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Single-nucleotide polymorphisms in the class II region of the major histocompatibility complex in Japanese patients with immunoglobulin A nephropathy

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Abstract Immunoglobulin A nephropathy (IgAN) is a form of chronic glomerulonephritis of unknown etiology and pathogenesis. Immunogenetic studies have not conclusively indicated that human leukocyte antigen (HLA) is

involved. As a first step in investigating a possible relationship between HLA class II genes and IgAN, we analyzed the extent of linkage disequilibrium (LD) in this region of chromosome 6p21.3 in a Japanese test population and found extended LD blocks within the class II locus. We designed a case-control association study of single-nucleotide polymorphisms (SNPs) in each of those LD blocks, and determined that SNPs located in the *HLA-DRA* gene were significantly associated with an increased risk of IgAN ($P = 0.000001$, odds ratio = 1.91 [95% confidence interval 1.46–2.49]); SNPs in other LD blocks were not. Our data imply that some haplotype of the *HLA-DRA* locus has an important role in the development of IgAN in Japanese patients.

Key words Single-nucleotide polymorphism · IgA nephropathy · Linkage disequilibrium · HLA class II · *HLA-DRA*

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Introduction

Immunoglobulin A nephropathy (IgAN [MIM161950]), a disease characterized by predominant IgA deposits in glomerular mesangial areas, is the most common type of glomerulonephritis (GN); its prevalence may be as high as 50% of all cases of GN in Asia, especially among the Japanese. Long-term follow-up studies of biopsy-proven cases of IgAN have revealed that 20%–30% of patients progress to end-stage renal disease within 20 years of GN onset (Galla 1995; Floege and Feehally 2000).

The pathogenesis of IgAN is unknown, but accumulated data suggest that some genetic factors are involved in disease susceptibility (Galla 2001). The prevalence of IgAN seems to reflect demographic and ethnic characteristics of the populations studied; moreover, several cases of familial IgAN (Julian et al. 1985; Scolari et al. 1999) and higher risk of identical twins to IgAN (Tolkoff-Rubin et al. 1978; Sabatier et al. 1979) have been reported. Investigators have

also observed an increased frequency of specific human leukocyte antigens (HLAs) in some patient populations (Hsu et al. 2000).

Although numerous studies have focused on HLAs encoded by the human major histocompatibility complex (MHC) locus with respect to possible linkage with susceptibility to IgAN, no consistent results have emerged (Hsu et al. 2000). Lately, however, genes encoding HLAs have come to be considered useful markers for identifying disease-susceptibility loci, rather than causing diseases themselves (Moore 1993; Schena 1995). This concept implies that loci linked to HLA genes could be associated with IgAN.

The present article takes a different approach to investigating the association of IgAN with the class II locus of the MHC, in view of the considerable interest that has arisen in understanding patterns of linkage disequilibrium (LD) in the human genome to facilitate association studies involving complex diseases (Jeffreys et al. 2001). Single-nucleotide polymorphisms (SNPs) in particular are receiving attention as having potential influence on susceptibility to complex diseases, including IgAN (Takei et al. 2002). The ethnically homogeneous population of Japan (Usami et al. 2000) presents an opportunity to study genetic factors other than race/ethnicity that might contribute to the incidence of IgAN. We provide here an estimation of the extent of LD in the HLA class II locus, and we demonstrate linkage of IgAN to a gene in this region by means of a case-control association study involving a large number of Japanese patients and controls.

Materials and methods

Materials

Peripheral blood samples were obtained from 313 patients (176 women and 137 men, mean age of 44.2 ± 14.3 years) who were diagnosed with IgAN on the basis of clinical manifestations as well as renal-biopsy findings at one of several surgical centers in Japan (Division of Clinical Nephrology and Rheumatology, Niigata University Graduate School of Medical and Dental Sciences; Department of Medicine, Kidney Center, Tokyo Women's Medical University; Department of Urology, Iwate Medical University; Department of Urology, Iwate Prefectural Ofunato Hospital; and Department of Urology, Sanai Hospital). Henoch-Schönlein purpura and secondary IgAN such as hepatic glomerulosclerosis were excluded from the analysis. The mean value of serum creatinine at the time of renal biopsy was 1.07 mg/dl, ranging from 0.3 to 2.5 mg/dl. We analyzed DNA from 816 volunteers (492 women and 324 men, mean age of 54.4 ± 14.5 years) as controls. These healthy subjects without hematuria, proteinuria, and renal dysfunction were randomly selected from the Japanese population. Genomic DNA was prepared from each sample according to standard protocols. Informed consent was obtained from all participants.

Markers and genotyping

Information about each SNP in the HLA class II region chosen for this study was obtained from the Japanese SNP (JSNP) database (<http://snp.ims.u-tokyo.ac.jp>). We amplified multiple genomic fragments using 20 ng of genomic DNA for each polymerase chain reaction (PCR), as described elsewhere (Ohnishi et al. 2000). Sequences of all primers are available at JSNP. Each PCR was performed in a 20- μ l solution containing 50 pmol of each primer, 10 units of Ex-Taq DNA polymerase (TaKaRa Shuzo, Tokyo, Japan), and 0.55 μ g of TaqStart (CLONTECH Laboratories, Tokyo, Japan) in the GeneAmp PCR system 9700 (Applied Biosystems, Foster City, CA, USA). Initial denaturation was at 94°C for 2 min, followed by 37 cycles of amplification at 94°C for 15 s and annealing at 60°C for 45 s, with a final extension for 2 min at 72°C. We genotyped each SNP by means of the Invader assay that combines a structure-specific cleavage enzyme with a universal fluorescent resonance energy transfer system (Mein et al. 2000).

Typing of *HLA-DRB1* by DNA sequencing

Using a technique of random sampling, we selected 82 of the IgAN patients and 253 of the controls. We typed these subjects for *HLA-DRB1* according to DNA sequence, using the *HLA-DRB* BigDye Terminator Sequencing-Based Typing Kit according to the manufacturer's instructions (Applied Biosystems).

Statistical analysis

Genotype distributions and allele frequencies of each selected SNP were compared, respectively, between cases and controls using the chi-square test. Significance was judged according to the guidelines of Lander and Kruglyak (1995). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by Woolf's method. Hardy-Weinberg equilibrium was assessed by χ^2 statistics (Nielsen et al. 1998). Frequencies of *HLA-DRB1* alleles were obtained by counting the total number of specific alleles. *HLA-DRB1* allele frequencies in IgAN patients were assessed for significant deviation from those of the control group by means of the χ^2 test, or by Fisher's exact test when criteria for the χ^2 test could not be applied.

Analysis of linkage disequilibrium

We estimated maximum-likelihood haplotype frequencies for each pair of SNP markers from the genotypic data of 94 controls. We used these frequencies to estimate the level of LD between each pair of SNPs, using D' value (Devlin and Risch 1995) for all pairs of markers with minor-allele frequencies of at least 0.10, except for SNPs not falling under the assumption of Hardy-Weinberg equilibrium.

Results

LD mapping in the HLA class II region

The region analyzed in the present study covered genomic DNA between the *DPB2* and *TSBP* genes on chromosome 6p21.3 (Fig. 1a). The LD patterns defined by 42 SNP markers are summarized in Fig. 1b. Because lower-frequency markers showed inconsistent LD patterns (Jeffreys et al. 2001), we selected markers with allelic frequencies of their minor alleles of greater than 10%. The LD map constructed in this study revealed five extended blocks of high disequilibrium that broke down at the *BTNL-2*, *DQA2*, *LMP2*, and *DOA* loci (Fig. 1b).

Case-control study in each domain

To investigate a possible association between IgAN and SNPs in each block, we genotyped 313 patients with IgAN and 816 controls at the five loci listed in Table 1. The genotype distributions we observed in controls did not differ from the expected frequency under the assumption of Hardy-Weinberg equilibrium (data not shown). A significant association to IgAN was observed at the *DRA* locus, but no association was found at the remaining four loci (Table 1).

In view of the strong association found at the *DRA* locus, we genotyped six SNPs present in the *HLA-DRA* gene (Fig. 2). The most significant difference in genotype distribution between patients with IgAN and controls was observed at the *DRA* SNP-5 locus (Table 2). Homozygosity for major

alleles was significantly more common in IgAN patients than in controls ($\chi^2 = 22.87$, $P = 0.000001$). The OR for patients with IgAN versus controls was 1.91 (95% CI 1.46–2.49) for homozygotes of the *DRA* SNP-5 major allele versus others. One of the three SNPs for which we found positive associations would alter an amino acid sequence: *DRA* SNP-6, which showed complete LD to *DRA* SNP-2, would substitute valine for leucine at codon 222 of the *HLA-DRA* gene ($\chi^2 = 19.96$, $P = 0.00004$). The OR for patients with IgAN versus controls was 1.77 (95% CI 1.36–2.31) for homozygotes of the *DRA* SNP-6 major allele versus others. In contrast, no significant differences were observed for *DRA* SNP-3 or *DRA* SNP-4.

Distribution of *HLA-DRB1* alleles

Because the *HLA-DRB* region lies in close vicinity to *DRA*, we also examined the relationship between the *DRB* region and SNPs for susceptibility to IgAN. Because *DRB1* is highly polymorphic, we determined the genotypes of 82 IgAN patients and 253 controls by direct DNA sequencing. As shown in Table 3, the frequency of *DRB1*04* tends to be higher in patients than in controls ($P = 0.034$), but the association of the *DRB1* gene to IgAN was less significant than that of the *DRA* gene.

Discussion

We have examined the extent and strength of LD within the class II locus of MHC in a Japanese population sample.

Table 1. Genotype frequencies and association tests of SNPs in the class II region (313 cases of IgAN vs 816 controls)

	<i>DOA</i>	<i>DMB</i>	<i>DQB2</i>	<i>DRA</i>	<i>TSBP</i>
SNP information					
Contig number	NT_007592.8	NT_007592.8	NT_007592.8	NT_007592.8	NT_007592.8
Location	15399187	15328808	15151100	14860033	14783966
Genetic variation	T>C	C>A	A>G	C>T	C>T
IgAN					
Major allele	0.61	0.45	0.68	0.66	0.65
Minor allele	0.39	0.55	0.32	0.34	0.35
Total	1.00	1.00	1.00	1.00	1.00
Major homozygous	0.36	0.23	0.49	0.46	0.44
Heterozygous	0.49	0.45	0.37	0.39	0.42
Minor homozygous	0.15	0.32	0.14	0.15	0.14
Total	1.00	1.00	1.00	1.00	1.00
Control					
Major allele	0.64	0.51	0.68	0.55	0.61
Minor allele	0.36	0.49	0.32	0.45	0.39
Total	1.00	1.00	1.00	1.00	1.00
Major homozygous	0.41	0.26	0.46	0.31	0.37
Heterozygous	0.45	0.50	0.44	0.48	0.48
Minor homozygous	0.14	0.24	0.10	0.21	0.15
Total	1.00	1.00	1.00	1.00	1.00
χ^2 [P]					
Genotype frequency (2 × 3 table)	2.32 [0.3]	7.37 [0.02]	6.52 [0.03]	23.04 [0.000009]	5.05 [0.08]
Allele frequency (major vs minor)	1.77 [0.1]	5.46 [0.01]	0.06 [0.8]	19.82 [0.000008]	3.64 [0.05]
Major homozygous vs others	2.32 [0.1]	1.13 [0.2]	0.79 [0.3]	22.87 [0.000001]	5.03 [0.02]
Minor homozygous vs others	0.23 [0.6]	7.35 [0.006]	3.86 [0.04]	4.37 [0.03]	0.36 [0.5]

SNP, Single-nucleotide polymorphism

a

b

Fig. 1. a The genomic region extending from *DPB2* to *TSBP* on human chromosome 6p21.3. **b** Distribution of linkage disequilibrium (LD) in the class II region, adjusted for physical distance. Single-nucleotide polymorphism (SNP) sites are indicated by *tick marks* at their locations in the respective genes. Domains showing strong LD are indicated *below* the chart in *light crimson*

Table 2. Genotype data and association tests of SNPs on the *HLA-DRA* gene

		DRA SNP-1 ^a	DRA SNP-2	DRA SNP-3	DRA SNP-4	DRA SNP-5	DRA SNP-6
SNP information		Exon 1 (5'UTR)	Exon 3	Intron 3	Intron 3	Intron 3	Exon 4
Location		-19	402	+64	+133	+280	724
Position		C/A	C>A	C>T	T>G	C>T	G>T
Genetic variation			Ile 134 Ile				Val 222 Leu
Substitution							
IgAN							
Major allele [%]			434 [69.3]	515 [82.3]	553 [88.3]	411 [65.7]	434 [69.3]
Minor allele [%]			192 [30.7]	111 [17.7]	73 [11.7]	215 [34.3]	192 [30.7]
Total			626 [100.0]	626 [100.0]	626 [100.0]	626 [100.0]	626 [100.0]
Major homozygous [%]			165 [52.7]	217 [69.3]	249 [79.5]	145 [46.3]	165 [52.7]
Heterozygous [%]			104 [33.2]	81 [25.9]	55 [17.6]	121 [38.7]	104 [33.2]
Minor homozygous [%]			44 [14.1]	15 [4.8]	9 [2.9]	47 [15.0]	44 [14.1]
Total			313 [100.0]	313 [100.0]	313 [100.0]	313 [100.0]	313 [100.0]
Control							
Major allele [%]			1009 [61.8]	1323 [81.1]	1436 [88.0]	903 [55.3]	1009 [61.8]
Minor allele [%]			623 [38.2]	309 [18.9]	196 [12.0]	729 [44.7]	623 [38.2]
Total			1632 [100.0]	1632 [100.0]	1632 [100.0]	1632 [100.0]	1632 [100.0]
Major homozygous [%]			315 [38.6]	537 [65.8]	634 [77.7]	254 [31.1]	315 [38.6]
Heterozygous [%]			379 [46.4]	249 [30.5]	168 [20.6]	395 [48.4]	379 [46.4]
Minor homozygous [%]			122 [15.0]	30 [3.7]	14 [1.7]	167 [20.5]	122 [15.0]
Total			816 [100.0]	816 [100.0]	816 [100.0]	816 [100.0]	816 [100.0]
χ^2 [P]							
Genotype frequency (2 × 3 table)			19.96 [0.00004]	2.79 [0.2]	2.64 [0.2]	23.04 [0.000009]	19.96 [0.00004]
Allele frequency (major vs minor)			11.04 [0.0008]	0.43 [0.5]	0.05 [0.8]	19.82 [0.000008]	11.04 [0.0008]
Major homozygous vs others			18.44 [0.00001]	1.26 [0.2]	0.46 [0.4]	22.87 [0.000001]	18.44 [0.00001]
Minor homozygous vs others			0.14 [0.7]	0.74 [0.3]	1.52 [0.2]	4.37 [0.03]	0.14 [0.7]
Odds ratio [95% CI]							
Major homozygous vs heterozygous			1.91 [1.43~2.54]	1.24 [0.92~1.67]	1.20 [0.86~1.68]	1.86 [1.40~2.49]	1.91 [1.43~2.54]
Major homozygous vs others			1.77 [1.36~2.31]	1.17 [0.89~1.55]	1.12 [0.81~1.54]	1.91 [1.46~2.49]	1.77 [1.36~2.31]
Major homozygous vs minor homozygous			1.45 [0.98~2.15]	0.81 [0.43~1.53]	0.61 [0.26~1.43]	2.03 [1.38~2.97]	1.45 [0.98~2.15]

SNP, Single-nucleotide polymorphism; UTR, untranslated region; CI, confidence interval

^a DRA SNP-1 was not in Hardy-Weinberg equilibrium

Fig. 2. Location of SNPs in the *HLA-DRA* gene

Table 3. Gene frequencies (%) of *HLA-DRB1* alleles in patients with IgAN and controls

<i>DRB1</i> allele	Group	
	IgAN (<i>n</i> = 82) 164 alleles	Controls (<i>n</i> = 253) 506 alleles
*01	3.1	5.7
*15	15.2	18.4
*04	26.2 [†]	18.4
*11	2.4	3.4
*12	3.1	4.7
*13	7.3	8.5
*14	13.4	11.5
*07	0.6	0.4
*08	11.0	12.1
*09	17.1	14.8
*10	0.6	1.4

[†] *P* = 0.034

Many factors influence the recombination rate and extent of LD, but a remarkable similarity of LD patterns in the MHC region has been observed in populations whose genetic and demographic histories are vastly different (Zavattari et al. 2000). The distribution of crossover events in the class II region tends to cluster in three hot spots, namely, between *DQB1* and *DQB3*, between *RING3* and *DOA*, and in a region within the *TAP2* gene (Zavattari et al. 2000). The LD blocks in our map were separated by corresponding intervals, defined as *DRA* and *DQA2*, *RING3* and *DOA*, and *TAP2* and *DMB*, indicating consistency with other studies (Jeffreys et al. 2001).

LD is a situation in which two closely located polymorphisms show association with each other. LD enables us to use an allele of one SNP to predict an allele of another (nearby) polymorphism. Any potential instance of LD between an SNP and a disease-causing, functional polymorphism (which might also be an SNP) is the basis for whole-genome association studies designed to detect genes involved in complex diseases (Remm and Metspalu 2002).

We demonstrate that the frequencies of *DRB1**04 was increased in patients with IgAN, consistent with other previous reports that HLA-DR4 was associated with IgAN in a Japanese population (*P* < 0.04), although the

reported *P* value was not significantly small (Hiki et al. 1982; Kashiwabara et al. 1982). Moreover, the apparent association between *HLA-DRA* alleles and IgAN has not been clarified in the Japanese or any other ethnic group; we have demonstrated here for the first time a significant association of three SNPs in the *HLA-DRA* gene with IgAN. However, because the *DQA1* and *DQB1* loci, which lie within the same LD domain, are highly polymorphic and remain untyped, we cannot exclude the possibility of an association of either or both of these genes with susceptibility to IgAN.

The class II region of the MHC contains a number of interesting candidates for susceptibility to a variety of diseases because of their polymorphic features and the antigenicity of their products. Strong associations exist between products of the polymorphic HLA-DR alleles and certain autoimmune diseases because HLA-DR molecules are of great importance in the selection and activation of CD4-positive T cells that regulate immune responses against protein antigens (Vyse and Todd 1996). However, the pathophysiology of these autoimmune disorders is not completely understood.

Class II molecules are composed of an alpha chain that is noncovalently associated with a beta chain encoded by the A and B gene loci, respectively, in MHC, and are expressed primarily on antigen-processing cells such as dendritic cells, B lymphocytes, and macrophages. The DR molecule consists a single alpha chain encoded by the *DRA* gene and four species of beta chain encoded by the *DRB1*, *DRB3*, *DRB4*, and *DRB5* genes. For Class II, both the A and B genes contribute to variable α -1 and β -1 domains that form a peptide-binding cleft (Williams 2001). The SNPs for which we found positive association with IgAN are not located in this variable α -1 domain. However, because the amino-acid substitution caused by the DRA SNP-6 occurs in the intracellular domain of the DRA molecule, it may affect the structures of peptides bound to HLA class II antigens.

The fundamental role of class II molecules is to bind to self and nonself peptides and transport them to the plasma membrane of cells for recognition by the T-cell antigen receptor. DRA SNP-6 may bring about individual differences in immune responses by influencing signals for alternative pathways involving internalization of HLA-DR molecules (Stern et al. 1994; Pinet et al. 1995). It is well known that, in autoimmune diseases, the activation of autoreactive CD4-positive T cells, which are inactivated under normal conditions, is considered to be a crucial step in the development of disease. Because the IgA antibody response is T-cell dependent, the MHC class II products encoded by DR genes might play a crucial role in the presentation of processed antigen to specific T cells (Hsu et al. 2000). However, the exact mechanism by which the DRA molecule contributes to the development of IgAN remains to be determined.

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