LETTERS

Protective effect of A at position -168 in the type III promoter of the *MHCIIA* gene in systemic lupus erythematosus

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The MHC class II transactivator (*MHCIIA*) gene was originally identified as a defective gene associated with bare lymphocyte syndrome, a severe combined immunodeficiency syndrome. Evidence indicates that *MHCIIA* is a master switch of antigen presentation in antigen-presenting cells.¹ A recent paper describes how a -168A →G polymorphism in the type III promoter of the *MHC2TA* gene was associated with increased susceptibility to rheumatoid arthritis, multiple sclerosis and myocardial infarction, as well as lower expression of *MHC2TA* after stimulation of leukocytes with interferon-gamma (IFN-γ).^{2,3} However, similar replicated studies in two other European populations did not find this association.^{4,5}

Systemic lupus erythematosus (SLE) is an autoimmune disease that is characterized by a complex set of immunological abnormalities that result in dysfunction of several organs. It has been reported that enhanced MHC class II antigen expression occurs in lupus nephritis in human and mice models.^{6,7} Therefore, particular alleles of the polymorphic gene involved in the regulation of MHC class II expression might be involved in the predisposition to SLE. We report here the association between a -168A →G polymorphism in the human *MHC2TA* gene and SLE. DNA samples were obtained from 180 Japanese patients with SLE (average age at onset: 26.4 ± 11.7 years) and 175 Japanese healthy controls. All the patients with SLE fulfilled the American College of Rheumatology criteria for SLE.⁸ Informed consent was obtained from each individual in this study. Genomic DNA was isolated from peripheral blood mononuclear cells. Genotypes of -168A →G (rs3087456) were determined by a TaqMan fluorogenic 5' nuclease assay (Applied Biosystems, Tokyo, Japan) as described elsewhere.⁹ Association between SLE susceptibility and -168A →G polymorphism was estimated by the Chi-square test that was implemented in R software package version 2.0.1 (<http://www.r-project.org/>).

As shown in table 1, we found a significant difference in allele frequencies for the single nucleotide polymorphism (SNP;

-168A →G) in individuals with SLE (p = 0.008). The presence of G at position -168 was frequent in normal Japanese individuals, in contrast to the study by Swanberg *et al.*² In SLE patients, A at position -168 was significantly associated with a decreased risk of developing SLE (p = 0.006; OR = 1.91). However, G at position -168 was not associated with an increased risk of developing SLE (p = 0.497). Therefore, we concluded that -168 A dominance is protective against the occurrence of SLE.

Upregulation of *CIITA* is reported to direct T cells differentiating to the Th1 but not to the Th2 lineage.¹⁰ The expression of *MHC2TA* mRNA has been shown to be lower in cells from individuals with genotype GG than in cells from individuals with other genotypes, by activation with IFN-γ (2). If that is the case, -168 A dominance might be associated with high expression of *MHCIIA*, resulting in the predominance of Th1 lineage over Th2, and this phenotype might be associated with protection against the occurrence of SLE. Further studies are needed to confirm the biological effects of SNP (-168A →G) in association with the differentiation of Th1 and Th2 lineage cells and also to study its role in the pathogenesis of SLE.

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Abbreviations: IFN-γ, interferon-gamma; *MHCIIA*, MHC class II transactivator; SLE, systemic lupus erythematosus

Table 1 Distribution of *MHC2TA* -168A →G in patients and controls

	SLE	Controls	p	OR (95% CI)
Allele frequencies				
A	44	68		
G	316	282	0.008	1.73 (1.14–2.61)
G-dominant model				
AA	3	5		
AG + GG	177	170	0.497	1.74 (1.15–2.61)
A-dominant model				
GG	139	112	0.006	1.91 (1.20–3.04)
AG + AA	41	63		

CI, confidence interval; OR, odds ratio; SLE, systemic lupus erythematosus.

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Crico-thyroid perichondritis leading to sore throat in patients with active adult-onset Still's disease

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A review of 341 adult-onset Still's disease (AOSD) patients noted that 69% of all reported cases¹ and 84% (69/82) of our series² displayed sore throat early in the disease course. Despite the presence of severe sore throat, physical examinations showed normal findings or only mild pharyngeal infection, and imaging studies (including computed tomography (CT) scans) of the neck were negative.^{1–4} The lesions responsible for sore throat in active AOSD patients have not yet been explored.

We performed magnetic resonance imaging (MRI) of the larynx⁵ in 6 active AOSD patients (3 females and 3 males; mean age 33.5 years; table 1) presenting with sore throat and fulfilling the Yamaguchi criteria.⁶ Our aim was to identify the lesions responsible for sore throat in AOSD patients. Throat swabs for bacterial cultures were negative and serological tests for viruses were non-diagnostic in all AOSD patients. Serum levels of C-reactive protein (CRP) were elevated in all of our active AOSD patients. Three AOSD patients were available for MRI examination both at the active phase when presenting with sore throat, and at the remission phase (defined as the absence of systemic manifestation and sore throat within 6

months of effective therapy). The Ethics Committee of Clinical Research, Taichung Veterans General Hospital, approved this study protocol.

A brief summary of clinical and MRI findings of our 6 AOSD patients during sore throat was shown in table 1. The T₁-weighted images showed increased thickness of soft tissue near the crico-thyroid cartilage (case 1 and fig 1A), and the post-contrast T₁-weighted images demonstrated marked enhancement at the perichondral tissue (fig 1B). In an AOSD patient presenting with odynophagia, the post-contrast T₁-weighted image showed marked enhancement at the soft tissue near cricoid-thyroid cartilages and the pharynx (case 5 and fig 1C). Gallium-67 scintigraphy showed an increased uptake intensity at the corresponding region (fig 1D). In a patient who had redness of the laryngeal mucosa shown by indirect laryngoscope, a T₂-weighted image illustrated increased signal intensity at the soft tissue surrounding the vocal cord (case 6). During a longitudinal

Abbreviations: AOSD, adult-onset Still's disease; CRP, C-reactive protein; CT, computed tomography; MRI, magnetic resonance imaging

Table 1 Summary of clinical and MRI findings of 6 patients with adult-onset Still's disease during sore throat

Case	Age/Sex	Clinical features of sore throat	Findings of indirect laryngoscopic examination	CRP levels (mg/dl)	MRI findings	
					T ₂ -weighted	Post-contrast T ₁
1	28/F	Left-sided sore throat	Normal	4.2	Increased signal intensity at left-sided crico-thyroid cartilage	Marked enhancement
2	34/F	Sore throat	Normal	1.6	Increased signal intensity at pre-epiglottic area	Mild enhancement
3	27/M	Sore throat	Normal	5.7	Increased signal intensity along bilateral thyroid cartilages	Marked enhancement
4	35/M	Sore throat	Normal	6.6	Increased signal intensity near cricoid cartilage	Mild enhancement
5	25/F	Severe sore throat with odynophagia	Redness of pharyngeal mucosa	10.7	Increased signal intensity at crico-thyroid cartilages and pharynx	Marked enhancement
6	52/M	Severe sore throat	Redness of laryngeal mucosa	11.3	Increased thickness with high signal intensity at the tissue surrounding vocal cord	Marked enhancement

M, male; F, female; CRP, C-reactive protein; MRI, magnetic resonance imaging.