Association of a polymorphism in the monocyte chemoattractant protein-1/CCL2 gene and lupus nephritis in systemic lupus erythematosus patients

Sirs,

Systemic lupus erythematosus (SLE) is an autoimmune disease and neuropsychiatric syndromes of systemic lupus erythematosus (NPSLE) and lupus nephritis (LN) are major contributors to morbidity and mortality in patients with SLE (1). There is growing evidence identifying the genetic factors that may predispose for the development of LN (2-5). MCP-1 (monocyte chemoattractant protein 1)/CCL2 (chemokine (C-C motif) ligand 2) is a CC chemokine which attracts leukocytes and other mediators into sites of inflammation. A previous study has examined the role of functional MCP-1/CCL2 polymorphisms in SLE and LN (6-8). To further investigate the role of this polymorphism in SLE, we studied genotype frequencies in Japanese patients with SLE and controls.

DNA samples were obtained from 159 Japanese patients with SLE (SLE; average age at onset is 27.4±12.6 years) (89 patients with LN (WHO II, III, IV, V) and 70 without L N (WHO I), 36 with NPSLE and 122 without NPSLE) and 187 Japanese healthy controls. Each of the patients with SLE fulfilled the American College of Rheumatology criteria for SLE. All the SLE patients underwent renal biopsy so that an assessment, according to WHO criteria, for lupus nephritis could be performed. Patients were divided into two groups based on LN. NPSLE was diagnosed under the American College of Rheumatology criteria for neuropsychiatric lupus syndromes (1). The genotype at position -2518 of CCL-2 (rs1024611) was determined by a TaqMan fluorogenic 5' nuclease assay (Applied Biosystems, Tokyo, Japan) as described elsewhere (9). The association between SLE susceptibility and the -2518A→G polymorphism was estimated by the Chi-square test implemented in R software package version 2.0.1 (http://www.r-project.org/).

Allele frequency for the CCL-2 -2518A→G polymorphism were determined in 140 (88.1%) Japanese SLE patients (81 patients with LN (91.0%) and 59 without LN (84.3%), 34 with NPSLE (94.4%) and 105 without NPSLE (86.2%)) and 177 (94.7%) controls. We did not find significant differences in allele frequency in individuals with SLE compared with controls (Table IA). The presence of the A/A genotype was significantly associated with a higher risk of LN (p=0.0441). The odds ratio (for the presence of A/A at position -2518 for LN cohorts) was 4.5 (95% CI = 0.954-21.03) (Table IB). We did not find a significant difference in allele frequency in individuals with NPSLE compared with non-NPSLE subjects (Table IC).

These data are inconsistent with the data presented by others. Tucci *et al*. suggested that an A/G or G/G genotype may predispose for the development of SLE and LN (6). Liao Ch *et al*. reported no significant difference in the frequency or in the distribution of genotypes of the -2518(A/G) MCP-1 in Chinese children (7). Brown KS *et al*. reported that the G allele was not significantly associated with SLE or LN in the whole study sample, while among Caucasians, G confers risk to develop SLE but not associated with LN (8). The presence of G at position -2518 in *CCL-2* was more frequent in healthy control Japanese, which is in contrast to the study by Tucci *et al*. (Table I) (6). Therefore, ethnic differences could well account for the difference in allelic frequencies observed in our group compared with others. Although we previously reported that MCP-1/CCL2

Table IA. Analysis of the MCP-1 -2518 genotype in SLE patients and controls*.

	SLE				
	Patients (n=140)	Controls (n=177)	p	OR	95% CI
Genotype					
A/A	13 (9)	17 (10)	0.8476	0.9	0.419-1.978
A/G	66 (47)	100 (56)	0.1131	0.7	0.450-1.104
G/G	61 (44)	60 (34)	0.0822	1.5	0.943-2.368
Presence of allele					
A	79 (56)	117 (66)	0.0822	0.7	0.422-1.060
G	127 (91)	160 (90)	0.8476	1.1	0.506-2.384
Allele frequency					
A	92 (33)	134 (38)			
G	188 (67)	220 (62)			

*Values are the number (%) of subjects. MCP-1: monocyte chemoattractant protein 1; SLE: systemic lupus erythematosus; OR: odds ratio; 95% CI: 95% confidence interval.

Table IB. Analysis of the MCP-1 -2518 genotype in SLE patients with and without LN*.

	SLE patients with LN (n=81)	SLE patients without LN (n=59)	p	OR	95% CI
Genotype					
A/A	11 (14)	2 (3)	0.0441	4.5	0.954-21.03
A/G	38 (47)	28 (47)	1.0000	1.0	0.500-1.916
G/G	32 (40)	29 (49)	0.3016	0.7	0.343-1.330
Presence of allele					
A	49 (60)	30 (51)	0.3016	1.5	0.752-2.914
G	70 (86)	57 (97)	0.0441	0.2	0.048-1.049
Allele frequency					
A	60 (37)	32 (27)			
G	102 (64)	86 (73)			

*Values are the number (%) of subjects. MCP-1: monocyte chemoattractant protein 1; SLE: systemic lupus erythematosus; LN: lupus nephritis; OR: odds ratio; 95% CI: 95% confidence interval.

Table IC. Analysis of the MCP-1 -2518 genotype in SLE patients with and without CNS*.

	SLE patients with CNS (n=34)	SLE patients without CNS (n=105)	p	OR	95% CI
Genotype					
A/A	4 (12)	8 (8)	0.2932	1.6	0.455-5.746
A/G	17 (50)	49 (47)	0.8438	1.1	0.527-2.478
G/G	13 (38)	48 (46)	0.5516	0.7	0.333-1.622
Presence of allele					
A	21 (62)	57 (54)	0.5516	1.4	0.617-3.001
G	30 (88)	97 (92)	0.2932	0.6	0.174-2.199
Allele frequency					
A	25 (37)	65 (31)			
G	43 (63)	145 (69)			

*Values are the number (%) of subjects. MCP-1: monocyte chemoattractant protein 1; SLE: systemic lupus erythematosus; LN: lupus nephritis; OR: odds ratio; 95% CI: 95% confidence interval.

levels in cerebral spinal fluids were higher in NPSLE patients than in non-NPSLE patients (10), we did not see any association of *CCL-2* gene polymorphisms with NPSLE in a Japanese population. Further studies are needed to confirm the functional effects of *CCL-2* gene polymorphisms in association with the development of SLE, LN and NPSLE in other ethnic groups.

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