KLK1 Gene Polymorphisms Are Not Associated with Lupus Nephritis in a Chinese Han Population

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To the Editor:

Lupus nephritis (LN) is one of the most serious manifestations of systemic lupus erythematosus (SLE) and is an important predictor of poor outcome. Susceptibility to LN is the end result of complex interactions between polygenic genetic factors involved in the regulation of immune responses. However, to date, a clear etiology is still obscure. Recently, it was reported that kallikrein genes, especially KLK1 gene, were associated with LN in mice and in Caucasians. However, such an association was not shown in all the investigated populations. This implies that different genetic influences exist in different ethnic groups, and it was decided to further validate the association of KLK1 gene polymorphisms with LN in a Chinese Han population.

A case-control association study was performed on 306 LN patients (age 32.2 ± 11.1 yrs, 84.2% female) and 338 matched healthy controls (age 31.7 ± 9.1 yrs, 55.8% female). LN patients were recruited from Peking University First Hospital; all were of Han ethnicity living in northern China and met revised SLE criteria of the American College of Rheumatology. LN was confirmed by renal biopsy (including 28, 64, 156, and 58 cases of class II, III, IV, V, respectively) according to the revised 2003 International Society of Nephrology/Renal Pathology Society classification system. Controls were geographically and ethnically matched. All samples were independent. Three tagging single-nucleotide polymorphisms were detected, including rs5516 (Gln145Glu, exon 3) and rs5517 (Glu186Lys, exon 4), which could efficiently tag 8 SNP (minor allele frequency > 0.1, from the 5' flanking sequence 1.5 kb upstream to the 3' flanking region) of the KLK1 gene, with r2 > 0.9 for both common haplotype and unmeasured variants of the KLK1 gene, based on the HapMap data of Han Chinese in a Beijing population, rs5516 and rs2740502 (intron 1) were formerly reported to be associated with LN in Caucasians.

Our study was approved by the medical ethics committee of Peking University. All patients gave informed consent. The overall 3 tSNP were genotyped by TaqMan allele discrimination assays (Assay ID: C__2932109_10 for rs2740502, C__2932115_20 for rs5517, and C__8705506_1 for rs5516; Applied Biosystems, Foster City, CA, USA) according to the manufacturer’s instructions. Concordance was checked against 5% samples and reached 100%. Disease associations were analyzed by chi-square tests using 2 × 2 as well as 2 × 3 contingency tables. Linkage disequilibrium (LD) was tested using Haploview (version 3.32, http://www.broad.mit.edu/mpg/haploview). Haplo.Stats software (version 1.4.3, http://cran.r-project.org/web/packages/haplo.stats) was used to test the association of statistically inferred haplotypes with LN. Power of the study was calculated by Power and Sample Size Calculations Software (version 3.0, http://biostat.mc.vanderbilt.edu/PowerSampleSize). Deviation from Hardy-Weinberg equilibrium was not observed for any of the SNP in the control or LN samples (p = 0.16 to 0.96). LD analysis in healthy controls revealed that r2 values between rs2740502, rs5516, and rs5517 were 0.05 and 0.32, respectively. In our case-control study, we had 0.978 (rs2740502), 0.965 (rs5516), and 0.992 (rs5517) power to detect a two-fold increased risk, assuming an α-level of 0.05. Allele type, genotype (Table 1), and haplotype (data not shown) distributions of identified polymorphisms were compared between patients and controls, but none of the 3 tSNP exhibited evidence of an association with susceptibility to LN in this Chinese population (p > 0.05).

The sample of LN in our study was large (306, comparable to 319 LN patients in total described by Liu, et al), homogeneous in ethnicity, proven by biopsy, and all enrolled from a single center; the selected tSNP could efficiently tag common alleles of KLK1 gene, all of which guaranteed reliability. We thus suggest that KLK1 gene is not associated with LN in a Chinese Han population.

The likely reason for the lack of association may be genetic heterogeneity. SLE is more common, more severe, of earlier onset, and has distinct clinical features in East Asians compared with Europeans. These clinical differences are independent of environment and are likely to be genetically determined, thus it was to be expected that SLE will have different genetic influences in different ethnic groups. This lack of association in our study provides information with respect to investigations for a role of members of the kallikrein system, at least of KLK1, in autoimmune diseases among different populations. Further study involving rare alleles of KLK1 and polymorphisms within other kallikrein genes will be needed.

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REFERENCES


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Table 1. KLK1 polymorphisms in LN patients and healthy controls in Han Chinese. Values are number (%).

<table>
<thead>
<tr>
<th>SNP</th>
<th>Patients, n = 306</th>
<th>Controls, n = 338</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2740502 Genotype frequency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G/G</td>
<td>13 (4.2)</td>
<td>20 (5.9)</td>
<td>0.246</td>
</tr>
<tr>
<td>C/G</td>
<td>119 (38.9)</td>
<td>112 (33.1)</td>
<td></td>
</tr>
<tr>
<td>C/C</td>
<td>174 (56.9)</td>
<td>206 (60.9)</td>
<td></td>
</tr>
<tr>
<td>Allele frequency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G (vs C)</td>
<td>145 (23.7)</td>
<td>152 (22.5)</td>
<td>0.607</td>
</tr>
<tr>
<td>G/G (vs C/G + C/C)</td>
<td>13 (4.2)</td>
<td>20 (5.9)</td>
<td>0.337</td>
</tr>
<tr>
<td>G/G + G/C (vs C/C)</td>
<td>132 (43.1)</td>
<td>132 (39.1)</td>
<td>0.293</td>
</tr>
</tbody>
</table>

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p values were calculated by chi-square analysis using 2 × 3 (comparison of genotype frequencies) or 2 × 2 (other comparisons) contingency tables.


