Association of human leukocyte antigen gene polymorphism and mesangial proliferative glomerulonephritis in a large population-based study

JING-JIE ZHAO[1*], XI-BING WANG[2*], YUN LUAN[3], JUN-LI LIU[1], LING LIU[1] and HONG-YING JIA[4]

[1]Clinical Molecular Biology Laboratory, The Second Hospital of Shandong University, Jinan, Shandong 250033; [2]Department of Gynaecology and Obstetrics, Maternal and Child Health Care Service Center of Zaozhuang, Shandong 277102; [3]Central Laboratory and [4]Department of Scientific Research, The Second Hospital of Shandong University, Jinan, Shandong 250033, P.R. China

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Abstract. The aim of the present study was to investigate the association of human leukocyte antigen (HLA) gene polymorphism and clinical phenotypes of patients with mesangial proliferative glomerulonephritis (MsPGN). The genotyping of HLA-A, HLA-B and HLA-DRB1 alleles was detected in 1,536 consecutive MsPGN patients during the previous five years and 2,027 age- and gender-matched healthy individuals by using the polymerase chain reaction-sequence-specific primers method. The clinical and pathological data of the patients were collected and the genotype frequencies (GF) and odds ratio (OR) were analyzed. The allele frequencies of HLA-A*23, A*25, B*15, B*40, B*53 and DRB1*18 were significantly higher in MsPGN patients than in the controls (P<0.05). These alleles were considered as the suspected susceptibility genes (SSG) for MsPGN. Of note, results of the follow-up survey study demonstrated poorer prognosis of patients with SSG than those without SSG. On the other hand, the frequencies of A*32, A*33, B*50, B*58, B*60, B*71, DRB1*16 were lower in MsPGN patients than in the controls (P<0.05). However, the alleles A*20, A*22, A*35, A*36, A*38, B*21, B*73 and B*78 were not expressed in MsPGN patients. HLA gene polymorphism is associated with hereditary susceptibility to MsPGN. Therefore, there might be corresponding susceptibility and protective genes associated with MsPGN.

Correspondence to: Professor Yun Luan, Central Laboratory, The Second Hospital of Shandong University, 247 North Park Avenue, Jinan, Shandong 250033, P.R. China
E-mail: y_luan@live.com

Professor Hong-Ying Jia, Department of Scientific Research, The Second Hospital of Shandong University, 247 North Park Avenue, Jinan, Shandong 250033, P.R. China
E-mail: jiahongying@sdu.edu.cn

*Contributed equally

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Introduction

The major histocompatibility complex (MHC) is located centromeric to human leukocyte antigen (HLA)-B and has >65 polymorphic alleles (IMGT/HLA database) (1). Their genes span 3,600 kb DNA on chromosome 6 and encode a group of cell-surface antigen-presenting proteins. These proteins constitute the most complex dominant hereditary system associated with polymorphisms in human, and there were dominant diversities among different ethnicities and geographical regions. This gene has been associated with susceptibility to various autoimmune diseases (2-8), including chronic glomerulonephritis (CGN) (9), which is the leading primary disease resulting in renal failure and death. HLA gene polymorphism is associated with the incidence of CGN in China (10). However, the majority of those results were based on small samples and were limited to specific populations or regions. Eastern China is the most populated region in China and has only 10,000 reported CGN patients. By contrast, mesangial proliferative glomerulonephritis (MsPGN) is the most common disease of CGN in China, however, an association between HLA polymorphism and MsPGN in this region has yet to be reported in a large population-based study. This epidemiological study therefore provided some basic information on the HLA genotypes of MsPGN patients in the eastern region of China. Its possible significance in the diagnosis and prognosis of CGN and in clarifying the mechanisms of the disease were also discussed.

Materials and methods

Patients and controls. In this study, 1,536 MsPGN patients (867 male and 669 female; aged, 13-75 years) were enrolled consecutively from the inpatient section in the Department of Nephrology and Kidney Transplant of 50 hospitals in Eastern China from January, 2007 to December, 2012. The diagnosis of MsPGN was based on clinical and histological findings

(in 1982, WHO pathological classification standards). A total of 2,027 age- and gender-matched healthy controls (HC) were also enrolled in this study. HC samples were obtained from unrelated healthy donors from the Hematopoietic Stem Cell Bank of Shandong, China. The study was approved by the ethics committee of the People's Republic of China and the Second Hospital of Shandong University. Informed consent was obtained from all patients and healthy individuals participating in this study. The samples were collected in a 5 ml Serum Separator Vacutainer Tube and centrifuged at 30 min at 249.75 x g for 5 min. The serum samples were then distributed into 0.5 ml aliquots and stored at -80˚C until analysis (11).

HLA-typing by DNA amplification. Genomic DNA was extracted from peripheral blood samples of patients and healthy individuals using the QIAamp DNA Blood Mini kit (Qiagen GmbH, Hilden, Germany) as previously described (12). Low-resolution HLA typing was performed by the polymerase chain reaction sequence-specific primers (PCR-SSP) techniques according to Micro SSP DNA Typing Trays HLA-A, HLA-B and HLA-DR (One Lambda Inc., Canoga Park, CA, USA). Amplified DNA fragments were detected by agarose gel electrophoresis (2.5% agarose gel), stained with ethidium bromide, and UV transillumination. One Lambda DNA/LMT software version 3.98 was used to detect specific alleles.

Table I. Demographic characteristics of mesangial proliferative glomerulonephritis patients.

Characteristics	No. of patients (n=1,536)
Gender	
Male	857
Female	679
Age at onset (year)	
>40	1,020
<40	516
Cr (μmol/l)	89.385±7.867
BUN (m/mol)	4.367±0.582
ALB (g/l)	20.846±3.481
Pro (g/24)	3.57±2.67

Cr, creatinine; BUN, blood urea nitrogen; ALB, albumin.

Table II. Comparison of human leukocyte antigen-A genotype frequencies in mesangial proliferative glomerulonephritis (MsPGN) patients and controls.

	Controls			MsPGN patients					
Genotype	No.	Antigen frequency	Gene frequency	No.	Antigen frequency	Gene frequency	χ^2	P-value	OR
A*01	89	0.0807	0.0412	79	0.0898	0.0461	0.85		1.13
A*02	541	0.4892	0.2765	447	0.5039	0.2947	0.47		1.04
A*03	92	0.0827	0.0461	84	0.0918	0.0483	0.92		1.12
A*11	286	0.2618	0.1409	210	0.2506	0.1289	1.06		0.89
A*20	0	0	0	2	0.0019	0.0009	12.9		34.58
A*22	0	0	0	3	0.0027	0.0014	20.5		47.23
A*23	5	0.0050	0.0025	13	0.0147	0.0059	15.7	<0.0001	3.08
A*24	323	0.2896	0.1607	242	0.2902	0.1536	0.19		0.85
A*25	1	0.0007	0.0003	5	0.0056	0.0028	18.1	<0.0001	8.19
A*26	69	0.0641	0.0325	51	0.0598	0.0301	0.25		0.85
A*29	31	0.0287	0.0152	30	0.0345	0.0183	1.28		1.36
A*30	222	0.2106	0.1068	217	0.2142	0.1310	0.37		1.08
A*31	87	0.0802	0.0397	78	0.0705	0.0349	1.45		0.79
A*32	44	0.0405	0.0213	36	0.0216	0.0125	6.84	<0.01	0.60
A*33	209	0.1894	0.1006	21	0.1584	0.0841	6.25	<0.05	0.80
A*34	1	0.0007	0.0003	0	0	0	0.92		0.63
A*35	0	0	0	1	0.0009	0.0005	6.89		20.75
A*36	0	0	0	1	0.0009	0.0005	6.91		20.75
A*38	0	0	0	1	0.0009	0.0005	6.84		20.75
A*66	3	0.0023	0.0011	1	0.0009	0.0005	0.85		0.59
A*68	19	0.0179	0.0091	13	0.0140	0.0070	0.87		0.79
A*69	3	0.0020	0.0010	1	0.0009	0.0005	0.62		0.67
A*74	2	0.0011	0.0005	0	0	0	1.34		0.41
Total		2,027				1,536			

Table III. Comparison of human leukocyte antigen genotype frequencies in mesangial proliferative glomerulonephritis (MsPGN) patients and controls.

	Controls			MsPGN patients					
Genotype	No.	Antigen frequency	Gene frequency	No.	Antigen frequency	Gene frequency	χ^2	P-value	OR
B*07	85	0.0948	0.489	72	0.0854	0.0427	0.72		0.90
B*08	23	0.0215	0.0107	17	0.0203	0.0105	0.00		1.01
B*13	249	0.2647	0.1429	215	0.2579	0.1406	0.07		0.94
B*14	7	0.0069	0.0036	3	0.0042	0.0012	1.02		0.67
B*15	1	0.0011	0.0005	30	0.0385	0.0187	243.7	<0.0001	36.07
B*18	8	0.0071	0.0036	9	0.0112	0.0056	1.58		1.54
B*21	0	0	0	1	0.0009	0.0005	6.86		21.62
B*27	290	0.0439	0.0218	29	0.0381	0.0191	1.17		0.91
B*35	39	0.0928	0.0472	94	0.1202	0.0620	7.62	<0.01	1.32
B*37	28	0.0265	0.0143	33	0.0369	0.0208	6.95	<0.01	1.48
B*38	38	0.04080	0.0202	32	0.0372	0.0184	0.18		0.94
B*39	32	0.0347	0.0176	24	0.0306	0.0147	0.55		0.88
B*40	1	0.0015	0.0008	15	0.0189	0.0088	73.05	<0.0001	10.74
B*41	2	0.0024	0.0012	4	0.0056	0.0028	3.28		2.47
B*42	1	0.0011	0.0005	0	0	0	1.16		0.41
B*44	102	0.1174	0.0605	87	0.1080	0.0451	0.64		0.92
B*45	2	0.0028	0.0013	6	0.0075	0.0037	6.53	<0.05	2.75
B*46	98	0.1078	0.0546	82	0.1048	0.0489	0.10		0.97
B*47	1	0.0007	0.0003	2	0.0028	0.0014	4.35	<0.05	4.76
B*48	70	0.0681	0.0327	59	0.0762	0.0385	0.96		1.14
B*49	4	0.0042	0.0021	6	0.0075	0.0037	2.20		1.87
B*50	16	0.0156	0.0078	4	0.0056	0.0028	6.59	<0.01	0.36
B*51	126	0.1371	0.0692	98	0.1201	0.0629	1.45		0.89
B*52	68	0.0642	0.0327	53	0.0669	0.0352	0.03		1.03
B*53	1	0.0011	0.0005	8	0.0102	0.0048	34.92	<0.0001	9.51
B*54	59	0.0582	0.0286	64	0.0806	0.0427	9.00	<0.005	1.39
B*55	35	0.0346	0.0175	31	0.0401	0.0202	0.81		1.17
B*56	5	0.0051	0.0026	6	0.0072	0.0038	0.95		1.53
B*57	33	0.0310	0.0156	21	0.0252	0.0121	0.77		0.85
B*58	98	0.0948	0.0486	50	0.0608	0.0317	12.09	<0.001	0.75
B*59	1	0.0015	0.0007	1	0.0009	0.0005	0.20		0.90
B*60	119	0.1174	0.0605	55	0.0689	0.0356	20.89	<0.0001	0.66
B*61	115	0.1401	0.0727	133	0.1686	0.0884	6.58	<0.01	1.18
B*62	128	0.1432	0.0743	94	0.1202	0.0620	3.89	<0.05	0.72
B*63	6	0.0058	0.0029	6	0.0084	0.0042	1.03		1.51
B*64	1	0.0013	0.0007	2	0.0037	0.0019	3.23		2.97
B*65	4	0.0061	0.0030	4	0.0056	0.0028	0.04		0.99
B*67	19	0.0251	0.0126	18	0.0233	0.0117	0.12		0.94
B*70	1	0.0004	0.0002	1	0.0019	0.0009	3.73		4.84
B*71	28	0.0341	0.0172	6	0.0084	0.0042	21.39	<0.0001	0.27
B*72	3	0.0026	0.0013	1	0.0009	0.0005	1.06		0.53
B*73	0	0.0000	0.0000	1	0.0009	0.0005	6.83	<0.01	19.86
B*75	74	0.0720	0.0367	55	0.0699	0.0356	0.06		0.97
B*76	1	0.0016	0.0008	1	0.0019	0.0009	0.03		1.38
B*77	2	0.0003	0.0001	1	0.0019	0.0009	4.69	<0.025	6.91
B*78	0	0	0	1	0.0009	0.0005	6.57	<0.01	21.02
B*81	3	0.0034	0.0017	1	0.0009	0.0005	1.82		0.43
Total		2,027				1,536			

Table IV. Comparison of human leukocyte antigen-DRB1 genotype frequencies in mesangial proliferative glomerulonephritis (MsPGN) patients and controls.

	Controls			MsPGN Patients					
Genotype	No.	Antigen frequency	Gene frequency	No.	Antigen frequency	Gene frequency	χ^2	P-value	OR
DR*01	61	0.0613	0.0286	76	0.0698	0.0354	3.02		1.25
DR*04	187	0.1895	0.1001	276	0.2562	0.1385	25.8	<0.0001	1.38
DR*07	283	0.2712	0.1398	277	0.2827	0.1409	0.61		0.92
DR*08	181	0.1143	0.0605	89	0.0818	0.0404	9.78	<0.001	0.65
DR*09	224	0.2268	0.1205	234	0.2162	0.1149	0.41		0.94
DR*10	30	0.0279	0.0145	45	0.0402	0.0218	5.42	<0.025	1.54
DR*11	113	0.1086	0.0581	164	0.1512	0.0806	17.5	<0.0001	1.43
DR*12	203	0.1862	0.1025	208	0.1926	0.1023	0.01		0.98
DR*13	150	0.1369	0.0682	130	0.1202	0.0620	4.49	<0.05	0.82
DR*14	113	0.1069	0.0498	124	0.1156	0.0596	0.39		1.05
DR*15	353	0.3206	0.1807	276	0.2563	0.1376	18.3	<0.0001	0.69
DR*16	45	0.0405	0.0202	22	0.0205	0.0103	12.6	<0.001	0.45
DR*17	83	0.0762	0.0388	57	0.0531	0.0270	7.27	<0.01	0.71
DR*18	1	0.0010	0.0005	12	0.0112	0.0056	78.0	<0.0001	152.35
Total		2,027				1,536			

Statistical analysis. Allele frequency distributions were confirmed by calculating the frequencies of the genotypes HLA-A, HLA-B, and HLA-DRB1 as being in Hardy-Weinberg equilibrium using Arlequin v.3.1 software. Analyses related to the case-control study were performed using the Statistical Package for the Social Sciences v.16 (SPSS Inc., Chicago, IL, USA). Differences between MsPGN patients and the controls were analyzed using the χ^2 and Fisher's exact tests for qualitative variables and the t-test for quantitative variables. The odds ratio (OR) was calculated to evaluate the association between the alleles and the disease. The Bonferroni method was used to adjust for type I errors due to multiple comparisons. P<0.05 was considered to indicate a statistically significant difference.

Results

Demographic characteristics of MsPGN patients. Table I summarizes the main clinical characteristics of the 1,536 unrelated MsPGN patients. The age at onset of disease was 13-75 years (mean, 35.62±13.5 years). The entire patient cohort had undergone a renal biopsy for an exact histological diagnosis.

Comparison of the HLA-A, HLA-B and HLA-DRB1 polymorphism between the MsPGN patients and the HC. The allele and genotype frequencies (GF) of the HLA-A, HLA-B and DRB1 gene polymorphisms of the MsPGN patients and the HC are presented in the Tables II-IV. The results demonstrated statistical differences of GF for HLA-A*23, A*25, B*15, B*40, B*53, and HLA-DRB1*18 in MsPGN patients as compared to the HC (P<0.0001, OR=3.08, 8.19, 36.07, 10.74, 9.51 and 152.35, respectively). Eight less frequent alleles (HLA-A*20, A*22, A*35, A*36, A*38, HLA-B*21, B*73 and B*78) were detected only in MsPGN patients, but not in the HC.

Allele frequencies of HLA-A*23, A*25, B*15, B*40, B*53 and DRB1*18 were higher in the MsPGN patients as compared to those in the HC, and thus considered as suspected susceptibility genes (SSG) for MsPGN.

Haplotype analysis. Statistical analysis of HLA-A, HLA-B and HLA-DRB1 haplotypes was performed between the patients and HC using the χ^2 test. The GF of the haplotypes A*23, B*44 and DRB1*18 (0.0091 vs. 0.0050); A*25, B*15 and DRB1*07 (0.0083 vs. 0.0043); A*03, B*70 and DRB1*11 (0.0074 vs. 0.0029); A*68, B*13 and DRB1*04 (0.0059 vs. 0.0020); and A*11, B*10 and DRB1*12 (0.0048 vs. 0.0015) were higher in MsPGN patients compared to the HC (P<0.05).

Follow-up survey. Forty-nine patients with SSG and 52 patients without SSG-carrying were randomly selected for follow-up, and a survival rate (SR) of 1, 3 and 5 years subsequent to kidney transplant was calculated. The results showed that the SR was 95.6%, 72.3 and 50.8% for SSG-carrying patients, and 98.4, 89.6 and 74.8% without SSG-carrying patients. Statistical differences were observed in SRs for patients with or without SSG according to results of the log-rank test (χ^2=6.6783, P<0.01).

Discussion

Mesangial proliferation is a basic pathologic process of various kidney diseases. MsPGN is the common pathological type that progresses to end-stage renal failure, and is histologically characterized by a marked mesangial increase and expansion of extracellular matrix in the glomeruli (13,14). The pathogenesis of MsPGN remains unclear, and genetic predisposition

may be a risk factor. Recent studies (15-18) have demonstrated that HLA alleles are associated with certain idiopathic renal diseases, including those detected in previous studies (19,20).

In the present study, we detected 23 alleles of HLA-A, 47 alleles of HLA-B and 14 alleles of HLA-DRB1 in 1,536 MsPGN patients in Eastern China. The results showed that the HLA-A*23, A*25, B*15, B*40, B*53 and DRB1*18 alleles were significantly higher in the MsPGN patients as compared to the HC. Results of the follow-up survey demonstrated these alleles to be SSG for MsPGN patients. However, the allele frequencies of A*32, A*33, B*50, B*58, B*60, B*71 and DRB1*16 were significantly lower in the MsPGN patients compared to the HC. This finding suggested that these alleles might be protective genes of MsPGN. Compared with ethnicities regions of China, our study proved that certain HLA alleles are potential hereditary risk factors for susceptibility to CGN (21,22). Thus, we observed that there were clear diversities of the highly polymorphic HLA system among ethnicities and regions. In addition, the alleles HLA-A*20, A*22, A*35, A*36, A*38, B*21, B*73 and B*78 were positive in rare cases of MsPGN (2, 3, 1, 1, 1, 1, 1 and 1 cases, respectively) although no alleles were identified to be positive in 2,027 HC. Their association with MsPGN remains to be clarified.

Previous studies have shown that HLA-DRB1, HLA-DQB1 and HLA-DPB1 alleles are associated with MsPGN disease anti-glomerular basement membrane disease (23) in Caucasian as well as Asian populations. The present study has proven that certain HLA alleles are potential hereditary risk factors for susceptibility to CGN. By contrast, we detected the GF of haplotypes A*30-B*13-DRB1*07, A*02-B*13-DRB1*07, A*33-B*44-DRB1*13, A*02-B*46-DRB1*09 and A*33-B*58- DRB1*13, findings consistent with those identified in Northern China (23). Previous reports (24) have identified the frequencies of haplotypes A*02-B*13-DRB1*07, A*33-B*44-DRB1*13, A*02-B*46-DRB1*09 and A*33-B*58-DRB1*13 to be high in Northern China, however, this was not the case in the present study. An analysis of the haplotypes revealed haplotypes A*23-B*44-DRB1*18, A*25-B*15-DRB1*07, A*03-B*70-DRB1*11, A*68-B*13-DRB1*04 and A*11-B*10-DRB1*12 to be significantly higher in MsPGN patients than the HC. An association of HLA polymorphism with the prognosis of MsPGN patients was also identified in this study. SRs of 1, 3 and 5 years for patients with SSGs (HLA-A*23, A*25, B*15, B*40, B*53 and DRB1*18) were lower than those of patients not carrying SSGs, and the difference was statistically significant.

In conclusion, in this large population-based study, we detected a strong association between HLA genotypes and MsPGN in Eastern China. Specific genotypes and haplotypes of HLA were closely associated with the incidence of common renal disorder and prognosis. The relationship may also be significant in revealing the immunological pathogenesis of CGN.

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