Diabetology & Metabolic Syndrome

RESEARCH

Open Access

Identifying therapeutic target genes for diabetic retinopathy using systematic druggable genome-wide Mendelian randomization

Long Xie[1*], Yu Qin Peng[2] and Xiang Shen[1]

Abstract

Introduction The treatment and prevention of diabetic retinopathy (DR) remain significant challenges. Mendelian randomization (MR) has been widely used to explore novel therapeutic targets. In this study, we conducted a systematic druggable genome-wide MR analysis to explore potential therapeutic targets for DR.

Methods We obtained data on druggable genes and screened for genes within blood expression quantitative trait loci (eQTL), which were then subjected to MR analysis and colocalization analysis with DR genome-wide association studies data to identify genes strongly associated with DR. Additionally, Gene Ontology (GO) analysis, Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis, protein-protein interaction (PPI) network construction, drug candidate prediction, and molecular docking were performed to provide valuable insights for the development of more effective and targeted therapeutic drugs.

Results MR analysis of blood eQTLs revealed 30 significant DR-associated druggable genes, with *PRKAB1* (OR = 0.935, 95% CI: 0.892 to 0.980) and *CNR1* (OR = 0.814, 95% CI: 0.696 to 0.951) being protective genes, whereas *CACNA1E* (OR = 1.282, 95% CI: 1.050 to 1.565), *NME1* (OR = 1.198, 95% CI: 1.028 to 1.397), and *CHRNA2* (OR = 1.192, 95% CI: 1.025 to 1.386) were associated with increased risk. KEGG analysis highlighted significant pathways, including adrenergic signaling in cardiomyocytes (hsa04261), the oxytocin signaling pathway (hsa04921), and arrhythmogenic right ventricular cardiomyopathy (hsa05412). PPI network analysis identified two key modules: one comprising *BIN1*, *CDH2*, *ACTN1*, *EPAS1*, *CEBPA*, and *CTSD* nodes, and the other consisting of *CACNG6*, *CACNA1E*, *CACNA2D3*, and *RASGRP3* nodes. Drug candidate prediction suggested ethanol and isoflupredone as potential therapeutic interventions, and molecular docking revealed C5's strong protein binding affinity.

Conclusions This study utilized MR and colocalization analysis to identify potential drug targets for DR. The findings provide promising leads for the treatments of DR, potentially reducing drug development costs.

Keywords Diabetic retinopathy, Mendelian randomization, GWAS, Druggable target genes

*Correspondence:
Long Xie
longxie_2020@163.com
[1]Department of Orthopedics, The Fourth Hospital of Changsha (Integrated Traditional Chinese and Western Medicine Hospital of Changsha), Hunan Normal University, Changsha, Hunan Province 410006, China
[2]Department of Ophthalmology, The Fourth Hospital of Changsha (Integrated Traditional Chinese and Western Medicine Hospital of Changsha), Hunan Normal University, Changsha, Hunan Province 410006, China

Introduction

Diabetes mellitus (DM) has emerged as a significant global health concern due to its increasing prevalence and associated complications [1]. Nearly half of individuals with type 2 diabetes mellitus (T2DM) eventually develop diabetic microvascular complications (DMCs), with diabetic retinopathy (DR) being the most common manifestation. These complications can lead to irreversible damage, including vision impairment, disability, and increased mortality [2]. Therefore, identifying effective treatments for DR is crucial for early prevention and intervention.

The management and prevention of DR present considerable challenges. Although novel pharmacological agents have been introduced, offering substantial benefits to patients, issues such as adverse effects and suboptimal response rates persist. Recent advancements in genetic research related to DR have identified numerous potential targets for drug development. However, substantial challenges impede the translation of these genetic discoveries into clinical applications. Although genome-wide association studies (GWAS) have identified various loci associated with DR, there is a significant gap in understanding the tissue-specific expression patterns of these genes, particularly in retinal endothelial cells. This lack of comprehensive knowledge severely limits the clinical utility of these genetic insights [3]. Additionally, the functional roles of many identified genes remain unclear, as most MR analyses have concentrated on genes linked to well-established metabolic pathways, such as VEGF signaling. Meanwhile, emerging factors like epigenetic regulators, including histone deacetylases, remain largely unexplored, despite their potential contributions to the progression of DR [4].Consequently, there is a pressing need to explore potential therapeutic targets for DR. Integrating genetic insights into drug development may offer innovative strategies. While GWAS have proven effective in identifying single nucleotide polymorphisms (SNPs) linked to DR risk [5], they often fall short of identifying causative genes or facilitating drug development without extensive downstream analyses.

Mendelian randomization (MR) is a robust analytical approach that leverages genetic variation as instrumental variables (IVs) to establish causal relationships between exposures and outcomes [6]. This analytical method has gained prominence in identifying novel therapeutic targets by integrating data from disease GWAS and expression quantitative trait loci (eQTL) studies [7]. A fundamental element of this methodology is the employment of eQTLs within the genomic regions of druggable genes. These eQTLs are frequently considered suitable proxies in this particular context, given that gene expression levels can be construed as a reflection of lifelong exposure to the effects of these genes [8]. This rationale underlies the frequent use of eQTLs of druggable genes as IVs in MR studies [8, 9]. In this study, we conducted a systematic druggable genome-wide MR analysis to identify potential therapeutic targets for DR. Initially, we compiled a comprehensive dataset of druggable genes and screened for those within blood eQTLs. These genes were subsequently analyzed using two-sample MR alongside DR GWAS data to identify those significantly associated with the disorder. To ensure the robustness of our findings, we performed a colocalization analysis. Additionally, we conducted enrichment analysis and constructed a protein-protein interaction network for all significant genes, offering valuable insights into their biological processes and regulatory mechanisms. Finally, we predicted potential candidate drugs and performed molecular docking studies, offering promising leads for the development of more effective and targeted therapeutic agents for DR.

Methods

An overview of this study is presented in Fig. 1. Ethics approval was not required for the study. The paper was prepared per the STrengthening the Reporting of Observational Studies in Epidemiology-MR (STROBE-MR) checklist for the study (Supplementary Material Table S1).

DGIdb: Drug-Gene Interaction Database; eQTL: expression quantitative trait loci; GWAS: genome-wide association studies; PPI: protein–protein interaction; DSigDB: Drug Signatures Database.

Druggable genes

Druggable genes were obtained from the Drug-Gene Interaction Database (DGIdb) (https://dgidb.org/) [10]. The DGIdb provides valuable information regarding drug-gene interactions and the potential for druggability. Specifically, we accessed the "Categories Data" from DGIdb, which was last updated in February 2022. Additionally, we included a list of druggable genes from a review by Finan et al. [11]. By integrating data from these two sources, we compiled a more comprehensive list of druggable genes, which has been employed in previous studies [12, 13].

eQTL datasets

The blood eQTL dataset was sourced from eQTLGen (https://eqtlgen.org/), which provided cis-eQTLs for 16,987 genes based on data from 31,684 blood samples collected from healthy individuals of European ancestry [9]. We selected cis-eQTL results that met a strict false discovery rate (FDR) threshold of less than 0.05 and included allele frequency data. All eQTLs meeting this FDR criterion were downloaded for genes with expression levels exceeding 0.1 fragments per kilobase per

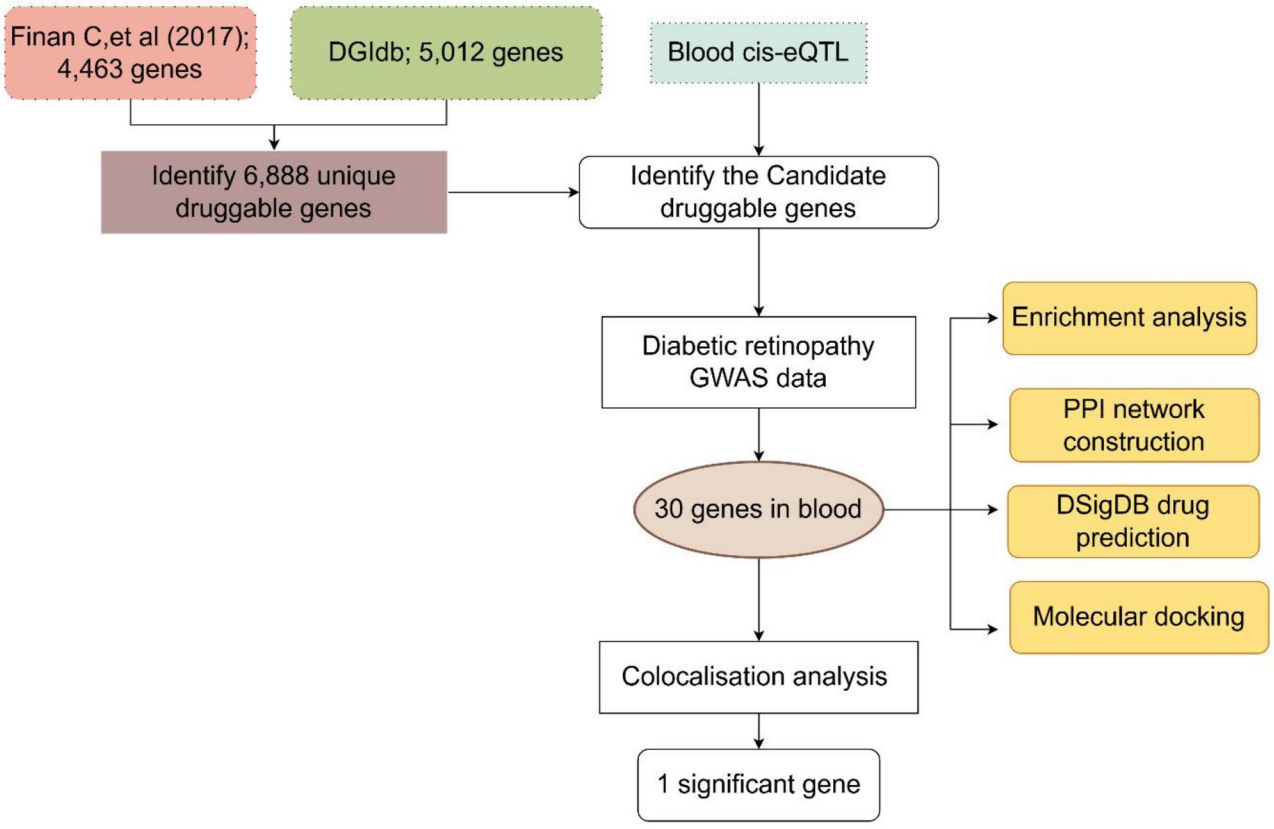

Fig. 1 Overview of this study design

Table 1 The details of eQTL and GWAS used in the study

Dataset	Sample size	Ancestry	Consortium	Web link
The blood cis-eQTL	31,684	European	eQTLGen	https://eqtlgen.org/
Diabetic retinopathy GWAS	12,681 cases and 71,596 controls	European	NA	https://r11.finngen.fi/pheno/DM_RETINOPATHY

million mapped reads in at least 10 samples. Additionally, complete SNP details were retrieved (Table 1).

Diabetic retinopathy GWAS dataset and SNP selection

Summary data on the association between SNPs and DR were extracted from the FinnGen consortium released on June 24, 2024 (https://r11.finngen.fi/) [14]. The GWAS of DR included 12,681 cases and 71,596 controls, all of European ancestry. For SNPs associated with druggable genes that were absent in the DR GWAS, proxy SNPs in strong linkage disequilibrium ($R^2 > 0.8$) were identified and included. A weak instrument, indicated by an F-value below 10, was excluded [15]. The exposure-outcome dataset was harmonized to exclude palindromic SNPs.

MR analysis

MR analyses were conducted using the "TwoSampleMR" package (version 0.5.7) in R [16]. The eQTLs of the druggable genome served as the exposure data. For IV construction, SNPs with an FDR below 0.05 and located within ± 100 kb of each gene's transcriptional start site (TSS) were selected. These SNPs were subsequently clumped at an R^2 threshold of less than 0.001 using European population data from the 1000 Genomes Project [17]. The R package "pheno-scanner" (version 1.0) was employed to identify phenotypes related to the IVs [18]. SNPs directly linked to DR or traits directly associated with it were excluded. The remaining SNPs were harmonized before MR analyses. For cases with only one SNP available, the Wald ratio method was used for MR estimation. When multiple SNPs were available, MR analysis was performed using the inverse-variance weighted (IVW) method with random effects [19]. Cochran's Q test was applied to evaluate heterogeneity among the causal effects of the SNPs [20]. while MR Egger's intercept was used to assess SNP pleiotropy [21]. P-values were adjusted using the FDR method, with 0.05 set as the significance threshold. The study conducted sensitivity analyses using the "leave-one-out" approach to assess

the robustness of the MR results [22]. Furthermore, target genes associated with medications commonly used to treat DR were selected, and their MR results were compared with those of significantly druggable genes.

Colocalization analysis

A single SNP may be located in the regions of multiple genes, meaning its effect on DR could be influenced by various genetic factors. To address this, colocalization analysis was performed to confirm shared causal genetic variations between DR and eQTLs at the same physical location. We specifically filtered SNPs located within ± 100 kb of each DR risk gene's TSS using data from DR GWAS [7] and blood eQTL datasets. The probability of an SNP being associated with DR was denoted as P1, the probability of an SNP being a significant eQTL as P2, and the probability of an SNP being both associated with DR and a significant eQTL as P12. Default probability values were applied: $P1 = 1 \times 10^{-4}$, $P2 = 1 \times 10^{-4}$, and $P12 = 1 \times 10^{-5}$ [23]. Posterior probabilities (PPs) were calculated to evaluate support for the following hypotheses: PPH0, SNP is unrelated to either trait; PPH1, SNP is related to gene expression but not to DR risk; PPH2, SNP is linked to DR risk but not to gene expression; PPH3, SNP is associated with both DR risk and gene expression, with clear causal variation; and PPH4, SNP is linked to both DR risk and gene expression, sharing a common causal variant. Given the limited capacity of colocalization analysis, we restricted our subsequent analyses to genes where PPH4 was greater than or equal to 0.75. Colocalization analysis was conducted using the R package "coloc" (version 5.2.3) [24].

Enrichment analysis

To investigate the functional characteristics and biological relevance of the predetermined prospective druggable genes, we utilized the R package "clusterProfiler" (version 4.10.1) to perform Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses [25]. The GO analysis encompassed three categories: Biological Process (BP), Molecular Function (MF), and Cellular Component (CC), which provide insights into gene functions and their roles in biological systems. KEGG pathway analysis offered information about metabolic.

PPI network construction

PPI networks were constructed to visually represent the relationships between the interactions of proteins encoded by significant druggable genes. These networks were generated using the STRING database (https://cn.string-db.org/) with a minimum required interaction confidence score set at 0.4. All other parameters were kept at their default settings to ensure consistency in the analysis.

Candidate drug prediction

The Drug Signatures Database (DSigDB, https://dsigdb.tanlab.org/DSigDBv1.0/) [26] is a sizable database containing 22,527 gene sets and 17,389 unique compounds associated with 19,531 genes. We uploaded previously identified significant druggable genes to DSigDB to predict candidate drugs and evaluate the pharmacological activity of target genes.

Molecular docking

Molecular docking was performed to evaluate the binding energies and interaction patterns between candidate drugs and their target proteins. This approach enabled the identification of ligands with high binding affinity and favorable interaction characteristics, which were then prioritized for further experimental validation and optimization in drug design. Drug structural data were sourced from the PubChem Compound Database (https://pubchem.ncbi.nlm.nih.gov/) [27] and downloaded in SDF format. These files were converted to pdb format using OpenBabel 2.4.1. Protein structural data were downloaded from the Protein Data Bank (PDB, https://www.rcsb.org/) [28]. The top five candidate drugs and their corresponding protein targets, encoded by significant genes, underwent molecular docking analysis using the CB-Dock2 online platform (https://cadd.labshare.cn/cb-dock2/index.php) [29].

Results

Druggable genome

A total of 5,012 druggable genes were identified from the DGIdb. In addition, 4,479 druggable genes were retrieved from prior literature reviews. By integrating these datasets, we compiled 6,888 unique druggable genes, all of which were annotated by the Human Genome Organization Gene Nomenclature Committee (HGNC). These genes were used for subsequent analyses (Table S2).

Candidate druggable genes

After intersecting blood eQTLs with druggable genes, 3,460 gene symbols were identified. MR analysis was conducted on these genes, resulting in the identification of 30 significant genes associated with DR (Fig. 2A). Protective genes were defined as those with odds ratios (OR) less than 1, indicating a potential reduction in the risk of developing a particular condition. For instance, genes such as *PRKAB1* (OR = 0.935, 95% CI: 0.892 to 0.980) and *CNR1* (OR = 0.814, 95% CI: 0.696 to 0.951) exhibited significant protective associations, as their confidence intervals exclude 1 and their p-values (0.005 and 0.010, respectively) indicate statistical significance. Conversely,

A

exposure	nsnp	method	pval	OR(95% CI)
PRKAB1	4	Inverse variance weighted	**0.005**	0.935 (0.892 to 0.980)
CNR1	2	Inverse variance weighted	**0.010**	0.814 (0.696 to 0.951)
ACTBP8	2	Inverse variance weighted	**0.012**	0.915 (0.854 to 0.981)
CHIT1	2	Inverse variance weighted	**0.012**	0.842 (0.735 to 0.963)
EPAS1	2	Inverse variance weighted	**0.015**	1.282 (1.050 to 1.565)
CTSD	2	Inverse variance weighted	**0.018**	0.789 (0.648 to 0.960)
SYNE3	2	Inverse variance weighted	**0.021**	1.198 (1.028 to 1.397)
CACNA2D3	2	Inverse variance weighted	**0.022**	0.898 (0.819 to 0.985)
ACTN1	2	Inverse variance weighted	**0.023**	1.192 (1.025 to 1.386)
CDH2	2	Inverse variance weighted	**0.023**	1.176 (1.023 to 1.352)
CEBPA	2	Inverse variance weighted	**0.024**	0.829 (0.704 to 0.976)
PPP2R5D	2	Inverse variance weighted	**0.026**	0.837 (0.716 to 0.979)
CACNA1E	2	Inverse variance weighted	**0.029**	0.882 (0.788 to 0.987)
SERPINB8	3	Inverse variance weighted	**0.031**	1.045 (1.004 to 1.087)
GALNT1	2	Inverse variance weighted	**0.032**	1.109 (1.009 to 1.218)
CAMK2D	4	Inverse variance weighted	**0.034**	1.087 (1.006 to 1.174)
LAMP3	2	Inverse variance weighted	**0.036**	0.836 (0.707 to 0.988)
MPI	2	Inverse variance weighted	**0.036**	1.082 (1.005 to 1.165)
VSIR	2	Inverse variance weighted	**0.038**	1.170 (1.008 to 1.357)
GGH	2	Inverse variance weighted	**0.039**	1.132 (1.006 to 1.274)
SDC2	2	Inverse variance weighted	**0.040**	1.231 (1.010 to 1.501)
CPD	2	Inverse variance weighted	**0.040**	0.932 (0.871 to 0.997)
SENP7	2	Inverse variance weighted	**0.042**	0.962 (0.927 to 0.999)
TGM1	2	Inverse variance weighted	**0.043**	0.915 (0.839 to 0.997)
CACNG6	2	Inverse variance weighted	**0.043**	1.177 (1.005 to 1.379)
NME1	3	Inverse variance weighted	**0.044**	1.058 (1.001 to 1.119)
SEMA3A	3	Inverse variance weighted	**0.045**	1.136 (1.003 to 1.287)
CHRNA2	2	Inverse variance weighted	**0.046**	1.191 (1.003 to 1.414)
BIN1	4	Inverse variance weighted	**0.047**	1.057 (1.001 to 1.117)
RASGRP3	2	Inverse variance weighted	**0.049**	1.117 (1.000 to 1.248)

B

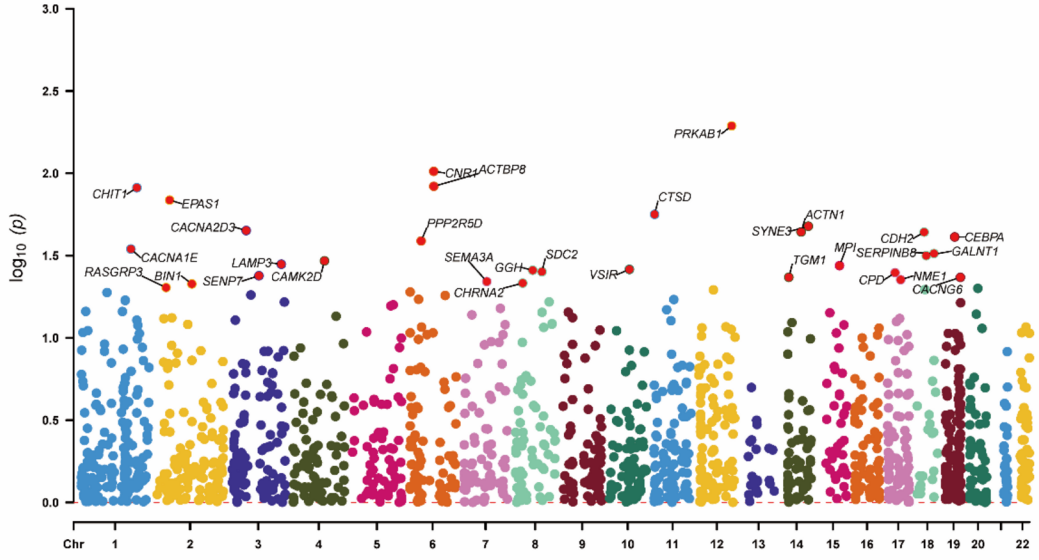

Fig. 2 Forest plot of 30 significant DR-associated genes identified by MR analysis, highlighting protective (e.g., *PRKAB1*, *CNR1*) and risk (e.g., *CACNA1E*) candidates with FDR < 0.05 (**A**). Manhattan plot of DR-related genes in blood (**B**)

risk genes were defined as those with OR greater than 1, suggesting an increased likelihood of disease development. For example, *CACNA1E* exhibited an OR of 1.282 (95% CI: 1.050 to 1.565) with a p-value of 0.015, indicating a significant association with increased risk of DR. Similarly, *NME1* (OR = 1.198, 95% CI: 1.028 to 1.397) and *CHRNA2* (OR = 1.192, 95% CI: 1.025 to 1.386) demonstrated significant risk associations, with confidence intervals excluding 1. The Manhattan plot is presented in Fig. 2B. Detailed results for the significant IVs of MR are available in Table S3. We have performed comprehensive sensitivity analyses (leave-one-out MR, MR-Egger, and MR-PRESSO), confirming the stability of associations (detailed in Supplementary Table S4), with no evidence of pleiotropy or influential outliers.

Enrichment analysis

GO analysis of the 30 potential targets revealed their involvement in BP such as regulation of calcium ion transmembrane transport via high voltage-gated calcium channels (GO: 1902514), calcium ion transmembrane transport via high voltage-gated calcium channels (GO: 0061577), regulation of action potential (GO: 0098900), and regulation of endopeptidase activity (GO: 0052548). The main MF included voltage-gated calcium channel activity (GO: 0005245), calcium channel activity (GO: 0005262), and gated channel activity (GO: 0022836). The main CC included sarcolemma (GO: 0042383), voltage-gated calcium channel complex (GO: 0005891), and tertiary granule lumen (GO: 1904724) (Fig. 3A). To explore the potential therapeutic pathways of DR-associated significant druggable genes, KEGG analysis was performed. The results indicated that the target genes were primarily enriched in pathways such as adrenergic signaling in cardiomyocytes (hsa04261), oxytocin signaling pathway (hsa04921), and arrhythmogenic right ventricular cardiomyopathy (hsa05412) (Fig. 3B).

PPI network construction

The PPI network was constructed using a minimum required interaction score of 0.400 (low confidence). Based on the interplay among 30 significant genes, the PPI network was found (Fig. 4A). Using the MCODE plugin in Cytoscape, two significant modules were identified within the PPI network based on their relative relevance. The two modules identified using the MCODE plugin are shown in Fig. 4B and included *BIN1*, *CDH2*, *ACTN1*, *EPAS1*, *CEBPA*, and *CTSD* nodes; Fig. 4C shows the *CACNG6*, *CACNA1E*, *CACNA2D3*, and *RASGRP3* nodes.

Candidate drug prediction and colocalization analysis

We used DSigDB to predict potentially effective intervention drugs and ranked the top 10 based on their adjusted p-values (Table 2). The results indicated that *ethanol* and *isoflupredone* were the two most significant drugs and were associated with *CNR1*, *CDH2*, *CEBPA*, *GGH*, *NME1*, *BIN1*, *SDC2*, *CPD*, and *BIN1*. To further explore these associations, a gene-drug interaction network was constructed, providing a comprehensive visualization of the relationships between the significant genes and the candidate drugs (Fig. 5). The results indicated that, of the previously identified 30 significant genes from blood, one gene had a PPH4 greater than 0.75 (Table 3).

Top predicted drugs: ethanol (targeting *CNR1*, *BIN1*) and isoflupredone (targeting *SDC2*, *CPD*). Edge thickness reflects binding affinity strength.

PPH0-PPH4 represent the posterior probabilities of different hypotheses, and PPH4 > 0.75 was considered as a significant colocalization result.

Molecular docking

This study employed molecular docking to evaluate the binding affinities of drug candidates to their respective targets and, consequently, to assess the druggability of the target proteins. The CB-Dock2 platform (https://cadd.labshare.cn/cb-dock2/php/index.php) was used to analyze the binding sites and interactions between the top five candidate drugs and the proteins encoded by the corresponding genes, generating the binding energy for each interaction. The docking results yielded eight effective interactions between the drugs and proteins, with the corresponding binding energies detailed in Table 4. Figure 6 illustrates the docking amino acid residues and hydrogen bond lengths for these interactions. Notably, previous studies have identified C5 as exhibiting the lowest binding energy (− 5 kcal/mol), which signifies highly stable binding interactions [30].

The lower the Binding energy, the better the binding effect and the higher the affinity.

Discussion

This study identified 30 unique druggable genes significantly associated with DR. Among these, genes such as *PRKAB1* and *CNR1* exhibited protective effects, indicating a reduced risk of developing DR, whereas genes like *CACNA1E*, *NME1*, and *CHRNA2* were associated with an increased risk. These findings provide crucial insights into the molecular mechanisms underlying DR and highlight potential therapeutic targets. Functional enrichment analysis revealed that these key genes are primarily involved in biological processes such as the regulation of calcium ion transmembrane transport, action potential regulation, and endopeptidase activity regulation. Furthermore, KEGG pathway analysis revealed that these genes are enriched in pathways related to adrenergic signaling in cardiomyocytes, oxytocin signaling, and arrhythmogenic right ventricular cardiomyopathy,

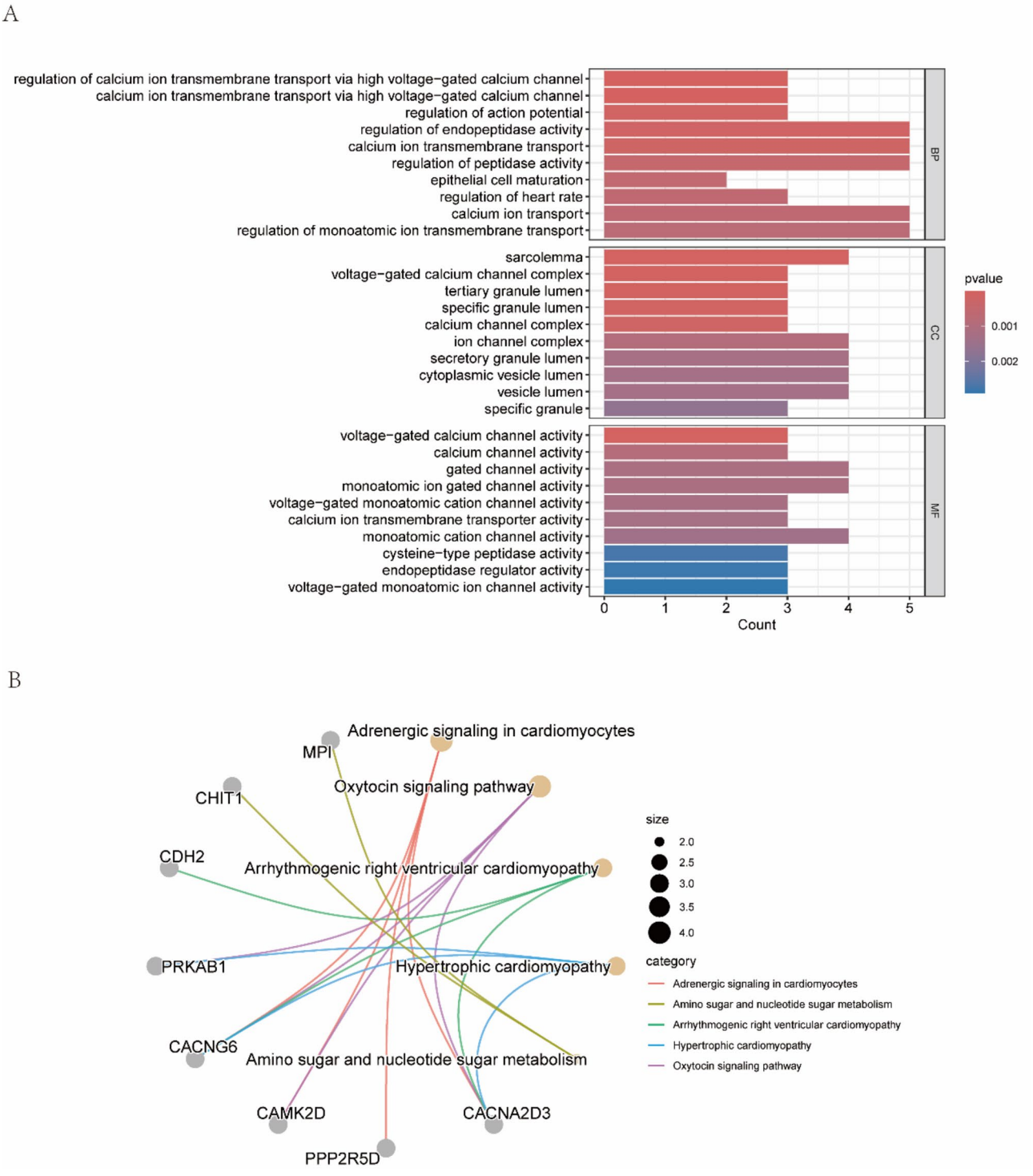

Fig. 3 The GO and KEGG enrichment analysis of the 30 genes from a cis-eQTL perspective in the MR analysis. **(A)** GO terms (BP: calcium transport; MF: voltage-gated channel activity). **(B)** KEGG pathways (adrenergic signaling, oxytocin signaling). Pathways directly linked to DR vascular dysfunction and inflammation

offering new perspectives for potential therapeutic interventions in DR.

The relationship between gene polymorphism and DR has been a subject of considerable interest in recent studies, underscoring the potential genetic underpinnings of this condition. Research reveals that specific gene polymorphisms are closely linked to the onset and progression of DR. For instance, polymorphisms in the

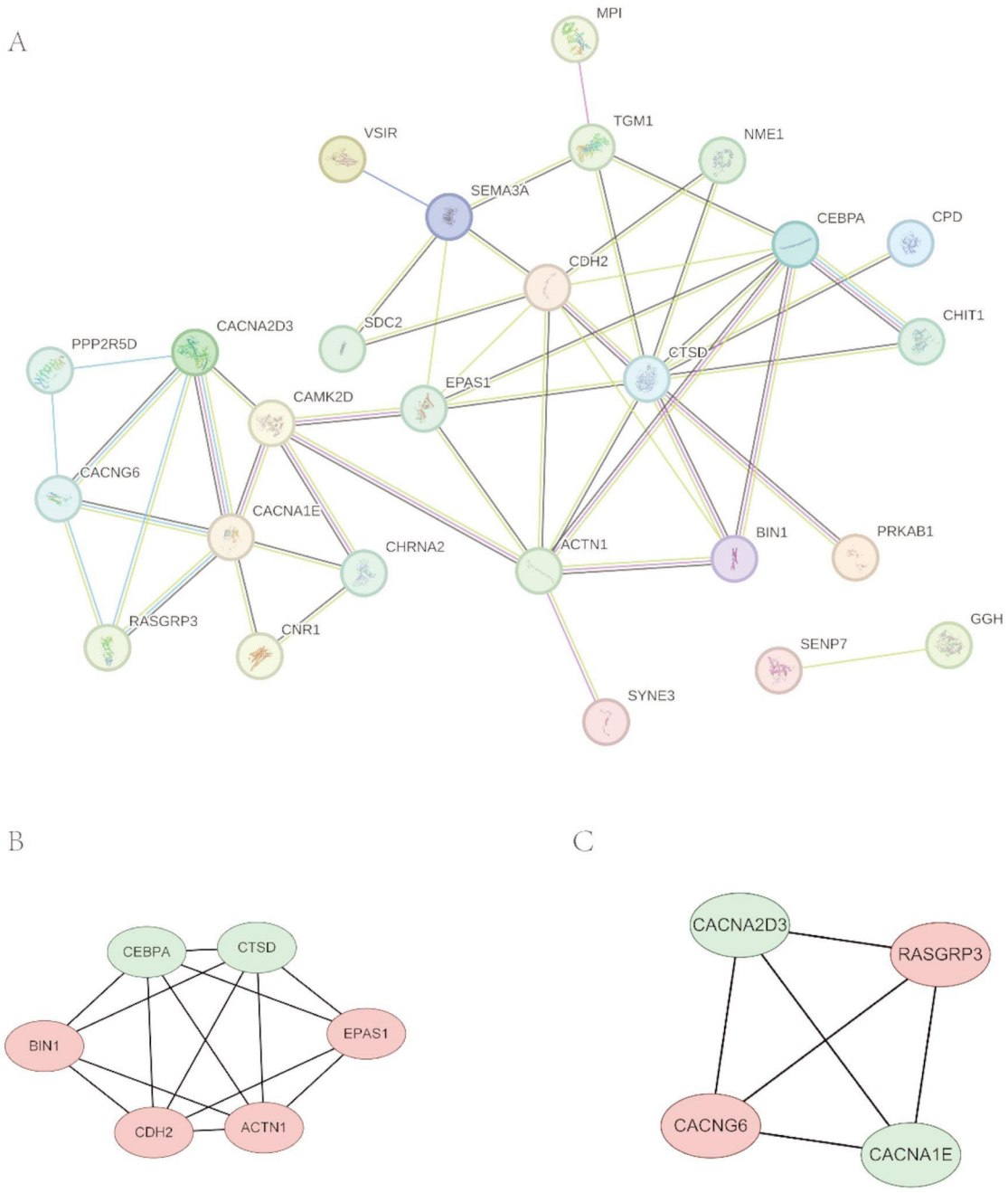

Fig. 4 Protein-protein interaction (PPI) network analysis: **(A)** Full network of 30 genes. **(B)** Module 1 (*BIN1*, *CDH2*, *ACTN1*): cytoskeletal regulation and endothelial integrity. **(C)** Module 2 (*CACNA1E*, *CACNG6*): calcium signaling and vascular contraction

Table 2 Candidate drug predicted by DsigDB

Drug name	pvalue	*p*.adjust	genes ID	Count
ethanol	1.62E-05	0.009073	CNR1/CDH2/CEBPA/GGH/NME1/BIN1	6
isoflupredone	0.000262	0.03466	SDC2/CPD/BIN1	3
GNF-Pf-2272	0.000329	0.03466	EPAS1/MPI/SENP7	3
Apomorphine hydrochloride	0.000366	0.03466	CNR1/GGH	2
Toxoflavin	0.000371	0.03466	EPAS1/MPI/SENP7	3

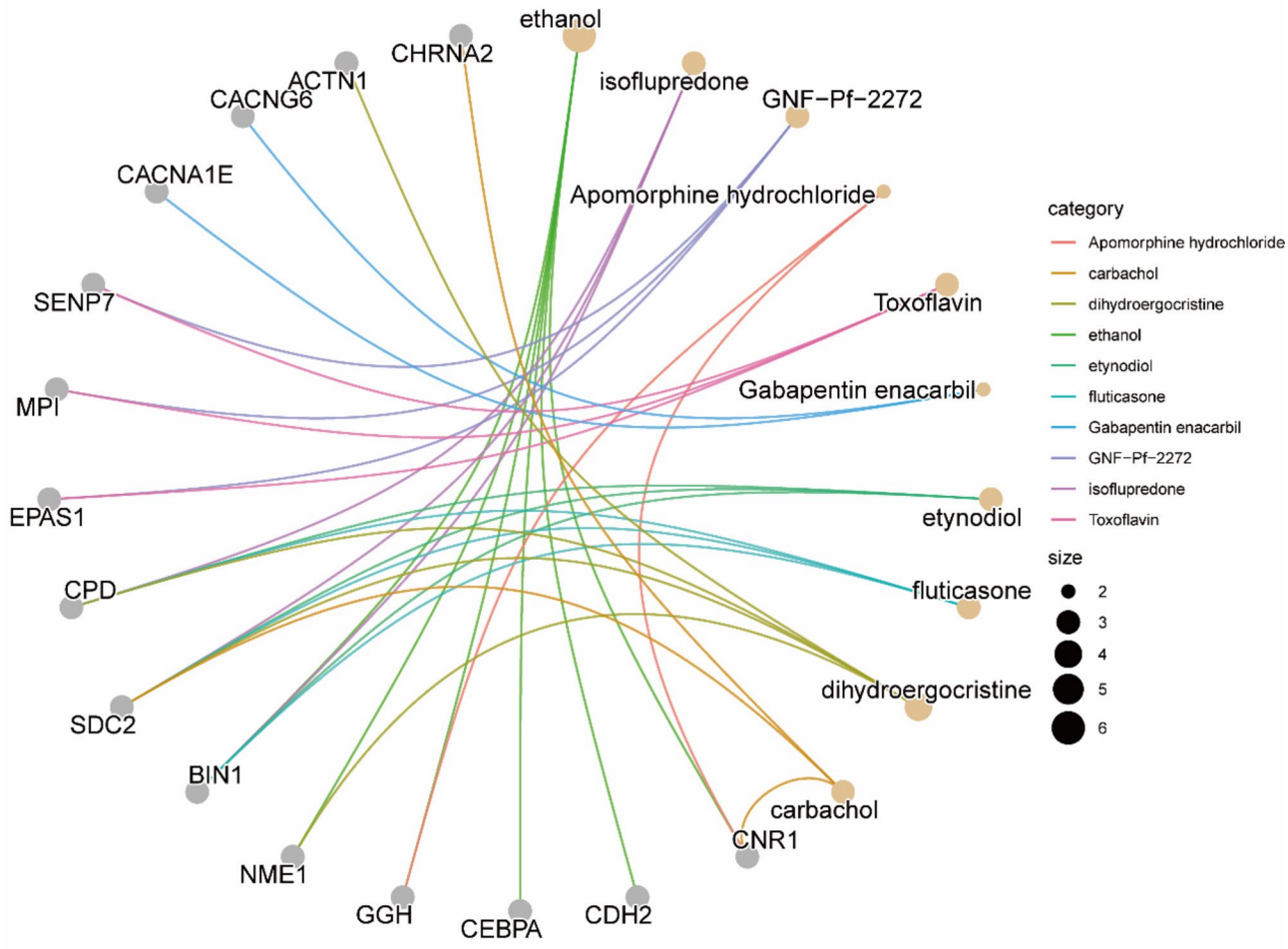

Fig. 5 Gene-Drug Interaction Network

Table 3 Colocalization results of one significant gene from blood

ID	Symbol		PP.H0	PP.H1	PP.H2	PP.H3	PP.H4
eqtl-a-ENSG00000170558	*CDH2*		0	0.100	0	0.047	0.852

Table 4 Molecular Docking results of available proteins and drugs

Target	PDB ID	Drug	PubChem ID	Binding energy(kcal/mol)
CNR1	8WU1	Apomorphine hydrochloride	9410	-9.8
BIN1	5I22	ethanol	702	-19.3
EPAS1	8CK8	GNF-Pf-2272	460,747	-5.3
SENP7	7R2E	GNF-Pf-2272	460,747	-5.9
BIN1	5I22	isoflupredone	127,516	-74.1
SDC2	6ITH	isoflupredone	127,516	-50.8
EPAS1	8CK8	Toxoflavin	66,541	-5.0
SENP7	7R2E	Toxoflavin	66,541	-5.9

erythropoietin gene have been associated with an elevated risk of developing DR [31], whereas variations in the tumor necrosis factor (*TNF*) gene are also implicated in its pathogenesis [32]. These findings underscore the importance of understanding the genetic background of DR, potentially paving the way for the development of targeted treatment strategies. In addition to gene polymorphisms, gene expression analysis has identified several genes that may play crucial roles in the pathophysiology of DR. Notable examples include *ARHGAP22*, *ICAM-1*, *VCAM-1*, *eNOS*, *UCP2*, and *LEF1*, whose expression levels correlate with both the development

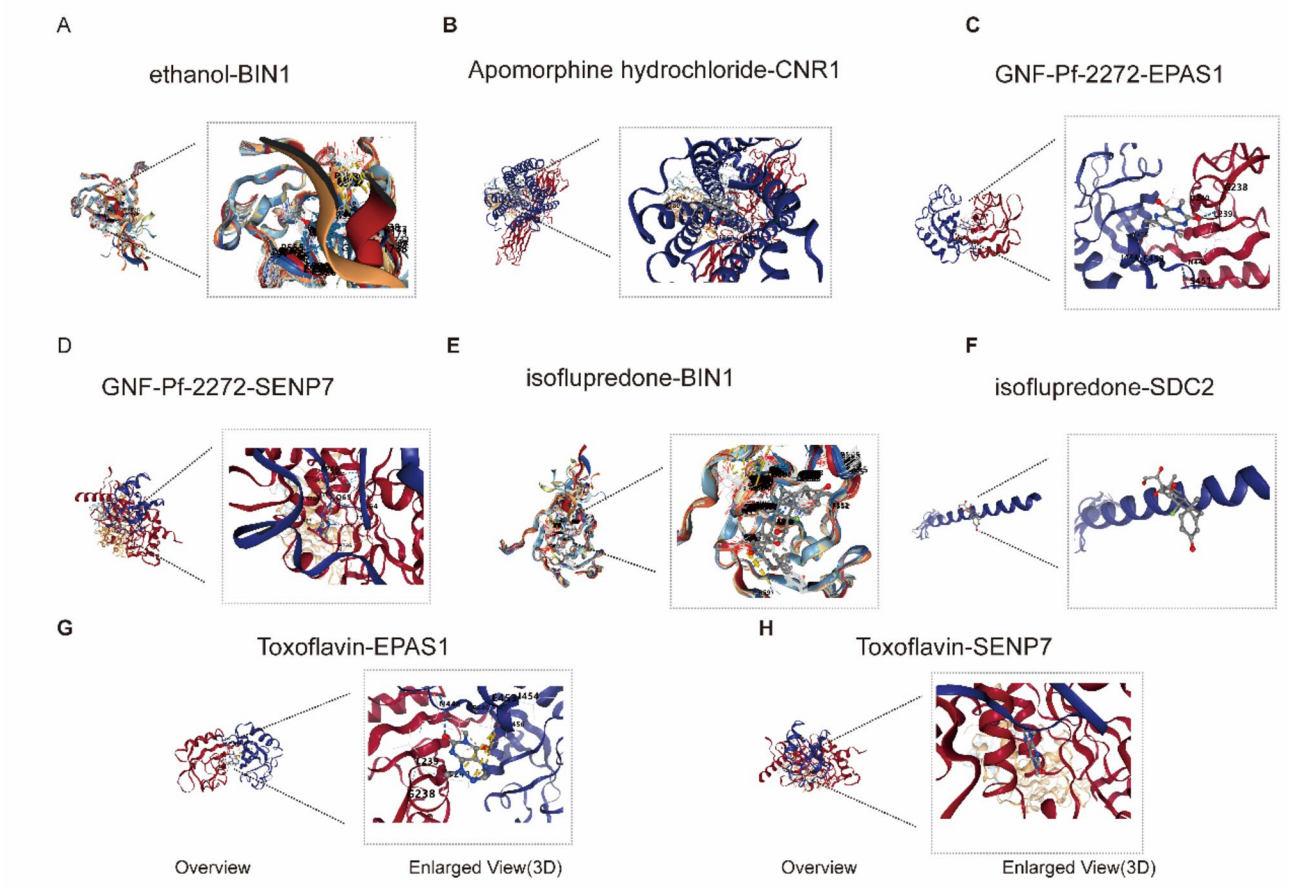

Fig. 6 Docking Analysis of Amino Acid Residues. **(A)** Ethanol binding to *BIN1* (PDB:5I22; energy = -19.3 kcal/mol). **(B)** Isoflupredone interaction with *SDC2* (PDB:6ITH; energy = -50.8 kcal/mol). Hydrogen bonds (dashed lines) stabilize key residues

and prognosis of DR. These genes are involved in key processes such as inflammatory responses, angiogenesis, and intercellular signaling, suggesting their potential as therapeutic targets [33]. The prospects of gene therapy in the context of DR are also becoming increasingly relevant. Advances in molecular diagnostic techniques have sparked interest in gene therapy for DR. While treatment strategies targeting specific gene mutations have shown promise in other hereditary retinal diseases, the application of gene editing technologies in DR remains in its early stages. However, these approaches hold considerable potential for enhancing patient outcomes [34]. Pharmacological interventions also play a vital role in DR management. Agents such as aflibercept have demonstrated protective effects, and innovative therapies, including antioxidant and vascular-targeted treatments, are under exploration. A deeper understanding of gene expression and regulatory mechanisms is crucial for the success of these therapeutic strategies [35]. Collectively, these insights highlight the intricate interplay between genetic factors and therapeutic interventions in the management of DR.

The *PRKAB1* protein serves as the *β1* subunit of AMP-activated protein kinase (AMPK), a critical regulator of energy metabolism [36]. In the context of DR, impaired energy metabolism in retinal cells is a key pathogenic mechanism. As a protective gene, *PRKAB1* enhances cellular energy metabolism and helps maintain intracellular energy homeostasis by activating the AMPK signaling pathway. This activation potentially alleviates retinal cell damage and reduces the risk of developing DR [37]. Also, the *CNR1* gene encodes the cannabinoid receptor 1 protein, which plays an essential role in regulating the nervous system and inflammatory responses [38]. Retinal neuronal dysfunction and inflammation are intricately linked to the onset and progression of DR. Research indicates that *CNR1* may confer neuroprotective effects by activating cannabinoid receptor 1, thereby mitigating damage to retinal neurons, suppressing inflammatory responses, and decreasing the production of inflammatory mediators, ultimately reducing the risk of DR [39]. In contrast, *CACNA1E* encodes the α1 subunit of L-type calcium channels, crucial for heart muscle function and brain signaling [40]. In DR, abnormal retinal blood vessel

contractions contribute to vascular complications. Dysregulated expression of *CACNA1E* may disrupt calcium channel function, exacerbating vascular irregularities and increasing the risk of DR [41]. A prior study identified cadherin-2 (*CDH2*) as a crucial regulator in DR, highlighting its significant role in the modulation of retinal vascular dysfunction and neuroretinal degeneration, thereby offering novel insights into the pathogenesis and therapeutic targeting of DR [42]. Several key pathways are also implicated in the pathogenesis of DR. For instance, the adrenergic signaling pathway (hsa04261) is closely associated with cardiovascular diseases and may influence DR [43]. Dysfunction in this pathway can impair cardiac function, disrupt circulation, and reduce retinal blood supply, thereby exacerbating DR [44, 45]. The oxytocin signaling pathway (hsa04921), known for its role in reproduction, cardiovascular regulation, and energy metabolism, is another relevant pathway [46]. Disruptions in this pathway may impair retinal blood flow and metabolism, promoting the progression of DR [47]. In addition, arrhythmogenic right ventricular cardiomyopathy (hsa05412) involves replacing heart muscle cells with fat and fibrous tissue, leading to arrhythmias [48]. Patients with DR often experience arrhythmias, potentially linked to the severity of their condition. Abnormalities in this pathway can alter the electrical properties of cardiac cells, affecting systemic circulation and worsening DR outcomes [49].

Research on pharmacological interventions for DR has been extensive, with numerous agents investigated for their potential therapeutic effects [50]. For instance, previous studies have identified BGP-15 as a promising candidate due to its ability to increase the expression of heat shock protein 70 and reduce levels of nuclear factor kappa B. These mechanisms help alleviate oxidative stress and inflammatory responses, suggesting that BGP-15 could serve as a future therapeutic agent for DR [51]. In our study, ethanol was identified as a potential therapeutic agent for DR, with effects likely mediated through multiple mechanisms. Ethanol may exhibit neuroprotective properties by modulating neurotransmitter release and neural signal transmission, thereby mitigating damage to retinal neurons and potentially slowing the progression of DR [52]. Furthermore, Ethanol Extract of Chinese Propolis demonstrates significant protective effects against early diabetic retinopathy by safeguarding the blood-retinal barrier, offering a promising therapeutic avenue for managing DR [53]. Besides, Ethanol extracts from Chinese propolis and *Osteomeles schwerinae* show promise as new treatments for early DR by reducing oxidative stress, maintaining blood-retinal barrier integrity, and preventing cell death [54]. Also, the ethanol extract of *Zingiber zerumbet rhizomes* may serve as a natural treatment for diabetic retinopathy by balancing angiogenesis (lowering VEGF and raising PEDF levels) and blocking inflammatory pathways like NF-κB and ERK1/2 [55]. Ethanol's toxicity limits its clinical use, but our findings highlight the potential of targeting its molecular interactors like *CNR1* and *BIN1* for therapy. Future research should focus on ethanol derivatives or receptor-specific agonists to utilize its benefits without side effects. Moreover, epidemiological studies are needed to explore the link between moderate alcohol consumption and diabetic retinopathy severity. Additionally, isoflupredone, an antagonist of the glucocorticoid receptor, may counteract the excessive activation of glucocorticoids, a process implicated in the pathogenesis of DR. Increased glucocorticoid activity in DR can exacerbate inflammatory responses and increase cellular death. By antagonizing the glucocorticoid receptor, isoflupredone may reduce these inflammatory reactions and cellular damage, highlighting its therapeutic potential in the management of DR [56].

This study offers several notable advantages. First, it is the pioneering study to utilize MR for identifying drug targets associated with DR, leveraging data from the most extensive publicly accessible DR risk GWAS to date. Additionally, the incorporation of colocalization analysis significantly enhances the robustness of the findings by minimizing the likelihood of false positives and false negatives. The enrichment analysis and PPI network analysis shed light on the functional characteristics and regulatory relationships of the identified target genes, offering valuable insights into potential therapeutic pathways for DR drug development. Drug prediction results underscore the therapeutic promise of these target genes, while the high binding activity observed in molecular docking further supports their potential as viable drug targets. Collectively, these findings provide compelling evidence for advancing drug discovery efforts in DR.

This study also has several notable limitations. First, the number of eQTL IVs used in the MR analysis is limited, with most analyses relying on fewer than three SNPs. This limitation reduces the robustness and credibility of the MR findings. The findings from MR analyses indicate a potential causal relationship between gene expression and DR; however, they do not confirm the reversibility of gene regulation or its suitability for pharmacological interventions, such as epigenetic modifications. MR primarily identifies targets for hypothesis generation, necessitating subsequent experimental validation to facilitate clinical translation. Additionally, while blood eQTLs provide a genome-wide perspective, tissue-specific regulatory mechanisms in the retina may influence the causal role of certain genes. the use of blood eQTLs for MR testing poses challenges in identifying the most relevant tissue for treatment. Different tissues may exhibit distinct genetic regulatory mechanisms,

and the exclusive reliance on blood eQTLs may not provide a comprehensive understanding of the disease or its potential treatments. Integrating colocalization and pathway enrichment addressed this limitation by highlighting cross-tissue conserved targets. Future research using multi-tissue eQTLs and spatial transcriptomics will enhance these results. Consequently, the MR findings may not fully reflect the effect sizes observed in clinical settings or accurately predict the impacts of therapeutic interventions. Further experimental validation and clinical trials are essential to confirm the therapeutic potential of the identified targets. While the FinnGen R11 GWAS dataset represented the most comprehensive resource available during our study period, we acknowledge the necessity of integrating more recent releases (e.g., R12) to encompass a broader spectrum of genetic variants. Notably, our colocalization methodology (PPH4 ≥ 0.75) effectively mitigates cohort-specific biases in the prioritization of targets. Collaborative initiatives aimed at harmonizing multi-ancestry GWAS data will be essential for enhancing the translational potential of these findings.

Conclusions

This study employed MR and colocalization analysis to identify 30 potential drug targets for DR. These findings offer promising avenues for the development of more effective treatments for DR, potentially reducing the costs associated with drug development. The study makes a valuable contribution to the field by emphasizing the significance of these druggable genes in the pathogenesis of DR. However, further clinical trials focusing on drugs targeting these genes are essential to validate their therapeutic potential.

Abbreviations

DR	Diabetic Retinopathy
HGNC	The Human Genome Organization Gene Nomenclature Committee
TSS	Transcriptional start site
MR	Mendelian randomization
eQTL	Expression quantitative trait loci
GWAS	Genome-wide association studies
SNP	Single nucleotide polymorphism
IVs	Instrumental variables
DGIdb	Drug-Gene Interaction Database
FDR	False discovery rate
IVW	Inverse-variance weighted
GO	Gene Ontology
KEGG	Kyoto Encyclopedia of Genes and Genomes
BP	Biological process
MF	Molecular function
CC	Cellular component
PPI	Protein–protein interaction
DSigDB	Drug Signatures Database
PDB	Protein Data Bank

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13098-025-01710-y.

Supplementary Material 1

Author contributions

Long Xie, Yu Qin Peng, Xiang Shen. wrote the main manuscript text and Long Xie, Yu Qin Peng prepared Figs. 1, 2 and 3. All authors reviewed the manuscript.

Funding

Not applicable.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 16 February 2025 / Accepted: 22 April 2025
Published online: 29 April 2025

References

1. American Diabetes Association Professional Practice C. 2. Diagnosis and classification of diabetes: standards of care in Diabetes-2024. Diabetes Care. 2024;47(Suppl 1):S20–42. https://doi.org/10.2337/dc24-S002.
2. Chauhan MZ, Elhusseiny AM, Kishor KS, Sanvicente CT, Ali AA, Sallam AB, et al. Association of primary Open-Angle Glaucoma with diabetic retinopathy among patients with type 1 and type 2 diabetes: A large global database study. Ophthalmology. 2024;131(7):827–35. https://doi.org/10.1016/j.ophtha.2024.01.016.
3. Taylor BE, Howell SJ, Lee C, Taylor Z, Barber K, Taylor PR. Diabetes-Mediated STEAP4 enhances retinal oxidative stress and impacts the development of diabetic retinopathy. Antioxid (Basel). 2025;14(2). https://doi.org/10.3390/antiox14020205.
4. Kowluru RA, Radhakrishnan R, Mohammad G. Regulation of Rac1 transcription by histone and DNA methylation in diabetic retinopathy. Sci Rep. 2021;11(1):14097. https://doi.org/10.1038/s41598-021-93420-4.
5. Mansour A, Mousa M, Abdelmannan D, Tay G, Hassoun A, Alsafar H. Microvascular and macrovascular complications of type 2 diabetes mellitus: Exome wide association analyses. Front Endocrinol (Lausanne). 2023;141143067.https://doi.org/10.3389/fendo.2023.1143067
6. Sanderson E, Glymour MM, Holmes MV, Kang H, Morrison J, Munafo MR et al. Mendelian randomization. Nat Rev Methods Primers. 2022;210. https://doi.org/10.38/s43586-021-00092-5.
7. Zhang C, He Y, Liu L. Identifying therapeutic target genes for migraine by systematic druggable genome-wide Mendelian randomization. J Headache Pain. 2024;25(1):100. https://doi.org/10.1186/s10194-024-01805-3.
8. Lloyd-Jones LR, Holloway A, McRae A, Yang J, Small K, Zhao J, et al. The genetic architecture of gene expression in peripheral blood. Am J Hum Genet. 2017;100(2):228–37. https://doi.org/10.1016/j.ajhg.2016.12.008.
9. Vosa U, Claringbould A, Westra HJ, Bonder MJ, Deelen P, Zeng B, et al. Large-scale cis- and trans-eQTL analyses identify thousands of genetic loci and polygenic scores that regulate blood gene expression. Nat Genet. 2021;53(9):1300–10. https://doi.org/10.1038/s41588-021-00913-z.
10. Freshour SL, Kiwala S, Cotto KC, Coffman AC, McMichael JF, Song JJ, et al. Integration of the Drug-Gene interaction database (DGIdb 4.0) with open crowdsource efforts. Nucleic Acids Res. 2021;49(D1):D1144–51. https://doi.org/10.1093/nar/gkaa1084.
11. Finan C, Gaulton A, Kruger FA, Lumbers RT, Shah T, Engmann J, et al. The druggable genome and support for target identification and validation in drug development. Sci Transl Med. 2017;9(383). https://doi.org/10.1126/scitranslmed.aag1166.
12. Su WM, Gu XJ, Dou M, Duan QQ, Jiang Z, Yin KF, et al. Systematic druggable genome-wide Mendelian randomisation identifies therapeutic targets for

Alzheimer's disease. J Neurol Neurosurg Psychiatry. 2023;94(11):954–61. https://doi.org/10.1136/jnnp-2023-331142.
13. Cao Y, Yang Y, Hu Q, Wei G. Identification of potential drug targets for rheumatoid arthritis from genetic insights: a Mendelian randomization study. J Transl Med. 2023;21(1):616. https://doi.org/10.1186/s12967-023-04474-z.
14. Kurki MI, Karjalainen J, Palta P, Sipila TP, Kristiansson K, Donner KM, et al. FinnGen provides genetic insights from a well-phenotyped isolated population. Nature. 2023;613(7944):508–18. https://doi.org/10.1038/s41586-022-05473-8.
15. Pierce BL, Ahsan H, Vanderweele TJ. Power and instrument strength requirements for Mendelian randomization studies using multiple genetic variants. Int J Epidemiol. 2011;40(3):740–52. https://doi.org/10.1093/ije/dyq151.
16. Pierce BL, Burgess S. Efficient design for Mendelian randomization studies: subsample and 2-sample instrumental variable estimators. Am J Epidemiol. 2013;178(7):1177–84. https://doi.org/10.1093/aje/kwt084.
17. Byrska-Bishop M, Evani US, Zhao X, Basile AO, Abel HJ, Regier AA, et al. High-coverage whole-genome sequencing of the expanded 1000 genomes project cohort including 602 trios. Cell. 2022;185(18):3426–40. https://doi.org/10.1016/j.cell.2022.08.004.
18. Kamat MA, Blackshaw JA, Young R, Surendran P, Burgess S, Danesh J, et al. PhenoScanner V2: an expanded tool for searching human genotype-phenotype associations. Bioinformatics. 2019;35(22):4851–3. https://doi.org/10.1093/bioinformatics/btz469.
19. Greco MF, Minelli C, Sheehan NA, Thompson JR. Detecting Pleiotropy in Mendelian randomisation studies with summary data and a continuous outcome. Stat Med. 2015;34(21):2926–40. https://doi.org/10.1002/sim.6522.
20. Sekula P, Del Greco MF, Pattaro C, Kottgen A. Mendelian randomization as an approach to assess causality using observational data. J Am Soc Nephrol. 2016;27(11):3253–65. https://doi.org/10.1681/ASN.2016010098.
21. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect Estimation and bias detection through Egger regression. Int J Epidemiol. 2015;44(2):512–25. https://doi.org/10.1093/ije/dyv080.
22. Xiang K, Wang P, Xu Z, Hu YQ, He YS, Chen Y, et al. Causal effects of gut Microbiome on systemic lupus erythematosus: A Two-Sample Mendelian randomization study. Front Immunol. 2021;12667097. https://doi.org/10.3389/fimmu.2021.667097.
23. Giambartolomei C, Vukcevic D, Schadt EE, Franke L, Hingorani AD, Wallace C, et al. Bayesian test for colocalisation between pairs of genetic association studies using summary statistics. PLoS Genet. 2014;10(5):e1004383. https://doi.org/10.1371/journal.pgen.1004383.
24. Giambartolomei C, Zhenli Liu J, Zhang W, Hauberg M, Shi H, Boocock J, et al. A bayesian framework for multiple trait colocalization from summary association statistics. Bioinformatics. 2018;34(15):2538–45. https://doi.org/10.1093/bioinformatics/bty147.
25. Yu G, Wang LG, Han Y, He QY. ClusterProfiler: an R package for comparing biological themes among gene clusters. OMICS. 2012;16(5):284–7. https://doi.org/10.1089/omi.2011.0118.
26. Yoo M, Shin J, Kim J, Ryall KA, Lee K, Lee S, et al. DSigDB: drug signatures database for gene set analysis. Bioinformatics. 2015;31(18):3069–71. https://doi.org/10.1093/bioinformatics/btv313.
27. Kim S, Chen J, Cheng T, Gindulyte A, He J, He S, et al. PubChem 2025 update. Nucleic Acids Res. 2024;53D1:D1516–25. https://doi.org/10.1093/nar/gkae1059. %J Nucleic Acids Research.
28. Chen CS, Zhou J, Wang F, Liu X, Dou D. Structure-aware protein self-supervised learning. Bioinformatics. 2023;39(4). https://doi.org/10.1093/bioinformatics/btad189.
29. Liu Y, Yang X, Gan J, Chen S, Xiao ZX, Cao Y. CB-Dock2: improved protein-ligand blind Docking by integrating cavity detection, Docking and homologous template fitting. Nucleic Acids Res. 2022;50(W1):W159–64. https://doi.org/10.1093/nar/gkac394.
30. Zhai Y, Li J, Zhang Q. Network Pharmacology and molecular Docking analyses of the potential target proteins and molecular mechanisms underlying the anti-arrhythmic effects of Sophora Flavescens. Med (Baltim). 2023;102(30):e34504. https://doi.org/10.1097/MD.0000000000034504.
31. Fan Y, Fu YY, Chen Z, Hu YY, Shen J. Gene-gene interaction of erythropoietin gene polymorphisms and diabetic retinopathy in Chinese Han. Exp Biol Med (Maywood). 2016;241(14):1524–30. https://doi.org/10.1177/1535370216645210.
32. Kumaramanickavel G, Sripriya S, Vellanki RN, Upadyay NK, Badrinath SS, Arokiasamy T, et al. Tumor necrosis factor allelic polymorphism with diabetic retinopathy in India. Diabetes Res Clin Pract. 2001;54(2):89–94. https://doi.org/10.1016/s0168-8227(01)00269-8.
33. Gong MT, Li WX, Zhang Q, Lv WW, He ZH, Zhou SL, et al. Comprehensive analysis of gene expression profiles associated with proliferative diabetic retinopathy. Exp Ther Med. 2018;16(4):3539–45. https://doi.org/10.3892/etm.2018.6635.
34. Zaneveld J, Wang F, Wang X, Chen R. Dawn of ocular gene therapy: implications for molecular diagnosis in retinal disease. Sci China Life Sci. 2013;56(2):125–33. https://doi.org/10.1007/s11427-013-4443-y.
35. Polewik K, Kosek M, Jamrozik D, Matuszek I, Smedowski A, Lewin-Kowalik J, et al. Rodent models of diabetic retinopathy as a useful research tool to study neurovascular Cross-Talk. Biology (Basel). 2023;12(2). https://doi.org/10.3390/biology12020262.
36. Kahn BB, Alquier T, Carling D, Hardie DG. AMP-activated protein kinase: ancient energy gauge provides clues to modern Understanding of metabolism. Cell Metab. 2005;1(1):15–25. https://doi.org/10.1016/j.cmet.2004.12.003.
37. Entezari M, Hashemi D, Taheriazam A, Zabolian A, Mohammadi S, Fakhri F, et al. AMPK signaling in diabetes mellitus, insulin resistance and diabetic complications: A pre-clinical and clinical investigation. Biomed Pharmacother. 2022;146112563. https://doi.org/10.1016/j.biopha.2021.112563.
38. Floreani A, Lazzari R, Macchi V, Porzionato A, Variola A, Colavito D, et al. Hepatic expression of endocannabinoid receptors and their novel polymorphisms in primary biliary cirrhosis. J Gastroenterol. 2010;45(1):68–76. https://doi.org/10.1007/s00535-009-0122-y.
39. El-Remessy AB, Rajesh M, Mukhopadhyay P, Horvath B, Patel V, Al-Gayyar MM, et al. Cannabinoid 1 receptor activation contributes to vascular inflammation and cell death in a mouse model of diabetic retinopathy and a human retinal cell line. Diabetologia. 2011;54(6):1567–78. https://doi.org/10.1007/s00125-011-2061-4.
40. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American college of medical genetics and genomics and the association for molecular pathology. Genet Med. 2015;17(5):405–24. https://doi.org/10.1038/gim.2015.30.
41. Kumar A, Mutter S, Parente EB, Harjutsalo V, Lithovius R, Mathavan S, et al. L-type calcium channel blocker increases VEGF concentrations in retinal cells and human serum. PLoS ONE. 2023;18(4):e0284364. https://doi.org/10.1371/journal.pone.0284364.
42. Chen H, Wang T, Wang E, Li N, Min H. Pursuing diabetic nephropathy through aqueous humor proteomics analysis. Oxid Med Cell Longev. 2022;20225945828. https://doi.org/10.1155/2022/5945828.
43. Yang JH, Saucerman JJ. Computational models reduce complexity and accelerate insight into cardiac signaling networks. Circ Res. 2011;108(1):85–97. https://doi.org/10.1161/circresaha.110.223602.
44. Yun JH, Kim JM, Jeon HJ, Oh TJ, Choi HJ, Kim B-J. Metabolomics profiles associated with diabetic retinopathy in type 2 diabetes patients. PLoS ONE. 2020;15(10):e0241365. https://doi.org/10.1371/journal.pone.0241365.
45. Gerstein HC, Nair V, Chaube R, Stoute H, Werstuck GH. Dysglycemia and the density of the coronary Vasa vasorum. Diabetes Care. 2019;42(5):980–2. https://doi.org/10.2337/dc18-2483.
46. Slattery MM, Morrison JJ. Preterm delivery. Lancet. 2002;360(9344):1489–97. https://doi.org/10.1016/s0140-6736(02)11476-0.
47. Ueda Y, Oxytocin. An expansive review of its mechanisms, functions, and therapeutic potential. World J Adv Res Reviews. 2023;19(1):1264–72. https://doi.org/10.30574/wjarr.2023.19.1.1499.
48. Fatkin D, Graham RM. Molecular mechanisms of inherited cardiomyopathies. Physiol Rev. 2002;82(4):945–80. https://doi.org/10.1152/physrev.00012.2002.
49. Vos SC, Aaron RV, Weng MH, Daw J, Rodríguez-Rivera E, Subauste CS. CD40 upregulation in the retina of patients with diabetic retinopathy: association with TRAF2/TRAF6 upregulation and inflammatory molecule expression. Invest Opthalmology Visual Sci. 2023;64(7):17. https://doi.org/10.1167/iovs.64.7.17.
50. Kaštelan S, Tomić M, Gverović Antunica A, Salopek Rabatić J, Ljubić S. Inflammation and Pharmacological treatment in diabetic retinopathy. Mediators Inflamm. 2013;2013213130. https://doi.org/10.1155/2013/213130.
51. Wachal Z, Szilágyi A, Takács B, Szabó AM, Priksz D, Bombicz M, et al. Improved survival and retinal function of aging ZDF rats in Long-Term, uncontrolled diabetes by BGP-15 treatment. Front Pharmacol. 2021;12650207. https://doi.org/10.3389/fphar.2021.650207.
52. Choi MR, Cho S, Kim DJ, Choi JS, Jin YB, Kim M, et al. Effects of ethanol on expression of coding and noncoding RNAs in murine neuroblastoma Neuro2a cells. Int J Mol Sci. 2022;23(13). https://doi.org/10.3390/ijms23137294.
53. Shi YZ, Liu YC, Zheng YF, Chen YF, Si JJ, Chen ML, et al. Ethanol extract of Chinese Propolis attenuates early diabetic retinopathy by protecting the

Blood-Retinal barrier in Streptozotocin-Induced diabetic rats. J Food Sci. 2019;84(2):358–69. https://doi.org/10.1111/1750-3841.14435.
54. Kim CS, Kim J, Kim YS, Jo K, Lee YM, Jung DH, et al. Improvement in diabetic retinopathy through protection against retinal apoptosis in spontaneously diabetic Torii rats mediated by ethanol extract of Osteomeles schwerinae C.K. Schneid. Nutrients. 2019;11(3). https://doi.org/10.3390/nu11030546.
55. Hong TY, Tzeng TF, Liou SS, Liu IM. The ethanol extract of Zingiber zerumbet rhizomes mitigates vascular lesions in the diabetic retina. Vascul Pharmacol. 2016. https://doi.org/10.1016/j.vph.2015.08.015.
56. Amin R, Ansyori AK, Erna R, Fauzi L. Anti-Receptor advanced glycation end products decreases inflammatory pathways in retinopathy diabetics: in vivo study. Open Access Macedonian J Med Sci. 2020;8(A):414–7. https://doi.org/10.3889/oamjms.2020.4293.

Publisher's note