HLA class II alleles may influence susceptibility to adult dermatomyositis and polymyositis in a Han Chinese population

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Abstract

Background: Polymyositis (PM) and dermatomyositis (DM) are idiopathic inflammatory myopathies (IIM), a group of autoimmune disorders characterized by inflammation present predominantly in muscle tissues. The chief clinical presentations include symmetric proximal muscle weakness, other organ involvement, and presence of autoantibodies [1]. Although the underlying pathogenesis for PM and DM remains unclear, evidence has suggested that, like many other autoimmune conditions, these disorders likely result from a combination of environmental exposure and genetic susceptibility [2]. Genetic variability in the human leukocyte antigen (HLA) genes is thought to play an important role in PM and DM pathogenesis [3,4]. This may be partly attributed to the influence of HLA molecules on T-cell receptor development, peripheral tolerance, and immune response to environmental agents. It has been established that geographic locations and ethnicities may affect susceptibility to autoimmune diseases [5,6]. The

Methods: We studied the influence of HLA polymorphisms on DM and PM susceptibility by analyzing HLA-DRB1, HLA-DQA1, and HLA-DQB1 alleles in 71 adult DM patients, 20 adult PM patients, and 113 controls in a Han Chinese population.

Results: A positive association was found between HLA-DQA1*0104 and DM (p = 0.01; corrected p (p corr) NS; odds ratio (OR) = 2.58; 95% confidence interval (CI): 1.18–5.64), while an inverse correlation was noted between HLA-DQB1*0303 and myositis patients with interstitial lung inflammation (p = 0.01; p corr NS; OR = 0.25; 95% CI: 0.07–0.73). A positive relationship was also observed between HLA-DRB1*07 and DM (p = 0.01; p corr NS; OR = 2.26; 95% CI: 1.12–4.59), while HLA-DRB1*03 seems to be protective against DM (p = 0.01; p corr NS; OR = 0.26; 95% CI: 0.06–0.81). The lung complication was closely associated with HLA-DRB1*04 (p = 0.01; p corr NS; OR = 2.82; 95% CI: 1.15–6.76) and HLA-DRB1*12 (p = 0.02; p corr NS; OR = 2.52; 95% CI: 1.02–6.07). The frequency of HLA-DRB1*07 was significantly higher among myositis patients with dysphagia than among controls (p = 0.01; p corr NS; OR = 4.78; 95% CI: 1.03–24.42). The putative haplotype DRB1*07-DQA1*01-DQB1*02 was positively correlated with DM (p = 0.03; p corr NS; OR = 2.90; 95% CI: 1.02–8.93) and the lung complication (p = 0.02; p corr NS; OR = 3.45; 95% CI: 1.04–11.58).

Conclusions: Our results demonstrate that HLA alleles may be involved in susceptibility to adult DM and PM in the Han Chinese population.

Keywords: Polymyositis, Dermatomyositis, HLA, Susceptibility, Chinese
HLA-DRB1*0301 and HLA-DQA1*0501 alleles have been reported as risk factors for myositis in Western populations [7,8], whereas DRB1*0803 may increase PM susceptibility among the Japanese population [9]. In studies of 52 DM and PM patients from Northern China, Han et al. reported positive associations between the HLA-DRB1*04, HLA-DRB1*07, and HLA-DRB1*12 alleles and DM development [10]. They also observed that HLA-DQB1*0401 is a risk factor for DM and PM [11]. However, the sample sizes of these studies were small; therefore, the possible role of HLA class II alleles in myopathies in Chinese patients requires further investigation.

To assess the effect of polymorphisms in HLA-DRB1, HLA-DQA1, and HLA-DQB1 on DM and PM susceptibility, we conducted a study of 91 adult patients with DM or PM and 113 healthy controls in a Han Chinese population. Our results demonstrate that HLA class II alleles may influence adult DM and PM susceptibility in the Han Chinese population.

**Methods**

**Study subjects**

Between August 2009 and March 2012, 71 and 20 patients were diagnosed with DM and PM, respectively, at the Huashan Hospital of Fudan University in Shanghai, China. The patients met probable or definite diagnosis of DM or PM according to the Bohan and Peter [12] criteria [12,13]. Lung lesions were examined by chest computed tomography, and a diagnosis of interstitial lung disease (ILD) or idiopathic interstitial pneumonitis was made by a pulmonologist. All patients were ethnic Han Chinese (25 males and 66 females, median age of 51 ± 15.8 years). One hundred and thirteen healthy Han Chinese subjects (36 males and 77 females, median age of 40.0 ± 8.6 years) with no history of autoimmune disease were enrolled in the study as controls. The study followed protocols set by the Declaration of Helsinki and was approved by the ethics committee of Huashan Hospital. All patients and controls provided written informed consent prior to the study.

**Experiments**

DNA was extracted from blood using the Qiagen DNA extraction kit (Qiagen; Hilden, Germany). Low- and high-resolution typing of the HLA-DRB1, HLA-DQA1, and HLA-DQB1 alleles were performed using the polymerase chain reaction (PCR)-sequence-specific primed (SSP) procedure described by Olerup et al. [14,15]. Serum was obtained from all patients for detection of myositis-specific antibodies (MSA; anti-Jo-1 autoantibodies) and myositis-associated antibodies (MAA; anti-Ro and anti-La autoantibodies). Autoantibodies were analyzed by an indirect immunofluorescence method using the kits from EUROIMMUN AG (Lubeck, Germany).

**Statistical analysis**

The allele, genotype, and haplotype frequencies of the HLA loci were compared between the patients and controls using the Fisher exact test or chi-square test, as appropriate. Data were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). A p-value ≤ 0.05 was considered statistically significant. In multiple comparisons, p-values were adjusted using the Bonferroni correction to give a corrected p-value (p_corr). A p-value ≤ 0.05 before correction for multiple comparisons was considered as possibly statistically significant. The Hardy–Weinberg equilibrium constant in the control group was confirmed using a chi-square test. Putative haplotypes were inferred from unphased genotype data using the Bayesian statistical method available in the PHASE program v2.1.1 [16]. Putative haplotypes with a frequency higher than 3% among the controls were selected for further comparisons between the patients and controls. Unless otherwise stated, Stata (version 7.0; Stata Corp.; College Station, TX, USA) statistical software was used to perform the statistical analyses.

**Results**

Of the 91 patients, 71 had been diagnosed with DM and 20 with PM (66 female and 25 male [2.64:1]). Although most of the patients were positive for antinuclear antibodies, few were positive for either MSA or MAA. The frequencies of MSA and MAA were higher in the PM group than in the DM group (10% vs. 1.4%, p = 0.06 for MSA; 20% vs. 5.63%, p = 0.05 for MAA). As expected, cutaneous involvement such as rash or cuticular overgrowth was present only in PM patients. Approximately half of the patients had ILD, with a higher prevalence among patients with PM than with DM (76.5% vs. 37.7%, p = 0.04). No significant differences in other clinical features were observed between the two groups (Table 1).

Genotyping analyses of the HLA-DQA1 and HLA-DQB1 loci were performed to study the relationship between the HLA class II alleles and susceptibility to DM and PM. Because there are several lines of evidence to suggest that DM and PM may be distinct diseases with different genetic backgrounds [17], we analyzed the influence of the HLA alleles on susceptibility to DM and PM individually rather than analyzing the combined DM/PM group (Table 2). Compared with the controls, the frequency of HLA-DQA1*0104 was significantly higher in the DM group than in the PM group (16.42% vs. 8.18%, p = 0.01, p_corr NS; OR = 2.58; 95% CI: 1.18–5.74), implying a possible positive correlation between HLA-DQA1*0104 and the risk of DM. Of the HLA-DQB1 alleles analyzed, only the HLA-DQB1*0303 frequency was lower in patients with ILD than in the controls (6.76% vs. 19.03%, p = 0.01, p_corr. NS; OR = 0.25; 95% CI: 0.07 – 0.73), implying that
patients with this allele are less likely to develop the lung complication. This was further confirmed by the fact that the HLA-DQB1*0303 frequency was lower among those who developed ILD (p < 0.01; OR = 0.19; 95% CI: 0.038–0.37) than those who did not develop ILD. HLA-DRB1 typing analysis showed that compared to controls, DM patients had a considerably lower prevalence of HLA-DRB1*03 (3.08% vs. 11.27%, p = 0.01, pcorr NS; OR = 0.26; 95% CI: 0.06–0.81) and a higher frequency of HLA-DRB1*07 (20.77% vs. 13.24%, p = 0.01, pcorr NS, OR = 2.26, 95% CI: 1.12–4.59). Both HLA-DRB1*04 and HLA-DRB1*12 alleles are linked to the lung disease (p = 0.01, pcorr NS; OR = 2.82; 95% CI: 1.15–6.76 and p = 0.02, pcorr NS; OR = 2.52; 95% CI: 1.02–6.07, respectively). A similar effect of HLA-DRB1*04 on ILD development was also observed when the allele frequencies between patients with and without the lung complication were compared (p = 0.026; OR = 3.32; 95% CI: 1.22–9.08). Comparison of HLA-DRB1*12 allele frequencies between myositis patients with and without ILD showed a similar trend of being higher among those with ILD than among those without, although the difference between the two groups was not statistically significant (p = 0.35; OR = 1.59; 95% CI: 0.63–4.00). This is likely attributable to the small numbers in the groups examined. Moreover, the HLA-DRB1*07 allele showed a possible influence on the development of esophageal/muscle complications (30.00% vs. 13.24%, p = 0.01, pcorr NS; OR = 4.78; 95% CI: 1.03–24.42). A similar trend for a higher HLA-DRB1*07 allele frequency was also noted among patients who had dysphagia as compared to those who did not (p = 0.057; OR = 3.55; 95% CI: 0.91–13.82).

We then examined the association between putative haplotypes involving the DRB1-DQA1-DQB1 loci and susceptibility to DM, PM, lung, and esophageal complications. In this analysis, only the putative haplotypes present in at least 3% of the controls were selected for further study. Of the 12 putative haplotypes selected, the frequency of DRB1*07-DQA1*01-DQB1*02 was higher in the DM group (p = 0.03, pcorr NS; OR = 2.90; 95% CI: 1.02–8.93) and in patients with ILD (p = 0.02, pcorr NS; OR = 3.45; 95% CI: 1.04–11.58) than in the controls, indicating that this putative haplotype might increase the risk of DM and the lung complication (Table 3). A further comparison of the DRB1*07-DQA1*01-DQB1*02 frequency in patients who developed dysphagia with those who did not showed a trend for a higher frequency of this haplotype among patients with dysphagia, although the difference between the groups was not statistically significant (p = 0.23; OR = 2.27; 95% CI: 0.68–7.72). Again, we consider that this result is likely due to the small sample sizes in both groups.

**Discussion**

There are differences in the clinical features of DM and PM between our cohort of Han Chinese patients and Western patients [1,18]. There are more DM cases in our cohort and among Mesoamerican patients, whereas PM is the major subtype among Caucasian patients [19]. Compared to Caucasian patients, our cohort had a higher prevalence of the lung complication [20]. The frequencies of dysphagia were comparable between our cohort and those reported in the West [1,21]. Approximately 30–40% of Caucasian and African American IIM patients are positive for MSA/MAA autoantibodies [19,22]. Although the proportion of patients who were positive for autoantibodies was relatively low in our cohort, it is nonetheless comparable to findings from other studies in Chinese patients [23,24].

There is a growing body of evidence to suggest that differences in the impact of HLA class II alleles on the susceptibility to DM and PM may exist among different ethnic groups and geographic locations [19,20,25–27]. It has been well documented that HLA class II alleles that form the 8.1 ancestral haplotype (8.1 AH), DRB1*03-DQA1*05-DQB1*02, are closely linked to DM and PM in Western populations [4,7,28]. Previous studies suggest that HLA-DQA1*0501 and HLA-DRB1*0301 may be risk factors for PM, whereas HLA-DQA1*0201 and HLA-DRB1*0401 confer protection against the disease in Caucasians [4,28-30]. Moreover, HLA-DRB1*07 has been reported to protect against PM and IIM in Caucasians and African Americans [4,22,28]. In their study of African American patients with IIM, O’Hanlon et al. [22]...
| Loci/alleles | DM     | PM     | Myositis with ILD | Myositis with dysphagia | Control | Control vs. indicated patients (p; OR (95% CI)) |
|-------------|--------|--------|-------------------|-------------------------|---------|-----------------------------------------------|
| **HLA-DRB1**|        |        |                   |                         |         |                                               |
| *01  | N = 65 | N = 19 | N = 37            | N = 10                  | N = 113 | n/s                                           |
| *03  | 1 (0.77) | 0 (0.00) | 1 (1.35)        | 0 (0.00)                | 5 (2.45) | n/s   |
| *04  | 4 (3.08) | 4 (10.53) | 4 (5.41)        | 1 (5.00)                | 23 (11.27) | 0.01; 0.26 |
| *07  | 17 (13.08) | 6 (15.79) | 15 (20.27)      | 2 (10.00)               | 22 (10.78) | n/s   |
| *08  | 13 (10.00) | 4 (10.53) | 7 (9.46)        | 2 (10.00)               | 17 (8.33) | n/s   |
| *09  | 20 (15.38) | 2 (5.26) | 3 (4.05)        | 3 (15.00)               | 26 (12.75) | n/s   |
| *10  | 2 (1.54) | 1 (2.63) | 2 (2.70)        | 0 (0.00)                | 3 (1.47) | n/s   |
| *11  | 3 (2.31) | 3 (7.89) | 2 (2.70)        | 0 (0.00)                | 9 (4.41) | n/s   |
| *12  | 20 (15.38) | 7 (18.42) | 14 (18.92)     | 6 (30.00)               | 27 (13.24) | 0.001; 2.26 |
| **HLA-DQA1**|        |        |                   |                         |         |                                               |
| *0101 | N = 67 | N = 20 | N = 39           | N = 12                  | N = 110 | n/s                                           |
| *0102 | 18 (13.43) | 10 (25.00) | 16 (20.51)     | 4 (16.67)               | 44 (20.00) | n/s   |
| *0103 | 26 (19.40) | 6 (15.00) | 10 (12.82)     | 6 (25.00)               | 28 (12.73) | n/s   |
| *0104 | 22 (16.42) | 4 (10.00) | 11 (14.10)     | 4 (16.67)               | 18 (8.18) | 0.001; 2.58 |
| **HLA-DQB1**|        |        |                   |                         |         |                                               |
| *0201 | 9 (6.72) | 0 (0.00) | 5 (6.41)        | 1 (4.17)                | 11 (5.00) | n/s   |
| *0202 | 18 (13.43) | 10 (25.00) | 16 (20.51)     | 4 (16.67)               | 44 (20.00) | n/s   |
| *0203 | 26 (19.40) | 6 (15.00) | 10 (12.82)     | 6 (25.00)               | 28 (12.73) | n/s   |
| *0204 | 22 (16.42) | 4 (10.00) | 11 (14.10)     | 4 (16.67)               | 18 (8.18) | 0.001; 2.58 |
| **Gao et al. BMC Dermatology 2014, 14:9**

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demonstrated that HLA-DRB1*14 and HLA-DRB1*0301 increase the risk of DM, while HLA-DRB1*0301 influences PM susceptibility. Furuya et al. [9,26] found that both HLA-DRB1*0803 and HLA-DQA1*0501 provide an increased risk of DM but a reduced risk of PM in a Japanese population. In a study of 25 Korean patients with IIM, Rider et al. [27] reported that HLA-DRB1*14 as a protective factor for DM and PM. To date, most studies on the subject have been focused on Western populations. In their studies of 52 DM and PM patients from Northern China, Han et al. reported that HLA-DRB1*04, HLA-DRB1*07, and HLA-DRB1*12 may render an increased risk of DM [10], while HLA-DQB1*0401 may have an impact on IIM susceptibility [11]. Our data demonstrate that the HLA-DQA1*0104 and HLA-DRB1*07 alleles are likely associated with an increased risk of DM, whereas HLA-DRB1*03 may provide protection against DM. Although 8.1 AH is known as a risk factor for IIM among individuals of Northwestern European descent [4,7,28], such an association has not been established in other ethnic groups [25].

It is interesting to note that HLA-DRB1*07 influences IIM susceptibility among various ethnic groups. In our study of Han Chinese patients, the HLA-DRB1*07 allele in the putative haplotype DRB1*07-DQA1*01-DQB1*02 was found to be a risk factor for DM, but the same allele present in the DRB1*07-DQA1*02-DQB1*02 haplotype was reported to be a protector against IIM in Caucasians and African Americans [4,22,25,28]. These findings imply that HLA-DRB1*07 might have opposite effects on the diseases in different ethnic groups. Similar phenomena have been observed for the effect of HLA-DQA1*0501 on IIM. This allele was reported as a protective factor against IIM in a Japanese population [9] but as a risk factor for IIM among US Caucasians [29]. Although it is unclear what might cause such different effects, possible explanations include referral bias, small sample sizes resulting in non-representative populations, different pathogeneses, various environmental risk triggers around the world, and unidentified genetic loci responsible for disease development.

Furuya et al. [26] reported a positive relationship between HLA-DRB1*0405 and anti-aminoacyl-tRNA synthetase

| Haplotypes               | DM (N =63) | PM (N = 18) | Myositis with ILD (N = 36) | Myositis with dysphagia (N = 9) | Control (N =100) |
|-------------------------|------------|-------------|-----------------------------|-------------------------------|------------------|
| DRB1-DQA1-DQB1          |            |             |                             |                               |                  |
| 03-05-02                | 2 (1.59)   | 2 (5.56)    | 2 (2.78)                    | 0 (0.00)                      | 11 (5.50)        |
| 04-03-03                | 6 (4.36)   | 1 (2.78)    | 5 (6.94)                    | 1 (5.56)                      | 9 (4.50)         |
| 04-03-04                | 5 (3.97)   | 2 (5.56)    | 5 (6.94)                    | 1 (5.56)                      | 6 (3.00)         |
| 07-01-02                | 12 (9.52)  | 1 (2.78)    | 8 (11.11)                   | 2 (11.11)                     | 7 (3.50)         |
| 07-03-02                | 6 (4.76)   | 0 (0.00)    | 3 (4.17)                    | 2 (11.11)                     | 11 (5.50)        |
| 08-01-06                | 13 (10.32) | 3 (8.33)    | 6 (8.33)                    | 2 (11.11)                     | 13 (6.50)        |
| 09-03-03                | 17 (13.49) | 2 (5.56)    | 3 (4.17)                    | 3 (16.67)                     | 20 (10.00)       |
| 11-05-03                | 3 (2.38)   | 1 (2.78)    | 1 (1.39)                    | 0 (0.00)                      | 7 (3.50)         |
| 12-01-03                | 11 (8.73)  | 2 (5.56)    | 8 (11.11)                   | 0 (0.00)                      | 11 (5.50)        |
| 13-01-06                | 7 (5.56)   | 0 (0.00)    | 2 (2.78)                    | 1 (5.56)                      | 7 (3.50)         |
| 14-01-05                | 2 (1.59)   | 1 (2.78)    | 0 (0.00)                    | 2 (11.11)                     | 7 (3.50)         |
| 15-01-06                | 7 (5.56)   | 3 (8.33)    | 3 (4.17)                    | 1 (5.56)                      | 19 (9.50)        |

n/s: not significant; n/a: not applicable; 1p corr greater than 0.05; ILD: interstitial lung disease.
autoantibodies in Japanese IIM patients. In addition, O'Hanlon et al. found that the HLA-DRB1*0302 allele is closely linked to myositis-specific anti-Mi-2 autoantibodies in DM [4]. In our study, the numbers of patients with MSA and MAA were too small to have sufficient statistical power for further analysis of the relationship between HLA alleles and MSA/MAA autoantibodies. It is also noteworthy that a greater frequency of myositis autoantibodies was found among PM patients from our cohort and the cohort reported by Chinoy and colleagues [20]. However, both cohorts were small in size, and in our study we analyzed only a limited number of autoantibodies.

Previous studies suggest that DM and PM may have different pathogeneses. It has been proposed that DM is likely the result of an autoimmune process induced by a humoral response, whereas PM may be caused by a cell-mediated autoimmune process [17]. Thus, it is plausible that DM and PM might have distinctive genetic susceptibilities. Further investigation is warranted to better understand the pathogeneses of these two diseases.

Possible explanations for the differences between the results from our study and those from other studies include the fact that the studies were conducted in different geographic locations with various environmental exposures, the heterogeneity in genetic backgrounds among the different ethnic groups and populations, the number of HLA polymorphic alleles analyzed, the different study methodologies used, referral bias, and the age and sex composition of the different study cohorts. The differences in the clinical and immunogenetic features between adult and childhood DM and PM are well documented [8,31].

Our study has some limitations. Although DM and PM are rare conditions and the number of patients in our cohort is the largest compared with similar studies in Chinese patients, it is still a relatively small cohort. It is likely that there are many genes and genetic polymorphisms that may influence DM and PM susceptibility, and we analyzed only a few of them. The data from our study should be validated by further analysis of multiple genes and alleles and their combined impacts on disease susceptibility. Nevertheless, our data shed some light on the genetic susceptibility of adult DM and PM, and may aid in stratifying disease subtypes according to genetic and ethnic backgrounds.

Conclusions
Our study of adult DM and PM in a Chinese population demonstrated that the putative haplotype DRB1*07-DQA1*01-DQB1*02 and the DRB1*07 and DQA1*0104 alleles are associated with an increased risk of DM, while DRB1*03 is associated with a reduced risk of DM. DQB1*0303 may confer protection against the lung complication, and DRB1*04, DRB1*12, and DRB1*07-DQA1*01-DQB1*02 are associated with an increased risk of developing the lung complication. Furthermore, DRB1*07 is associated with an increased risk of developing dysphagia.

Abbreviations
PM: Polymyositis; DM: Dermatomyositis; HLA: Human leukocyte antigen; IIM: Idiopathic inflammatory myopathies.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
LB, LL and XG conceived the study design and manuscript preparation; LB, LL, XG, LY, LH, HS, and YY participated in data interpretation; XG, YY, LH, LY, HS, and GG collected data and conducted experiments and data analysis. All authors read and approved the final manuscript.

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