Investigation of the diagnostic performance of a machine learning model based on anti-PLA2R antibodies and SNPs in IMN

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Abstract

[Objective] To construct a noninvasive diagnostic model based on anti-PLA2R antibodies, single nucleotide polymorphisms (SNPs), and clinical indicators, in order to optimize the diagnostic strategy for idiopathic membranous nephropathy (IMN) and reduce dependence on renal biopsy. Methods A total of 100 patients with IMN and 100 non-IMN patients who were definitively diagnosed by renal biopsy in Yuebei People's Hospital from November 2021 to November 2024 were enrolled. Clinical and laboratory parameters were collected. Anti-PLA2R antibodies were measured by ELISA, and six SNP loci (rs4664308, rs3828323, rs35771982, rs3749117, rs3749119, rs2187668) were analyzed by gene sequencing. Feature variables were selected using LASSO regression, and eight machine learning models were constructed. The optimal model was identified based on AUC, accuracy, and other performance metrics. Results There were significant differences between IMN and non-IMN patients in age, hypertension status, anti-PLA2R antibody, urinary protein quantification, and eight other laboratory indicators ($P < 0.05$). The optimal cutoff value of anti-PLA2R antibodies for diagnosing IMN was 10.5 RU/ml (AUC = 0.83, 95% CI: 0.76–0.89, sensitivity 0.71, specificity 0.94). The genotype and allele frequencies of the six SNP loci differed significantly between the two groups ($P < 0.05$). Among them, the rs2187668-C allele was a protective factor for IMN (OR = 0.02, 95% CI = 0.001–0.34, P = 0.006). The LightGBM model was identified as the optimal diagnostic model (AUC = 0.951, accuracy 0.883, sensitivity 0.9, specificity 0.867). The core features, in order of importance, were anti-PLA2R antibody concentration, age, Scr, serum albumin, serum IgG, and rs2187668. [Conclusion] The optimal cutoff value of anti-PLA2R antibodies measured by ELISA to distinguish IMN from non-IMN is 10.5 RU/ml. The loci rs4664308, rs3828323, rs35771982, rs3749117, rs3749119, and rs2187668 are associated with IMN, and the rs2187668-C allele is a protective factor for IMN in the Chinese population. The LightGBM model

constructed based on anti-PLA2R antibodies, age, serum creatinine, serum albumin, serum IgG, and SNP (rs2187668) selected by LASSO regression has good clinical application value.

Full Text

Exploration of the Efficacy of Machine Learning Models Based on Anti-PLA2R Antibodies and SNPs in the Diagnosis of IMN

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Abstract

[Objective] To construct a non-invasive diagnostic model based on anti-PLA2R antibodies, single nucleotide polymorphisms (SNPs), and clinical indicators to optimize the diagnostic strategy for idiopathic membranous nephropathy (IMN) and reduce dependence on renal biopsy.

Methods A total of 100 IMN patients and 100 non-IMN patients who underwent renal biopsy at Yuebei People' s Hospital between November 2021 and November 2024 were enrolled. Clinical and laboratory indicators were collected, anti-PLA2R antibodies were detected by ELISA, and six SNP loci (rs4664308, rs3828323, rs35771982, rs3749117, rs3749119, rs2187668) were analyzed via gene sequencing. LASSO regression was employed to screen feature variables, and eight machine learning models were constructed. The optimal model was selected based on metrics including AUC and accuracy.

Results Significant statistical differences were observed between IMN and non-IMN patients in eight parameters including age, hypertension status, anti-PLA2R antibody levels, and quantitative urine protein ($P < 0.05$). The optimal cut-off value for anti-PLA2R antibody in diagnosing IMN was 10.5 RU/ml (AUC = 0.83, 95% CI: 0.76–0.89, sensitivity = 0.71, specificity = 0.94). Genotype and allele frequencies of the six SNP loci differed significantly between the two groups ($P < 0.05$), with the rs2187668-C allele identified as a protective factor against IMN (OR = 0.02, 95% CI = 0.001–0.34, P = 0.006). The LightGBM model emerged as the optimal diagnostic model (AUC = 0.951, accuracy = 0.883, sensitivity = 0.9, specificity = 0.867), with core features ranked as follows: anti-PLA2R antibody concentration, age, serum creatinine (Scr), serum albumin, serum IgG, and rs2187668.

[**Conclusions**] The optimal diagnostic cut-off value for anti-PLA2R antibody detected by ELISA to distinguish IMN from non-IMN is 10.5 RU/ml. The loci rs4664308, rs3828323, rs35771982, rs3749117, rs3749119, and rs2187668 are associated with IMN, with the rs2187668-C allele serving as a protective factor in the Chinese population. The LightGBM model constructed based on LASSO regression-selected features (anti-PLA2R antibody, age, serum creatinine, serum albumin, serum IgG, and SNP rs2187668) demonstrates excellent clinical applicability.

Keywords: idiopathic membranous nephropathy; anti-PLA2R antibody; single nucleotide polymorphism; machine learning

Classification: R692.6

Introduction

Membranous nephropathy (MN) is the leading cause of nephrotic syndrome in adults, with 80% of cases classified as idiopathic membranous nephropathy (IMN) [1]. The incidence of MN has been rising annually in China, making it the second most common glomerular disease after IgA nephropathy [2]. Renal biopsy remains the gold standard for IMN diagnosis; however, in early disease stages, pathological specimens may show no obvious morphological abnormalities under light microscopy despite significant proteinuria [3]. Additionally, renal biopsy is invasive and carries risks of complications such as gross hematuria and renal loss. Some patients cannot undergo biopsy due to contraindications or refusal. Therefore, there is an urgent need for non-invasive diagnostic alternatives.

In 2009, Beck et al. identified an autoantibody from glomerular extracts that interacted with a 155 kDa protein in over 70% of IMN patients, which was confirmed via mass spectrometry to be the M-type phospholipase A2 receptor (PLA2R) [4]. The KDIGO 2021 guidelines acknowledge its potential value as an alternative to renal biopsy in certain patients [5]; however, reported diagnostic cut-off values vary considerably across studies, limiting clinical application. Furthermore, IMN pathogenesis is closely linked to genetic background. Genome-wide association studies (GWAS) have demonstrated that SNPs in the PLA2R1 and HLA-DQA1 genes are associated with IMN susceptibility [6], though the underlying biological mechanisms remain unclear. Currently, SNP loci are primarily used for risk prediction and lack dynamic integration with clinical phenotype data.

Machine learning (ML) can integrate multi-dimensional data to construct precise prediction models and has shown promise in nephrological diagnostics. This study aims to integrate anti-PLA2R antibodies, six SNP loci, and clinical-biochemical indicators, using LASSO regression to screen core features and construct machine learning diagnostic models, thereby providing a novel tool

for non-invasive IMN diagnosis.

Methods

Study Subjects

This study enrolled 100 IMN patients and 100 non-IMN patients who underwent renal biopsy at the Department of Nephrology, Yuebei People' s Hospital, between November 2021 and November 2024.

Inclusion criteria: (1) All patients underwent renal biopsy to confirm renal pathology; (2) Age $\geq$ 18 years; (3) Pre-treatment serum anti-PLA2R antibody detection by ELISA; (4) All participants provided informed consent.

Exclusion criteria: (1) Incomplete baseline clinical data; (2) Prior treatment with glucocorticoids or immunosuppressants before biopsy; (3) Severe infection or acute kidney injury; (4) Malignancy, viral hepatitis, HIV infection, systemic lupus erythematosus, or pregnancy.

This study was approved by the Ethics Committee of Yuebei People' s Hospital (Approval No.: KY-2021-151), and all participants provided written informed consent.

Experimental Methods

(1) Data Collection. Clinical data included gender, age, systolic/diastolic blood pressure at admission, history of hypertension, diabetes mellitus, anemia, and hyperuricemia. Laboratory parameters included serum creatinine (Scr), serum albumin, total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), quantitative urine protein, serum IgG, serum IgA, serum IgM, complement C3, complement C4, and glomerular filtration rate (GFR).

(2) ELISA Detection. Serum anti-PLA2R antibody titers were measured by enzyme-linked immunosorbent assay (ELISA) using kits from EUROIMMUN AG according to the manufacturer' s instructions.

(3) Genomic DNA Extraction. Genomic DNA was extracted using the Magnetic Bead Multi-Type Sample DNA Extraction Kit from Shanghai Yinglaidun Biotechnology Co., Ltd.

(4) SNP Genotyping. Primers were designed based on relevant literature and the Primer3 online software, synthesized by Shanghai Yinghe Applied Biotechnology Co., Ltd. Details of the polymorphic loci and corresponding amplification primers are provided in .

(5) Statistical Analysis. All data were analyzed using SPSS 26.0 and R 4.4.2. For continuous variables, normally distributed data were expressed as mean $\pm$ standard deviation and compared between groups using independent samples t-tests; non-normally distributed data were expressed as median (Q_1, Q_3) and

compared using Mann-Whitney U tests. Categorical data were expressed as n(%) and analyzed using Chi-square or Fisher' s exact tests, with $P < 0.05$ considered statistically significant. ROC curve analysis was performed to determine the optimal cut-off value for anti-PLA2R antibody in distinguishing IMN from non-IMN, using the maximum Youden index. Hardy-Weinberg equilibrium was assessed using Chi-square tests. LASSO regression was employed for feature selection and predictive model construction. Model development and validation involved randomly splitting the sample in a 7:3 ratio (seed = 3) using the caret package in R, creating a training cohort (n = 140) and a validation cohort (n = 60). Eight machine learning algorithms were developed and evaluated based on F1 scores, decision curve analysis, and calibration plots to identify the optimal model. Feature importance was analyzed using SHAP (SHapley Additive exPlanations) values generated from the best-performing model, with SHAP summary plots illustrating feature impacts.

Results

Comparison of Baseline and Clinical Indicators Between IMN and Non-IMN Groups

The IMN group had a median age of 55.5 years, with 58% male patients and a hypertension prevalence of 57%. The non-IMN group had a median age of 36.5 years, 43% male patients, and a hypertension prevalence of 29%. Age and hypertension status differed significantly between groups ($P < 0.05$). Laboratory indicators showed that anti-PLA2R antibody levels, quantitative urine protein, and total cholesterol were significantly higher in the IMN group, while serum albumin, serum IgG, and IgA were significantly lower (all $P < 0.05$). Other indicators showed no significant differences. Detailed results are presented in .

Comparison of Baseline and Clinical Indicators Between Anti-PLA2R Antibody-Positive and -Negative IMN Patients

Among the 100 IMN patients, 63.37% were anti-PLA2R antibody-positive and 36.63% were negative. Antibody levels were 159.50 (68.75, 306.00) RU/ml in the positive group versus 2.00 (1.00, 10.00) RU/ml in the negative group ($P < 0.05$). No significant differences were observed in other clinical features ($P > 0.05$). Details are provided in .

Optimal Cut-off Value of Anti-PLA2R Antibody for IMN Diagnosis

ROC curve analysis of anti-PLA2R antibody for IMN diagnosis yielded an area under the curve of 0.83 (95% CI: 0.76–0.89, $P < 0.05$). Various cut-off values are shown in , with the optimal value determined to be 10.5 RU/ml, achieving sensitivity of 0.71, specificity of 0.94, positive predictive value of 0.92, and negative predictive value of 0.76. The ROC curve is illustrated in [Figure 1: see original paper].

SNP Quality Control Results

(1) Multiplex PCR Agarose Electrophoresis. PCR products were examined using 3% agarose gel electrophoresis. The DNA ladder ranged from 100 to 500 bp. Library fragments appeared at approximately 400 bp, indicating satisfactory quality control, as shown in [Figure 2: see original paper].

(2) Agilent 2100 Bioanalyzer Quality Control. After library purification, quality control was performed using the Agilent 2100 Bioanalyzer. The main peak appeared at 400 bp, confirming satisfactory quality, as depicted in [Figure 3: see original paper].

Genotype and Allele Frequency Distribution of PLA2R and HLA-DQA1 Genes

All six loci in the control group conformed to Hardy-Weinberg equilibrium ($P > 0.05$), confirming that study subjects originated from the same Mendelian population. Significant differences in genotype and allele frequencies were observed between IMN and non-IMN patients at all six loci ($P < 0.05$), as detailed in .

Genotype and Allele Frequency Distribution in Anti-PLA2R Antibody-Positive vs. -Negative IMN Patients

No statistically significant differences were found in genotype or allele frequencies of the six SNPs between anti-PLA2R antibody-positive and -negative IMN patients ($P > 0.05$).

Variable and Predictor Selection via LASSO Regression

Among the 28 variables analyzed, LASSO regression with 10-fold cross-validation selected six variables with non-zero coefficients: anti-PLA2R antibody concentration, age, serum creatinine, serum albumin, serum IgG, and rs2187668. The LASSO regression analysis is illustrated in [Figure 4: see original paper].

Detailed Performance Metrics of Each Model

Using the six variables selected by LASSO regression, eight machine learning models were constructed. The LightGBM model demonstrated optimal performance with AUC = 0.951, accuracy = 0.883, recall = 0.9, F1-score = 0.885, sensitivity = 0.9, and specificity = 0.867, significantly outperforming Logistic regression (AUC = 0.898) and single anti-PLA2R antibody diagnosis (AUC = 0.83). Model performance metrics are summarized in . Calibration curves showed the LightGBM model performed best among the eight models ([Figure 5: see original paper] and [Figure 6: see original paper]). Decision curve analysis (DCA) demonstrated that the LightGBM model provided greater net benefit and a wider threshold probability range compared to other models ([Figure 7: see original paper]).

Feature Importance and Model Interpretability Analysis of the LightGBM Model

In the LightGBM model, features were ranked by importance as follows: anti-PLA2R antibody concentration, serum albumin, rs2187668, age, serum IgG, and serum creatinine ([Figure 8: see original paper]). SHAP analysis generated a summary plot ([Figure 9: see original paper]) showing that blue regions represent samples with significant positive contributions to model predictions, while red regions indicate significant negative contributions. Higher antibody concentrations and older age increased SHAP values (positive contribution), whereas lower serum albumin, serum IgG, and serum creatinine decreased SHAP values (negative contribution).

A SHAP local interpretability plot ([Figure 10: see original paper]) illustrates how each feature contributes to IMN diagnosis for an individual patient sample. The baseline risk (E[f(x)]) of 0.5 indicates a 50% default probability without feature input, while f(x) represents the final predicted probability. Features in yellow with "+" signs positively contribute to IMN diagnosis, while red features with "-" signs negatively contribute. In this example, f(x) = 0.963 indicates a 96.3% probability of IMN, with high-weight yellow features (anti-PLA2R antibody, age) and red features (serum creatinine) driving the prediction.

Discussion

This study revealed significant differences in age and hypertension prevalence between IMN and non-IMN groups, with a median IMN onset age of 55.5 years, consistent with previous research [7]. Hypertension is common in autoimmune disease-related kidney disorders [8], and its prevalence increases with age. IMN patients frequently present with hyperlipidemia, which may indirectly increase hypertension risk by promoting atherosclerosis. As a common cause of nephrotic syndrome, IMN in this study was characterized by higher total cholesterol, triglycerides, LDL-C, and quantitative urine protein, and lower serum albumin compared to non-IMN patients. Additionally, lower serum IgG and IgA levels in IMN patients likely reflect loss of immunoglobulins through damaged glomerular filtration barriers.

Anti-PLA2R antibody concentrations were significantly higher in the IMN group (median 62.5 vs. 1 RU/ml), establishing it as a sensitive biomarker for distinguishing IMN from non-IMN. The ELISA kit manufacturer recommends $ $20 RU/mL as positive and <14 RU/mL as negative, with intermediate values considered equivocal. However, optimal thresholds vary across populations. Cheng et al. reported that $ $2.05 RU/mL yielded superior performance (AUC = 0.899, specificity = 0.945, sensitivity = 0.854) compared to the 20 RU/mL threshold [9]. Another single-center Chinese study of 252 IMN and 521 non-IMN patients identified 2.5 RU/mL as the optimal cut-off (sensitivity = 0.85, specificity = 0.88) [10]. Our ROC analysis confirmed an AUC of 0.83 with sensitivity 0.71 and specificity 0.94 at the 10.5 RU/ml threshold. This value

offers higher sensitivity than 14 or 20 RU/ml without compromising specificity, achieving a clinically practical balance. Variations in optimal thresholds across studies likely reflect population-specific genetic backgrounds influencing antibody expression. A limitation of this analysis is the lack of independent cohort validation, which may reduce reliability. While the positive predictive value suggests reliable positive results, negative results require integration with other markers, underscoring the importance of multimodal approaches for accurate non-invasive diagnosis.

In this study, only anti-PLA2R antibody status differed significantly between antibody-positive and -negative IMN groups, while other indicators such as urine protein and lipid profile showed no differences—contrasting with most published literature [9,11,12]. However, both groups in our cohort exhibited severe clinical manifestations. Possible explanations include: (1) some patients with antibody levels <20 RU/ml may still develop IMN, but high cut-off values classify them as negative; (2) involvement of alternative antigens such as THSD7A or NELL-1; or (3) false-negative antibody results. These findings suggest that anti-PLA2R antibody status may not be the sole determinant of baseline clinical phenotype, though its pathological significance warrants further mechanistic and prognostic investigation.

IMN is not a classic Mendelian disorder, but genetic contributions are increasingly recognized. A 2011 European GWAS identified strong associations between adult IMN and risk alleles in HLA-DQA1 (chromosome 6) and PLA2R1 (chromosome 2) [6], though the pathophysiological mechanisms remain unclear. Tian et al. validated higher prevalence of rs35771982, rs3749117, and rs4664308 in Chinese IMN cohorts, while rs3749119 and rs3828323 showed no significant differences. Notably, allele frequencies of rs4664308 differed between anti-PLA2R antibody-positive and -negative IMN patients [13]. Wang et al. reported that variants rs35771982, rs4664308, and rs3749117 were closely associated with IMN susceptibility in a Chinese population, while rs2187668 showed no significant correlation [14]. In contrast, Lv and Wang demonstrated strong associations between rs2187668 and IMN, with rs2187668-A as the susceptibility allele [15,16]. Our study examined six SNP loci (rs4664308, rs3828323, rs35771982, rs3749117, rs3749119, rs2187668) and found significant associations with IMN at both genotype and allele levels. The rs4664308-A allele significantly increased IMN risk, consistent with Tian' s findings [13]. The rs2187668-C allele emerged as a protective factor in our Chinese cohort, contradicting previous reports [14-16] and differing from GWAS findings in Caucasian populations where this locus conferred higher risk than PLA2R alleles [6]. Unlike Tian' s study [13], we found that the rs3828323-C allele significantly increased IMN risk, aligning with conclusions from Caucasian populations [17]. Some studies suggest rs3828323 may influence hypertension and renal outcomes in IMN patients [18]. Our finding that the rs35771982-G allele increased IMN risk aligns with Wang et al. [14] but contrasts with Tian et al., who identified the C allele as high-risk [13]. In African-American populations, this locus shows no association with IMN [19]. A meta-analysis of seven case-control studies reported associations

between rs3749117 and rs3749119 and IMN susceptibility in Asian populations, with T and C as risk alleles respectively [20], consistent with our results.

Within IMN patients, we found no significant differences in the six SNPs between anti-PLA2R antibody-positive and -negative groups, suggesting no clear association between genetic variation and antibody expression. This contrasts with Tian' s two-cohort study, which identified significant differences in allele distribution of rs4664308 and genotype/allele distributions of rs35771982 and rs4664308 between antibody-positive and -negative groups [13].

In summary, our genetic analysis concludes: (1) Risk alleles and genotypes in PLA2R (SNPs rs4664308, rs3828323, rs35771982, rs3749117, rs3749119) and HLA-DQA1 (SNP rs2187668) are closely associated with IMN susceptibility, with rs2187668-C serving as a protective factor in Chinese populations; (2) Genetic variation is not associated with anti-PLA2R antibody expression levels; (3) Discrepancies across studies likely stem from varying sample sizes, ethnicities, and study designs, particularly given the genetic heterogeneity among Chinese geographic populations.

LASSO regression selected six variables: anti-PLA2R antibody, age, serum creatinine, serum albumin, serum IgG, and rs2187668. Among eight ML models, LightGBM, Random Forest, and Xgboost achieved accuracy of 0.883, with LightGBM showing the highest AUC (0.951) and optimal F1-score, establishing it as the final diagnostic model.

The LightGBM model significantly outperformed antibody-alone diagnosis (AUC 0.951 vs. 0.83) and traditional logistic regression (AUC 0.951 vs. 0.898). Previous studies reported Xgboost models for IMN differentiation with accuracy 0.94 and AUC 0.985 [21]. Our feature importance and SHAP analysis identified core diagnostic variables as anti-PLA2R antibody, serum albumin, rs2187668, age, serum IgG, and serum creatinine, confirming the central value of the antibody. Cao et al. identified serum IgG, albumin, and antibody as key variables in their Xgboost model [21], indicating that IMN diagnosis requires multi-factor dynamic assessment.

Study limitations: (1) Single-center retrospective data may introduce selection bias, and larger sample sizes are needed to improve model generalizability; (2) Model performance requires validation in multi-center, prospective cohorts to confirm robustness across different populations; (3) High SNP detection costs may limit application in primary care settings.

In conclusion, anti-PLA2R antibody holds core value in non-invasive IMN diagnosis, particularly for patients at high risk for renal biopsy complications, with 10.5 RU/ml recommended as the optimal cut-off. PLA2R SNPs (rs4664308, rs3828323, rs35771982, rs3749117, rs3749119) and HLA-DQA1 SNP rs2187668 are associated with IMN susceptibility, with the rs2187668-C allele serving as a protective factor in Chinese populations. The LightGBM model constructed using LASSO-selected features (anti-PLA2R antibody, age, serum creatinine, serum albumin, serum IgG, and SNP rs2187668) demonstrates excellent clinical

value, providing an efficient and translatable multi-dimensional tool for precision diagnosis of IMN.

References

[1] Ronco P, Beck L, Debiec H, et al. Membranous nephropathy[J]. Nat Rev Dis Primers, 2021, 7(1): 69.

[2] Xu X, Wang G, Chen N, et al. Long-Term Exposure to Air Pollution and Increased Risk of Membranous Nephropathy in China[J]. J Am Soc Nephrol, 2016, 27(12): 3739-3746.

[3] Fogo A B, Lusco M A, Najafian B, et al. AJKD Atlas of Renal Pathology: Membranous Nephropathy[J]. Am J Kidney Dis, 2015, 66(3): e15-17.

[4] Beck L H, Bonegio R G B, Lambeau G, et al. M-Type Phospholipase A2 Receptor as Target Antigen in Idiopathic Membranous Nephropathy[J]. N Engl J Med, 2009, 361(1): 11-21.

[5] Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases[J]. Kidney Int, 2021, 100(4S): S1-S276.

[6] Stanescu H C, Arcos-Burgos M, Medlar A, et al. Risk HLA-DQA1 and PLA(2)R1 alleles in idiopathic membranous nephropathy[J]. N Engl J Med, 2011, 364(7): 616-626.

[7] Couser W G. Primary Membranous Nephropathy[J]. CJASN, 2017, 12(6): 983-997.

[8] Boesen E I, Kakalij R M. Autoimmune-mediated renal disease and hypertension[J]. Clin Sci (Lond), 2021, 135(17): 2165-2196.

[9] Cheng W, Cheng H, Wang G, et al. PLA2R-related membranous nephropathy serum anti-PLA2R antibody detection diagnostic threshold and influencing factors[J]. Chinese Journal of Practical Internal Medicine, 2022, 42(09): 761-765.

[10] Guo H, Yao Y, Zhou J, et al. The cutoff value and prognosis of anti-PLA2R antibody for idiopathic membranous nephropathy: a single-center retrospective study in China[J]. Ren Fail, 2023, 45(2): 2253922.

[11] Chu X, Xu X, He X, et al. Value of serum phospholipase A2 receptor antibody in remission of idiopathic membranous nephropathy[J]. Chinese Journal of Nephrology, 2018, 34(10): 752.

[12] Pan Y, Chen W D, Liu L, et al. Clinical Features and Pathology of PLA2R and THSD7A-Associated Membranous Nephropathy: A Single-Center Study from China[J]. Immunotargets Ther, 2024, 13: 385-398.

[13] Tian C X, Li L, Qiu P, et al. Association of SNPs in PLA2R1 with idiopathic and secondary membranous nephropathy in two Chinese cohorts[J]. Br J Biomed

Sci, 2020, 77(1): 24-28.

[14] Wang F, Wang T T, Liang X W, et al. PLA2R1 and HLA-DQA1 gene variations in idiopathic membranous nephropathy in South China[J]. Ann Acad Med Singap, 2021, 50(1): 33-41.

[15] Lv J, Hou W, Zhou X, et al. Interaction between PLA2R1 and HLA-DQA1 variants associates with anti-PLA2R antibodies and membranous nephropathy[J]. J Am Soc Nephrol, 2013, 24(8): 1323-1329.

[16] Wang W, Fan S, Li G, et al. Interaction between PLA2R1 and HLA-DQA1 variants contributes to the increased genetic susceptibility to membranous nephropathy in Western China[J]. Nephrology (Carlton), 2019, 24(9): 919-925.

[17] Coenen M J H, Hofstra J M, Debiec H, et al. Phospholipase A2 receptor (PLA2R1) sequence variants in idiopathic membranous nephropathy[J]. J Am Soc Nephrol, 2013, 24(4): 677-683.

[18] Fan S, Wang Q, Wang A Y, et al. The association between variants in PLA2R and HLA-DQA1 and renal outcomes in patients with primary membranous nephropathy in Western China[J]. BMC Med Genomics, 2021, 14(1): 123.

[19] Saeed M, Beggs M L, Walker P D, et al. PLA2R-associated membranous glomerulopathy is modulated by common variants in PLA2R1 and HLA-DQA1 genes[J]. Genes Immun, 2014, 15(8): 556-561.

[20] Sheng Q, Jian X, Zhang J, et al. Meta-analysis of PLA2R1 gene loci rs3749117 and rs3749119 single nucleotide polymorphisms and susceptibility to idiopathic membranous nephropathy[J]. Journal of Clinical Nephrology, 2021, 21(8): 636-642.

[21] Cao S, Yang S, Chen B, et al. Establishing a differential diagnosis model between primary membranous nephropathy and non-primary membranous nephropathy by machine learning algorithms[J]. Ren Fail, 2024, 46(2): 2253922.

Author Contributions

He Min: Conceptualized the study and designed the research protocol.

Liu Zhaoqi, Hong Libo, Wang Yutong: Conducted the experiments.

Huang Tingyu, Cai Tanying, Yao Ziyi: Collected, cleaned, and analyzed the data.

Liu Zhaoqi, Lin Juhua: Drafted the manuscript.

He Min: Revised the final version of the manuscript.

Note: Author contributions can be categorized as: (1) Study conception and design, including specific ideas or methods; (2) Study implementation, such as

conducting experiments or surveys; (3) Data acquisition, provision, and analysis; (4) Manuscript drafting or final revision. Each paper should specify individual contributions across these four categories. For multi-author papers, specific contributions must be detailed.

Note: Figure translations are in progress. See original paper for figures.