypothesis generating. Future work should replicate results in pediatric or age stratified datasets and in ocular tissue specific resources, and also use gene by age analyses and robust MR methods to assess consistency.

6. Conclusions

Using complementary genetic and systems-level analyses, this study highlights PDGFRA, LRRTM2, and PCOLCE as candidates for further

investigation in myopia and PM. MR and colocalization support possible roles in ECM remodeling, retinal neurotransmission, and scleral biomechanics. Docking and MD simulations suggest chemotypes such as 1,3-Propanediol, Cis-9-Octadecenoic Acid, and 17-Beta-Estradiol that warrant prioritization, but these results remain hypothesis-generating and do not establish therapeutic efficacy. Future work should include cell-based and in vivo validation, exploration of target modulation, and delivery strategies to assess translational potential.

Ethics approval and consent to participate

The study received approval from the Ethics Review Board of Tianjin Eye Hospital (No. KY-2023WJW011).

Authors contributions

Original draft writing, Jingwen Hui and Xuehao Cui. Data analysis, Xuehao Cui and Jingwen Hui. Idea: Xuehao Cui and Quanhong Han. Scheme design: Xuehao Cui and Quanhong Han, Manuscripts review, Jingwen Hui and Quanhong Han. All authors read and approved of the final manuscript.

Consent for publication

All authors have read and approved the final version of this manuscript for submission and publication.

Informed consent

Not applicable.

Data sources and software URLs

FinnGen R12 (https://r12.finngen.fi); UK Biobank (https://www.ukbiobank.ac.uk); ARIC (https://www2.cscc.unc.edu/aric/); deCODE genetics (https://www.decode.com); GTEx Portal (https://gtexportal.org); eQTLGen (https://www.eqtlgen.org); OpenGWAS (https://gwas.mrcieu.ac.uk); STRING (https://string-db.org); KEGG (https://www.kegg.jp); HMDB (https://hmdb.ca); AutoDock Vina/AutoDock Tools (http://autodock.scripps.edu);

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Competing interests

All the authors declare no interest conflicts among them.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.apjo.2026.100277.

Data availability

The data presented in this study are available in this article and supplementary materials.

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