Replicated association of a regulatory polymorphism in the interferon γ gene with lupus susceptibility

Single-nucleotide polymorphisms (SNPs) of the human interferon γ gene (IFNG) were found to be associated with susceptibility to systemic lupus erythematosus (SLE) in our recent case–control study on 1759 unrelated Korean participants (742 SLE patients and 1017 controls). In particular, the SLE-susceptible (minor) allele in an SNP (rs2430561) located on an NF-κB binding site in the first intron was associated with elevated IFNG expression, consistent with previous functional implications of high expression levels of IFNG in lupus pathogenesis in human disease and murine models, although this SNP showed no association in several previous small studies.

In our original study, the effect size of this SNP was marginal with an OR of 2.48 in a recessive model, but its association was significant (p=0.022). When the effect sizes of the two study results still showed a significant association (adjusted OR 1.61 and p=0.0066 in a recessive model; p in Q-statistic=0.094).

The participants in this validation cohort were recruited from six hospitals (Hanyang University Hospital for Rheumatic Diseases, Kyungpook National University Hospital, Eulji University Hospital, Ajou University Hospital, Yonsei University Severance Hospital and Chungnam National University Hospital) and the patients fulfilled the American College of Rheumatology criteria. Genomic DNA was obtained from the peripheral blood cells of the subjects and genotyped using the MassARRAY platform of Sequenom, Inc. (San Diego, California). OR and p values were calculated using logistic regression analysis with adjustment for age and gender. The average call rate was 97.7% and the control subject genotypes were under Hardy–Weinberg equilibrium (p≥0.33). The combined effect sizes were calculated by fixed-effects meta-analysis (p values in Q-statistic ≥0.094).

In summary, SLE association of the cis-regulatory SNP rs2430561 in IFNG was reproduced in two independent cohorts, supporting the previous association of increased expression of IFNG with increased susceptibility to SLE.

Table 1 Meta-analysis showing the association of rs2430561 and rs2069705 with SLE susceptibility

<table>
<thead>
<tr>
<th>SNP/cohort</th>
<th>SLE cases</th>
<th>Controls</th>
<th>Codominant model</th>
<th>Recessive model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p</td>
<td>OR (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td>rs2430561 (T&gt;A)</td>
<td>T/T</td>
<td>A/A</td>
<td>1.28 (1.04 to 1.58)</td>
<td>0.029</td>
</tr>
<tr>
<td>Original study</td>
<td>503/167/18</td>
<td>765/225/11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>This study</td>
<td>629/177/19</td>
<td>1146/301/15</td>
<td>1.20 (0.99 to 1.45)</td>
<td>0.060</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td></td>
<td></td>
<td>1.24 (1.08 to 1.42)</td>
<td>0.0029</td>
</tr>
<tr>
<td>rs2069705 (C&gt;T)</td>
<td>C/C</td>
<td>T/T</td>
<td>1.28 (1.07 to 1.53)</td>
<td>0.0047</td>
</tr>
<tr>
<td>Original study</td>
<td>406/240/38</td>
<td>634/338/26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>This study</td>
<td>541/265/37</td>
<td>953/468/52</td>
<td>1.07 (0.91 to 1.25)</td>
<td>0.58</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td></td>
<td></td>
<td>1.16 (1.03 to 1.30)</td>
<td>0.015</td>
</tr>
</tbody>
</table>

OR, 95% CI and p values were calculated using logistic regression analysis with adjustment for age and gender or using meta-analysis. SLE, systemic lupus erythematosus; SNP, single-nucleotide polymorphism.

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Competing interests None.

Patient consent Obtained.

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