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ORIGINAL ARTICLE

Shared epitope and radiologic progression are less prominent in elderly onset RA than young onset RA

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Abstract The aim of this study was to determine the influence of HLA-DRB1 and HLA-DQB1 genes on the disease susceptibility and the disease severity in elderly onset rheumatoid arthritis (EORA) compared with young onset rheumatoid arthritis (YORA) in Korean patients. Genetic analysis of HLA-DRB1 and HLA-DQB1 alleles was performed in three groups. Group 1 included 63 patients who were diagnosed with (rheumatoid arthritis) RA after the age of 60 (EORA). Group 2 consisted of 109 patients who were diagnosed with RA before the age of 60 (YORA). Group 3 involved 133 normal controls. The shared-epitope-coding alleles included the members of the HLA-DRB1*04 allele group (*0401, *0404, *0405, *0408, *0410), HLA-DRB1*01 allele group (*0101,*0102), HLA-DRB1*1001, and HLA-DRB1*1402. The disease severity was assessed by the modified total sharp score (mTSS). The shared-epitope-coding alleles were more frequently observed in the RA patients than in the normal controls. The shared-epitope-coding alleles were less frequently found in EORA group than YORA group (31/63 (49.2 %) in group 1, 72/109 (66.1 %) in group 2, 45/133 (33.8 %) group 3, $p = 0.02$). Although the mTSS of the group 1 was higher than group 2 at symptom onset, the overall mean mTSS of the group 1 was lower than that of group 2 (26.8 vs. 57.5, $p < 0.05$). HLA-DQ*04 showed the higher frequency in the patients group than in normal controls ($p < 0.001$). And HLA-DQ*04 was less commonly found in the patients with EORA than YORA ($p < 0.05$). The influence of shared epitope and HLA-DQ*04 alleles may be less significant on disease susceptibility in EORA. The presence of shared-epitope-coding alleles did not appear to influence on disease severity in EORA patients as well as in YORA patients. Radiologic deterioration in EORA group was less severe than in YORA group. The presence of shared epitope and radiologic progression are less prominent in EORA patients than YORA patients.

Keywords Shared epitope · HLA-DQ*04 · Elderly onset rheumatoid arthritis · Mean mTSS

Eun-Ji Kim/Jennifer Lee and Tai-Gyu Kim/Ho-Youn Kim have contributed equally to this work.

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Introduction

Rheumatoid arthritis (RA) is one of the most common autoimmune diseases characterized by chronic destructive polyarthritis. Its incidence peaks at age 35–55, and many patients develop their first manifestation of RA before the age of 60. As a subset rheumatoid arthritis, EORA is defined as a disease whose symptoms begin after the age of 60 [1]. EORA differs slightly at presentation from YORA by a more equal gender distribution, a higher frequency of acute onset with systemic features, more frequent involvement of the shoulder, and higher disease activity. And EORA is usually accompanied by a high erythrocyte

sedimentation rate (ESR), a tendency of a lower positive rate of rheumatoid factor (RF), and different clinical outcomes compared with YORA [2–4].

Many investigators have reported that EORA is associated with a different genetic background than YORA [5]. All of these alleles, including the HLA-DRB1*04 group (0401, 0404, 0405, 0408, and 0410), HLA-DR*01 group (0101 and 0102), HLA-DR*10 group (1001), and HLA-DRB1*14 group (1402), share a sequence of amino acids at position 70–74 in the third hypervariable region of the HLA-DRB1 gene, the so-called "shared epitope" [6, 7]. The shared epitopes may be associated with both the susceptibility to and severity of RA. EORA as a subset of RA has a lower association with HLA-DR4 compared with YORA. And some studies have reported that radiologic progression is less prominent in EORA in long-term follow-up studies, but one interesting observation in a 1-year short-term follow-up study after the onset of disease was that EORA was more likely than YORA to be associated with greater bone erosion [8–11].

And many investigators reported that HLA-DQ is associated with RA susceptibility, and several studies have reported that HLA-DQ4 and HLA-DQ6 are associated with RA susceptibility [12–14].

Our studies focused on shared epitope and radiologic progression in elderly onset RA. And we also examined the association of HLA-DQ in elderly onset RA.

Methods

Study population

The study was a retrospective study of 172 patients who fulfilled the 1987 American College of Rheumatology criteria for RA and who had visited the Department of Rheumatology at Seoul St. Mary's Hospital between October 1, 2009 and October 1, 2010. All patients had undergone radiological and immunogenetic assessment.

Two groups of Korean patients were selected based on their age at disease onset. The disease had begun after the age of 60 in the EORA group ($n = 63$) and before the age of 60 in the YORA group ($n = 109$). The medical records of these patients were reviewed retrospectively. The control group comprised 133 healthy blood donors recruited from the Department of Microbiology, Catholic University of Korea.

Immunogenetic analysis

Low-resolution analysis of HLA-DR/DQ was conducted by polymerase chain reaction amplification with sequence-specific primers (PCR-SSP). High-resolution analysis of HLA-DR/DQ was conducted by PCR amplification with sequence-based typing (PCR-SBT).

Radiographic analysis

The modified total sharp score (mTSS) was calculated from simple X-rays of the hands and the wrists.

Statistical method

The data were analyzed by Student's t test and chi-square test using SPSS for Windows version 12.0 (SPSS Inc., Chicago, IL, USA). A $p \leq 0.05$ was considered significant.

Results

Demographic characteristics

The total number of target subjects was 305 patients comprising 63 patients with EORA, 109 patients with YORA, and 133 healthy controls. In the EORA group, the mean age at the time of the study was 69.2 years and the mean age at onset was 65.7 years. In the YORA group, the mean age at the time of the study was 47.2 years and the mean age at onset was 40.9 years. The EORA group included 21 men (33.3 %) and 42 women (66.7 %), giving a 1:2 gender ratio. The YORA group included 12 men (11 %) and 97 women (89 %), giving a 1:8 gender ratio. The mean period of disease morbidity was 3.5 years in the EORA group and 6.3 years in the YORA group. There were no differences between the two patient groups in RF-positive rate, anti-CCP Ab level, and the acute phase response markers such as ESR and C-reactive protein (CRP) (Table 1).

The shared-epitope-coding alleles were less frequently found in EORA group than YORA onset group

The HLA-DR analysis showed a lower frequency of shared epitopes in the EORA group (30 patients, 47.6 %) than in the YORA group (72 patients, 66.1 %) ($p = 0.02$) (Table 2A).

Among these shared epitopes, HLA-DR*0405 type had the highest frequency in both patient groups, followed by HLA-DR*0101 type (Table 2B). A comparison of the shared epitopes after dividing them into two allelic groups showed shared epitopes from both alleles in 7 patients (11.1 %) in the EORA group and in 17 patients (15.6 %) in the YORA group. Shared epitopes from only one allele were found in 23 patients (36.5 %) in the EORA group and in 55 patients (50.5 %) in the YORA group, such case found with shared epitopes from the one allele only, had

Table 1 Demographics in patients

	EORA ($n = 3$)	YORA ($n = 109$)	p value
Mean age (years)	69.22	47.16	<0.001
Mean age at onset	65.71	40.88	<0.0001
Women (%)	42 (66.7 %)	97 (89 %)	<0.001
Disease duration (years)	3.50	6.34	<0.001
RF positivity (%)	51 (81 %)	82 (82.85)	0.83
RF titer[a]	80.64 ± 34.77	54.59 ± 18.33	0.11
Anti-CCP AB positivity (%)	49 (81.7)	76 (84.4 %)	0.66
Anti-CCP AB titer[a]	90.89 ± 7.16	77.37 ± 6.97	0.27
ESR (mm/h)[a]	63 ± 2.87	95 ± 2.53	0.49
CRP (mg/dl)[a]	2.43 ± 0.17	2.91 ± 0.96	0.52

[a] Disease duration adjusted values

Table 2 Distribution of shared-epitope-coding alleles in EORA and YORA

	EORA ($n = 63$)	YORA ($n = 109$)	p value
A			
SE (Total number, %)	30 (47.6 %)	72 (66.1 %)	0.02*
SE–SE	7 (11.1 %)	17 (15.6 %)	0.49
DRB1*0405/0405	2	6	
DRB1*0405/RALA	1	9	
RALA/RALA	4	2	
SE–DR_X	23 (36.5 %)	55 (50.5 %)	0.02*
DRB1*0101/X	3	10	
DRB1*0401/X	0	5	
DRB1*0404/X	2	4	
DRB1*0405/X	14	29	
DRB1*0408/X	2	1	
DRB1*0410/X	1	1	
DRB1*1001/X	1	3	
DRB1*1402/X	0	1	
DR_X–DR_X	33 (52.4 %)	37 (33.9 %)	0.02*

	RA		Total ($n = 102$)
	EORA ($n = 30$)	YORA ($n = 72$)	
B			
HLA-DRB1*0101 (%)	7 (23.3 %)	18 (25.0 %)	25 (24.5 %)
HLA-DRB1*0401 (%)	1 (3.3 %)	6 (8.3 %)	7 (6.8 %)
HLA-DRB1*0404 (%)	4 (13.3 %)	6 (8.3 %)	10 (9.8 %)
HLA-DRB1*0405 (%)	17 (56.6 %)	46 (63.8 %)	63 (61.7 %)
HLA-DRB1*0408 (%)	2 (6.6 %)	1 (1.3 %)	3 (2.9 %)
HLA-DRB1*0410 (%)	1 (3.3 %)	1 (1.3 %)	2 (1.9 %)
HLA-DRB1*1001 (%)	2 (6.6 %)	4 (5.5 %)	6 (5.8 %)
HLA-DRB1*1402 (%)	0 (0 %)	1 (1.3 %)	1 (0.9 %)

RALA RA-associated alleles excluding *0405

X not RA-associated alleles

shown statistically significant inter-group differences (Table 2A).

In the HLA-DQ analysis, HLA-DQ*03 type was the most prevalent type in all subjects. This type was found in 103 patients (59.9 %) in the combined RA group and in 69 healthy controls (51.9 %) (Table 3A). HLA-DQ*04 type had a significantly higher frequency in the RA group ($p < 0.001$), and HLA-DQ*06 type had a lower frequency in the RA group ($p < 0.05$) (Table 3A). A comparison between the EORA and YORA groups showed a lower frequency of HLA-DQ*04 type in the EORA group (p value <0.05) (Table 3B).

The radiographic progression was less prominent in EORA group than in YORA group

We used the mTSS to assess disease severity using the radiographs of hands in the EORA and YORA groups. The mTSS score was 30.16 ± 5.41 points in the EORA group and 65.18 ± 9.64 points in the YORA group ($p < 0.05$) (Table 4). Intriguingly, when the patients were subdivided by the presence of RF, YORA group showed higher mTSS only in patients with positive RF. Likewise, in ACPA-negative patients, there was no difference of mTSS between EORA and YORA group while mTSS of YORA was higher in ACPA-positive patients (data not shown). In addition, when we subdivided the EORA group according to shared-epitope status, the mTSS did not differ significantly between the shared-epitope-positive group (29.82 ± 7.48 points) and shared-epitope-negative group (30.51 ± 7.75 points). Similarly, in the YORA group, the mTSS did not differ significantly between the shared-epitope-positive

Table 3 HLA-DQ subtype in RA patients

	RA ($n = 172$)	Control
A		
HLA-DQ*02 (%)	22 (12.8 %)	26 (19.5%)
HLA-DQ*03 (%)	103 (59.9 %)	69 (51.9 %)
HLA-DQ*04 (%)	66 (38.4 %)*	30 (22.6 %)
HLA-DQ*05 (%)	45 (26.25%)	45 (33.8 %)
HLA-DQ*06 (%)	58 (33.7 %)*	64 (48.1 %)
	EORA ($n = 63$)	YORA ($n = 109$)
B		
HLA-DQ*02 (%)	11 (17.5 %)	11 (10.1 %)
HLA-DQ*03 (%)	35 (55.6 %)	68 (62.4 %)
HLA-DQ*04 (%)	18 (28.6 %)‡	48 (44 %)
HLA-DQ*05 (%)	12 (19.0 %)	33 (30.3 %)
HLA-DQ*06 (%)	26 (41.3 %)	32 (29.4 %)

* p value versus control: $p < 0.05$

‡ p value versus YORA: $p < 0.05$

group (65.88 ± 10.10 points) and shared-epitope-negative group (63.77 ± 14.41 points).

We analyzed the mean mTSS in the EORA and YORA groups according to the period of disease morbidity. The overall mean mTSS was lower in the EORA than in the YORA group. The mean mTSS at the time of symptom onset differs significantly between patient groups, but had worsened more in YORA than in EORA patients 6 years after the onset of symptoms (Table 4; Fig. 1).

Discussion

The gender ratio of EORA in patients ≥60 years of age has been reported more equally [14]. In a comparison of the clinical profiles between EORA and YORA patients, Kim et al. [4] found a male/female ratio of 1:2.5 in EORA patients and 1:5.6 in YORA patients. We found similar ratios of 1:2 in EORA and 1:8 in YORA patients.

Most patients with RA have a shared epitope comprising a common amino acid sequence at the location 70–74 in the third hypervariable region (QKRAA/QRRAA) in the HLA-DR β chain. Since Gregersen et al. [15] proposed the "shared-epitope hypothesis" in 1987, a number of studies have reported that the shared epitopes are related to the susceptibility to and the severity of RA [16]. Hong et al. [17] also investigated the frequency of shared epitopes in patients with RA in Korea and found frequencies of 57 % in the patient group and 25 % in the control group. Minn et al. [7] reported a 56 % frequency of shared epitopes in a patient group. Taken together, these data suggest an association between shared epitopes and RA.

Massardo et al. [8] tried to explain the effects of shared epitopes on the severity of RA. They used the Steinbrocker radiological staging system to assess bone erosion in the hands to assess disease severity. Ten of the 11 patients shown to have shared epitopes had bone erosion, but only three of the 14 patients who did not have shared epitopes had bone erosion. Massardo et al. [8] concluded that the shared epitopes might affect the severity of RA. In Korea, research into the association between RA and the severity of disease has been performed. In 1997, Kim et al. [9] performed HLA-DR analysis on patients with RA in Korea and reported that the HLA-DR*0405-type group showed many symptoms such as bone erosion, joint deformity, and other symptoms unrelated to joints.

Studies of the association between HLA-DR type and RA have been extended to the study of HLA-DR type in EORA, because EORA as a subset of RA presented different demographic, clinical, and laboratory findings compared with YORA.

In 2001, Hellier et al. [1] performed an HLA-DR analysis of 62 patients with EORA and 262 patients with YORA. In their study, both the EORA and YORA groups had high frequencies of shared epitopes, but the frequencies did not differ significantly between these two groups. In the HLA-DR analysis of Hellier et al. [1] the frequency of HLA-DR*04 and HLA-DR*01 was compared in the EORA and YORA groups. Twenty-two patients (37 %) in the EORA group and 135 patients (52 %) in the YORA group had the HLA-DR*04 type. By contrast, 22 patients (37 %) in EORA group and 78 patients (30 %) in the YORA group had the HLA-DR*01 type. These data suggested that EORA is associated less with HLA-DR*04 than is YORA. In our HLA-DR analysis, the frequency of shared epitopes differed significantly between groups. The epitopes were found in 31 patients (49.2 %) in the EORA group and 72 patients (66.1 %) in the YORA group. Our data suggest that the shared epitopes have less influence on the susceptibility to RA in the EORA group than in the YORA group, but there is no significant difference in the frequency of HLA-DR*04 in the EORA and YORA group.

To identify the effects of shared epitopes on disease severity, radiological bone erosion was assessed in this study by classifying the subjects according to the presence or absence of shared epitopes, but we found no significant differences between groups. The same comparison was performed by classifying EORA patients according to the presence or absence of shared epitopes. Similarly, there was no difference between groups. Our data suggest that the shared epitopes are not related to the severity of RA, including EORA.

In a study of the severity of EORA, Bukhari et al. [11] assessed radiological bone erosion over a 1-year period in patients with EORA. The short-term follow-up observation after 1 year showed severe bone erosion in patients with EORA. In a similar study, Peltomaa et al. [18] reported high levels of bone erosion, ESR, and CRP at the time of onset of EORA. However, the clinical prognosis and radiological evidence of disease progression over 3 years were similar between EORA and YORA patients. This may reflect more severe bone erosion during the initial stage of disease in EORA patients, but similar disease progression in both EORA and YORA patients after the start of

Table 4 Modified total sharp score in EORA and YORA patients according to the presence of shared epitope

	mTSS	
	EORA ($n = 63$)	YORA ($n = 109$)
SE positive	29.82 ± 7.48*	65.88 ± 10.10*
SE negative	30.51 ± 7.75*	63.77 ± 14.41*
Total	30.16 ± 5.41*	65.18 ± 9.64*

mTSS modified total sharp score

* p value < 0.05

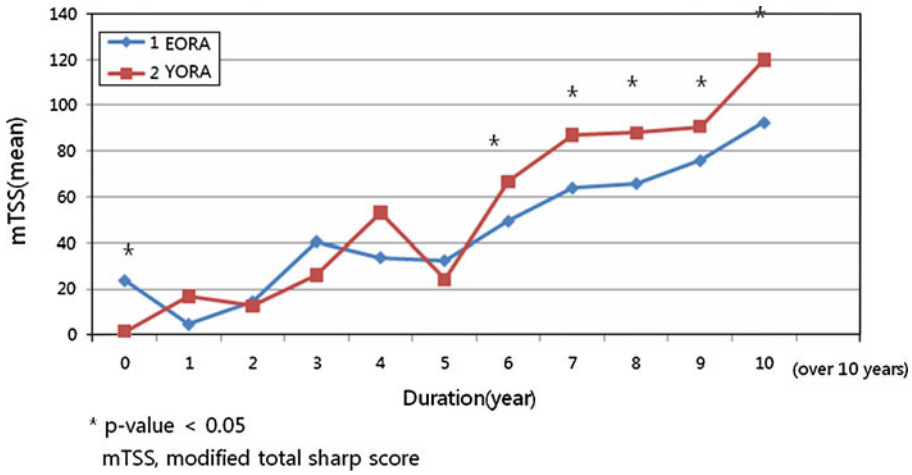

Fig. 1 Modified total sharp score in EORA and YORA patients according to the presence of shared epitope

treatment. In our study, hand radiographs examined at the onset of symptoms showed that EORA patients had greater bone erosion. However, after a prolonged period of disease morbidity, a low level of bone erosion was found in EORA patients. Thus, it appears that EORA shows a different pattern of progression in terms of clinical prognosis and radiological variation compared with YORA patients.

In addition to studies of HLA-DR, studies have been conducted on the association between HLA-DQ and RA, but no clear conclusion has been established about the effects of HLA-DQ on susceptibility to RA. De Vries et al. [19] reported in 1999 that HLA-DQ was not related to RA in their study of HLA-DQ and susceptibility to RA. Milicic et al. [13] concluded that the shared epitopes were closely associated with susceptibility to RA but not with HLA-DQ. Fugger et al. [20] compared the frequencies of HLA-DQ*07 and HLA-DQ*08 in HLA-DR*04-positive patients with RA and a control group. They concluded that HLA-DQ*07 and HLA-DR*08 are not associated with susceptibility to RA. However, Ali et al. [21] found a significant difference in the frequency of HLA-DQ*06 between RA patients and a healthy control group. Yuan et al. [22] also found a significant difference in HLA-DQ*04 frequency between RA patients and a healthy control group. Thus, there are contrasting opinions on the relationship between HLA-DQ and susceptibility to RA.

In this study, HLA-DQ analysis was performed on patients with RA and a healthy control group. Among the RA patients, 103 (59.9 %) had HLA-DQ*03 and 69 (51.9 %) controls had HLA-DQ*03; HLA-DQ*03 was the most frequently identified allele in both groups. However, 66 patients (38.4 %) with HLA-DQ*04 had RA, and 30 controls (22.6 %) had this type, indicating that the frequency of HLA-DQ*04 was higher in the RA patients than in people without RA. HLA-DQ*06 was found in 58 RA patients (33.7 %) and in 64 controls (48.1 %), indicating that this allele is more frequent in healthy controls. In our study of patients with EORA and YORA, the HLA-DQ*04 frequency was higher in patients with RA than in healthy controls and in patients with YORA than in those with EORA: HLA-DQ*04 was found in 18 patients (28.6 %) with EORA and in 48 patients (44 %) with YORA that the frequency of HLA-DQ*04 was higher in YORA patients than in EORA patients. It was possible to identify that HLA-DQ*04 was likely to be associated with susceptibility to RA and seemed to be more closely associated with YORA group than in the EORA group.

Limitation is that the study was based on the medical records of patients who had genetic test results and were randomly selected from patients who had visited only one hospital. This study was a retrospective study, and we were unable to observe progression of bone erosion from onset of the disease. Further studies which are multicenter based and have large sample sizes are needed to examine HLA-DR/DQ in EORA/YORA patients, and prospective studies are needed to understand its relationship with bone erosion in EORA/YORA patients.

Conclusion

The influence of shared epitope and HLA-DQ*04 alleles may be less significant on disease susceptibility in EORA. The presence of shared-epitope-coding alleles does not seem to influence on disease severity in EORA patients as well as YORA patients. Radiologic deterioration in EORA group was less severe and progressed differently from YORA group. The presence of shared epitope and radiologic progression are less prominent in EORA patients than YORA patients.

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Conflict of interest The authors have no conflict of interest to declare.

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