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

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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 al1 showing tyrosine kinase 2 (TYK2) is associated with systemic lupus erythematosus (SLE). Similar results have been reported in different Caucasian populations2,3,4, but not in a recently published Japanese study5. 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 reported6,7. 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, rs2304256, and rs2304255, which were not included in the Illumina Beadchip procedure. The rs12720270 was reported to be associated with SLE in a Caucasian population7. The rs2304255 and rs2304245 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 function2. 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 SLE3, 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 Haplovie8 (Figure 1). The rs280519, rs2304256, and rs12720270 were in moderate LD (r² = 0.62–0.85).

MAF of these 3 SNP in our cohort were found to be different from those reported in Caucasian3 and Japanese2 populations. In the control groups, the minor allele of rs2304256 was G in Chinese 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 with SLE in Asian populations 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 SLE10 (data not shown). The rs2304256 was 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 × 10⁻4 and p = 2.9 × 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 skin11. 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 Chinese. On the other hand, the negative association of the SNPs with SLE could not be replicated.

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Letters

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

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

* Data from Graham, et al; ** data from Kyogoku, et al; † 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.
REFERENCES

Figure 1. LD r2 prime charts from HaploView of TYK2 SNP in Hong Kong Chinese.