Supplemental Material

Supplemental Table 1. List of hazard ratios of HLA alleles in Cox proportional hazards models to assess associations between HLA alleles and kidney outcome event (≥40% eGFR decline during follow-up) in patients with PLA2R-related membranous nephropathy.

Supplemental Table 2. The carrying rate of HLA alleles in patients and healthy controls in this study. More information would be found in previous publications [J Am Soc Nephrol. 2016;27(10): 3195-3203.].

Supplemental Table 3. Risk factors for assessing risk of ≥ 50% eGFR decline in patients with PLA2R2-related Membranous Nephropathy (n = 392).

Supplemental Table 4. Relationship between the susceptible alleles and the four identified progressive risk alleles.

Supplemental Figure 1. Kaplan–Meier analysis of kidney survival curves (≥ 50% decline in eGFR) in PLA2R-related membranous nephropathy patients. HLA risk alleles: DRB1*13:01, DQB1*06:03, DRB1*04:05 or DQB1*03:02.

Supplemental Figure 2. Kaplan–Meier analysis of kidney survival curves (≥ 40% decline in eGFR) in PLA2R-related membranous nephropathy patients. (A) Patients with positive HLA DRB1*13:01 had worse kidney outcome than those with negative HLA DRB1*13:01 during follow-up. (B) Patients with DRB1*13:01^{+}DRB3*02:02^{+} had a significant higher rate of kidney failure than those with DRB1*13:01^{-} DRB3*02:02^{+}.

Supplemental Figure 3. Kaplan–Meier analysis of kidney survival curves (≥ 40% decline in eGFR) in PLA2R-related membranous nephropathy patients. Patients with positive HLA DRB1*04:05 had worse kidney outcomes during follow-up. eGFR, estimated glomerular filtration.

Supplemental Figure 4. Kaplan–Meier analysis of kidney survival curves (≥ 40% decline in eGFR) in PLA2R-related membranous nephropathy patients. Patients with positive HLA DQB1*03:02 had worse kidney outcomes during follow-up. eGFR, estimated glomerular filtration.

Supplemental Figure 5. Linkage map of HLA-DRB3/4/5 with HLA-DRB1 in the National Marrow Donor Program (NMDP) of Chinese population.

Supplemental Table 1. List of hazard ratios of HLA alleles in Cox proportional hazards models to assess associations between HLA alleles and kidney outcome event (≥40% eGFR decline during follow-up) in patients with PLA2R-related membranous nephropathy.

	allele name	HR	Lower95	Upper95	P-value
1	DRB1*13:01	3.71	1.77	7.80	0.000533757
2	DQB1*06:03	3.71	1.77	7.80	0.000533757
3	DRB1*04:05	3.80	1.52	9.50	0.004281035
4	DQB1*03:02	3.06	1.40	6.72	0.005238834
5	DQA1*01:03	2.14	1.19	3.87	0.011502572
6	DQA1*03:03	2.94	1.26	6.83	0.012265818
7	DQB1*04:01	2.91	1.16	7.27	0.022356019
8	DQA1*03:01	2.41	1.04	5.58	0.040849005
9	DRB1*01:01	4.07	0.99	16.68	0.051568479
10	DQB1*NEW	7.04	0.97	51.25	0.054057101
11	DQB1*05:01	2.69	0.98	7.42	0.055859951
12	DRB1*04:06	3.09	0.97	9.88	0.056905942
13	DRB5*01:01	0.62	0.37	1.03	0.062510271
14	DQA1*01:02	0.64	0.39	1.07	0.087053781
15	DRB1*15:01	0.65	0.39	1.07	0.090301761
16	DQB1*05:02	0.19	0.03	1.40	0.103833444
17	DQB1*02:02	0.33	0.08	1.33	0.118412983
18	DQB1*03:01	0.59	0.30	1.15	0.119947467
19	DRB1*04:03	2.95	0.72	12.06	0.133138663
20	DRB1*07:01	0.52	0.19	1.43	0.203051095
21	DQA1*01:05	2.48	0.60	10.25	0.20816465
22	DRB1*10:01	2.48	0.60	10.25	0.20816465
23	DQA1*02:01	0.52	0.19	1.44	0.211171188
24	DQB1*06:41	3.46	0.48	25.08	0.218599473
25	DQA1*01:04	0.59	0.25	1.37	0.218680717
26	DQA1*01:01	2.04	0.50	8.35	0.321723626
27	DQB1*06:02	0.79	0.48	1.28	0.336109714
28	DRB1*08:03	1.54	0.62	3.84	0.351222694

29	DRB1*12:10	2.48	0.34	17.90	0.368157969
30	DQA1*05:05	0.72	0.33	1.57	0.403801619
31	DRB1*08:09	2.31	0.32	16.76	0.407142644
32	DQB1*06:01	0.77	0.41	1.44	0.415070046
33	DRB1*14:05	0.70	0.25	1.92	0.487563594
34	DRB3*01:01	1.49	0.36	6.09	0.581720231
35	DQA1*05:01	1.14	0.68	1.89	0.620435666
36	DQB1*05:03	0.85	0.39	1.86	0.686411822
37	DQB1*03:03	1.17	0.54	2.57	0.689762717
38	DRB1*13:02	0.75	0.18	3.08	0.691763891
39	DRB3*02:02	1.11	0.65	1.90	0.701256078
40	DRB3*03:01	0.84	0.34	2.09	0.704472408
41	DQA1*04:01	1.41	0.20	10.22	0.730774431
42	DQB1*04:02	1.41	0.20	10.22	0.730774431
43	DQB1*02:01	1.07	0.65	1.78	0.786371147
44	DRB1*03:01	1.07	0.65	1.78	0.786371147
45	DRB1*11:01	0.91	0.42	2.00	0.817074574
46	DRB1*12:01	0.79	0.11	5.72	0.817363959
47	DQA1*06:01	1.11	0.45	2.76	0.822879491
48	DRB1*12:02	1.10	0.44	2.75	0.830935734
49	DQB1*06:04	1.21	0.17	8.75	0.848656946
50	DQA1*03:02	1.09	0.44	2.72	0.850157228
51	DRB1*09:01	0.92	0.33	2.54	0.874180266
52	DRB1*14:04	1.10	0.15	7.96	0.922385012
53	DRB1*15:02	0.00	0.00	Inf	0.994542239
54	DRB5*01:02	0.00	0.00	Inf	0.994591966
55	DQB1*06:09	0.00	0.00	Inf	0.994706299
56	DQA1*05:03	0.00	0.00	Inf	0.994789757
57	DRB1*12:28	0.00	0.00	Inf	0.995004853
58	DRB1*16:02	0.00	0.00	Inf	0.995004853
59	DRB1*13:12	0.00	0.00	Inf	0.995236083
60	DQB1*03:05	0.00	0.00	Inf	0.995511227
61	DRB1*04:01	0.00	0.00	Inf	0.995586627
62	DRB1*11:04	0.00	0.00	Inf	0.995755597
63	DRB1*14:14	0.00	0.00	Inf	0.995756127
64	DRB5*01:08	0.00	0.00	Inf	0.995881579
65	DRB1*04:02	0.00	0.00	Inf	0.996034593

66	DQA1*NEW	0.00	0.00	Inf	0.996045314
67	DRB1*08:04	0.00	0.00	Inf	0.996060511
68	DRB1*14:03	0.00	0.00	Inf	0.996090356
69	DQA1*05:09	0.00	0.00	Inf	0.996105861
70	DRB1*11:11	0.00	0.00	Inf	0.996105861
71	DRB1*14:07	0.00	0.00	Inf	0.996139592
72	DRB1*08:02	0.00	0.00	Inf	0.996194995
73	DRB1*15:04	0.00	0.00	Inf	0.996283702
74	DRB1*11:03	0.00	0.00	Inf	0.99654845
75	DQA1*05:08	0.00	0.00	Inf	0.996617549
76	DQA1*05:06	0.00	0.00	Inf	0.996671806
77	DQB1*03:13	0.00	0.00	Inf	0.996804383
78	DRB1*14:54	1.00	0.31	3.19	0.997734601
79	DRB1*04:04	NA	NA	NA	NA

DQA1*NEW, new DQA1 allele identified by HLA target sequencing; DQB1*NEW, new DQB1 allele identified by HLA target sequencing. NA, the result is not available in the Cox analysis for there is only one patient carrying the DRB1*04:04. Inf, infinity.

Supplemental Table 2. The carrying rate of HLA alleles in patients and healthy controls in this study. More information would be found in previous publications [J Am Soc Nephrol. 2016;27(10): 3195-3203.].

Alleles	Cases (N = 392)	Health Controls (n=385)
DQA1*01:01	0.02	0.05
DQA1*01:02	0.73	0.30
DQA1*01:03	0.10	0.19
DQA1*01:04	0.16	0.09
DQA1*01:05	0.01	0.04
DQA1*02:01	0.09	0.21
DQA1*03:01	0.05	0.14
DQA1*03:02	0.06	0.28
DQA1*03:03	0.04	0.16
DQA1*04:01	0.01	0.01
DQA1*05:01	0.34	0.08
DQA1*05:03	0.01	0.00
DQA1*05:05	0.15	0.18
DQA1*05:06	0.01	0.01
DQA1*05:08	0.01	0.02
DQA1*05:09	0.00	0.00
DQA1*06:01	0.07	0.15
DQA1*NEW	0.01	0.00
DQB1*02:01	0.34	0.08
DQB1*02:02	0.07	0.18
DQB1*03:01	0.25	0.34
DQB1*03:02	0.05	0.15
DQB1*03:03	0.08	0.30
DQB1*03:05	0.00	0.01
DQB1*03:13	0.00	0.00
DQB1*04:01	0.03	0.13
DQB1*04:02	0.01	0.03
DQB1*05:01	0.03	0.09
DQB1*05:02	0.08	0.08

DQB1*05:03	0.14	0.08
DQB1*06:01	0.22	0.21
DQB1*06:02	0.51	0.15
DQB1*06:03	0.03	0.02
DQB1*06:04	0.02	0.04
DQB1*06:09	0.02	0.02
DQB1*06:41	0.00	0.00
DQB1*NEW	0.00	0.01
DRB1*01:01	0.01	0.03
DRB1*01:02	0.00	0.01
DRB1*03:01	0.34	0.07
DRB1*04:01	0.01	0.01
DRB1*04:02	0.01	0.00
DRB1*04:03	0.01	0.05
DRB1*04:04	0.00	0.02
DRB1*04:05	0.03	0.14
DRB1*04:06	0.02	0.05
DRB1*04:07	0.00	0.01
DRB1*04:08	0.00	0.00
DRB1*04:10	0.00	0.01
DRB1*07:01	0.09	0.21
DRB1*08:02	0.01	0.01
DRB1*08:03	0.05	0.14
DRB1*08:04	0.00	0.00
DRB1*08:09	0.01	0.00
DRB1*09:01	0.06	0.30
DRB1*10:01	0.01	0.04
DRB1*11:01	0.12	0.10
DRB1*11:03	0.00	0.00
DRB1*11:04	0.02	0.00
DRB1*11:06	0.00	0.00
DRB1*11:11	0.00	0.00
DRB1*12:01	0.02	0.09
DRB1*12:02	0.07	0.15
DRB1*12:10	0.01	0.01
DRB1*12:28	0.00	0.00
DRB1*13:01	**0.03**	**0.02**

DRB1*13:02	0.04	0.06
DRB1*13:03	0.00	0.00
DRB1*13:12	0.01	0.00
DRB1*14:03	0.01	0.01
DRB1*14:04	0.01	0.01
DRB1*14:05	0.09	0.03
DRB1*14:07	0.01	0.01
DRB1*14:141	0.00	0.00
DRB1*14:54	0.05	0.05
DRB1*15:01	0.72	0.21
DRB1*15:02	0.03	0.06
DRB1*15:04	0.00	0.00
DRB1*16:02	0.00	0.04
DRB3*01:01	0.02	0.11
DRB3*02:02	0.70	0.26
DRB3*03:01	0.09	0.18
DRB5*01:01	0.73	0.25
DRB5*01:02	0.03	0.03
DRB5*01:03	0.00	0.01
DRB5*01:08	0.00	0.01
DRB5*02:02	0.00	0.01
DRB5*02:03	0.00	0.00

Supplemental Table 3. Risk factors for assessing risk of ≥ 50% eGFR decline in patients with PLA2R2-related Membranous Nephropathy (n = 392).

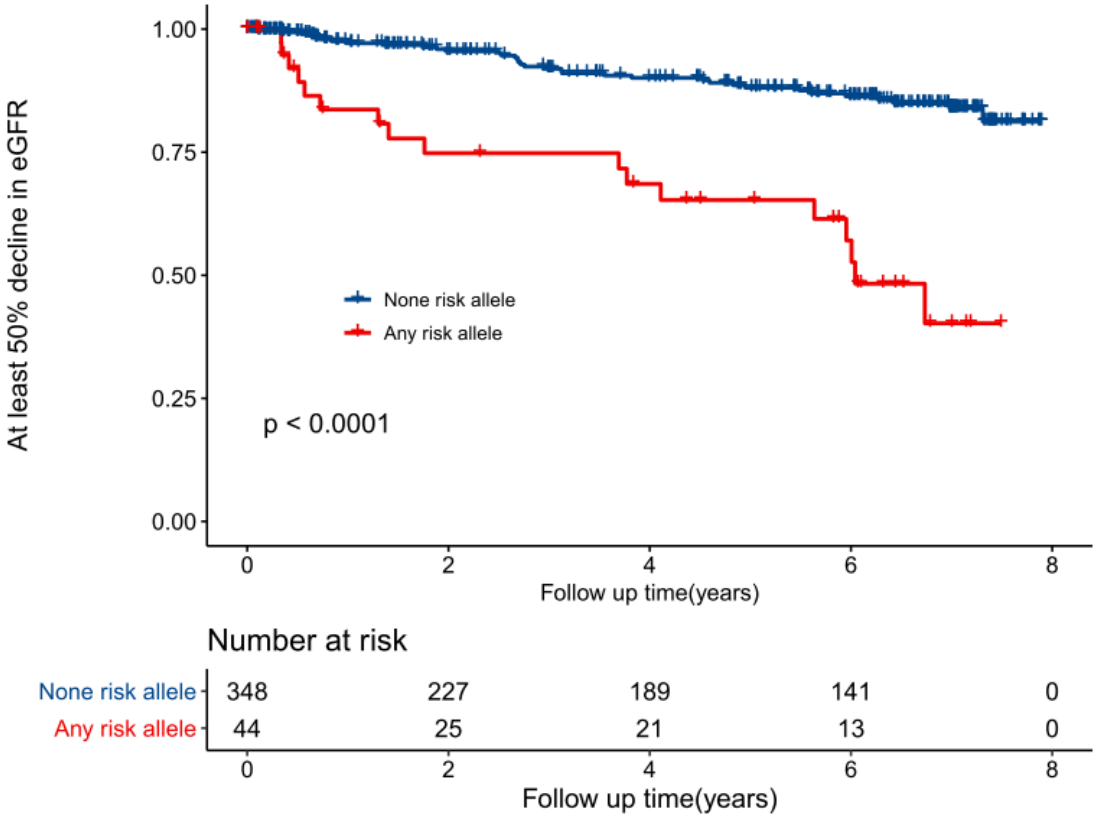
	Univariate Cox regression			Multivariate Cox regression		
Models and Factors	HR	95% CI	*P* value	HR	95% CI	*P* value
Any HLA risk allele possession #	4.6	2.6 - 8.2	2.9×10^{-7}	4.5	2.4 - 8.3	1.6×10^{-6}
Sex (Female)	0.46	0.24 - 0.90	0.02	0.61	0.30 - 1.2	0.17
Age at baseline (For every 10 yrs)	1.2	0.98 - 1.4	0.08	0.95	0.75 - 1.2	0.68
Proteinuria at baseline (g/24h)	1.2	1.1 - 1.4	< 0.001	1.1	0.99 - 1.3	0.07
Albumin at baseline (g/l)	0.93	0.88 - 0.98	0.008	0.99	0.93 - 1.06	0.74
eGFR at baseline (For every 10 ml/min per 1.73 m^2)	0.80	0.73 - 0.89	< 0.001	0.84	0.73 - 0.96	0.01
anti-PLA2R antibodies (For every 10 U/ml)	1.02	1.01 - 1.03	< 0.001	1.02	1.01 - 1.03	0.002

HLA risk alleles: DRB1*13:01, DQB1*06:03, DRB1*04:05 or DQB1*03:02. HR, hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate.

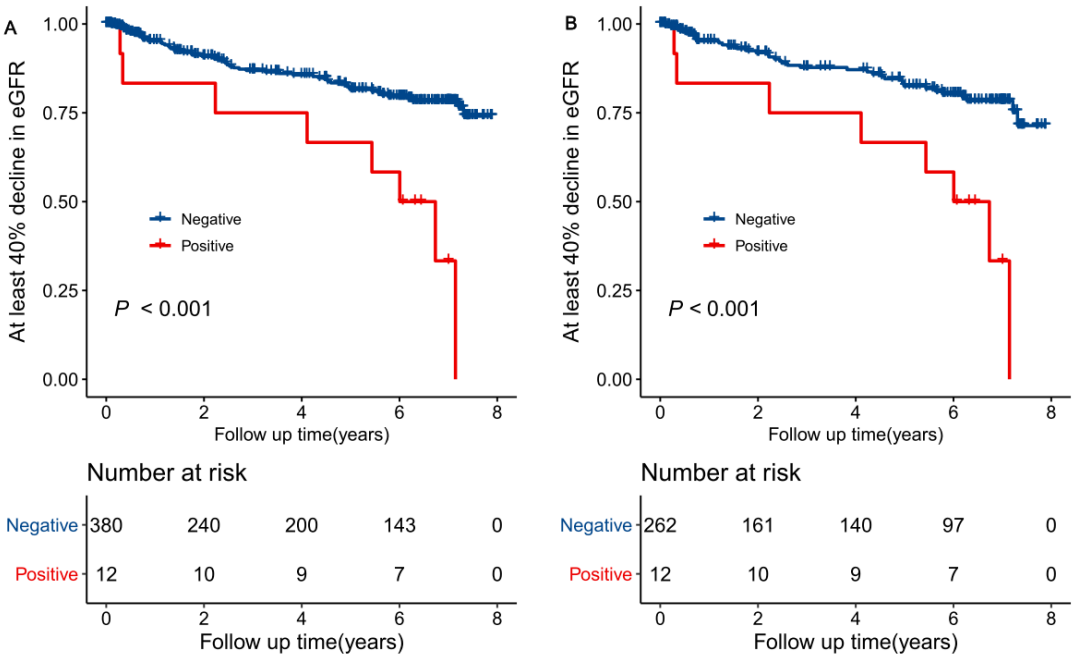
Supplemental Table 4. Relationship between the susceptible alleles and the four identified progressive risk alleles.

Alleles	Total (n = 392)	DRB1*15:01+ (n=283)	DRB3*0202+ (n= 274)	DRB1*0301+ (n= 135)
DRB1*13:01+	12	4 (33.3%)	12 (100%)	0 (0%)
DQB1*06:03+	12	4 (33.3%)	12 (100%)	0 (0%)
DRB1*04:05+	12	4 (33.3%)	8 (66.7%)	5 (41.7%)
DQB1*03:02+	21	12 (57.1%)	8 (38.1%)	4 (19.0%)
Any risk HLA allele	44	20 (45.5%)	27(61.4%)	8 (18.2%)

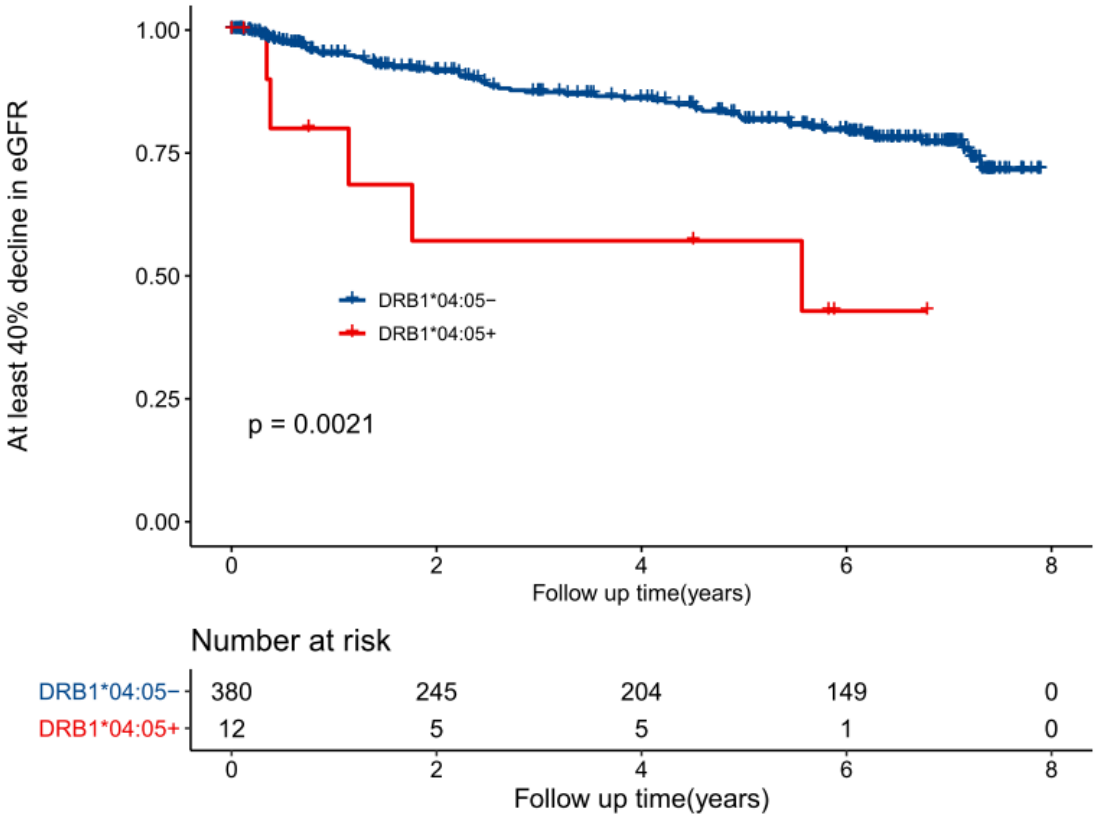
Supplemental Figure 1. Kaplan–Meier analysis of kidney survival curves (≥ 50% decline in eGFR) in PLA2R-related membranous nephropathy patients. HLA risk alleles: DRB1*13:01, DQB1*06:03, DRB1*04:05 or DQB1*03:02.



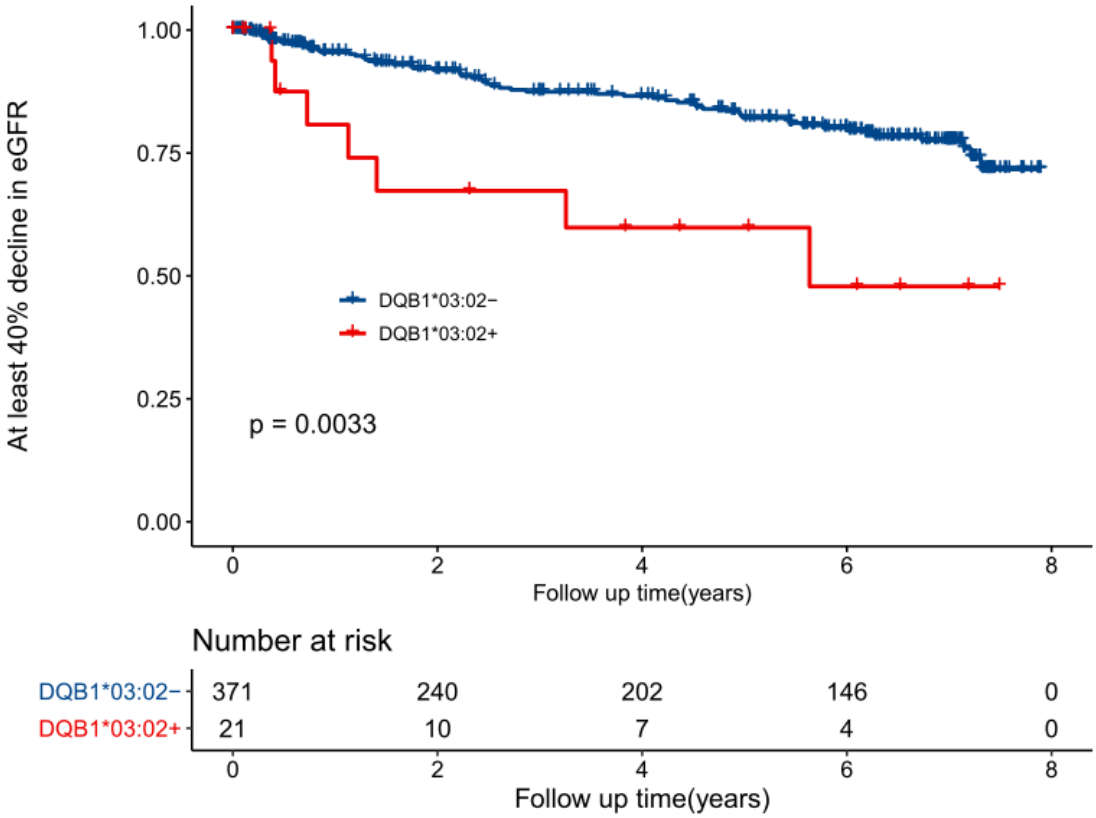
Supplemental Figure 2. Kaplan–Meier analysis of kidney survival curves (≥ 40% decline in eGFR) in PLA2R-related membranous nephropathy patients. (A) Patients with positive HLA DRB1*13:01 had worse kidney outcome than those with negative HLA DRB1*13:01 during follow-up. (B) Patients with DRB1*13:01^{+}DRB3*02:02^{+} had a significant higher rate of kidney failure than those with DRB1*13:01^{-} DRB3*02:02^{+}.



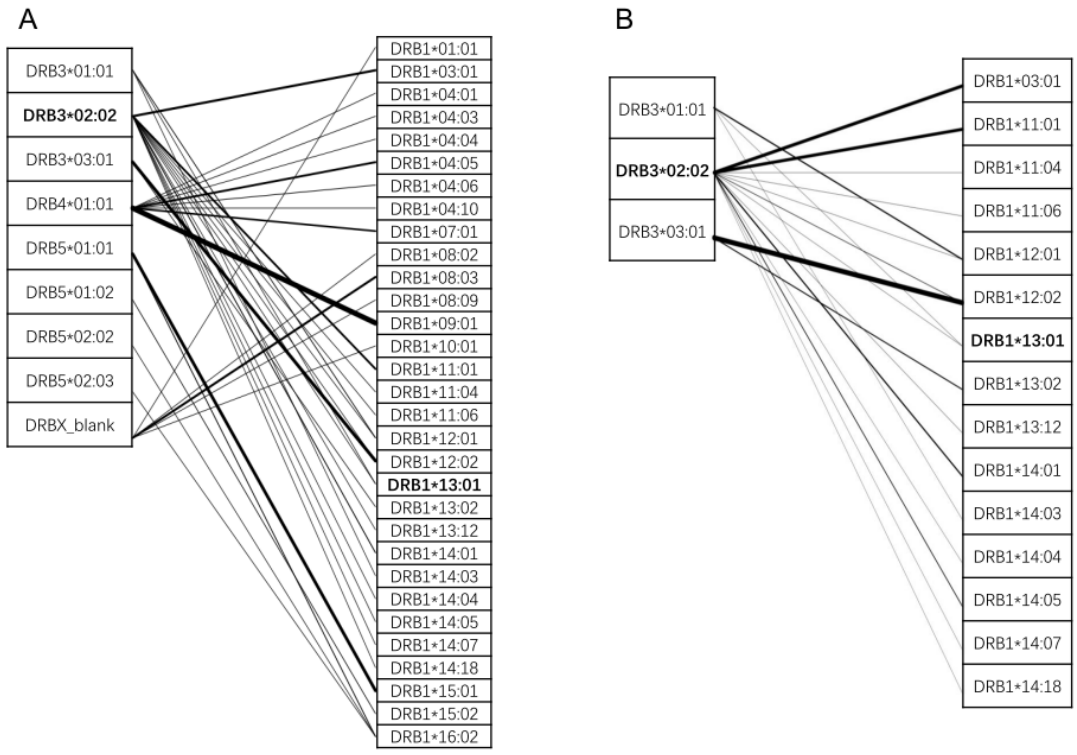
Supplemental Figure 3. Kaplan–Meier analysis of kidney survival curves (≥ 40% decline in eGFR) in PLA2R-related membranous nephropathy patients. Patients with positive HLA DRB1*04:05 had worse kidney outcomes during follow-up. eGFR, estimated glomerular filtration.



Supplemental Figure 4. Kaplan–Meier analysis of kidney survival curves (≥ 40% decline in eGFR) in PLA2R-related membranous nephropathy patients. Patients with positive HLA DQB1*03:02 had worse kidney outcomes during follow-up. eGFR, estimated glomerular filtration.



Supplemental Figure 5. Linkage map of HLA-DRB3/4/5 with HLA-DRB1 in the National Marrow Donor Program (NMDP) of Chinese population.



The line width represents the frequency of each haplotype. Panel A shows the linkage of HLA-DRB3/4/5 with HLA-DRB1; Panel B shows the linkage of HLA-DRB3 with HLA-DRB1. HLA DRB1*13:01 allele was mostly lined with DRB3*02:02 and DRB3*0101 in general Chinese population. DRB3*02:02 allele was linked with a number of DRB1 alleles, while DRB1*03:01 allele was almost completely linked with DRB3*02:02. Data were collected from Hum Immunol, 74: 1313-1320, 2013 10.1016.