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# Association of SNPs in *PLA2R1* with idiopathic and secondary membranous nephropathy in two Chinese cohorts

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**ABSTRACT**

**Objectives**: Specific single-nucleotide polymorphisms (SNPs) in the M-type phospholipase A2 receptor-1 (*PLA2R1*) are associated with increased risk of idiopathic membranous nephropathy (IMN) in European populations. We hypothesized links between IMN and SMN with these SNPs in two Chinese cohorts.

**Methods**: A cohort of 166 IMN patients and 144 controls from southern China (Group A) and a cohort of 212 IMN patients, 118 SMN patients, and 162 controls from northwestern China (Group B) were recruited. SNPs within *PLA2R1* (rs3749119, rs3749117, rs35771982, rs3828323, and rs4664308) were identified and the frequencies of genotypes and alleles were determined for the different groups.

**Results**: Relative to controls, IMN patients had a greater prevalence of rs35771982, rs3749117, and rs4664308 in Group A (OR = 1.61, 95% CI = 1.13–2.31, $P = 0.011$; OR = 1.62 (1.15–2.29), $P = 0.006$ and OR = 1.17 (1.06–1.28), $P = 0.001$, respectively) and in Group B (OR = 1.58 (1.13–2.22), $P = 0.009$; OR = 1.68 (1.22–2.33), $P = 0.002$ and OR = 1.15 (1.06–1.25), $P < 0.001$, respectively). Genotype and allele distributions of rs4664308 differed significantly between SMN patients and controls in Group B (OR = 1.58 (1.10–2.26), $P = 0.012$). Genotype and allele distribution of rs35771982 and rs4664308 differed significantly between PLA2R-Ab(+) and PLA2R-Ab(-) IMN patients in Group B (OR = 1.59 (1.09–2.31), $P = 0.018$ and OR = 1.15 (1.03–1.29), $P = 0.005$, respectively).

**Conclusion**: This study of two cohorts from different regions of China indicate that specific *PLA2R1* polymorphisms are associated with IMN and SMN.

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Idiopathic membranous nephropathy; secondary membranous nephropathy; PLA2R; single nucleotide polymorphism; susceptibility; alleles

## Introduction

Membranous nephropathy (MN), the main cause of nephrotic syndrome in adults, is characterized by deposition of subepithelial immune complexes and thickening of the glomerular basement membrane (GBM). MN is classified as idiopathic (IMN) or secondary (SMN) depending on its aetiology [1–3]. About 70% of MN patients have IMN, one the most common pathologic types of primary glomerulonephritis. Numerous autoimmune diseases, such as systemic lupus erythematosus (SLE), hepatitis B and hepatitis C infections, and malignancies, are major causes of SMN [4]. The clinical consequences of IMN are varied. About one-third of patients with mild symptoms experience spontaneous remission [5]. Nearly 30 to 40% develop thrombotic or thromboembolic events, urinary tract infection, or cardiovascular disease [6]. Progressive decline of renal function occurs in other patients, who have refractory MN; about 35% of these refractory MN patients develop end-stage renal disease within 10 years [7].

Clinicians now consider IMN to be an autoimmune disease that targets the kidneys, in which there are circulating autoantibodies. The major target of these autoantibodies is the M-type phospholipase A2 receptor (PLA2R), which are not detectable in patients with SMN or with other autoimmune diseases [8]. PLA2R, a subtype of IgG4, is a type-I transmembrane protein that occurs in glomerular podocytes and binds to autoantibodies in patients with MN, leading to subepithelial deposits [9]. A recent genome-wide association study (GWAS) of British, Dutch, and French cohorts identified significant associations of specific single-nucleotide polymorphisms (SNPs) within *PLA2R1* and IMN [10]. Although previous studies of individuals in South Asia and Korea have also reported associations of *PLA2R1* polymorphisms with IMN [11,12], there are few genetic studies of IMN in Chinese populations.

In the present study, we hypothesized links between 5 SNPs within *PLA2R1* (rs3749119, rs3749117, rs35771982, rs3828323, and rs4664308), which have known associations with IMN in European cohorts, and the presence of IMN and SMN in two independent and geographically separated cohorts in China.

## Materials and methods

Two groups of study subjects were recruited. Group A was 166 IMN patients and 144 healthy controls from Nanfang Hospital, enrolled from September 2015 to

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February 2016. Group B was 212 IMN patients, 118 SMN patients, and 162 age and sex matched healthy controls from Shiyan Renmin Hospital, enrolled from January 2016 to December 2017. IMN and SMN were diagnosed by renal biopsy. Diagnostic criteria for IMN [13] were documented absence of SLE, hepatitis B virus (HBV) infection, tumours, and drug-induced SMN. Diagnostic criteria for SMN [13] were MN with a known secondary cause based on clinical evaluation and medical history, including membranous lupus nephritis, HBV-related glomerulonephritis, malignancies, and other well-documented conditions. None of the participants were closely related, and all were of Han ethnicity. This study was approved by the Ethics Committee of Hubei University of Medicine and Southern Medical University and was conducted in accordance with the Declaration of Helsinki. Informed written consent was obtained from each participant.

Serum anti-PLA2R antibodies were measured using a commercial indirect immunofluorescence staining kit (Euroimmun, Luebeck, Germany) according to the manufacturer's instructions. Five *PLA2R1* SNPs (rs3749119, rs3749117, rs35771982, rs3828323, and rs4664308) were sequenced in each study subject. First, genomic DNA was isolated from the peripheral blood leukocytes using a DNA isolation kit from Tiangen Biotech (Beijing, China). Primers were designed using Primer version 3.21. The SNP rs35771982 was detected using primers F5′-GAAGCTCCATAATTTTCATTTCAGAGC-3′ and R 5′-GGCAAAGAAAACACTGCGGGTA-3′. The SNP rs3749117 was detected using primers F5′-GCTTATCTTCCTGGTCCC TATTTT-3′ and R5′- ATTCTGTGCACCTTTCCCGTCATT-3′. The SNP rs3749119 was detected using primers F5′-CTGGGAGACTCACCCTGCCACT-3′ and R5′- TTCTCAAATC GCTCACCCACAACT-3′. The SNP rs3828323 was detected using primers F5′-TGTAAGTTCTGTTTCCATATTCTAAG-3′ and R5′- CTGATCAACATGGATCATAGTGAC-3′. The SNP rs4664308 was detected using primers F5′-CGGAGGAT CACCAGCACATA-3′ and R5′- GAGGGGGACAGGAGGG AGT-3′. Amplification was performed on an ABI Vii7 Dx real-time PCR system (Applied Biosystems). The PCR amplification protocols were: step 1, denaturation at 95°C for 5 min; step 2, 20 cycles of 95°C for 30 s, 65°C for 30 s and 72°C for 30 s, with a taper of the annealing temperature by 0.5°C with each cycle; step 3, 20 cycles of 95°C for 30 s, 55°C for 30 s, and 72°C for 30 s; step 4, extension at 72°C for 5 min and then transferred to 4°C. PCR products were purified using Multiscreen Filter Plates from Millipore (Carrigtwohill, Ireland) and were sequenced using the BigDye Terminator Cycle Sequencing Kit (Applied Biosystems, Tokyo, Japan) with an automated DNA sequencer (ABI 3130 DNA analyser; Applied Biosystems, Foster City, CA, USA). Sequences and mutations were analysed using DNASIS for Mac (Hitachi, Tokyo, Japan).

Data are presented as means with standard deviations, medians with ranges, or counts with percentages, as appropriate. The significance of comparisons was determined using Student's *t*-test, the non-parametric Mann-Whitney U test, and a one-way ANOVA for continuous variables. The genotype frequencies of cases and controls were compared using a chi-squared test or Fisher's exact test, as appropriate. Deviation from the Hardy-Weinberg equilibrium was determined using chi-squared test. Odds ratios (ORs) and 95% confidence intervals (CIs) were also calculated. Statistical analysis was performed using SPSS version 19 (Chicago, IL, USA), and a two-tailed *P*-value below 0.05 was considered significant.

## Results

Group A had 166 patients with IMN and 144 healthy controls; 69 patients received immunosuppressive therapy. Group B had 212 patients with IMN, 118 patients with SMN, and 162 healthy controls (Table 1); none of the patients received immunosuppressive therapy. Among the patients with SMN in Group B, 51 had SLE, 45 had hepatitis B, 2 had psoriasis, 3 had Sjögren syndrome, 2 had hepatitis B and SLE, and the other 15 had malignancies. All groups were age and sex matched, and differences in serum albumin, were as expected, although there were no differences in serum creatinine.

We initially determined the allele frequencies and genotype distributions of 5 SNPs in IMN patients and controls in Group A (Table 2). The genotype frequencies of all 5 SNPs in the controls indicated no significant deviations from Hardy-Weinberg equilibrium. The genotype and allele distributions of rs35771982, rs3749117, and rs4664308 differed significantly between IMN patients

Table 1. Baseline characteristics of patients in Group A and Group B.

| | IMN (Group A) | Control (Group A) | P(a) | IMN (Group B) | SMN (Group B) | Control (Group B) | P(b1) | P(b2) |
|---|---|---|---|---|---|---|---|---|
| Patients (n) | 166 | 144 | ND | 212 | 118 | 162 | ND | ND |
| Age, years (mean ± SD) | 49.1 ± 15.5 | 50.5 ± 14.0 | 0.405 | 49.4 ± 9.6 | 48.5 ± 11.8 | 47.3 ± 11.7 | 0.072 | 0.421 |
| Males/females | 105/61 | 85/59 | 0.446 | 144/68 | 56/62 | 95/67 | 0.064 | 0.064 |
| Proteinuria (g/24 h) | 5.7 ± 3.0 | ND | ND | 5.2 ± 2.0 | 4.7 ± 2.1 | ND | ND | ND |
| Albumin (g/L) | 27 ± 5 | 40 ± 4 | <0.001 | 26 ± 4 | 27 ± 5 | 41 ± 3 | <0.001 | <0.001 |
| SCr (μmol/L) | 74 ± 21 | 76 ± 15 | 0.341 | 73 ± 21 | 74 ± 22 | 75 ± 12 | 0.806 | 0.344 |
| Anti-PLA2R-Ab(+) | 101(60.8%) | ND | ND | 153(72.2%) | 11(9.3%) | ND | ND | ND |
| Imunosuppressant treatment | 69(41.6%) | ND | ND | 0(0%) | 0(0%) | ND | ND | ND |

Abbreviations here and below: IMN: idiopathic membranous nephropathy; ND: not determined; SCr: serum creatinine; SMN: secondary membranous nephropathy. P(a): IMN *vs*. Control in Group A. P(b1): IMN *vs*. Control in Group B. P(b2): SMN *vs*. Control in Group B.

Table 2. Genotype and allele distributions of *PLA2R1* SNPs in IMN patients and healthy controls (Group A).

| SNP | Genotype | IMN (n = 166) | Control (n = 144) | P | Allele | IMN | Control | OR (95%CI) | P |
|---|---|---|---|---|---|---|---|---|---|
| rs35771982 | CC | 101(60.8) | 68(47.2) | 0.036 | C | 258(77.7) | 197(68.4) | 1.61(1.13–2.31) | 0.011 |
| | CG | 56(33.7) | 61(42.4) | | G | 74(22.3) | 91(31.6) | | |
| | GG | 9(5.4) | 15(10.4) | | | | | | |
| rs3749117 | TT | 95(57.2) | 65(45.1) | 0.029 | T | 249(75.0) | 187(64.9) | 1.62(1.15–2.29) | 0.006 |
| | CT | 59(35.5) | 57 (39.6) | | C | 83(25.0) | 101(35.1) | | |
| | CC | 12(7.2) | 22(15.3) | | | | | | |
| rs3749119 | CC | 86(51.8) | 65(45.1) | 0.410 | C | 238(71.7) | 192(66.7) | 1.27(0.90–1.78) | 0.191 |
| | CT | 66(39.8) | 62(43.1) | | T | 94(28.3) | 96 (33.3) | | |
| | TT | 14(8.4) | 17(11.8) | | | | | | |
| rs3828323 | TT | 12(7.2) | 16(11.1) | 0.283 | T | 76(22.9) | 83(28.8) | 0.73(0.51–1.05) | 0.098 |
| | CT | 52(31.3) | 51(35.4) | | C | 256(77.1) | 205(71.2) | | |
| | CC | 102(61.4) | 77(53.5) | | | | | | |
| rs4664308 | GG | 8(4.8) | 15(10.4) | 0.005 | G | 64(19.3) | 89(30.9) | 1.17(1.06–1.28) | 0.001 |
| | GA | 48(28.9) | 59(41.0) | | A | 268(80.7) | 199(69.1) | | |
| | AA | 110(66.3) | 70(48.6) | | | | | | |

and controls. However, the genotype and allele distributions of rs3749119 and rs3828323 had no significant differences between IMN patients and controls. We also determined the allele frequencies and genotype distributions of the same 5 SNPs in IMN patients, SMN patients, and controls in Group B (Table 3). As in Group A, the genotype frequencies of all 5 SNPs in the controls indicated no significant deviations from Hardy-Weinberg equilibrium.

As in Group A, the genotype and allele distributions of rs35771982, rs3749117, and rs4664308 differed significantly between IMN patients and controls. The genotype and allele distributions of rs3749119 and rs3828323 had no significant differences between IMN patients and controls. The genotype and allele distributions of rs4664308 also differed significantly between SMN patients and controls, but the genotype and allele distributions of the other 4 SNPs were similar in SMN patients and controls.

Comparison of the allele frequencies and genotype distributions of the 5 SNPs in PLA2R-Ab(+) and PLA2R-Ab (-) IMN patients in Group A (Table 4) indicated a significant difference in the allele frequency of rs4664308. However, the genotype and allele distributions of the other 4 SNPs and the genotype frequency of rs4664308 were not significantly different in these two groups. The same analysis in Group B (Table 5) indicated significant differences in the genotype and allele distributions of rs35771982 and rs4664308. The allele frequencies and genotype distributions of the other 3 SNPs were not significantly different between these two groups.

## Discussion

We previously reported that 71.7% of patients with IMN and 9.3% of patients with SMN were PLA2R-Ab(+) [14]. Several recent studies identified the association of several common variants in *PLA2R1* with IMN in European and Asian populations [10–12]. In this study, we examined the relationships of *PLA2R1* and IMN and SMN in two geographically distinct Chinese cohorts. We found that the genotype and allele distributions of rs35771982, rs3749117, and rs4664308 were significantly associated with IMN, and that genetic variants of rs4664308 were also associated with SMN.

The rs35771982 SNP within *PLA2R1* is in a coding region of exon 5 [15]. Numerous publications reported that this SNP had the strongest association with IMN in cohorts from Korea, South Asia, Taiwan, China, and Japan [11–12, 16–19]. Some [11,18] reported the C allele in rs35771982 was the high-risk allele, in agreement with our results, whereas others [12,16,17,19] reported the

Table 3. Genotype and allele distributions of *PLA2R1* SNPs in IMN patients, SMN patients, and healthy controls (Group B).

| SNP | Genotype | IMN (n = 212) | SMN (n = 118) | Controls (n = 162) | P | Allele | IMN | SMN | Controls | OR(95%CI) | P |
|---|---|---|---|---|---|---|---|---|---|---|---|
| rs35771982 | CC | 137(64.6) | 60(50.8) | 80(49.4) | 0.012[a] | C | 339(80.0) | 170(72.0) | 232(71.6) | 1.58(1.13–2.22)[a] | 0.009[a] |
| | CG | 65(30.7) | 50(42.4) | 72(44.4) | 0.934[b] | G | 85(20.0) | 66(28.0) | 92(28.4) | 1.02(0.70–1.48)[b] | 0.925[b] |
| | GG | 10(4.7) | 8(6.8) | 10(6.2) | | | | | | | |
| rs3749117 | TT | 134(63.2) | 66(55.9) | 77(47.5) | 0.009[a] | T | 329(77.6) | 172(72.9) | 218(67.3) | 1.68(1.22–2.33)[a] | 0.002[a] |
| | CT | 61(28.8) | 40(33.9) | 64(39.5) | 0.373[b] | C | 95(22.4) | 64(27.1) | 106(32.7) | 1.31(0.90–1.89)[b] | 0.164[b] |
| | CC | 17(8.0) | 12(10.2) | 21(13.0) | | | | | | | |
| rs3749119 | CC | 130(61.3) | 67(56.8) | 87(53.7) | 0.326[a] | C | 330(77.8) | 180(76.3) | 239(73.8) | 1.25(0.90–1.75)[a] | 0.226[a] |
| | CT | 70(33.0) | 46(39.0) | 65(40.1) | 0.734[b] | T | 94(22.2) | 56(23.7) | 85(26.2) | 1.14(0.78–1.69)[b] | 0.554[b] |
| | TT | 12(5.7) | 5(4.2) | 10(6.2) | | | | | | | |
| rs3828323 | TT | 21(9.9) | 12(10.2) | 20(12.3) | 0.219[a] | T | 104(24.5) | 65(27.5) | 98(30.2) | 0.75(0.54–1.04)[a] | 0.082[a] |
| | CT | 62(29.2) | 41(34.7) | 58(35.8) | 0.803[b] | C | 320(75.5) | 171(72.5) | 226(69.8) | 0.88(0.61–1.27)[b] | 0.511[b] |
| | CC | 129(60.8) | 65(55.1) | 84(51.9) | | | | | | | |
| rs4664308 | GG | 9(4.2) | 20(16.9) | 13(8.0) | 0.002[a] | G | 73(17.2) | 90(38.1) | 91(28.1) | 1.15(1.06–1.25)[a] | <0.001[a] |
| | GA | 55(25.9) | 50(42.4) | 65(40.1) | 0.039[b] | A | 351(82.8) | 146(61.9) | 233(71.9) | 1.58(1.10–2.26)[b] | 0.012[b] |
| | AA | 148(69.8) | 48(40.7) | 84(51.9) | | | | | | | |

[a]IMN *vs.* Controls; [b]SMN *vs.* Controls. IMN = idiopathic membranous nephropathy; SMN = secondary membranous nephropathy.

**Table 4.** Genotype and allele distributions of *PLA2R1* SNPs in PLA2R-Ab(+) and PLA2R-Ab(-) IMN patients (Group A).

| SNP | Genotype | PLA2RAb(+) (n = 101) | PLA2R-Ab(-) (n = 65) | P | Allele | PLA2R-Ab(+) | PLA2R-Ab(-) | OR(95%CI) | P |
|---|---|---|---|---|---|---|---|---|---|
| rs35771982 | CC | 60(59.4) | 41(63.1) | 0.869 | C | 155(76.7) | 103(79.2) | 1.12(0.74–1.70) | 0.593 |
| | CG | 35(34.7) | 21(32.3) | | G | 47(23.3) | 27(20.8) | | |
| | GG | 6(5.9) | 3(4.6) | | | | | | |
| rs3749117 | TT | 59(58.4) | 36(55.4) | 0.927 | T | 153(75.7) | 96(73.8) | 1.11(0.67–1.84) | 0.697 |
| | CT | 35(34.7) | 24(36.9) | | C | 49(24.3) | 34(26.2) | | |
| | CC | 7(6.9) | 5(7.7) | | | | | | |
| rs3749119 | CC | 49(48.5) | 40(56.9) | 0.493 | C | 140(69.3) | 98(75.4) | 0.74(0.45–1.21) | 0.230 |
| | CT | 42(41.6) | 27(36.9) | | T | 62(30.7) | 32(24.6) | | |
| | TT | 10(9.9) | 5(6.2) | | | | | | |
| rs3828323 | TT | 8(7.9) | 4(6.2) | 0.415 | T | 51(25.2) | 25(19.2) | 1.42(0.83–2.43) | 0.203 |
| | CT | 35(34.7) | 17(26.2) | | C | 151(74.8) | 105(80.8) | | |
| | CC | 58(57.4) | 44(67.7) | | | | | | |
| rs4664308 | GG | 2(2.0) | 6(9.2) | 0.057 | G | 31(15.3) | 33(25.4) | 1.14(1.01–1.27) | 0.024 |
| | GA | 27(26.7) | 21(32.3) | | A | 171(84.7) | 97(74.6) | | |
| | AA | 72(71.3) | 38(58.5) | | | | | | |

Abbreviations: IMN = idiopathic membranous nephropathy.

**Table 5.** Genotype and allele distributions of *PLA2R1* SNPs in PLA2R-Ab(+) and PLA2R-Ab(-) IMN patients (Group B).

| SNP | Genotype | PLA2RAb(+) (n = 153) | PLA2R-Ab(-) (n = 59) | P | Allele | PLA2R-Ab(+) | PLA2R-Ab(-) | OR(95%CI) | P |
|---|---|---|---|---|---|---|---|---|---|
| rs35771982 | CC | 106(69.3) | 30(50.8) | 0.043 | C | 252(82.4) | 85(72.0) | 1.59(1.09-2.31) | 0.018 |
| | CG | 40(26.1) | 25(42.4) | | G | 54(17.6) | 33(28.0) | | |
| | GG | 7(4.6) | 4(6.8) | | | | | | |
| rs3749117 | TT | 94(61.4) | 40(67.8) | 0.149 | T | 237(77.5) | 92(78.0) | 0.97(0.58-1.62) | 0.909 |
| | CT | 49(32.0) | 12(20.3) | | C | 69(22.5) | 26(22.0) | | |
| | CC | 10(6.5) | 7(11.9) | | | | | | |
| rs3749119 | CC | 97(63.4) | 33(55.9) | 0.601 | C | 242(79.1) | 88(74.6) | 1.29(0.78-2.12) | 0.317 |
| | CT | 48(31.4) | 22(37.3) | | T | 64(20.9) | 30(25.4) | | |
| | TT | 8(5.2) | 4(6.8) | | | | | | |
| rs3828323 | TT | 14(9.2) | 7(11.9) | 0.838 | T | 73(23.9) | 31(26.3) | 0.88(0.54-1.43) | 0.604 |
| | CT | 45(29.4) | 17(28.8) | | C | 233(76.1) | 87(73.7) | | |
| | CC | 94(61.4) | 35(59.3) | | | | | | |
| rs4664308 | GG | 4(2.6) | 5(8.5) | 0.028 | G | 43(14.1) | 30(25.4) | 1.15(1.03-1.29) | 0.005 |
| | GA | 35(22.9) | 20(33.9) | | A | 263(85.9) | 88(74.6) | | |
| | AA | 114(74.5) | 34(57.6) | | | | | | |

Abbreviations: IMN = idiopathic membranous nephropathy.

G allele in rs35771982 was the high-risk allele. Saeed et al. [20] reported no association between rs35771982 and IMN in a cohort of PLA2R-Ab(+) African Americans. Thus, there are significant variations in the effect of rs35771982 on MN in geographically distinct populations.

The rs3749117 SNP within *PLA2R1* is also in a coding region of exon 5. This SNP is significantly more common in cohorts of white Europeans [15] with IMN, and in Caucasians, African Americans [20], and Japanese [19] who are PLA2R-Ab(+). These previous results are concordant with our results. On the contrary, Ramachandran et al. [12] reported no association of IMN with rs3749117 and IMN in a cohort from India. The rs3749119 SNP within *PLA2R1* is in the 5′ untranslated region of exon 1. Three previous studies reported this SNP was significantly associated with IMN in cohorts of white Europeans [15], Indians [12], and Japanese [21]. However, there was no such association in our two Chinese cohorts and in a Japanese cohort [19]. The rs3828323 SNP within *PLA2R1* is in a coding region of exon 24. Although this SNP was significantly associated with IMN in cohorts of white Europeans [15] and Indians [12], it was not associated with IMN in our two Chinese cohorts and in a Japanese cohort [19].

The rs4664308 SNP was first examined in French, Dutch, and British populations [10]. Ramachandran et al. [12], Lv et al. [17] and Bullich et al. [22] subsequently reported an association of this SNP with IMN. Our study confirmed that Chinese individuals with the rs4664308-A allele had an increased risk of IMN, but those with the rs4664308-G allele had an increased risk of SMN. We hypothesize that IMN and SMN may have similarities in their pathogeneses that are related to genetic variants in *PLA2R1*.

Furthermore, we found that the C allele in rs35771982 and the A allele in rs4664308 were associated with PLA2R-Ab(+) in IMN patients from Hubei Province (northwestern China). However, analysis of IMN patients from Nanfang Hospital (southern China) indicated that the allele frequency of rs4664308, but not rs35771982, was significantly different for those who were PLA2R-Ab(+) and PLA2R-Ab(-). We speculate that MN treatments (imunosuppressants) could affect the rate of PLA2R-Ab(+), as 41.6% of the patients in Group A received imunosuppressant therapy, but none of the patients in Group B received immunosuppressants. Therefore, the results of Group B better reflect the true relationship between PLA2R-Ab (+) and the SNPs in *PLA2R1*.

In conclusion, our study of two geographically distinct Chinese cohorts indicated that 3 SNPs within *PLA2R1* (rs35771982, rs3749117, and rs4664308) were associated with increased susceptibility to IMN, and that there was also a strong association of rs4664308 with susceptibility to SMN. These findings may help to identify individuals with increased risk for IMN and SMN so that clinicians can perform early interventions and make better treatment decisions. However, our knowledge of the contribution of *PLA2R1* genetic variants to the pathogenesis of IMN is limited. The relationships between these genetic variants and the clinical outcomes of patients with IMN and SMN require validation.

This work represents an advance in biomedical science because it shows that specific *PLA2R1* gene polymorphisms are associated with IMN and SMN in Chinese cohorts.

## Summary table

*What is known about this subject*:
- Genetic and environmental factors are associated with susceptibility to idiopathic membranous nephropathy (IMN).
- The circulating level of anti-PLA2R autoantibody is a highly specific diagnostic biomarker for IMN.
- Recent research identified PLA2R as the major target antigen in IMN.

*What this paper adds*:
- SNPs within the *PLA2R1* gene (rs35771982, rs3749117, and rs4664308) are linked with IMN.
- The rs4664308 SNP is linked with secondary membranous nephropathy (SMN).
- The rs35771982 and rs4664308 SNPs appear to influence the expression of anti-PLA2R-Ab in IMN.

## Disclosure statement

No potential conflict of interest was reported by the authors.

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