HLA-DRB1 Alleles as Genetic Risk Factors for the Development of Anti-MDA5 Antibodies in Patients with Dermatomyositis

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ABSTRACT. ***Objective.*** Patients with polymyositis/dermatomyositis (PM/DM) who express anti-melanoma differentiation associated protein 5 (anti-MDA5) antibodies frequently present with interstitial lung disease (ILD). The aim of this study was to investigate the association of HLA-DRB1 with anti-MDA5 expression in PM/DM.

Methods. The frequency of DRB1 alleles was compared among 70 patients with PM, 104 patients with DM, and 400 healthy controls in a Han Chinese population.

Results. Frequencies of DRB1*04:01 [17.0% vs 1.3%, corrected p value (p_c) = 3.8×10^{-8}, OR 16.2, 95% CI 6.6–39.7] and *12:02 (42.6% vs 19.3%, p_c = 0.008, OR 3.1, 95% CI 1.7–5.7) were significantly higher in anti-MDA5–positive patients with PM/DM compared with the controls. The frequencies of DRB1*04:01 ($p = 5.2 \times 10^{-6}$, OR 17.1, 95% CI 5.3–54.9) and *12:02 ($p = 3.8 \times 10^{-4}$, OR 3.1, 95% CI 1.7–5.7) in anti-MDA5–positive patients with DM-ILD were higher than in the controls, whereas the frequencies of DRB1*04:01 and *12:02 did not differ between the anti-MDA5–negative patients with DM-ILD and controls. No difference in the frequency of DRB1 alleles, other than *04:01, carrying the "shared epitope" (SE), i.e., *01:01, *01:02, *04:05, and *10:01, was observed between the controls and patients with DM stratified by the presence of anti-MDA5 and ILD.

Conclusion. DRB1*04:01 and *12:02 confer susceptibility to anti-MDA5 antibody production in DM, which cannot be explained by the SE hypothesis. (First Release July 15 2017; J Rheumatol 2017;44:1389–93; doi:10.3899/jrheum.170165)

Key Indexing Terms:
POLYMYOSITIS DERMATOMYOSITIS
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Polymyositis (PM) and dermatomyositis (DM) are autoimmune diseases characterized by inflammation of skeletal muscle and other organ systems[1]. Disease-related death is generally associated with malignancy and/or interstitial lung disease (ILD), and a high mortality rate of patients with PM/DM has been confirmed in the Chinese population[2]. Myositis-specific autoantibodies (MSA) are a group of autoantibodies specifically found in PM/DM, but not in other autoimmune diseases. Studies have revealed that stratification of PM/DM according to the presence of MSA is useful because these autoantibodies are usually expressed in a mutually exclusive fashion in PM/DM and are closely

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associated with the clinical phenotype[3]. Patients with DM who are positive for anti-melanoma differentiation-associated gene 5 (MDA5) antibody frequently have rapidly progressive ILD (RP-ILD), and their 6-month survival rate is only 41%[4], demonstrating the poor prognosis of this clinical entity.

Both genetic and environmental factors may be involved in the etiopathology of PM/DM. The first genome-wide association study of DM revealed a strong signal in the MHC region[5]. It has also been reported that the presence of ILD and MSA in patients with DM is largely controlled by the HLA class II haplotype, rather than by the myositis subtype[6]. In previous studies, we reported the high risk of DM patients with anti-MDA5 antibodies for developing RP-ILD and for high mortality[4]. We also observed a significantly higher frequency of anti-MDA5 antibodies in Chinese patients when compared with Japanese patients[7].

To date, only 1 study has investigated the association of anti-MDA5 expression with HLA-DRB1; in that study, DRB1*01:01 and *04:05 were reported to be associated with anti-MDA5 positivity in Japanese patients with DM[8]. However, because the number of participants was only 17, the findings should be replicated in other cohorts to confirm the association. To clarify the HLA-linked genetic factor for anti-MDA5, we performed an association study of HLA-DRB1 with anti-MDA5 antibodies in a Han Chinese population. Our study suggested that DRB1*04:01 and *12:02 are genetic predisposing factors for anti-MDA5 antibody production in DM.

MATERIALS AND METHODS

Participants. A total of 574 participants, consisting of 104 patients with DM, 70 patients with PM, and 400 healthy controls, were enrolled. All participants were of Han ethnicity and were from the Affiliated Drum Tower Hospital, Nanjing, China. Diagnosis of probable or definite PM, classic DM, and clinically amyopathic DM was made, as described previously[4,9]. Four hundred healthy controls with no history of autoimmune diseases were recruited from the health examination center of Drum Tower hospital. This study was approved by the Ethics Committee of Affiliated Drum Tower Hospital, Nanjing University Medical School (2015004), and written informed consent was obtained from each participant.

HLA-DRB1 genotyping and anti-MDA5 antibody detection. Genotyping of HLA-DRB1 was performed using the sequencing-based typing method on a GeneAmp PCR System 9700 (Applied Biosystems). Sequencing data were collected using a 3730XL Genetic Analyzer (Applied Biosystems) and DRB1 allele assignments were interpreted using uTYPE Dx Sequencing Analysis Software (Thermo Fisher Scientific). Levels of anti-MDA5 were measured using recombinant MDA5 antigen, as described previously. This ELISA method showed an analytical sensitivity of 85% and analytical specificity of 100%, in comparison with the gold standard immunoprecipitation (IPP) assay[10].

Statistical analysis. Frequencies of HLA-DRB1 alleles were compared between the patients and controls using a chi-square test or Fisher's exact test. To compensate for multiple testing, the corrected p value (p_c) was calculated by multiplying the p value by 33, because 33 different HLA-DRB1 alleles were detected in the study participants. A p_c value < 0.05 was considered to be statistically significant.

RESULTS

As shown in Table 1, there were no differences between patients with PM and DM in their age at diagnosis, sex, and prevalence of ILD. Consistent with our previous report[7], anti-MDA5 antibodies were exclusively expressed in the patients with DM, but not in those with PM ($p < 0.001$). In this cohort, anti-MDA5 antibodies were detected in 47 (45.2%) patients with DM. ILD was found in 31 of 70 patients with PM (44.3%) and 66 of 105 patients with DM (63.5%).

First, we compared the HLA-DRB1 allele frequencies between patients with PM/DM and controls. As shown in Table 2, a total of 33 HLA-DRB1 alleles were detected in the analyzed participants. Compared with the controls, the allele frequencies of DRB1*04:06 (0.0 vs 6.3%, OR 0.1, 95% CI 0.0–0.8, p = 0.037) and *11:01 (4.8% vs 12.3%, OR 0.4, 95% CI 0.1–0.9, p = 0.03) were lower in the patients with PM and DM, respectively. The allele frequencies of DRB1*07:01 (23.1% vs 12.0%, OR 2.2, 95% CI 1.3–3.8, p = 0.004) and *08:03 (21.2% vs 11.8%, OR 2.0, 95% CI 1.2–3.5, p = 0.013) in the patients with DM were higher than those in the controls. However, these differences did not reach statistical significance after the correction for multiple testing ($p_c > 0.05$). These results indicated that DRB1 polymorphisms were not significantly associated with the presence of PM/DM overall.

In anti-MDA5–positive patients with PM/DM, the frequency of DRB1*09:01 was lower than in the controls (6.4% vs 26.3%, OR 0.2, 95% CI 0.1–0.6, p = 0.003), although this did not reach statistical significance after correction ($p_c > 0.05$). In contrast, we observed significantly higher frequencies of DRB1*04:01 (17.0% vs 1.3%, $p = 1.2 \times 10^{-9}$, $p_c = 3.8 \times 10^{-8}$, OR 16.2, 95% CI 6.6–39.7) and *12:02 (42.6% vs 19.3%, p = 0.0002, $p_c = 0.008$, OR 3.1, 95% CI: 1.7–5.7) in anti-MDA5–positive patients with PM/DM than in the controls, suggesting a potential association of these 2 alleles with anti-MDA5 antibody production in patients with PM/DM.

Given that nearly all patients with anti-MDA5 antibodies develop ILD (45 of 47 patients in our present study), it is not clear whether DRB1*04:01 and *12:02 contribute to the

Table 1. Clinical characteristics of patients with PM/DM. Values are n (%) unless otherwise specified.

Characteristics	PM, n = 70	DM, n = 104	p
Mean age at diagnosis, yrs	54.8	50.2	ns
Male/female, n	36/34	26/78	ns
Anti-MDA5–positive	0	47 (45.2)	< 0.001
ILD	31 (44.3)	66 (63.5)	ns
With anti-MDA5 antibodies	0 (0.0)	45 (42.3)	
Without anti-MDA5 antibodies	31 (44.3)	21 (20.2)	

PM: polymyositis; DM: dermatomyositis; ILD: interstitial lung disease; anti-MDA5: anti-melanoma differentiation-associated gene 5; ns: not significant.

Table 2. Comparisons of HLA-DRB1 allele frequencies between patients with PM/DM and controls. Values are % unless otherwise specified.

DRB1 Allele	PM	DM	Anti-MDA5–positive PM/DM	Controls	Controls vs Indicated Patients [p, p_c, OR (95% CI)]		
					PM	DM	Anti-MDA5–positive PM/DM
*01:01	1.4	4.8	6.4	4	ns	ns	ns
*01:02	0.0	1.0	0.0	0.3	ns	ns	ns
*03:01	10.0	9.6	8.5	10.5	ns	ns	ns
*04:01	2.9	8.7	17.0	1.3	ns	ns	1.2×10^{-9}; 3.8×10^{-8}; 16.2 (6.6–39.7)
*04:02	0	0	0	1.3	ns	ns	ns
*04:03	4.3	3.9	4.3	3.3	ns	ns	ns
*04:05	12.9	14.4	14.9	13.3	ns	ns	ns
*04:06	0.0	6.7	10.6	6.3	0.037; ns	ns	ns
*04:07	1.4	1.9	2.1	0	ns	ns	ns
*04:10	0	0	0	0.8	ns	ns	ns
*07:01	14.3	23.1	21.3	12.0	ns	0.004; ns	ns
*08:02	2.9	0.0	0.0	1.3	ns	ns	ns
*08:03	18.6	21.2	14.9	11.8	ns	0.013; ns	ns
*08:09	0	0	0	0.3	ns	ns	ns
*09:01	28.6	19.2	6.4	26.3	ns	ns	0.003; ns
*10:01	7.1	0	0	3	ns	ns	ns
*11:01	14.3	4.8	4.3	12.3	ns	0.03; ns	ns
*11:04	2.9	0	0	0.3	ns	ns	ns
*12:01	5.7	3.9	2.1	8.0	ns	ns	ns
*12:02	12.9	24.0	42.6	19.3	ns	ns	0.0002; 0.008; 3.1 (1.7–5.7)
*12:10	1.4	0	0	0.3	ns	ns	ns
*13:01	7.1	2.9	6.4	2.8	ns	ns	ns
*13:02	5.7	10.6	10.6	7.3	ns	ns	ns
*13:12	0.0	1.9	0	1	ns	ns	ns
*14:03	1.4	0	0	0.3	ns	ns	ns
*14:04	0	0	0	1.5	ns	ns	ns
*14:05	0	1.0	0	5.5	ns	ns	ns
*14:07	0	1.0	0	0.3	ns	ns	ns
*14:54	2.9	0	0	4.3	ns	ns	ns
*15:01	14.3	18.3	17.0	20.8	ns	ns	ns
*15:02	5.7	5.8	4.3	5	ns	ns	ns
*16:01	0	1.0	0	0.3	ns	ns	ns
*16:02	8.6	0	0	7.8	ns	ns	ns

PM: polymyositis; DM: dermatomyositis; anti-MDA5: anti-melanoma differentiation-associated gene 5; p_c: corrected p value; ns: not significant.

susceptibility to ILD or to the production of anti-MDA5. To clarify this issue, we compared the frequencies of DRB1*04:01 and *12:02 in patients with DM, stratified by the presence of ILD or anti-MDA5 antibodies. We focused solely on DM, because anti-MDA5 antibodies are exclusively detected in patients with DM, but not in those with PM, and the frequencies of DRB1*04:01 and *12:02 were not significantly different between the patients with PM-ILD and the controls (data not shown). As shown in Table 3, the frequencies of DRB1*04:01 ($p = 4.7 \times 10^{-8}$, OR 12.5, 95% CI 5.0–30.9) and *12:02 ($p = 0.04$, OR 1.8, 95% CI 1.0–3.2) in patients with DM-ILD were significantly higher than those in the controls. The frequencies of DRB1*04:01 ($p = 5.2 \times 10^{-6}$, OR 17.1, 95% CI 5.3–54.9) and *12:02 ($p = 3.8 \times 10^{-4}$, OR 3.1, 95% CI 1.7–5.7) in the anti-MDA5–positive patients with DM-ILD were also significantly higher than those in the controls. However, the frequencies of both DRB1*04:01 and *12:02 were not significantly different between the patients with DM without ILD and the controls, or between the anti-MDA5–negative patients with DM-ILD and the controls. These results suggested that both DRB1*04:01 and *12:02 are associated with anti-MDA5 production in DM, which results in a secondary association with ILD, because nearly all anti-MDA5–positive patients developed ILD. Because the OR value for *04:01 was higher than that for *12:02, DRB1*04:01 may make a greater contribution to the production of anti-MDA5 antibodies than DRB1*12:02.

The DRB1*0401 allele contains amino acid sequences in a DRβ chain, known as a shared epitope (SE) predisposing to rheumatoid arthritis (RA). To clarify whether other HLA-DRB1 alleles carrying the SE are associated with ILD or anti-MDA5 production in DM, we compared the frequencies of combined SE alleles other than DRB1*04:01, i.e., DRB1*01:01, *01:02, *04:05, and *10:01, between the

Table 3. Comparisons of HLA-DRB1*04:01, *12:02, and SE allele frequencies in patients with DM, stratified by presence of ILD or anti-MDA5 antibody. Values are n (%) unless otherwise specified.

DRB1Allele	Control, n = 400	DM-ILD, n = 66	DM without ILD, n = 38	Anti-MDA5–positive DM-ILD, n = 45	Anti-MDA5–negative DM-ILD, n = 21	p; OR (95% CI) DM-ILD vs Control	DM without ILD vs Controls	Anti-MDA5–positive DM-ILD vs Controls	Anti-MDA5–negative DM-ILD vs Controls
*04:01	5 (1.3)	9 (13.6)	0	8 (17.8)	1 (4.8)	4.7×10^{-8}; 12.5 (5.0–30.9)	ns	5.2×10^{-6}; 17.1 (5.3–54.9)	ns
*12:02	77 (19.3)	20 (30.3)	5 (13.2)	19 (42.2)	1 (4.8)	0.04; 1.8 (1.0–3.2)	ns	3.8×10^{-4}; 3.1 (1.7–5.7)	ns
Combined SE alleles other than *04:01[†]	77 (19.3)	15 (22.7)	5 (13.2)	9 (20.0)	6 (28.6)	ns	ns	ns	ns

[†]DRB1*01:01, *01:02, *04:05, and *10:01. SE: shared epitope; DM: dermatomyositis; ILD: interstitial lung disease; anti-MDA5: anti-melanoma differentiation-associated gene 5; ns: not significant.

controls and the stratified patients with DM as mentioned above, but no significant difference was observed in any comparison.

DISCUSSION

It is well known that the production of MSA is closely associated with HLA polymorphisms and other genetic risk factors. The relatively high prevalence of anti-MDA5 antibodies in Asian patients with PM/DM, especially in Chinese patients with DM, suggests that genetic predisposing factors may be involved in the production of this antibody. In our present study, we performed high-resolution sequence-based genotyping of DRB1 in Chinese patients with PM/DM. Our results identified HLA-DRB1*04:01 and *12:02 as the risk factors for ILD and the development of anti-MDA5 antibodies in DM. Our results are in part consistent with the report by Gao, *et al*, in which they reported that DM-ILD was closely associated with DRB1*04 and *12 serotypes[11]. On the other hand, our findings differ from the previous report by Gono, *et al*[8]. In their study of 17 anti-MDA5–positive cases, Gono, *et al* reported that the frequencies of DRB1*01:01 and *04:05 were increased. Because both DRB1*01:01 and *04:05 are SE alleles, associated with the susceptibility to RA, the authors proposed HLA-DRB1 as an immunogenetic factor shared by RA and anti-MDA5 antibody–positive DM. However, their sample size was small and the statistical difference in allele frequencies was not corrected for multiple comparisons, indicating the necessity of a replicated study to establish the association of HLA-DRB1 and anti-MDA5 antibody–positive DM. It is interesting to note that the frequencies of both DRB1*04:01 and *12:02 were higher in the anti-MDA5–positive patients in the study of Gono, *et al*[8], although the statistical power was not sufficient to provide statistically significant differences owing to the small sample size. It is noteworthy that the frequencies of DRB1*04:01 and *12:02 are higher in Han Chinese than in Japanese individuals, which may explain the higher prevalence of ILD and anti-MDA5 antibody in Chinese patients than in Japanese patients.

The DRB1 alleles containing SE (QRRAA, QKRAA, or RRRAA sequences at positions 70–74 of the HLA-DRβ chain) are well-established risk factors for RA and are closely associated with the presence of rheumatoid factors or anti-citrullinated protein antibodies (ACPA), whereas alleles containing aspartic acid at residue 70 may protect against RA or favor a less erosive disease[12]. Recent advances have elucidated that a model including amino acids at positions 11 or 13 (which are in tight linkage disequilibrium), 71, and 74 may better explain the association of HLA-DRB1 alleles with the susceptibility to RA. In particular, valine at position 11 shows the greatest effect on RA inflammation, while serine at the same position is protective[13]. Although ILD is often accompanied by RA, most patients with RA present ILD with a chronic course rather than the RP-ILD seen in anti-MDA5–positive patients with PM/DM. A study showed that DRB1 alleles carrying SE were associated with a reduced risk of ILD in Japanese patients with RA[14], implying that SE may not be a risk factor for ILD in patients with RA. On the other hand, we found that both DRB1*04:01 carrying SE (containing valine at position 11 and glutamine at position 70) and *12:02 not carrying SE (containing serine at position 11 and aspartic acid at position 70) were associated with the susceptibility to ILD in patients with DM. In addition, the frequency of combined DRB1 alleles carrying SE alleles other than *04:01 was not significantly different between the controls and patients stratified by the presence of ILD or anti-MDA5 antibodies. Moreover, a large metaanalysis demonstrated that DRB1*12:02 was not associated with RA in the Han Chinese population[15]. These findings clearly indicate that the associations between DRB1 and ILD and anti-MDA5 antibodies cannot be simply explained by the SE hypothesis and suggest that the immunogenetic mechanisms involved in the pathogenesis of ILD differ between RA and DM, as well as in the autoantibody production between ACPA and anti-MDA5.

In addition to anti-MDA5 antibodies, anti-PM-Scl and anti-aminoacyl-transfer RNA synthetase (anti-ARS) antibodies may also be a biomarker of ILD in patients with PM/DM. In whites, anti-PM-Scl and anti-ARS antibodies are associated with HLA-DRB1*03[6]. A subset of cases in our present study had been investigated previously using the IPP method for the presence of anti-ARS antibodies, and no anti-PM-Scl antibody was detected in this subset of cases[7]. Among 18 patients with anti-ARS, 4 patients (22.2%) carried DRB1*03. The frequency of DRB1*03 in anti-ARS–positive Chinese patients did not significantly differ from that in the controls, and was much lower than that reported in white patients (84.6%)[6], suggesting a different genetic background between Chinese and whites in association with MSA. In this regard, it will be interesting to analyze the association between anti-MDA5 antibody and HLA in white patients in the future.

Although anti-MDA5 antibody is closely associated with ILD, the mechanisms of MDA5 itself and anti-MDA5 antibody in eliciting lung tissue damage remain unclear. MDA5 is a member of the cytoplasmic RNA helicases family that senses viral RNA and mounts antiviral innate immunity by producing type I interferons and inflammatory cytokines. Serum interferon-α can be a useful biomarker in patients with anti-MDA5–positive DM[16]. The binding of the viral dsRNA to MDA5 and the consequent induction of type I interferon responses might be a possible mechanism leading to the autoimmune response.

We found that HLA-DRB1*04:01 and *12:02 confer susceptibility to anti-MDA5 antibody production in DM. Our results highlight the different immunogenetic mechanisms in DM and RA that underlie both ILD and autoantibody production.

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