Life Sciences 229 (2019) 124–131

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Review article

Gene polymorphism and risk of idiopathic membranous nephropathy

Dongwei Liu, Jiahui Zhang, Yan Shi, Zhangsuo Liu*

Department of Nephrology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China
Research Institute of Nephrology, Zhengzhou University, Zhengzhou, China
Key Laboratory of Precision Diagnosis and Treatment for Chronic Kidney Disease in Henan Province, Zhengzhou, China
Core Unit of National Clinical Medical Research Center of Kidney Disease, Zhengzhou, China

ARTICLE INFO

Keywords:
Gene
MN
HLA
PLA2R
THSD7A
Gene marker

ABSTRACT

Membranous nephropathy (MN) is the most common primary glomerular disease (PGD) in the world. Currently, MN still lacks specific diagnostic markers and effective treatment strategy. It is speculated that the occurrence of MN is mainly related to environmental and genetic factors. The pathological manifestations of MN patients are diverse, significant differences in response to treatment options, and more reports on young MN patients suggest the importance of genes in the pathogenesis and diagnosis of MN. We will propose a novel perspective on the important role of genes in the pathogenesis of MN baced on the latest research.

1. Introduction

Membranous nephropathy (MN) is a nomenclature of pathological diagnosis, first described in 1959. In 1959, Heymann et al. first established the classic MN rat model, Heymann nephritis model, and they uncovered that the pathogenesis of MN is due to the deposition of immune complexes in situ in podocytes, and the target antigen is megalin, which is a rat podocyte antigen [1]. However, megalin is absent in the epithelial cells of MN patients, and anti-megalin antibody is not detected in the serum. Until 2002, the first podocyte antigen of human MN, the neonatal-neutral endopeptidase (NEP) was first found in a neonate born with membranous nephropathy. Maternal antibodies of neutral endopeptidase crossed the placenta and bound to fetal podocytes, then the immune complex was formed on the epithelial, induced the disease, neonatal MN, antenatally [2].

In 2009, Beck et al. demonstrated that the M-type phospholipase A2 receptor 1 (PLA2R1) is the major human target antigen of IMN. The anti-PLA2R1 antibodies were found in 70% of the IMN patients [3]. In 2014, Tomas et al. found the antibody of THSD7A in the serum of European and Boston PLA2R1-negative IMN patients [4]. The discovery of PLA2R1 and THSD7A autoantibodies has made us more convinced that the immune system plays an important role in the pathogenesis of MN. At present, MN is considered to be an autoimmune disease, which is mainly caused by autoantibodies recognizing glomerular podocyte target antigen. Electron compact deposits under the foot process and the epithelium can activate the complement system to form a membrane attack complex that causes podocyte damage. Systematically detection of target antigens is a key to uncover the pathogenesis of MN. The discoveries and researches of potential target antigens of the pathogenesis of MN may contribute to the specific and targeted diagnosis and treatment of MN patients [5].

The incidence of MN has increased rapidly in recent years. The kidney biopsy data from Nanjing, China, showed that the prevalence of MN increases from 8.89% in 1979–2002 to 18.42% in 2003–2013 [6]. And, from 1983 to 2015, MN in Hong Kong, China has accounted for 23.6% of nephrotic syndrome (NS) was reported in 2018 [7]. MN overlaps in 20% of cases of nephrotic syndrome in adults, and it is the leading cause of recurrent glomerulopathy after kidney transplantation (approximately 40%) [8]. And, MN is the most common primary glomerular disease (PGD) in Shandong, China which was reported in 2017 (about 43.3%) [9]. In Chinese elderly (≥65 years old), MN is also the most common PGD reported in 2014 [10].

Moreover, idiopathic membranous nephropathy (IMN) accounts for about 70–80% of MN [8]. And a data of 43.7 million Chinese hospitalized patients showed that the proportion of IMN in hospitalized PGN patients was increasing (from 4.5% in 2010 to 8.8% in 2015) [11].

It is speculated that the increase of MN may relate to the environmental pollution and the genetic anticipation of risk genes. The kidneys are particularly susceptible to environmental pollution and 20% cardiac output is delivered to the kidneys. Therefore, the environmental toxins will be concentrated while the kidneys are filtering the blood. The study by Hou et al. suggested that the occurrence of MN is related to PM2.5 [12]. A large cohort study of 2 million US veterans found that long-term exposure to PM2.5, PM10, nitrogen dioxide and carbon monoxide is

* Corresponding author at: No. 1, Jianshe East Road, Zhengzhou 450052, Henan Province, China.
E-mail address: zhangsuoliu@zzu.edu.cn (Z. Liu).

https://doi.org/10.1016/j.lfs.2019.05.010
Received 24 March 2019; Received in revised form 30 April 2019; Accepted 6 May 2019
Available online 07 May 2019

associated with the development of CKD [13].

Particulate matter of environmental pollution can be inhaled through the respiratory tract, and particles with a diameter of 5 μm or less are easily deposited in the bronchioles and alveoli. Thereby the particles can destroy the airway epithelial barrier by several pathways, induced oxidative stress, phagocytosis impairment of alveolar cells, inflammatory cell infiltration and immune dysfunction. Lung inflammatory mediators may spill into the circulation, cause systemic inflammation, oxidative stress and other organ damage. PM2.5 deposited in the alveoli can also activate the autonomic nervous system. Thus, the particulate matter cause autonomic nervous system dysfunction, systemic oxidative stress and organ damage. In addition, deposited ultrafine particles may be transferred directly to the circulatory or lymphatic system then lead to coagulation and fibrinolysis dysfunction and non-pulmonary tissue impairment [14]. Importantly, several studies have unraveled that inhaled particles whose diameter is 30 nm or less can be transferred from the lungs to the circulation system, and will be selectively accumulated in the inflammation site of vascular, while it be filtered and excreted by the kidneys [15].

However in places where PM2.5 is relatively low, such as southwestern China, the incidence of MN also increases. Fig. 1 showed that the environmental factors were excluded, while genetic factors played a major role in the progress of MN. With the development of genomics, we have more information of the genes involved in the disease. It has been found that the polymorphism of C1Q is related to the genetic anticipation of renal amyloidosis in Japan and Portugal [16]. MN is also a disease that tends to be younger. It is mainly observed in the middle-aged and elderly population past, however, it is still predisposed in youth as well as some children now, a study has collected 7962 renal biopsy data from children aged 0–18 in 115 hospitals in China between 2004 and 2014, the study found that MN is the third leading cause of NS in girls and the second leading cause of NS in children aged 13–18 [17]. This phenomenon might be related to the early onset of the biological manifestation of the genotypes that appear in the middle-aged and elderly. We speculate that the risk genes associated with MN are involved in the phenomenon of MN genetic anticipation, as a result of the MN patients became younger and younger. Unfortunately, there is no relevant research report yet, and our team is working on patients with familial membranous nephropathy. And there is no report on the risk genes involved in the genetic anticipation of MN, and our team is working in the field, familial membranous nephropathy as well.

Although we know the importance of gene polymorphism in the progress of MN, and PLA2R and TSHD7A have a high sensitivity and specificity, albeit without genetic diagnosis markers. Immunosuppressive agents and non-specific reduction in proteinuria are the criteria used in the clinical treatment of MN [18]. On the other hand, we found that some patients with MN have different responses to hormones and immunosuppressive agents, although the clinical and pathological features are similar. Some patients do not respond to immunosuppressive therapy, and some II-III IMN patients are better than I IMN in clinical immunosuppressive therapy. A third of IMN patients went into remission spontaneously, a third went into remission after treatment, and a third exhibited continuous aggravation after treatment. This suggested that individual heterogeneity and genetic polymorphism might be crucial factors that lead to differences in efficacy, necessitating an in-depth interpretation of the genetic polymorphism of MN for a clinically precise treatment and individualized medication (Fig. 1).

Genetic polymorphism refers to the simultaneous or frequent presence of ≥2 different genotypes or alleles in the same biological population [19]. This polymorphism is derived from the difference in the copy number of the repeats in the genome or from single copy sequence variation, known as copy number variant (CNV) and single nucleus polymorphism (SNP); the most common and deeply investigated polymorphism is SNP [20]. In recent years, the gene polymorphism of IMN has been studied extensively [21,22]. Thus, herein, we presented recent

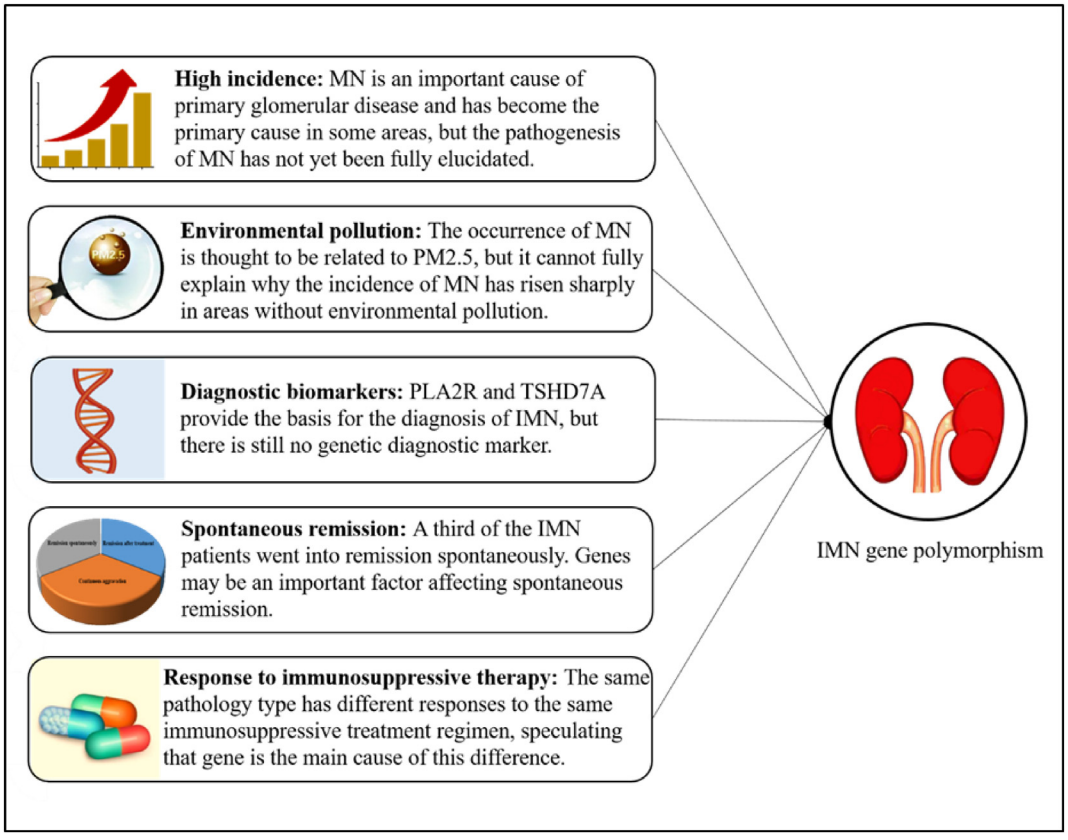

Fig. 1. The necessity of conducting IMN gene polymorphism research.

Table 1
Risk genes of IMN in different races.

Gene name	SNP database ID	Location	Race	Published year	Author
DQA1	SNP rs9272729	2:3942806	European ancestry	2016	Sekula P
	SNP rs28383345	2:3938519	Chinese Han	2017	Qin XS
	SNP rs2187668	2:3939169	French/Dutch/Chinese Han/British/Spanish/South Asians	2011;	Stanescu HC;
				2017;	Qin XS;
				2017;	Cui Z;
				2015;	Ramachandran R;
				2014	Bullich G
DQB1*0602			Japanese	2016	Thiri M
DRB1*1501		6p21.32	Japanese, Chinese Han	2017;	Cui Z;
				2016;	Thiri M;
				2017	Le WB
DRB1*0301		6p21.32	Chinese Han	2017	Cui Z
DRB3*0202		6p21.3	Chinese	2017	Le WB
TNF-α −308A		6p21.23	Bergamo	2007	Thibaudin D
TNFd2		6p21.23	Caucasians	2007	Thibaudin D
TAP1B				1994	Chevrier D
THSD7A		7p21.3		2016;	Larsen CP;
				2014;	Tomas NM;
				2018;	Ren S;
				2017	Wang J
PLA2R	SNP rs35771982	2:160028907	Chinese/Japanese/Caucasians	2018;	Kaga H;
				2014;	Saeed M;
				2013	Lv J
	SNP rs17830558	2:160021853	European ancestry	2016	Sekula P
	SNP rs4664308	2:160060986	Chinese/Spanish/Rench/Dutch/British/South Asians/Indian	2017;	Cui Z;
				2014;	Bullich G;
				2017;	Sanjana G;
				2013	Lv J
	SNP rs3749119	2:160062509	Japanese/South Asians/Indian	2015;	Ramachandran R;
				2016;	Thiri M;
	SNP rs3749117	2:160028931	Chinese/South/Asians/Dutch/Indian	2015;	Ramachandran R;
				2017;	Sanjana G;
				2013	Lv J
	SNP rs3792189	2:160029361	Dutch	2017	Sanjana G
	SNP rs3792192	2:160030364	Dutch	2017	Sanjana G
	SNP rs6722275	2:160036749	Dutch	2017	Sanjana G
	SNP rs2715928	2:160057088	Japanese	2016	Thiri M
	SNP rs16844715	2:160058595	Japanese	2016	Thiri M
IL-4590T		5q31.1	Bergamo	2015	Giacomelli M
IL-4 −33T		5q31.1	Bergamo	2015	Giacomelli M
IL-10 −1082G		1q32.1	Bergamo	2015	Giacomelli M
IL-6 C-572G	SNP rs1800796	7:22726627	Taiwanese Han	2010	Chen SY
STAT4	SNP rs3024912	2:191028361		2011	Chen SY
	SNP rs3024908	2:191029415		2011	Chen SY
MBL2 O allele of exon 1		10q21.1	Brazilian	2018	do Nascimento Costa DM
MBL2 A/O genotype		10q21.1	Brazilian	2018	do Nascimento Costa DM
TLR9	SNP rs352139	3:52224356	Taiwanese	2013	Chen YT
	SNP rs352140	3:52222681	Taiwanese	2013	Chen YT
TLR4	SNP rs10983755	9:117702392	Taiwanese	2010	Chen SY
	SNP rs1927914	9:117702447	Taiwanese	2010	Chen SY
	SNP rs10759932	9:117702866	Taiwanese	2010	Chen SY
	SNP rs11536889	9:117715853	Taiwanese	2010	Chen SY
UG G38A			Taiwanese children	2018	Kılıc BD
NPHS1	SNP rs401824	19:35852007	Taiwanese	2010	Lo WY
	SNP rs437168	19:35843517	Taiwanese	2010	Lo WY
MYH9	SNP rs12107	22:36281936	Taiwanese/Xinjiang Uygur	2013;	Chen YT;
				2016	Guo Y
PAI-1 4G5G/4G4G		7q22.1	Chinese	2008	Chen CH

evidence from both preclinical and clinical studies to propose a genetic polymorphism perspective on IMN.

2. Genes localized on HLA complex class II and III

Human lymphocyte antigen (HLA) is a highly polymorphic allogeneic antigen. It belongs to the class of glycoproteins and is noncovalently bound by an α heavy chain (glycosylated) and a β light chain, localized on chromosome 6p21-23. HLA antigen has become an emerging research area in immunogenetics, immunobiology, and biochemistry [23]. HLA is classified into class I, II, and III antigens, according to the location and function [24]. The gene of HLA class I is in the order of three positions B, C, and A, class II is composed of three sub-regions, DP, DQ, and DR, and class III is mainly composed of C2, C4A, C4B, and Bf. The HLA locus was first described to be related to MN in 1979 [25].

2.1. Genes located on HLA class II

HLA-DQ a-chain 1 (*HLA-DQA1*) is one of the maximally studied genes located on HLA class II. Some researchers explored the association between HLA complex genes and MN in 323 MN patients of European ancestry and 345 healthy controls. In addition, HLA-DQA1 rs9272729 was founded to be significantly associated with MN patients

of European ancestry by a combined approach of GWAS, genotype imputation, HLA imputation. However, the study could not deduce whether the MN patients were IMN or SMN or both [26].

Some researchers performed independent genome-wide association studies of single nucleotide polymorphisms (SNPs) in patients with IMN in 3 Caucasian, 75 French, 146 Dutch, and 335 British patients. The results revealed that the HLA complex class II HLA-DQA1 (SNP rs2187668), located on chromosome 6p21, was significantly associated with IMN patients in 3 Caucasians ($P = 1.8 \times 10^{-9}$, $P = 5.6 \times 10^{-27}$, and $P = 5.2 \times 10^{-36}$ in the French, Dutch, and British patients, respectively); also, the HLA-DQA1 rs2187668 is closely related to IMN in Caucasians. This allele can promote an autoimmune response against some targets such as PLA2R1 [27]. Also, another study was conducted on the association between HLA SNPs and IMN in Chinese Han population, and the HLA-DQA1 rs2187668 and rs28383345 were correlated with IMN in 509 patients and 601 healthy controls independently and significantly [28]. Moreover, HLA-DQA1 rs2187668 was associated with IMN in another case-control study with 261 IMN patients and 599 healthy controls of Han Chinese origin [29]. HLA-DQA1 rs2187668 was also validated as a risk factor of IMN in Spanish and South Asians cohorts [30,31]. The mechanism stated that the HLA-DQA1 was significantly associated with high circulating anti-PLA2R1 antibodies in a European cohort [32].

HLA-DRB1 also is one of the most studied genes located on HLA class II. DRB1*1501 and DRB1*0301 were identified as independent risk alleles for IMN in a case-control study with 261 IMN patients and 599 healthy controls of Chinese Han origin. Also, interaction between rs4664308 of PLA2R and HLA-DRB1*1501/DRB1*0301 facilitated the same among arginine13, alanine71 encoded by DRB1*1501, lysine71 encoded by DRB1*0301, and T cell epitopes of PLA2R. Furthermore, these structural models suggested that the association between HLA and IMN might be related to the interaction between HLA and circulating anti-PLA2R1 antibodies [29]. HLA-DRB1*1501 and HLA-DQB1*0602 are strongly associated with IMN in a study with 53 patients and 419 healthy controls of Japanese ethnicity [33].

HLA-DRB1*1501 and HLA-DRB3*0202 confirmed the increased risk of IMN related to PLA2R, independently and strongly. However, no significant increase in the risk of IMN was noted after adjusting for HLA-DRB1*1501 and HLA-DRB3*0202. This evidence demonstrated a robust and independent association between HLA-DRB1*1501 and HLA-DRB3*0202 with IMN related to PLA2R in the Chinese population. The study also validated the findings in another independent experiment with 293 IMN patients related to PLA2R and 285 healthy controls [34].

The risk SNPs of HLA in different races are shown in Table 1.

TAP gene is localized on the HLA class II gene region, and the product encoded by the *TAP* gene is involved in the initiation and regulation of the immune response [35]. Another study reported that the frequency of *TAP1* B allele was significantly higher in patients with MN as compared to the controls (44 MN patients and 70 healthy controls) [36]. However, the study did not provide information whether the MN patients were IMN or SMN or both.

2.2. Genes located on HLA class III

TNF-α is a pro-inflammatory factor produced by macrophages and monocytes. The human *TNF-α* gene is localized at 6p21.33 and is linked to the *HLA* gene in the HLA class III region between the HLA-B and HLA-C2 sites, consisting of TNFα and TNFβ. The biological activity of TNFα accounts for 70–95% of the total activity of TNF [37]. The −308A of *TNF-α* gene was significantly increased in IMN patients as compared to healthy controls in a study of Bergamo with 45 IMN patients and 124 healthy controls, thereby suggesting that the polymorphism of *TNF-α* is related to IMN in Bergamo species.

The polymorphism and distribution of −308 TNF-α and TNFd were analyzed in a case-control study comprising of 100 Caucasians patients with IMN and 232 Caucasians controls. The results showed that TNFd2 allele was significantly associated with the occurrence/initiation of IMN in Caucasians [38]. In addition, high-frequency A-allele of TNF-α was associated with high serum levels of TNF-α in IMN patients [39]. The HLA risk genes of IMN are shown in Table 1.

3. *PLA2R* gene: highly anticipated in detection and treatment

M-type phospholipase A2 receptor 1 (PLA2R1) is a type I transmembrane receptor and belongs to the mammalian mannose receptor family, and is mainly expressed in podocytes [40]. The in situ immune complex is formed by the binding of PLA2R autoantibodies that are expressed in IMN patients on the surface of podocytes. Subsequently, the complement system will be activated through the bypass and mannose-binding lectin pathway, resulting in the formation of C5b9 attacking membrane complex, which damages the podocytes [41]. The M-type *PLA2R* gene is located on chromosome 2q23-24. The polymorphism might affect the function of the *PLA2R* gene, and the genetic variation encoding the PLA2R protein is related to the development of IMN [42]. Also, many SNPs within PLA2R were studied among different races.

In 2009, the main target antigen of IMN was found to be the M-type phospholipase A2 receptor 1 (PLA2R1). The anti-PLA2R1 antibodies were found in 70% of the IMN patients, but no anti-PLA2R antibodies were found in the secondary membranous nephropathy (SMN), disease control, and healthy subjects, suggesting that M-type PLA2R is closely related to the occurrence of IMN [3]. Reportedly, the detection rate of PLA2R was 82% in Chinese IMN patients [43], 74% in Iranian IMN patients, and 53% in Japanese IMN patients [44,45].

A study from Japan included 58 patients with IMN, 26 patients with secondary MN (SMN), and 50 patients with other diseases. The investigators selected 6 SNPs in PLA2R1, and the genomic DNA of peripheral monocytes from each patient was used for sequencing. The results showed a strong genetic association between IMN and SNP rs35771982 within PLA2R1 in 2017. The study also found a common variant in PLA2R1, especially rs35771982 that regulates the progress of IMN with HLA-DQA1 in Caucasians [46]. A large case-control study involving 1512 participants explored the relevance of different subtypes in MN patients with PLA2R-positive and negative. Subsequently, four independent analyses were conducted, and the most relevant SNP was found to be PLA2R1 SNP rs35771982 in MN patients with PLA2R-positive ($P = 1.4 \times 10^{-14}$, odds ratio = 1.98); the PLA2R1 polymorphism was associated with PLA2R-positive MN patients, predominantly in Caucasians, while no association with MN was detected in African Americans [47]. The only drawback is the study does not provide information that the MN patients were IMN or SMN or both.

A prospective study analyzed the association of PLA2R with IMN among Indians. A total of 114 adult IMN patients were enrolled, and PLA2R was assessed by enhanced glomerular staining on fresh frozen tissue before treatment and after 6 and 12 months of therapy. 5 SNPs (rs4664308, rs3749119, rs3749117, rs3828323, and rs2187668) were genotyped by TaqMan assay, and 95 healthy participants served as the controls. The result demonstrated that > 2/3rd of the Indians are PLA2-positive as assessed by enhanced glomerular staining, and SNPs rs3749119, rs3749117, and rs4664308 in PLA2R1 were significantly associated with IMN. The patient containing risk genes have high levels of PLA2R [30].

A Spanish study recruited 89 IMN patients and 286 individuals without renal dysfunction. A case-control study was performed, and the effect of PLA2R1 rs4664308 on the clinical prognosis and renal function was analyzed; the PLA2R1 rs4664308 was confirmed as a risk factor of IMN [31]. Thus, PLA2R1 rs4664308 is found to be a robust SNP associated with IMN in Rench, Dutch, and British cohort [48].

A study about PLA2R1 polymorphism was conducted in Japan in 2016. A total of 15 PLA2R1 SNPs were precisely positioned among 53 IMN patients and 419 healthy controls, of which SNP rs3749119

showed a strong correlation with IMN in Japan. The study demonstrated that PLA2R1 rs2715928 and rs16844715 were strongly associated with IMN [42]. Also, PLA2R1 SNP rs3749119 was significantly associated with IMN in South Asians [39].

Furthermore, three SNPs rs35771982, rs3749117, and rs4664308 of PLA2R1 were genotyped in 2132 Chinese individuals, including 1112 patients with IMN and 1020 healthy controls. The results showed that these SNPs are related to the occurrence of IMN in Chinese individuals; among those carrying the two risk SNPs, 73% had anti-PLA2R antibodies, and 75% expressed PLA2R in the glomeruli [49]. The SNP rs3749117 showed a significant association with IMN in Dutch and South Asian cohort [30,48].

Another study showed that SNPs rs3792189, rs3792192 and rs6722275 on chromosome 2 were localized within PLA2R1 and were significantly associated with IMN in the Dutch cohort [48]. Also, the PLA2R1 rs17830558 was demonstrated as a risk locus for MN as detected by genome-wide association studies (GWAS) in 323 MN European ancestry cases and 345 controls except for the MN patients involved in this study are IMN or SMN patients or both is not known [26].

Patients with a high-risk genotype had high anti-PLA2R levels [30]. IMN caused by PLA2R might causes changes in amino acids, which alters the molecular structure of PLA2R, exposing the epitope of PLA2R, stimulating the body to produce specific anti-PLA2R antibodies, and leading to the onset of IMN. Fig. 1 illustrates the risk SNPs of PLA2R in different races. The PLA2R risk genes of IMN are shown in Table 1.

4. *THSD7A*: new prospects for genetic diagnosis

Thrombospondin type-1 domain-containing 7A (THSD7A) is expressed in placental vascular endothelial cells and plays a role in endothelial cell migration and angiogenesis. A previous study evaluated the expression of THSD7A by immunofluorescence staining of kidney biopsy samples and concluded that THSD7A is expressed in podocyte foot processes [50].

The antibodies of THSD7A were detected by Tomas et al. in 2014 in European and Boston IMN patients' serum using anti-PLA2R1-negative. Simultaneously, immunohistochemistry of renal biopsy samples showed that THSD7A is a 250-kDa glomerular protein localized to podocytes. The study proved that THSD7A is the second self-antigen involved in the pathogenesis of adult IMN [4]. Another meta-analysis in 2017 showed that the detection rate of THSD7A was about 3% in all IMN patients and 10% in PLA2R1-negative IMN patients. Moreover, in patients with THSD7A-positive, the incidence of malignancies varied from 6% to 25% [51]. Reportedly, about 2% were THSD7A-positive among 578 Chinese patients with IMN, and 16% were THSD7A-positive in PLA2R1-negative IMN patients [52]. Similarly, enhanced granular expression of THSD7A was 9.1% as detected in 92 Japanese IMN patients [53].

Although there is no relevant report on the polymorphism of THSD7A gene, THSD7A has already revealed its potential as a marker for genetic diagnosis in related IMN research. The combined application of THSD7A and PLA2R gene detection is expected to provide important reference value for the diagnosis of IMN.

5. Genes related to cytokines

5.1. IL-4, IL-6, and IL-10

IL-4 is a cytokine produced by activated T cells and mast cells. It enhances the expression of HLA class II antigen. IL-10 is primarily produced by Th2 cells that play an immunoregulatory role by inhibiting the macrophages [54]. The frequencies for −590T and −33T alleles of *IL-4* gene were significantly increased in IMN patients as compared to healthy controls in the study with 45 IMN patients and 124 healthy controls from Bergamo race. Also, the frequency of −1082G allele of the *IL-10* gene was increased in the subgroup of patients with CD4/CD8 ratio > 2. Thus, it was deduced that the polymorphic variants of *IL-4* and *IL-10* genes are associated with the pathogenesis of IMN [55].

Some researchers investigated the effect of IL-6C-572G SNP rs1800796 on MN in Taiwanese Han population, which included 265 controls and 106 IMN patients. The IL-6C-572G SNP was genotyped by restriction fragment length polymorphism assay. The result showed a significant difference between the genotype and allele frequency distributions of IL-6C-572G SNP between IMN patients and controls. Individuals with IL-6C-572G SNP C allele or CC genotype showed a high risk of IMN [56].

5.2. STAT4 gene polymorphisms

Signal transducer and activator of transcription 4 (STAT4) is a member of the STAT family. STAT is involved in a variety of cytokine-mediated JAK/STAT signaling pathways and is closely related to cell proliferation, apoptosis, and immune regulation [57]. The association between three *STAT4* gene polymorphisms (rs3024912, rs3024908, and rs3024877) and the susceptibility to MN was analyzed in 403 Taiwanese individuals (138 MN patients and 265 healthy controls). The result showed a different distribution of *STAT4* rs3024912 and rs3024908, and the MN patients with GG genotype at rs3024912 SNP have a high risk of renal failure. The pity is that the author does not provide information that the MN patients involved in this study were IMN or SMN or both, still, this phenomenon also indicated that STAT4 rs3024912 and rs3024908 are the underlying reasons for MN [58].

6. Other susceptibility genes

6.1. Mannose-binding lectin2 (MBL2) gene polymorphisms

Mannose-binding lectin (MBL) is a glycoprotein widely distributed in plants and animals. It causes the cells to aggregate or precipitate glycoconjugates. Also, it can identify N-galactosamine and mannose on the surface of various pathogenic microorganisms, and then, activate MASP-1, MASP-2, C4, C2, and C3, which activates the complement system [59].

The polymorphisms of exon 1 (codons 52, 54, and 57) in *MBL2* gene and single base polymorphisms at positions −550 (HL) and −221 (XY) in the promoter region were analyzed in 60 patients (35 IMN and 25 SMN) and 101 controls from Brazilian. The results showed that MN patients carry the O allele of exon 1 variant at a frequency of 2.54-fold and the A/O genotype at a frequency of 11.16-fold as compared to the control group. The MN patients with combined genotypes (YA/O, XA/O, and O/O) are often associated with defective MBL production [60].

6.2. Urokinase plasminogen activator (uPA) gene polymorphism

The human *uPA* gene is localized on chromosome 10. uPA binds to uPA receptor (uPAR), triggers the cleavage of plasminogen to plasmin, and reduces the fibrinolysis of the kidney [61].

The level of urinary uPA in patients with fibrotic deposits in the glomeruli was significantly lower than in those without fibrotic deposits. Moreover, the decreased levels of urinary uPA and plasminogen activity in the glomeruli contribute to the process of glomerular disease [62].

The association between the 3′-UTR C/C genotype of the urokinase gene and end-stage renal disease (ESRD) or acquired immune system tumor in IMN patients in Taiwan has been reported. Another study about the association between 3′-UTR and IMN was conducted in 91 patients and 105 healthy controls from Taiwan. Although no significant difference was observed in the distribution of 3′-UTR genotype in IMN patients and healthy controls, the urokinase gene 3′-UTR C/C genotype was correlated with ESRD or acquired immune system tumor in IMN Taiwanese patients [63].

6.3. Toll-like receptor 9 (TLR9) and Toll-like receptor 4 (TLR-4) gene polymorphisms

TLR9 belongs to the Toll-like receptor family and is expressed on the organelles' membrane of innate immune cells. It mainly recognizes the bacterial or viral unmethylated CpG DNA in the cytoplasm and induces the production of pro-inflammatory cytokines by triggering the MyD88-dependent signal transduction pathway [64]. Previous studies showed that the level of TLR9 increased in lupus nephritis and glomerulus [65].

A study investigated the *TLR9* gene polymorphisms in 397 Taiwanese individuals (134 MN patients and 263 healthy controls) as detected by polymerase chain reaction. The result showed that AA genotype at SNP rs352139 and GG genotype at SNP rs352140 were significantly associated with Taiwanese IMN patients; also, IMN patients with A-G type were susceptible to the decrease in renal function. These SNPs are promising markers of the susceptibility to IMN in Taiwanese patients after 27 years of follow-up [66].

TLR4 is localized on 9q32-33. TLR4 recognizes Gram-negative lipopolysaccharide (LPS) and heat-shock proteins (HSP) released by host necrotic cells [67].

A study analyzed the association between *TLR4* gene polymorphism and clinical manifestations and pathogenesis of IMN, constituting 134 MN patients and 263 healthy controls. The *TLR4* gene polymorphism was typed by a specific polymerase chain reaction method. Although, whether the MN patients are IMN or SMN patients or both is not provided in this study. A significant differences in *TLR4* gene rs10983755 A/G ($P < .001$) and rs1927914 A/G ($P < .05$) between control and MN patients was founded in this study. Also, the distribution of rs10759932 C/T and rs11536889 C/T polymorphisms were significantly different in both groups. The proteinuria ratio of patients with non-AA genotype was significantly higher than that of AA. These results suggested that the genotype distribution of the *TLR4* gene in MN patients and healthy controls are related to the pathogenesis of MN [68].

6.4. Uteroglobin (UG) gene polymorphism

UG regulates the concentration of progesterone into the blastocyst [69]. *UG* gene polymorphism (G38A) has a critical role in the development of childhood idiopathic nephrotic syndrome (INS) after investigating the distribution of AA, GG, and AG genotypes in the *UG* gene, and the polymorphism of G38A was related to the steroid response in Taiwanese children [70].

6.5. NPHS1 gene polymorphisms

Nephrin is a cell adhesion protein specifically expressed in the rhizosphere membrane of renal podocytes. The normal structural function of the podocytes and the integrity of the glomerular filtration barrier is maintained by the adhesion of Nephrin protein and signal transduction composed of Nephrin and podocin [71]. The association between SNPs (rs401824, rs437168, and rs3814995) at chromosomal loci 41034749 (5′ UTR), 41026259 (exon17), and 41034052 (exon 3) and MN was assessed in 389 Taiwanese individuals (132 MN patients and 257 healthy subjects). The results showed a significantly different distribution of rs437168 in MN patients and healthy controls, and the AA genotype of rs401824 and GG genotype of rs437168 was associated with the low remission in MN patients [72]. However, the present study did not provide the information on whether the MN patients involved were IMN or SMN or both.

6.6. MYH9 gene polymorphisms

MYH9 gene is localized on chromosome 22 [73]. It encodes non-muscle myosin IIA (NMMHC-IIA) protein, a hexamer composed of two heavy chains and two pairs of light chains, expressed in glomerular podocytes and mesangial cells [74,75]. A study with 135 MN patients and 265 healthy controls analyzed the association between *MYH9* gene polymorphisms (rs7078 and rs12107) and the susceptibility to MN in Taiwanese individuals. The results implied that rs12107 might be related to the occurrence of MN in Taiwanese patients, and those with AA genotype at the rs12107 SNP have a higher risk of renal failure as compared to other MN patients [76]. However, that the study did not demonstrate whether the MN patients were IMN or SMN or both. In addition, some studies reported that *MYH9* gene rs12107 locus CC genotype and C allele are associated with the susceptibility to IMN as observed in Xinjiang Uygur population [77].

6.7. PAI-1 gene polymorphisms

Plasminogen activator inhibitor-1 (PAI-1) is a major regulator of the fibrinolytic system. It acts as an antifibrinolytic agent by binding to plasminogen activator that reduces the fibrin degradation and maintains the balance between fibrinolytic and coagulation systems in human blood. The PAI-1 activity plays a major role in renal tissue fibrosis [78]. Some studies investigated the correlation between *PAI-1* gene polymorphisms and IMN in 246 individuals (104 IMN patients and 142 healthy controls) and found that patients with IMN carrying 4G5G and 4G4G of the *PAI-1* gene have a high risk of vascular-related complications and reduced renal function as compared to patients with 5G5G of the *PAI-1* gene [79].

6.8. ACE, AGT, eNOS

Association between *ACE/AGT/eNOS* genes and IMN patients in Chinese Xinjiang Uygur was explored in 135 Xinjiang Uygur (45 IMN patients, 45 Uygur patients, and 45 Uygur healthy controls) in 2016. The results showed that *ACE/AGT/eNOS* genes are not the risk factors of IMN patients in Chinese Xinjiang, but are associated with the progress of IMN [80]. The risk genes of IMN are shown in Table 1.

The diagnosis of MN has made a breakthrough, and the discovery of PLA2R antibody makes the non-invasive diagnosis of MN possible.

However, the mechanism of IMN is yet unknown. IMN is not only related to environmental factors but also genetic factors. Large sample validation experiments and mechanism need further exploration with respect to IMN studies. At present, our center has started the gene sequencing of early-onset IMN patients in order to further understand the influence of gene polymorphism on the occurrence and treatment response of young and early-onset IMN patients. Nevertheless, IMN gene polymorphism and individualized medication need further investigation to achieve accurate the treatment of MN, to improve the clinical efficacy of IMN patients, to reduce the side effects of immunosuppressive therapy, and to improve the outcome of IMN patients. In addition, the exploration of biomarkers and gene polymorphisms is essential in pla2R and TSHD7A double-negative IMN patients.

Funding

This work was supported by grants from the Natural Science Foundation of Henan Province (Grant No. 162300410282).

Declarations of interest

All authors declare no conflicts of interest.

Author's contribution

Dongwei Liu searched the literature and write this article, Jiahui Zhang and Yan Shi searched the literature and participate in discussions, Zhangsuo Liu participated in the discussion and revised the article.

References

[1] W. Heymann, D.B. Hackel, S. Harwood, et al., Production of nephrotic syndrome in rats by Freund's adjuvants and rat kidney suspensions, Proc. Soc. Exp. Biol. Med. 100 (4) (1959) 660–664.

[2] H. Debiec, V. Guigonis, B. Mougenot, et al., Antenatal membranous glomerulonephritis due to anti-neutral endopeptidase antibodies, N. Engl. J. Med. 346 (26) (2002) 2053–2060, https://doi.org/10.1056/NEJMoa012895.

[3] L.H. Beck Jr., R.G. Bonegio, G. Lambeau, et al., M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy, N. Engl. J. Med. 361 (2009) 11–21, https://doi.org/10.1056/NEJMoa0810457.

[4] N.M. Tomas, L.H. Beck Jr., C. Meyer-Schwesinger, et al., Thrombospondin type-1 domain-containing 7A in idiopathic membranous nephropathy, N. Engl. J. Med. 371 (24) (2014) 2277–2287, https://doi.org/10.1056/NEJMoa1409354.

[5] P. Ronco, H. Debiec, A podocyte view of membranous nephropathy: from Heymann nephritis to the childhood human disease, Pflugers Arch. 469 (7–8) (2017) 997–1005, https://doi.org/10.1007/s00424-017-2007-x.

[6] J.H. Hou, H.X. Zhu, M.L. Zhou, et al., Changes in the spectrum of kidney diseases: an analysis of 40,759 biopsy-proven cases from 2003 to 2014 in China, Kidney Dis. 4 (1) (2018) 10–19, https://doi.org/10.1159/000484717.

[7] J.K.C. Ng, T.K.W. Ma, F.M.M. Lai, et al., Causes of nephrotic syndrome and nephrotic-range proteinuria are different in adult Chinese patients: a single centre study over 33 years, Nephrology 23 (6) (2018) 565–572, https://doi.org/10.1111/nep.13061.

[8] P. Ronco, H. Debiec, Pathophysiological advances in membranous nephropathy: time for a shift in patient's care, Lancet 385 (9981) (2015) 1983–1992, https://doi.org/10.1016/S0140-6736(15)60731-0.

[9] L. Tang, J. Yao, X. Kong, et al., Increasing prevalence of membranous nephropathy in patients with primary glomerular diseases: a cross-sectional study in China, Nephrology 22 (2) (2017) 168–173, https://doi.org/10.1111/nep.12739.

[10] B. Jin, C. Zeng, Y. Ge, et al., The spectrum of biopsy-proven kidney diseases in elderly Chinese patients, Nephrol. Dial. Transplant. 29 (12) (2014) 2251–2259, https://doi.org/10.1093/ndt/gfu239.

[11] J. Li, Z. Cui, J. Long, et al., Primary glomerular nephropathy among hospitalized patients in a national database in China, Nephrol. Dial. Transplant. (2018), https://doi.org/10.1093/ndt/gfy022.

[12] X. Xu, G. Wang, N. Chen, et al., Long-term exposure to air pollution and increased risk of membranous nephropathy in China, J. Am. Soc. Nephrol. 27 (12) (2016) 3739–3746, https://doi.org/10.1681/ASN.2016010093.

[13] B. Bowe, Y. Xie, T. Li, et al., Particulate matter air pollution and the risk of incident CKD and progression to ESRD, J. Am. Soc. Nephrol. 29 (1) (2018) 218–230, https://doi.org/10.1681/ASN.2017030253.

[14] X. Xu, S. Nie, H. Ding, et al., Environmental pollution and kidney diseases, Nat. Rev. Nephrol. 14 (5) (2018) 313–324, https://doi.org/10.1038/nrneph.2018.11.

[15] M.R. Miller, J.B. Raftis, J.P. Langrish, et al., Inhaled nanoparticles accumulate at sites of vascular disease, ACS Nano 11 (5) (2017) 4542–4552, https://doi.org/10.1021/acsnano.6b08551.

[16] L. Lobato, A. Rocha, Transthyretin amyloidosis and the kidney, Clin. J. Am. Soc. Nephrol. 7 (8) (2012) 1337–1346, https://doi.org/10.2215/CJN.08720811.

[17] S. Nie, W. He, T. Huang, et al., The spectrum of biopsy-proven glomerular diseases among children in China a national, cross-sectional survey, Clin. J. Am. Soc. Nephrol. (2018), https://doi.org/10.2215/CJN.11461017 CJN-11461017.

[18] L. Peng, S.Y. Wei, L.T. Li, et al., Comparison of different therapies in high-risk patients with idiopathic membranous nephropathy, J. Formos. Med. Assoc. 115 (1) (2016) 11–18, https://doi.org/10.1016/j.jfma.2015.07.021.

[19] P. Milesi, M. Weill, T. Lenormand, et al., Heterogeneous gene duplications can be adaptive because they permanently associate overdominant alleles, Evol. Lett. 1 (3) (2017) 169–180, https://doi.org/10.1002/evl3.17.

[20] L. Xu, Y. Hou, D.M. Bickhart, et al., Population-genetic properties of differentiated copy number variations in cattle, Sci. Rep. 6 (2016) 23161, , https://doi.org/10.1038/srep23161.

[21] N. Mladkova, K. Kiryluk, Genetic complexities of the HLA region and idiopathic membranous nephropathy, J. Am. Soc. Nephrol. 28 (5) (2017) 1331, https://doi.org/10.1681/ASN.2017030283.

[22] M.J. Coenen, J.M. Hofstra, H. Debiec, et al., Phospholipase A2 receptor (PLA2R1) sequence variants in idiopathic membranous nephropathy, J. Am. Soc. Nephrol. 24 (4) (2013) 677, https://doi.org/10.1681/ASN.2012070730.

[23] J. Dausset, Iso-leuco-anticorps, Acta Haematol. 20 (1–4) (1958) 156–166, https://doi.org/10.1159/000205478.

[24] D.S. Monos, R.J. Winchester, The Major Histocompatibility Complex[M]//Clinical Immunology, fifth edition, (2019), pp. 79–92 (e1).

[25] P.T. Klouda, E.J. Acheson, F.S. Goldby, et al., Strong association between idiopathic membranous nephropathy and HLA-DRW3, Lancet 314 (8146) (1979) 770–771.

[26] P. Sekula, Y. Li, H.C. Stanescu, et al., Genetic risk variants for membranous nephropathy: extension of and association with other chronic kidney disease aetiologies, Nephrol. Dial. Transplant. 32 (2) (2016) 325–332, https://doi.org/10.1093/ndt/gfw001.

[27] H.C. Stanescu, M. Arcos-Burgos, A. Medlar, et al., Risk HLA-DQA1 and PLA2R1 alleles in idiopathic membranous nephropathy, Clin. J. Am. Soc. Nephrol. 364 (7) (2011) 616–626, https://doi.org/10.2215/CJN.05310513.

[28] X.S. Qin, J.H. Liu, G.T. Lyu, et al., Variants in the promoter region of HLA-DQA1 were associated with idiopathic membranous nephropathy in a Chinese Han population, Chin. Med. J. 130 (14) (2017) 1677, https://doi.org/10.4103/0366-6999.209884.

[29] Z. Cui, L. Xie, F. Chen, et al., MHC class II risk alleles and amino acid residues in idiopathic membranous nephropathy, J. Am. Soc. Nephrol. 28 (5) (2017) 1651–1664, https://doi.org/10.1681/ASN.2016020114.

[30] R. Ramachandran, V. Kumar, A. Kumar, et al., PLA2R antibodies, glomerular PLA2R deposits and variations in PLA2R1 and HLA-DQA1 genes in primary membranous nephropathy in South Asians, Nephrol. Dial. Transplant. 31 (9) (2015) 1486–1493, https://doi.org/10.1093/ndt/gfv399.

[31] G. Bullich, J. Ballarín, A. Oliver, et al., HLA-DQA1 and PLA2R1 polymorphisms and risk of idiopathic membranous nephropathy, Clin. J. Am. Soc. Nephrol. 9 (2) (2014) 335–343, https://doi.org/10.2215/CJN.05310513.

[32] D. Kanigicherla, J. Gummadova, E.A. McKenzie, et al., Anti-PLA2 Rantibodies measured by ELISA predictlong-term outcomeina prevalent populationof patients with idiopathic membranous nephropathy, Kidney Int. 83 (2013) 940–948.

[33] M. Thiri, K. Honda, K. Kashiwase, et al., High-density association mapping and interaction analysis of PLA2R1 and HLA regions with idiopathic membranous nephropathy in Japanese, Sci. Rep. 6 (2016) 38189, , https://doi.org/10.1038/srep38189.

[34] W.B. Le, J.S. Shi, T. Zhang, et al., HLA-DRB1* 15: 01 and HLA-DRB3* 02: 02 in PLA2R-related membranous nephropathy, J. Am. Soc. Nephrol. 28 (5) (2017) 1642–1650, https://doi.org/10.1681/ASN.2016060644.

[35] I. Djilalisaiah, S. Caillatzucman, J. Schmitz, et al., Polymorphism of antigen processing (TAP, LMP) and HLA class II genes in celiac disease, Hum. Immunol. 40 (1) (1994) 8–16.

[36] D. Chevrier, M. Giral, V. Braud, et al., Membranous nephropathy and a TAP1 gene polymorphism, N. Engl. J. Med. 331 (2) (1994) 133–134, https://doi.org/10.1056/NEJM199407143310218.

[37] E. Ghamari, P. Farnia, S. Saif, et al., Susceptibility to pulmonary tuberculosis: host genetic deficiency in tumor necrosis factor alpha (TNF-α) gene and tumor necrosis factor receptor 2 (TNFR2), Int. J. Mycobacteriol. 5 Suppl 1 (5) (2016) S136, https://doi.org/10.1016/j.ijmyco.2016.09.038.

[38] D. Thibaudin, L. Thibaudin, P. Berthoux, et al., TNFA2 and d2 alleles of the tumor necrosis factor alpha gene polymorphism are associated with onset/occurrence of idiopathic membranous nephropathy, Kidney Int. 71 (5) (2007) 431–437, https://doi.org/10.1038/sj.ki.5002054.

[39] C. Bantis, P.J. Heering, S. Aker, et al., Tumor necrosis factor-α gene G-308A polymorphism is a risk factor for the development of membranous glomerulonephritis, Am. J. Nephrol. 26 (1) (2006) 12–15, https://doi.org/10.1159/000090706.

[40] Y. Dong, L. Cao, H. Tang, et al., Structure of human M-type phospholipase A2 receptor revealed by cryo-electron microscopy, J. Mol. Biol. 429 (24) (2017), https://doi.org/10.1016/j.jmb.2017.10.019.

[41] H. Debiec, P. Ronco, Immune response against autoantigen PLA2R is not gambling: implications for pathophysiology, prognosis, and therapy, J. Am. Soc. Nephrol. 27 (5) (2016) 1275–1277, https://doi.org/10.1681/ASN.2015101170.

[42] X. Zhang, Z. Cui, M. Zhao, The genetic and environmental factors of primary membranous nephropathy: an overview from China, Kidney Dis. 4 (2) (2018) 65–73, https://doi.org/10.1159/000487136.

[43] W. Qin, L.H. Beck, C. Zeng, et al., Anti-phospholipase A2 receptor antibody in membranous nephropathy, J. Am. Soc. Nephrol. 22 (6) (2011) 1137–1143.

[44] M. Ardalan, A. Ghafari, F. Hamzavi, et al., Anti-phospholipase A2 receptor antibody in idiopathic membranous nephropathy: a report from Iranian population, J. Nephropathol. 18 (6) (2013) 241–248, https://doi.org/10.12860/JNP.2013.38.

[45] S. Akiyama, M. Akiyama, E. Imai, et al., Prevalence of anti-phospholipase A2 receptor antibodies in Japanese patients with membranous nephropathy, Clin. Exp. Nephrol. 19 (4) (2015) 653–660, https://doi.org/10.1007/s10157-014-1054-2.

[46] H. Kaga, A. Komatsuda, A. Omokawa, et al., Analysis of PLA2R1 and HLA-DQA1 sequence variants in Japanese patients with idiopathic and secondary membranous nephropathy, Clin. Exp. Nephrol. 22 (2) (2018) 275–282, https://doi.org/10.1007/s10157-017-1471-0.

[47] M. Saeed, M.L. Beggs, P.D. Walker, et al., PLA2R-associated membranous glomerulopathy is modulated by common variants in PLA2R1 and HLA-DQA1 genes, Genes Immun. 15 (8) (2014) 556, https://doi.org/10.1038/gene.2014.50.

[48] G. Sanjana, K. Anna, H. Elion, et al., Genetics of membranous nephropathy, Nephrol. Dial. Transplant. (2017) 1–9.

[49] J. Lv, W. Hou, X. Zhou, et al., Interaction between PLA2R1 and HLA-DQA1 variants associates with anti-PLA2R antibodies and membranous nephropathy, J. Am. Soc. Nephrol. (2013), https://doi.org/10.1681/ASN.2012080771 ASN. 2012080771.

[50] C.P. Larsen, L.N. Cossey, L.H. Beck, THSD7A staining of membranous glomerulopathy in clinical practice reveals cases with dual autoantibody positivity, Mod. Pathol. 29 (4) (2016) 421, https://doi.org/10.1038/modpathol.2016.32.

[51] S. Ren, C. Wu, Y. Zhang, et al., An update on clinical significance of use of THSD7A in diagnosing idiopathic membranous nephropathy: a systematic review and meta-analysis of THSD7A in IMN, Ren. Fail. 40 (1) (2018) 306–313, https://doi.org/10.1080/0886022X.2018.1456457.

[52] J. Wang, Z. Cui, J. Lu, et al., Circulating antibodies against thrombospondin type-I domain-containing 7A in chinese patients with idiopathic membranous nephropathy, Clin. J. Am. Soc. Nephrol. 12 (10) (2017) 1642–1651, https://doi.org/10.2215/CJN.01460217.

[53] T. Iwakura, N. Ohashi, A. Kato, et al., Prevalence of enhanced granular expression of thrombospondin type-1 domain-containing 7A in the glomeruli of Japanese patients with idiopathic membranous nephropathy, PLoS One 10 (9) (2015) e0138841, , https://doi.org/10.1371/journal.pone.0138841.

[54] I.C. Ho, S.C. Miaw, Regulation of IL-4 expression in immunity and diseases[M]//, Regulation of Cytokine Gene Expression in Immunity and Diseases, Springer Dordrecht, 2016, pp. 31–77, , https://doi.org/10.1007/978-94-024-0921-5_3.

[55] M. Giacomelli, R. Kumar, G. Tampella, et al., IL-4, IL-10 and TNF-α polymorphisms in idiopathic membranous nephropathy (IMN), Open J. Immunol. 5 (05) (2015) 233.

[56] S.Y. Chen, C.H. Chen, Y.C. Huang, et al., Effect of IL-6 C-572G polymorphism on idiopathic membranous nephropathy risk in a Han Chinese population, Ren. Fail. 32 (10) (2010) 1172–1176, https://doi.org/10.3109/0886022X.2010.516857.
[57] J. Zhou, X.Z. Xu, Y.R. Hu, et al., Cryptotanshinone induces inhibition of breast tumor growth by cytotoxic CD4+ T cells through the JAK2/STAT4/perforin pathway, Asian Pac. J. Cancer Prev. 15 (6) (2014) 2439–2445.
[58] S.Y. Chen, C.H. Chen, Y.C. Huang, et al., Association of STAT4 polymorphisms with susceptibility to primary membranous glomerulonephritis and renal failure, Clin. Chim. Acta 412 (21 – 22) (2011) 1899–1904, https://doi.org/10.1016/j.cca.2011.06.020.
[59] J. Dobó, G. Pál, L. Cervenak, et al., The emerging roles of mannose-binding lectin-associated serine proteases (MASPs) in the lectin pathway of complement and beyond, Immunol. Rev. 274 (1) (2016) 98, https://doi.org/10.1111/imr.12460.
[60] D.M. do Nascimento Costa, L.M. Valente, G.V. Fernandes, et al., Mannose-binding lectin2 gene polymorphism and IgG4 in membranous nephropathy, Nephron 139 (2) (2018) 181–188, https://doi.org/10.1159/000486552.
[61] A.W. Van Der Velden, A.A.M. Thomas, The role of the 5′ untranslated region of an mRNA in translation regulation during development, Int. J. Biochem. Cell Biol. 31 (1) (1999) 87–106.
[62] R.P. Jansen, mRNA localization: message on the move, Nat. Rev. Mol. Cell Biol. 2 (4) (2001) 247, https://doi.org/10.1038/35067016.
[63] C.H. Chen, S.Y. Chen, K.H. Shu, et al., Urokinase gene 3′-UTR T/C polymorphism is associated with malignancy and ESRD in idiopathic membranous nephropathy, Biomed. Res. Int. (2014) 425095, , https://doi.org/10.1155/2014/425095.
[64] Y. Wang, Q. Liu, D. Chen, et al., Chlamydial lipoproteins stimulate toll-like receptors 1/2 mediated inflammatory responses through MyD88-dependent pathway, Front. Microbiol. 8 (2017) 78, https://doi.org/10.3389/fmicb.2017.00078.
[65] F. Conti, F.R. Spinelli, S. Truglia, et al., Kidney expression of toll like receptors in lupus nephritis: quantification and clinicopathological correlations, Mediat. Inflamm. 2 (2016) 7697592, , https://doi.org/10.1155/2016/7697592.
[66] Y.T. Chen, C.C. Wei, K.L. Ng, et al., Toll-like receptor 9 SNPs are susceptible to the development and progression of membranous glomerulonephritis: 27 years follow-up in Taiwan, Ren. Fail. 35 (10) (2013) 1370–1375, https://doi.org/10.3109/0886022X.2013.828264.
[67] H. Fang, H.S. Mun, A. Kikumura, et al., Toxoplasma gondii-derived heat shock protein 70 induces lethal anaphylactic reaction through activation of cytosolic phospholipase A2 and platelet-activating factor via Toll-like receptor 4/myeloid differentiation factor 88, Microbiol. Immunol. 52 (7) (2008) 366–374, https://doi.org/10.1111/j.1348-0421.2008.00047.x.
[68] S.Y. Chen, W.C. Chen, Y.H. Chen, et al., Association of toll-like receptor 4 gene polymorphisms with primary membranous nephropathy in a high prevalence renal disease area in Taiwan, ScienceAsia 36 (2) (2010) 130–136.
[69] C. Garcia, E. Calvo, A. Nieto, The transcription factor SOX17 is involved in the dtranscriptional control of the uteroglobin gene in rabbit endometrium, J. Cell. Biochem. 102 (3) (2007) 665–679, https://doi.org/10.1002/jcb.21324.
[70] B.D. Kılıc, M. Buyukcelik, S.O. Balcı, et al., Uteroglobin gene polymorphism (G38A) may be a risk factor in childhood idiopathic nephrotic syndrome, Pediatr. Nephrol. 33 (2) (2018) 295–303, https://doi.org/10.1007/s00467-017-3800-7.
[71] X. Li, P.Y. Chuang, V.D. D'Agati, et al., Nephrin preserves podocyte viability and glomerular structure and function in adult kidneys, J. Am. Soc. Nephrol. 26 (10) (2015) 2361, https://doi.org/10.1681/ASN.2014040405.
[72] W.Y. Lo, S.Y. Chen, H.J. Wang, et al., Association between genetic polymorphisms of the NPHS1 gene and membranous glomerulonephritis in the Taiwanese population, Clin. Chim. Acta 411 (9–10) (2010) 714–718, https://doi.org/10.1016/j.cca.2010.02.004.
[73] M. Marini, M. Bruschi, A. Pecci, et al., Non-muscle myosin heavy chain IIA and IIB interact and co-localize in living cells: relevance for MYH9-related disease, Int. J. Mol. Med. 17 (5) (2006) 729–736.
[74] C. Arrondel, N. Vodovar, B. Knebelmann, et al., Expression of the nonmuscle myosin heavy chain IIA in the human kidney and screening for MYH9 mutations in Epstein and Feehtner syndromes, J. Am. Soc. Nephrol. 13 (1) (2001) 65–74.
[75] N. Singh, N. Nainani, P. Arora, et al., CKD in MYH9-related disorders, Am. J. Kidney Dis. 54 (4) (2009) 732–740, https://doi.org/10.1053/j.ajkd.2009.06.023.
[76] Y.T. Chen, C.H. Chen, C.H. Yen, et al., Association between MYH9 gene polymorphisms and membranous glomerulonephritis patients in Taiwan, Sci. Asia 39 (6) (2013) 625–630.
[77] Y. Guo, L.I. Lu, G.U. Kai-Hong, et al., Association of MYH9,STAT4 and uPA gene single nucleotide polymorphism with idiopathic membranous nephropathy, J. Pract. Med. 32 (3) (2016) 376–381.
[78] T. Han, G. Zhang, Y. Dong, et al., Modulation of plasminogen activator inhibitor-1 (PAI-1) by the naphthoquinone shikonin, Fitoterapia 113 (2016) 117–122, https://doi.org/10.1016/j.fitote.2016.07.010.
[79] C.H. Chen, K.H. Shu, M.C. Wen, et al., Impact of plasminogen activator inhibitor-1 gene polymorphisms on primary membranous nephropathy, Nephrol. Dial. Transplant. 23 (10) (2008) 3166–3173, https://doi.org/10.1093/ndt/gfn258.
[80] Y. Guo, Reziwan Abudula, Z.F. Zhao, et al., Association of ACE, AGT, eNOS genes single nucleotide polymorphisms with idiopathic membranous nephropathy, Hainan Med. J. (2016), https://doi.org/10.1016/j.humpath.2013.07.032.