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Investigating potential drug targets for IgA nephropathy and membranous nephropathy through multi-queue plasma protein analysis: a Mendelian randomization study based on SMR and co-localization analysis

Xinyi Xu[1,2,3†], Changhong Miao[1,2,3†], Shirui Yang[1,2†], Lu Xiao[1,2*†], Ying Gao[1,2,3], Fangying Wu[4] and Jianbo Xu[5*]

†Xinyi Xu, Changhong Miao, Shirui Yang and Lu Xiao contributed equally to this work and are co-first authors.

*Correspondence:
Lu Xiao
xljhy1987@126.com
Jianbo Xu
1659268376@qq.com
[1]First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin 300381, China
[2]National Clinical Research Center for Chinese Medicine Acupuncture and Moxibustion, Tianjin, China
[3]Tianjin University of Traditional Chinese Medicine, Tianjin 301617, China
[4]The Second School of Clinical Medicine, Zhejiang Chinese Medical University, Hangzhou 310053, China
[5]Department of Clinical Laboratory, Jinhua Maternal and Child Health Care Hospital, Jinhua, Zhejiang 321000, China

Abstract

Background Membranous nephropathy (MN) and IgA nephropathy (IgAN) pose challenges in clinical treatment with existing therapies primarily focusing on symptom relief and often yielding unsatisfactory outcomes. The search for novel drug targets remains crucial to address the shortcomings in managing both kidney diseases.

Methods Utilizing GWAS data for MN (ncase = 2150, ncontrol = 5829) and IgAN (ncase = 15587, ncontrol = 462197), instrumental variables for plasma proteins were derived from recent GWAS. Sensitivity analysis involved bidirectional Mendelian randomization analysis, MR Steiger, Bayesian co-localization, and Phenotype scanning. The SMR analysis using eQTL data from the eQTLGen Consortium was conducted to assess the availability of selected protein targets. The PPI network was constructed to reveal potential associations with existing drug treatment targets.

Results The study, subjected to the stringent Bonferroni correction, revealed significant associations: four proteins with MN and three proteins with IgAN. In plasma protein cis-pQTL data from two cohorts, an increase in one standard deviation in PLA2R1 (OR = 2.01, 95%CI = 1.83–2.21), AIF1 (OR = 9.04, 95%CI = 4.69–17.41), MLN (OR = 3.79, 95%CI = 2.12–6.78), and NFKB1 (OR = 29.43, 95%CI = 7.73–112.0) was associated with an increased risk of MN. Additionally, in plasma protein cis-pQTL data, a standard deviation increase in FCGR3B (OR = 1.15, 95%CI = 1.09–1.22) and BTN3A1 (OR = 4.05, 95%CI = 2.65–6.19) correlated with elevated IgAN risk, while AIF1 (OR = 0.58, 95%CI = 0.46–0.73) exhibited IgAN protection. Bayesian co-localization indicated that PLA2R1 (coloc.abf-PPH4 = 0.695), NFKB1 (coloc.abf-PPH4 = 0.949), FCGR3B (coloc.abf-PPH4 = 0.909), and BTN3A1 (coloc.abf-PPH4 = 0.685) share the same variants associated with MN and IgAN. The SMR analysis indicated a causal link between NFKB1 and BTN3A1 plasma protein eQTL in both conditions, and BTN3A1 was validated externally.

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Conclusion Genetically influenced plasma levels of PLA2R1 and NFKB1 impact MN risk, while FCGR3B and BTN3A1 levels are causally linked to IgAN risk, suggesting potential drug targets for further clinical exploration, notably BTN3A1 for IgAN.

Keywords Membranous nephropathy$_1$, IgA nephropathy$_2$, Mendelian randomization$_3$, Drug targets$_4$, pQTL$_5$

Introduction

IgA nephropathy (IgAN) and membranous nephropathy (MN) are common primary glomerulonephritis worldwide (IgAN at least 25/1000000 annually), with IgAN being the leading cause of primary glomerular diseases [1, 2], followed closely by MN [3]. IgAN is pathologically characterized by mesangial deposition of granular IgA. Clinical manifestations of IgAN vary, ranging from asymptomatic macroscopic hematuria to acute glomerulonephritis [4]. While most IgAN patients follow a benign course, 26-50% may progress to end-stage renal disease (ESRD) within 10–30 years [5, 6], with faster renal function decline and poorer prognosis in Asian populations, imposing a significant burden on families and national economies [7, 8]. Currently, there is no effective and safe treatment specifically for IgAN, and widespread and optimized supportive therapy remains the cornerstone of IgAN patient management [9].

MN is an autoimmune disease characterized by immune complex deposition beneath the epithelial cells of the glomerular basement membrane, with diffuse thickening of the basement membrane. 60% of MN cases are attributed to circulating autoantibodies targeting glomerular podocyte antigens, such as phospholipase A2 receptor type 1 (PLA2R1) and thrombospondin type 1 domain 7 A (THSD7A) [4]. Mechanistically, membranous nephropathy can be classified into idiopathic membranous nephropathy (IMN), representing about 75% of cases, and secondary membranous nephropathy (SMN) [4]. IMN is the most common type among non-diabetic adult nephrotic syndrome patients globally. Current clinical treatment for membranous nephropathy primarily involves immunosuppressive regimens. However, traditional immunosuppressive therapies, including corticosteroids, cyclophosphamide, tacrolimus, cyclosporine, and rituximab, are associated with high recurrence rates and infection risks. Due to their toxic effects, these therapies are limited to high-risk MN patients with clinical presentations of nephrotic syndrome [10]. Supportive therapy remains the primary treatment approach for non-nephrotic proteinuria patients clinically, underscoring the importance of exploring mild yet effective treatment modalities.

Human proteins play a crucial role as the most important components within the biological organism, participating in a myriad of biochemical reactions, cellular activities, and phenotypic expressions. The majority of known drug targets are proteins, with approximately 20,000 proteins encoded by the human genome [11], and around one-fourth of them potentially regulated by small molecules [12]. However, the number of human targets identified to date is still less than 1,000 [13]. Nelson et al. demonstrated that proteins associated with diseases, supported by genetic linkage, doubled the success rate of clinical development [14]. In recent years, Mendelian randomization (MR) analysis has been widely used in drug target development and drug repurposing [15]. MR is a genetic instrumental variable analysis that typically employs single nucleotide polymorphisms (SNPs) from Genome-Wide Association Studies (GWAS) as genetic instruments to estimate the causal effects of exposure on outcomes. Compared to observational

studies, MR can avoid the influence of confounding factors. With advancements in high-throughput genomics and proteomics technologies in plasma, MR-based strategies have facilitated the identification of potential therapeutic targets for various diseases (e.g., heart failure [16] and stroke [17]). However, to date, few MR studies have integrated GWAS and protein quantitative trait locus (pQTL) data for IgAN and MN. Therefore, this study aims to integrate research on plasma proteomics data, utilizing two-sample MR and Bayesian co-localization to explore potential drug treatment targets for IgAN and MN.

Materials and methods

Study design

This study is a MR and co-localization study based on summary data from multiple cis-pQTL GWAS to explore potential drug targets for MN and IgAN. The study follows the STROBE-MR guidelines for MR analysis and operates under three fundamental assumptions: (1) the instrument variables are closely associated with the selected plasma proteins; (2) the chosen instrument variables are independent of any potential confounding factors; (3) genetic variation is unrelated to the selected kidney disease outcomes, except through plasma proteins. Additionally, other assumptions, including the absence of statistical interactions, must be met [18].

The study proceeds in three main steps: first, the summary data of cis-pQTL for plasma proteins and MR studies for MN and IgAN are separately gathered; second, co-localization analysis and related sensitivity analyses are conducted to ensure the accuracy of results and the suitability of selected protein targets; third, based on Summary Data-based Mendelian Randomization (SMR) analysis, large-scale eQTL data from the eQTLGen Consortium are utilized to determine if the identified potential drug targets for MN and IgAN have a causal association with kidney disease outcomes. Finally, the study performs Protein-Protein Interaction (PPI) network analysis to investigate the association between the potential drug targets identified in this study and existing research on treatment targets for MN and IgAN.

The study utilizes GWAS summary-level data, and all informed consents and ethical approvals were obtained in the original studies. The study design flowchart is illustrated in Fig. 1.

Data sources

QTL GWAS data source

For the initial MR analysis, plasma pQTL data come from Zheng et al. [19] integrating studies from five GWAS research cohorts [20–24]. The instrumental variable must meet specific criteria: (1) significant genome-wide correlation ($P<5e-8$); (2) independent association (linkage disequilibrium (LD) set at $r2<0.001$); (3) only cis-acting pQTLs are included in this study; (4) located outside the major histocompatibility complex boundaries (CHR6, 26–34 Mb) [25]. Finally, the study includes 738 cis-acting pQTLs for 734 proteins. Additionally, plasma pQTL data from Ferkingstad, E [26] (measuring 4907 plasma proteins in 35559 participants) are used for validation and integration, extracting cis-acting pQTLs for each protein based on transcription start and end points ± 1 MB.

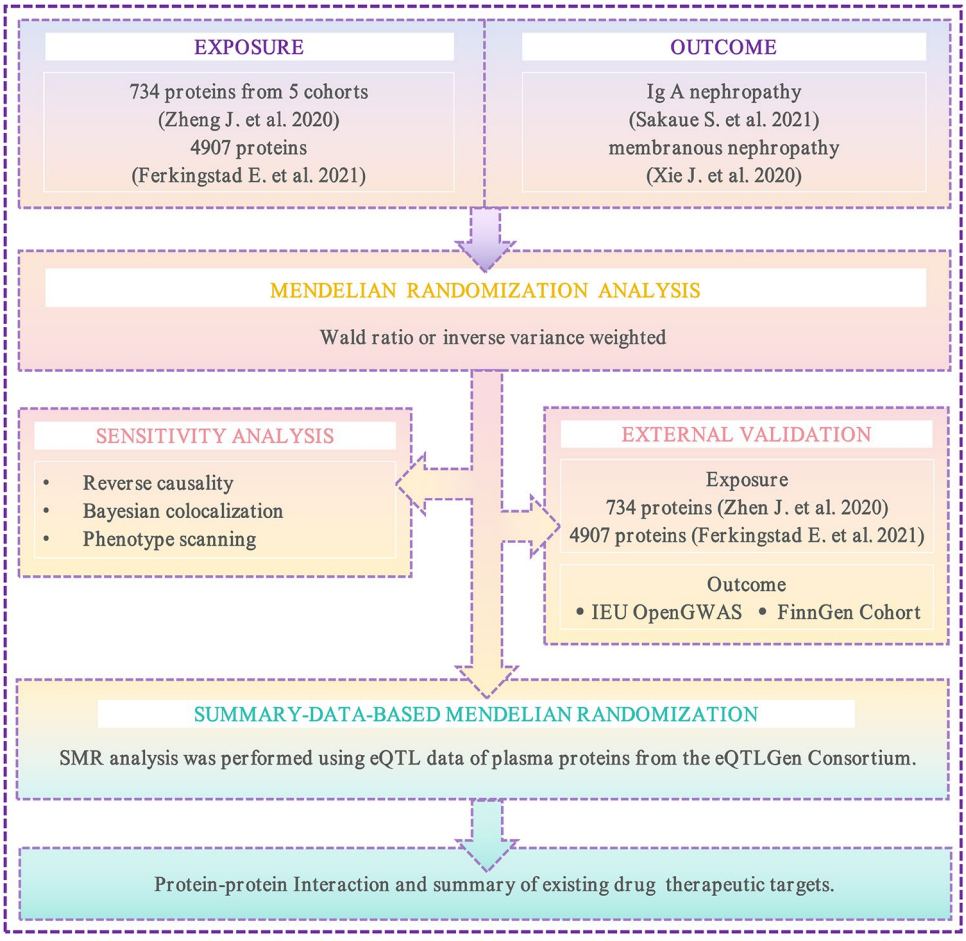

Fig. 1 The schematic diagram of the study design

For the eQTL data used in SMR analysis, data are obtained from the eQTLGen Consortium, including summary data from 37 datasets involving 31,684 individuals [27]. The study utilizes cis-eQTLs and lead SNPs for SMR analysis.

Missing information such as effect allele frequencies in the QTL GWAS summary statistics is imputed using the matched human genome construct as a reference.

Summary GWAS data for MN and IgAN

The GWAS summary data for membranous nephropathy (MN) used in this study were obtained from the largest meta-analysis of GWAS published in IEU OpenGWAS, involving 2,150 cases and 5,829 controls. All cases in the study were defined based on kidney biopsy diagnosis of idiopathic MN, with any secondary cases excluded. The control group comprised healthy individuals, with any known cases of nephropathy excluded (GWAS ID: ebi-a-GCST010005).

The GWAS summary data for IgA nephropathy (IgAN) used in this study were derived from the latest GWAS summary data published in IEU OpenGWAS, involving 15,587 cases and 462,197 controls. The diagnosis of IgAN was determined based on ICD criteria, defined as chronic glomerulonephritis characterized by predominant immunoglobulin A deposition in the mesangial region of the glomerulus (GWAS ID: ebi-a-GCST90018866).

The validation GWAS dataset for IgAN in this study was sourced from the Finngen database, involving 592 cases and 376,685 controls (GWAS ID: finngen_R8_N14_IGA_NEPHROPATHY), and from the IEU database, involving 977 cases and 5,957 controls (GWAS ID: ieu-a-1081). The diagnosis of IgAN in both datasets was determined according to ICD criteria.

Statistical analysis

Mendelian randomization (MR) study

The study employs Wald ratio and Inverse Variance Weighted (IVW) methods to validate the causal relationship between plasma pQTL and MN/IgAN. IVW is the primary analysis method for MR, providing a weighted average of results based on the variance and covariance of effect estimates for each genetic variant, assuming unbiased instrument variables and a common causal effect [28]. The study sets a threshold P value of 0.05/2415 ($P<2.07e-5$) after Bonferroni correction for result prioritization and further analysis. MR is performed only for initially identified proteins, and the threshold P value is set at 0.05 for external validation.

Sensitivity analysis and reverse causal inference

Cochrane's Q test is utilized to assess heterogeneity among instrument variables. Reverse MR is conducted to ensure the reliability of study results. MR Steiger analysis is performed to verify the directionality of the association between proteins and MN/IgAN [29]. Additionally, to assess the close correlation between a single SNP and MN/IgAN, the study conducts a search for each SNP's secondary phenotypes in GeneATLAS [30].

Bayesian co-localization analysis

Bayesian co-localization analysis is a statistical method for evaluating the probability that two or more different features or traits share common genetic causes or causal variations [31]. The analysis is conducted under five basic hypotheses: H0 (no association), H1 (association with the protein but not the kidney disease outcome), H2 (association with the kidney disease outcome but not the protein), H3 (independent association with both), and H4 (shared association with both). The study defines H4 as the main basis for Bayesian co-localization, considering a posterior probability (PPH4) greater than 60% as evidence for H4, and PPH4 greater than 90% as strong evidence for co-localization.

Summary data-based mendelian randomization (SMR)

In SMR analysis, the HEIDI test is used to assess heterogeneity-dependent tools, validating whether observed associations between gene expression and outcomes are due to linkage scenarios [32]. External validation is performed using plasma pQTL data and IgAN GWAS data from the Finngen and IEU databases. Additionally, eQTL data from the eQTLGen Consortium are utilized for SMR analysis to ensure the accuracy of study results.

PPI network analysis

This study investigated the interactions between genes associated with MN and IgAN and the currently available potential drug targets. We identified eight drugs for improving MN from recent high-quality research [33] and obtained information on six

therapeutic drugs for IgAN from a high-quality review study [34]. Subsequently, we retrieved corresponding drug targets from the DrugBank database (https://www.drugbank.ca) [35].

All PPI analyses were conducted using the Search Tool for the Retrieval of Interacting Genes (STRING) database (https://string-db.org/). The minimum requirement for inte raction score was set at 0.15 to ensure the inclusion of gene interactions with a certain level of correlation. Subsequently, to further elucidate the potential signaling pathways involved in protein interactions relevant to the treatment of MN and IgAN, we utilized GeneMANIA to annotate these potential pathways. Finally, this study screened the identified drug targets using the Enrichr platform in conjunction with the DSigDB database to identify chemical compounds associated with these targets. Enrichr then generated a results table containing information on drug-target associations, including enrichment scores, p-values, and adjusted significance levels. Highly relevant drug compounds were identified based on statistical significance, and the results were quantified to illustrate the strength of associations between the drugs and their targets.

Results

Instrument variable selection

The information on instrument variables that meet the criteria is presented in Table S1 and Table S2. To avoid weak instrument bias, the study ensures that F-statistics are all greater than 10. We ultimately identified 738 and 1,681 cis-pQTLs in the two plasma protein datasets, respectively.

MR Analysis results for 738 and 1681 Cis-acting plasma protein pQTLs with IgAN and MN

Under the multiple corrected P value threshold ($P<2.07e-5$), significant causal associations were found in the 738 cis-pQTLs dataset, showing a significant causal association between Phospholipase A2 Receptor 1 (PLA2R1) and MN (OR=2.01, 95%CI=1.83–2.21, $P=2.78e-46$), and a significant causal association between Fc Fragment Of IgG Receptor IIIb (FCGR3B) and IgAN (OR=1.15, 95%CI=1.09–1.22, $P=8.98e-7$). To ensure the reliability of the study, subsequent analysis in the 1681 cis-pQTLs dataset revealed significant causal associations between Allograft Inflammatory Factor 1 (AIF1) (OR=9.04, 95%CI=4.69–17.41, $P=4.78e-11$), Motilin-Like Neuropeptide (MLN) (OR=3.79, 95%CI=2.12–6.78, $P=7.25e-06$), Nuclear Factor Kappa B Subunit 1 (NFKB1) (OR=29.43, 95%CI=7.73–112.0, $P=7.06e-07$) and MN; and AIF1 (OR=0.58, 95%CI=0.46–0.73, $P=7.15e-6$), FCGR3B (OR=1.17, 95%CI=1.10–1.24, $P=4.56e-7$), Butyrophilin Subfamily 3 Member A1 (BTN3A1) (OR=4.05, 95%CI=2.65–6.19, $P=1.10e-10$) and IgAN. The MR analysis results are presented in Fig. 2; Table 1.

Sensitivity analysis and bayesian co-localization analysis

Sensitivity analysis is a crucial step in MR studies to detect potential pleiotropy. The Cochrane's Q test p-values for MR analysis results in this study are all greater than 0.05, indicating the absence of heterogeneity. Furthermore, MR Steiger tests ensure the correct directionality of the relationship between the instrumental variable and exposure and outcome variables. To minimize interference from confounding factors, a manual search of secondary phenotypes controlled by the included SNPs in this study showed no clear interference from confounding factors. Subsequently, Bayesian co-localization

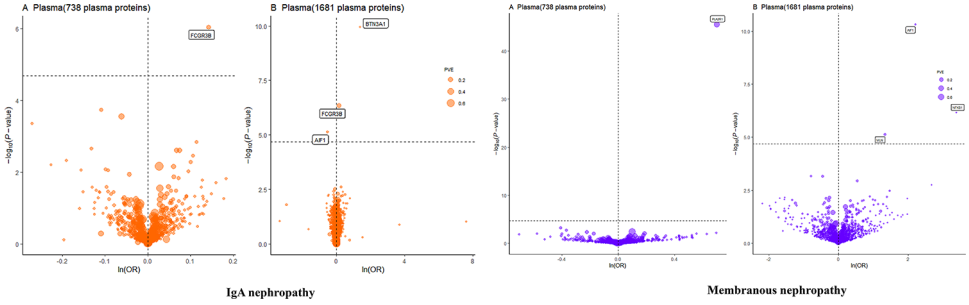

Fig. 2 Volcano plots illustrating the results of all Mendelian randomization analyses conducted in this study

Table 1 This study conducted inverse variance-weighted(IVW) significance analysis for all mendelian randomization outcomes

Study	Exposure	Outcome	Gene	Method	OR	95%CI	P_value
Zheng et al. [19]	738 plasma proteins	MN	PLA2R1	IVW	2.01	1.83–2.21	2.78e-46
Zheng et al. [19]	738 plasma proteins	IgAN	FCGR3B	IVW	1.15	1.09–1.22	8.98e-7
Ferkingstad, E et al. [26]	1681 plasma proteins	MN	AIF1	IVW	9.04	4.69–17.41	4.78e-11
Ferkingstad, E et al. [26]	1681 plasma proteins	MN	MLN	IVW	3.79	2.21–6.78	7.25e-6
Ferkingstad, E et al. [26]	1681 plasma proteins	MN	NFKB1	IVW	29.43	7.73–112	7.06e-7
Ferkingstad, E et al. [26]	1681 plasma proteins	IgAN	AIF1	IVW	0.58	0.46–0.73	7.15e-6
Ferkingstad, E et al. [26]	1681 plasma proteins	IgAN	FCGR3B	IVW	1.17	1.10–1.24	4.56e-7
Ferkingstad, E et al. [26]	1681 plasma proteins	IgAN	BTN3A1	IVW	4.05	2.65–6.19	1.10e-10

Table 2 All sensitivity analysis outcomes of mendelian randomization analyses performed in this study

Outcome	Exposure (Zheng et al.[19])	heterogeneity test		MR Steiger	
		Cochran's Q	Pval	Steiger direction	Steiger pval
IgA nephropathy	FCGR3B	-	-	TRUE	4.88e-62
Membranous nephropathy	PLA2R1	-	-	TRUE	< 0.01
Outcome	**Exposure (Ferkingstad et al.[26])**	**heterogeneity test**		**MR Steiger**	
		Cochran's Q	**Pval**	**Steiger direction**	**Steiger pval**
IgA nephropathy	AIF1	1.88	0.17	TURE	1.61e-7
IgA nephropathy	FCGR3B	0.43	0.51	TURE	1.14e-14
IgA nephropathy	BTN3A1	-	-	TURE	< 0.0003
Membranous nephropathy	AIF1	-	-	TRUE	< 0.01
Membranous nephropathy	MLN	0.02	0.89	TRUE	< 0.01
Membranous nephropathy	NFKB1	-	-	TRUE	< 0.01

analysis was conducted, suggesting a close association between PLA2R1 (coloc.abf-PPH4=0.695) and MN in the 738 cis-pQTLs dataset; and a strong association between NFKB1 (coloc.abf-PPH4=0.949), FCGR3B (coloc.abf-PPH4=0.909), and BTN3A1 (coloc.abf-PPH4=0.685) and IgAN in the 1681 cis-pQTLs datasets. Sensitivity analysis results are shown in Table 2, and co-localization results are shown in Fig. 3.

SMR Analysis of plasma protein eQTL data based on eQTLGen Consortium and external validation

Firstly, MR analysis was conducted using pQTL data for selected proteins (AIF1, FCGR3B, BTN3A1) and IgAN GWAS data from the Finngen and IEU databases for external validation. Additionally, the largest plasma protein eQTL data from the eQTL-Gen Consortium (no eQTL data for PLA2R1 were found in this dataset) were used for

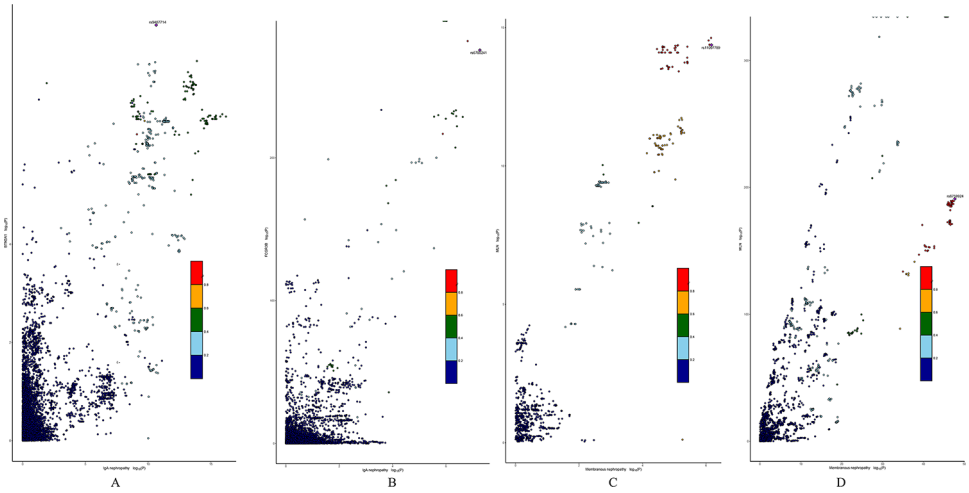

Fig. 3 Scatter plot of the results of Bayesian colocation analysis conducted in this study

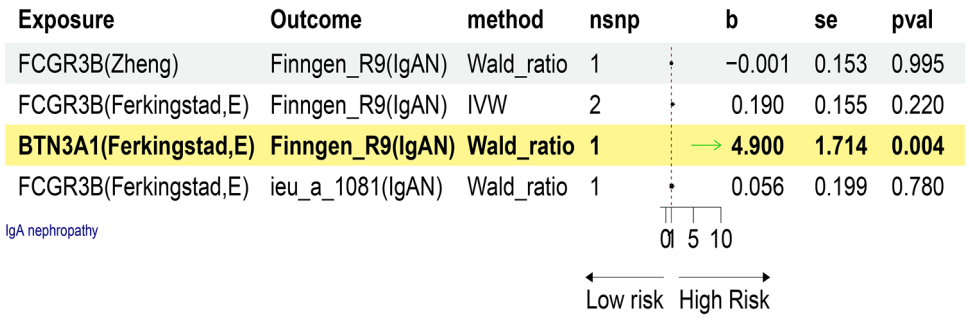

Fig. 4 A forest plot depicting the external validation analysis results for all Mendelian randomization analyses conducted in this study

SMR analysis in this study. The study found a strong causal association between NFKB1 eQTL data and MN (PSMR=1.57e-92), and between BTN3A1 eQTL data and IgAN (PSMR=3.20e-04) (SMR analysis for FCGR3B protein's pQTL data was already validated in the aforementioned datasets). External validation MR analysis results are shown in Fig. 4, and SMR analysis results are shown in Table 3.

Association of Potential Drug Targets with current MN and IgAN drugs

The study explored existing drugs and targets for MN and IgAN, and all possible drugs and targets are listed in the Table 4. Finally, using PPI network analysis, the study investigated the interaction between potential drug targets identified in this study and existing targets for MN and IgAN. BTN3A1 in IgAN may be a new drug target for the disease. The interaction between potential drug targets identified in this study and current protein targets for IgAN and MN is shown in Fig. 5.

Candidate drug prediction

The candidate drug prediction results indicate that, through analysis of the PPI network and the DSigDB database, we identified several potential drugs targeting proteins associated with MN and IgAN. In MN, PLA2R1 and NFKB1 were identified as the major associated proteins, with relevant candidate drugs including: Menadione; tert-Butyl

Table 3 Results of SMR analysis conducted in this study

Outcome	Gene	chr	top eQTL SNP	pos	A1	A2	eaf	eQTL association			GWAS association			SMR association			HEIDI Test	
								b	se	*P*	b	se	*P*	b	se	*P*	*P*	nSNPs
MN	NFKB1	4	rs4648011	103,475,444	G	T	0.42	0.17	0.08	1.56e-92	0.04	9.26e-6	7.97e+3	**0.26**	**0.01**	**1.57e-92**	2.92e-7	10
IgAN	BTN3A1	6	rs4320356	26,423,560	T	C	0.45	0.35	0.008	0.0e+0	-0.04	0.01	2.94e-4	-0.12	0.03	3.2e-4	3.18e-6	20

chr, chromosome; A1, Effect allele; A2, Other allele; pos, SNP base pair; eaf, Effect allele frequency; b, beta; P, p value

Hydroperoxide; Decitabine and Hydrogen Peroxide. Additionally, specific drugs targeting NFKB1, such as Butein, Tyrphostin AG 1478, Dihydrexidine, N-phenyl-1 H-pyrazole-3-carboxamide, and Chlorpropamide, exhibited high Combined Scores (13617.26). In IgAN, BTN3A1 and FCGR3B were identified as the major associated proteins. Candidate drugs include Ciclopirox; Clozapine and Meclofenoxate. These results provide new directions for potential treatments of IgAN and MN through candidate drugs (Table 5).

Discussion

Traditional treatment approaches for IgAN include supportive care, tonsillectomy, and the use of steroids and immunosuppressive agents. Tonsillectomy aims to reduce the number of IgA production sites and decrease circulating IgA levels. However, its widespread application is limited, and recent studies suggest that combining tonsillectomy with steroid pulses does not significantly increase clinical remission rates or reduce hematuria [36]. Due to the risks associated with tonsillectomy in adults and the lack of robust randomized controlled trials, the 2021 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines do not recommend its routine use [37]. Instead, the focus of IgAN treatment according to the 2021 KDIGO guidelines is on optimizing supportive care, including blood pressure management, the use of maximum tolerated doses of renin-angiotensin system inhibitors (RASI), and lifestyle changes. For those IgAN patients at risk of disease progression after at least 90 days of optimized supportive care, a six-month course of corticosteroid treatment may be considered [38]. However, the long-term efficacy and safety of glucocorticoids remain controversial. The STOP-IgAN study revealed that intensifying immunosuppressive therapy in high-risk IgAN patients did not delay the decline in estimated glomerular filtration rate (eGFR), and adverse reactions significantly increased [39]. The TESTING study demonstrated that adequate steroid treatment for IgAN significantly reduced proteinuria and decreased the risk of kidney failure events by 63%, but the risk of severe adverse events increased by 4.63 times [40]. Additionally, targeted release formulations of budesonide, aimed at reducing adverse reactions, have received regulatory approval. In Chinese patients, mycophenolate mofetil (MMF) has shown efficacy in clinical trials, with research indicating that adding subcutaneous MMF injections significantly reduce the risk of disease progression in progressive IgAN patients [41], aligning with our study results.

Currently, Western medicine lacks specific drugs for the treatment of MN, and the most common approach involves a combination of glucocorticoids and immunosuppressants. Guidelines also indicate that many complications of glomerular diseases result from clinical manifestations rather than specific histopathological patterns. These complications can significantly alter the incidence and even mortality rates, underscoring the importance of actively managing such complications in clinical practice. This proactive approach positively impacts the natural course of the disease and the prognosis for patients. Specific measures include controlling edema, reducing proteinuria, managing blood pressure, controlling blood sugar, addressing.

other metabolic issues, minimizing thrombosis formation, and slowing disease progression. These treatments may, to some extent, reduce or modulate the need for immunosuppressive drugs during therapy, thereby mitigating the potential side effects associated with immunosuppressive agents. Given the high cost of most

Table 4 The drug treatment targets identified in existing studies for MN and IgAN were retrieved in this study

Existing studies have shown that the treatment of membranous nephropathy related drugs and their targets	
Drugs	**Targets**
Anti-PLA2R1 antibodies	PLA2R1
Anti-CD19 antibodies	CD19
Anti-CD38 antibodies	CD38
Rituximab	MS4A1
Tacrolimus	FKBP1A
Belimumab	TNFSF13B
Cyclosporine	CAMLG、PPP3R2、PPIA、PPIF
Cyclophosphamide	NR1I2
Existing studies have shown that the treatment of IgA nephropathy related drugs and their targets	
Drugs	**Targets**
Budesonide	NR3C1、ANXA1
atrasentan	EDNRA
mannose-binding lectin-associated serine protease 2 inhibitor	MASP2
Hydroxychloroquine	TLR7、TLR9、ACE2
Valsartan	AGTR1
Miconazole	IMPDH1、IMPDH2、PTS

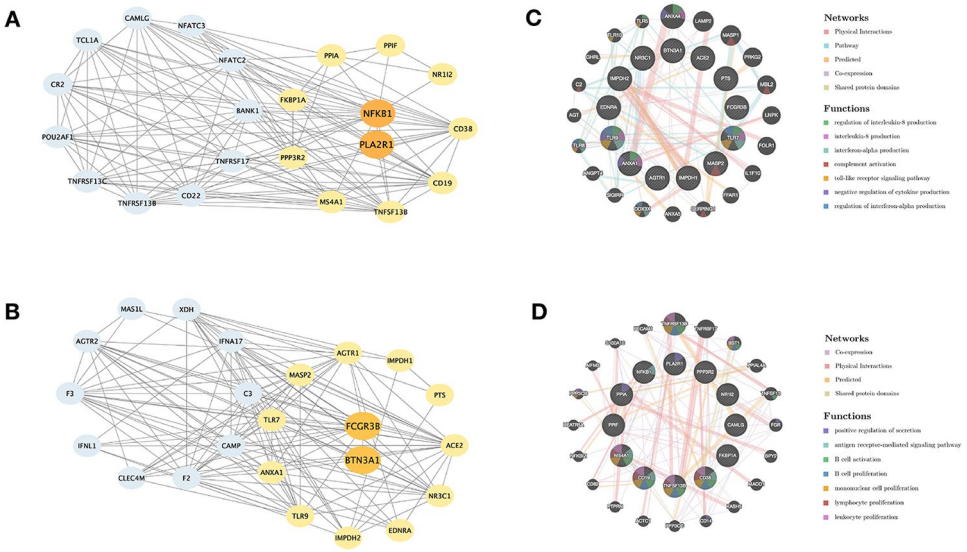

Fig. 5 The potential drug targets discovered in this study were assessed for protein interactions with the current proteins associated with IgAN and MN. (**A**. The figure presents the interactions of PLA2R1 and NFKB1 in MN with existing drug targets and related proteins. **B**. The figure illustrates the interactions of FCGR3B and BTN3A1 in IgAN with existing drug targets and related proteins. **C**. The figure displays the current potential signaling pathways and mechanisms of FCGR3B and BTN3A1 in IgAN. **D**. The figure showcases the current potential signaling pathways and mechanisms of PLA2R1 and NFKB1 in MN)

immunosuppressive drugs, reducing their usage can also alleviate economic pressure on patients, enhance medical compliance, and improve overall prognosis.

The Fc gamma receptors (FCGR), which bind to the Fc segment of immunoglobulin G (IgG), constitute a protein family expressed by various immune cells. FCGR3B is the sole inhibitory member of the FcγR immune regulator family [42] and is primarily expressed by neutrophils and eosinophils. Research indicates that FCGR3B binds to and mediates the uptake of immune complexes in a dose-dependent manner [43]. Previous

Table 5 Candidate drug prediction in this study

Outcome	Term	*P*-value	Odds Ratio	Combined Score	Genes
MN	menadione CTD 00007386	0.003	37,720	216,145	PLA2R1;NFKB1
	TERT-BUTYL HYDROPEROXIDE CTD 00007349	0.004	37,318	201,717	PLA2R1;NFKB1
	Decitabine CTD 00000750	0.008	36,400	175,317	PLA2R1;NFKB1
	hydrogen peroxide CTD 00006118	0.019	34,654	139,496	PLA2R1;NFKB1
	7646-79-9 CTD 00000928	0.023	33,812	126,214	PLA2R1;NFKB1
	butein CTD 00001872	0.001	1998.8	13,617	NFKB1
	Tyrphostin AG 1478 TTD 00011607	0.001	1998.8	13,617	NFKB1
	DIHYDREXIDINE TTD 00007580	0.001	1998.8	13,617	NFKB1
	N-phenyl-1 H-pyrazole-3-carboxamide TTD 00009559	0.001	1998.8	13,617	NFKB1
	chlorpropamide CTD 00005649	0.001	1998.8	13,617	NFKB1
IgAN	ciclopirox HL60 DOWN	0.006	332.3	1695	BTN3A1
	clozapine CTD 00005693	0.012	160.3	703	FCGR3B
	meclofenoxate HL60 UP	0.038	50.8	166	FCGR3B

reports have suggested an association between copy number variations (CNVs) in the FCGR3B gene and susceptibility to systemic lupus erythematosus (SLE) [44, 45]. SLE is an immune complex-mediated disease, and a decrease in FCGR3B copy numbers results in reduced expression of neutrophil FcγRIIb, diminishing the clearance of immune complexes. This leads to their deposition in the kidneys and joints, promoting inflammatory reactions. IgAN is characterized by the deposition of immune complexes as well. Recent clinical studies have shown a downregulation of extracellular vesicle lncRNA G21551 [46], which is the closest protein-coding gene to FCGR3B, in IgAN patients. This supports the aforementioned disease correlation. Additionally, a Chinese study has suggested potential pathogenic roles for FCGR2B and FCRLB in IgAN [47], indicating that Fc family proteins may play a crucial role in the pathogenesis of IgAN.

Butyrophilin (BTN) belongs to the immunoglobulin (Ig) superfamily and is a transmembrane protein. The BIN3A family, also known as CD277, is a subfamily of BIN molecules [48]. The significance of BTN3A in vivo is associated with its regulatory role in immune cells. Vγ9Vδ2 T cells are considered the first line of defense during infection and have been confirmed to possess potent anti-tumor activity [49]. Upon activation, they release various cytotoxic molecules and inflammatory factors [50]. Additionally, these cells play a role in antigen presentation and regulation of other immune cells, such as dendritic cells, T cells, and B cells [51, 52], crucial in infectious diseases [53], tumors [54, 55], and maintaining autoimmune balance [56]. Moreover, research indicates that IgAN is associated with clonal expansion of γδ T cells in the blood and kidneys. This expansion is correlated with disease progression and may contribute to immunopathology [57]. Studies suggest that Vγ9Vδ2 T cells are specifically activated by small molecule intermediates, phosphoantigens (pAgs), in the mevalonate pathway. This process heavily depends on the cytoplasmic B30.2 domain of BTN3A [58]. Recent research published in NATURE suggests that selective blockade of the interaction between BTN3A1 and BTN2A1 may selectively inhibit abnormal activation of Vγ9Vδ2 T cells in autoimmune diseases [59]. Clinical studies have confirmed the effectiveness of the humanized anti-BTN3A monoclonal antibody (ICT01) against solid tumors [60] and hematological malignancies. However, there is currently no research elucidating the direct relationship between BIN3A and IgA nephropathy. Our study results indicate for the first time

that BIN3A may be an important potential drug target for IgA nephropathy, but further research is needed to confirm this.

In 2009, M-type phospholipase A2 receptor 1 (PLA2R1) was identified as the primary antigen for adult membranous nephropathy (MN), significantly advancing both basic and clinical research [61, 62]. PLA2R1 belongs to the mannose receptor family, with a relative molecular weight of 180 kDa. Its extracellular segment contains one fibronectin type II domain (FNI). The FNI domain is highly conserved in molecular structure and plays a role in binding and clearing collagen [63]. PLA2R can bind to collagen I and IV under the mediation of FNII, and this interaction may be one of the mechanisms leading to proteinuria in PLA2R-associated MN [64–66]. The association between PLA2R1 gene variations and susceptibility to idiopathic membranous nephropathy (IMN) has been well established. This association has proven valuable in the diagnosis of IMN, serving as an important diagnostic hint and, to some extent, a substitute for renal biopsy. Thus, relevant indicators have been rapidly applied in clinical practice, aligning with our research findings. Additionally, clinical studies have shown a significant correlation between the titers of anti-PLA2R1 antibodies and the severity of MN deposition, making it a prognostic biomarker for MN [67]. Traditional nonspecific and toxic immunosuppressive regimens for MN treatment often lead to side effects such as bone marrow toxicity, infections, cancer, and kidney toxicity, raising concerns. Further research focusing on interventions targeting podocyte PLA2R, such as the use of anti-CD20 monoclonal antibody rituximab, provides a clear pathophysiological basis for specific targeting of B cell lineages to prevent antibody production and subepithelial deposition, offering a promising alternative in the management of MN [68].

Nuclear Factor Kappa-B (NFKB) is a widely distributed transcription factor family that includes RelA (p65), RelB, p52, p50, and c-Rel subunits [69]. This family selectively binds to the B cell κ-light chain enhancer, regulating downstream gene expression. The NFKB pathway activation can be classified into two types: classical and non-classical. The classical type exhibits rapid and transient transcriptional activity after NFKB activation, regulating the expression of various pro-inflammatory genes critical for inflammatory response mediation [70]. Non-classical NFKB pathway activation occurs through TNF receptor superfamily-related signaling pathways, processing NFKB precursor protein p100 into mature NFKB dimers, mediating sustained NFKB dimer functionality, potentially playing a crucial role in immune response regulation [71]. The association between NFKB genes and susceptibility to membranous nephropathy (MN) has been validated in several studies. A genome-wide association study (GWAS) on primary MN identified NFKB1 as a significantly risk-associated locus for MN (OR=1.25, P=3.4×10–12) [28]. Consistent with this result, another study using microarray datasets identified NFKB1 as a differentially expressed gene (DEG) in MN [72]. Elevated serum levels of NFKB were observed in patients with chronic glomerulonephritis (CGN), including focal segmental glomerulosclerosis, minimal change disease, and membranous nephropathy, although urinary NFKB levels were not correlated with CGN [73]. The underlying mechanisms of MN renal pathology are not fully elucidated, but oxidative stress and.

inflammation are involved in downstream molecular mechanisms triggered by immune complex deposition and complement activation. Recent research has identified podocyte-specific genes expressed in the glomeruli of MN patients, enriched with NFKB targets [74]. Increased expression of phosphorylated NFKB p65 protein in MN

serum receptors suggests activation of the inflammatory pathway [75]. Highlighting the disease mechanisms aims to discover new therapeutic drugs, with many traditional Chinese medicines (Moshen granule [76], Sanqi oral solution [77], and Zhen-Wu-tang [78]) and compounds isolated from herbal medicines (such as Tripterygium wilfordii multiglycosides [79], curcumin [80], betulinic acid [81], and coumarin glycosides [82]) being considered potential regulators of the NFKB molecular pathway.

Additionally, it is crucial to acknowledge the limitations of this study. (1) This study relies on GWAS data and pQTL analysis, with the interpretation of these data influenced by the associations between genotype and phenotype. Although MR analysis can reveal causal relationships to some extent, its conclusions depend on the effects of genetic variation on the target proteins. Therefore, the identified drug targets mainly reflect protein changes under genetic influences and may not comprehensively represent all influencing factors, especially environmental and other non-genetic factors. (2) The samples used in GWAS and pQTL studies are predominantly from European populations, which may limit the generalizability of the results to other ethnic groups. (3) Limitations of external validation: Although we utilized data from multiple sources for external validation, the identified drug targets and their interactions require further experimental validation and clinical research to confirm their clinical relevance and therapeutic potential. (4) In drug target prediction, the DSigDB database relies on known interactions between drugs and proteins. Since the prediction of drug-target interactions is based on existing gene expression data, this approach may lead to false positives. (5) Further molecular docking and animal experiments should be conducted in future studies to validate the findings.

Conclusions

In conclusion, a series of studies in this research indicate that genetically. determined levels of plasma proteins PLA2R1 and NFKB1 causally impact the risk of membranous nephropathy, while levels of FCGR3B and BTN3A1 causally relate to the risk of IgA nephropathy.

Supplementary Information

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Supplementary Material 1

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Xinyi Xu, Changhong Miao, Shirui Yang and Lu Xiao contributed equally to this work and are co-first authors.

Author contributions
XX, CM, LX and SY conceived the present idea and were responsible for the design of the study. CM, XX and YG access all the data in the study and took responsibility for the accuracy of the data analysis. SY, FW and XJ performed the statistical analysis and manuscript writing. All authors were involved in the writing and revision of the article, and all authors approved the submitted version to be published.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable. This study was conducted based on publicly available GWAS data and did not require ethical approval.

Consent for publication
All authors were involved in the writing and revision of the article, and all authors approved the submitted version to be published.

Competing interests
The authors declare no competing interests.

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