Lack of Association of *TYK2* Gene Polymorphisms in Chinese Patients with Systemic Lupus Erythematosus

To the Editor:

We read with interest the study of Hellquist, *et al*[1] showing tyrosine kinase 2 (*TYK2*) is associated with systemic lupus erythematosus (SLE). Similar results have been reported in different Caucasian populations[2,3,4], but not in a recently published Japanese study[5]. Interestingly, we also found *TYK2* polymorphisms were not associated with SLE in Hong Kong Chinese, although subphenotype analysis revealed it may be associated with the development of photosensitivity and discoid rash.

Our study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster. The study included 669 patients with SLE and 2538 controls, as reported[6,7]. Genotyping with the Illumina 610-Quad Human Beadchip (Illumina, San Diego, CA, USA) from 612 patients and 2193 healthy controls included 9 single-nucleotide polymorphisms (SNP) within 10 kilobases spanning *TYK2*. Additional genotyping by direct sequencing on 150 patients and 345 healthy controls was performed for rs12720270, rs2304356, and rs2304255, which were not included in the Illumina Beadchip procedure. The rs12720270 was reported to be associated with SLE in a Caucasian population[3]. The rs2304255 and rs2304256 were selected because they are both nonsynonymous substitutions (Gly>Ser at amino acid position 13433 and Val>Phe at amino acid position 13430, respectively) within *TYK2*, which may constitute significance in gene function[2]. Out of the 150 patients genotyped by direct sequencing, 93 were also genotyped in the Illumina Beadchip; with this overlap, a total of 669 patients were included in this study.

The genotype frequencies of all studied SNP were in Hardy-Weinberg equilibrium. Considering a minor allele frequency (MAF) > 0.05, a population prevalence of 0.06% for SLE[8], and a significance level of 0.05, our study had sufficient power to detect association with an odds ratio ≥ 1.2. Out of all the 12 SNP genotyped, rs280519, rs2304256, and rs12720270 had MAF > 0.05 in our population; the allelic associations are summarized in Table 1. None of the SNP was shown to be associated with SLE ($p > 0.05$). Based on the 93 overlapping patients genotyped both in the Illumina Beadchip and by direct sequencing, linkage disequilibrium (LD) between the 12 SNP was analyzed by Haploview[9] (Figure 1). The rs280519, rs2304256, and rs12720270 were in moderate LD ($r^2 = 0.62–0.85$).

MAF of these 3 SNP in our cohort were found to be different from those reported in Caucasian[3] and Japanese[5] populations. In the control groups, the minor allele of rs2304256 was G in Chinese instead of T in Japanese and Caucasians; and the minor allele of rs121720270 was C instead of T. The MAF of rs280519 was also different (Table 1). These differences could be attributed to the different genetic backgrounds. From the International HapMap Project (http://www.hapmap.org), the MAF of rs280519 and rs2304256 in Han Chinese are 0.415 and 0.463 respectively, similar to the findings of our study. The LD patterns derived from the HapMap Project also show a big contrast between Japanese, Han Chinese, and Caucasians in the *TYK2* region (data not shown). These genetic differences in allele frequencies and LD patterns among populations could explain the discrepancies between association of *TYK2* SNP in Caucasians and Asians. Neither the Japanese study nor our study could replicate the associations of *TYK2* SNP with SLE, which may suggest that *TYK2* is a specific risk factor for Caucasians. On the other hand, the negative association from the studied SNP cannot exclude the association of *TYK2* in Chinese because of the different LD patterns between Chinese and Caucasians; these markers may not tag the functional SNP in Chinese as in Caucasians and thus associations could not be replicated.

Subphenotype analysis was also performed for the 11 criteria from the revised American College of Rheumatology diagnostic criteria for SLE[10] (data not shown). The rs2304256 and rs12720270 were found to be associated with photosensitivity and discoid rash in patients with SLE. After adjustment by Bonferroni correction, the association of rs2304256 and rs12720270 with photosensitivity was still maintained ($p = 5.9 \times 10^{-4}$ and $p = 2.9 \times 10^{-3}$, respectively), whereas that with discoid rash became marginal ($p = 0.010$ and $p = 0.026$, respectively). In a previous study, rs2304256 was found to be associated with increased risk of discoid lupus erythematosus (DLE) and *TYK2* was expressed in macrophage-like cells and neutrophils of DLE, subcutaneous lupus erythematosus, and SLE skin[11]. Although rs2304256 was not associated with increased risk of SLE in this study, its association with cutaneous manifestations suggests that *TYK2* may be a minor risk factor for SLE in Chinese.

Our results verified that *TYK2* polymorphisms were not associated with SLE in Hong Kong Chinese, but that rs2304256 and rs12720270 may be associated with photosensitivity and discoid rash. This lack of association may be due to ethnic differences in susceptibility genes, which may be elucidated in future studies involving denser genotyping in different populations.

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Table 1. Allelic associations and frequencies of SNP of *TYK2* in Hong Kong Chinese subjects.

SNP	A1	A2	MAF, Controls	MAF, Cases	p	Caucasians*, MAF (Minor allele)	Japanese**, MAF (Minor allele)
rs8108236	A	G	0.012	0.008			
rs12720279	T	C	0.040	0.042			
rs280519†	A	G	0.357	0.349	0.5923	0.50 (A)	0.48 (G)
rs6511695	T	C	0.012	0.009			
rs12720253	T	G	0.025	0.020			
rs6511696	T	C	0.012	0.009			
rs280500	G	A	0.044	0.046			
rs2304259	G	T	0.045	0.043			
rs280502	T	G	0.045	0.046			
rs2304255	A	G	0.039	0.028			
rs2304256†	G	T	0.424	0.413	0.7055	0.25 (T)	0.38 (T)
rs12720270†	C	T	0.453	0.443	0.7181	0.17 (T)	0.37 (T)

* Data from Graham, *et al*[3]; ** data from Kyogoku, *et al*[5]. † SNP with minor allele frequencies > 0.05 selected for statistical analysis. A1: minor allele in Chinese population; A2: major allele in Chinese population; MAF: minor allele frequency.

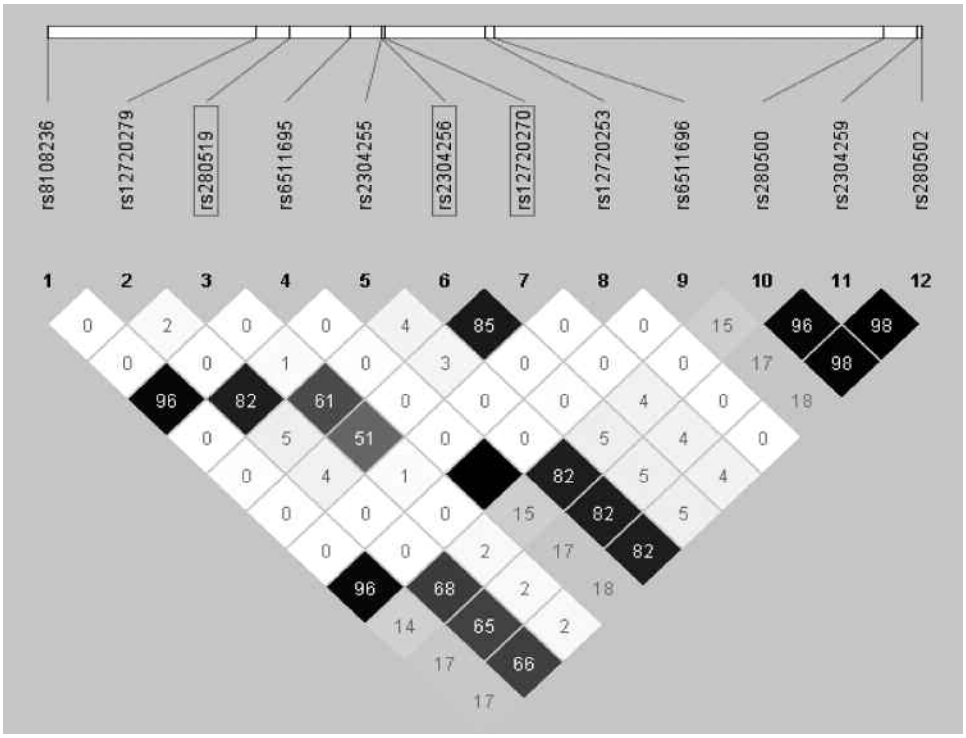

Figure 1. LD r^2 prime charts from HaploView of *TYK2* SNP in Hong Kong Chinese.

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