Functional Haplotype Frequencies of the Interleukin-1B Promoter in the Korean Population

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Abstract

Single nucleotide polymorphisms (SNPs) in the promoter region of the *IL-1B* (interleukin-1) gene have been implicated in a variety of diseases that have an inflammatory component. However, there has been significant heterogeneity among study results, especially between Caucasian and Asian populations. Recently, it has been reported that SNPs in the *IL-1B* gene affect transcription, according to haplotype context, and genetic association studies may be more informative if functional SNP haplotypes of population are analyzed. Therefore, we estimated the distribution of IL-1B promoter haplotypes in 433 Koreans using the three major functional IL-1B promoter SNPs (*IL-1B*-1464, -511, and -31) and compared the results with those in Caucasians. The difference in IL-1B promoter haplotype frequency between Korean and Caucasian populations was statistically significant. The potentially more inflammatory haplotypes had higher frequencies in Koreans when compared with Caucasians. These Korean haplotype data will be useful for future association studies between *IL-1B* SNPs and disease risk.

Keywords: Interleukin-1B; polymorphism; haplotype; Korean

SNPs in the promoter region of *IL-1B* gene have been implicated in a variety of diseases that have an inflammatory component, including cardiovascular disease, gastric cancer, Alzheimer disease, and periodontal disease (Iacoviello et al., 2005; Camargo et al., 2006; Griffin et al., 2000; Korman et al., 1997). The *IL-1B* gene is highly polymorphic, and several SNPs have been frequently associated with several diseases (Iacoviello et al., 2005; Francis et al., 1999; El-Omar et al., 2000). However, there has been significant heterogeneity among study results, especially between Caucasian and Asian populations (Camargo et al., 2006; Lee et al., 2004; Yang et al., 2004; Zeng et al., 2003; Chang et al., 2005; Ma et al., 2003; Hodge et al., 2001).

Recently, Chen et al. (Chen et al., 2006) reported that SNPs in the *IL-1B* gene affect transcription according to haplotype context, and genetic association studies may be more informative if functional SNP haplotypes are analyzed, rather than individual functional SNPs. Further, they showed that the functional haplotypes differ by ethnic population. These findings underline the relevance of population haplotypes in the design of genetic studies (Chen et al., 2006). In view of these findings, we estimated the distribution of *IL-1B* promoter haplotypes in 433 Koreans using three major functional *IL-1B* promoter SNPs (*IL-1B*-1464, -511, and -31) and compared the results with those in Caucasian and African populations. Although the *IL-1B*-3737 polymorphism also had allele-specific differences in nuclear protein binding, no differences in promoter activity were observed with different alleles of this SNP on a background of the other SNP sets that showed higher promoter activity (Chen et al., 2006). Because it has been suggested that the functional significance of *IL-1B*-3737 might depend on a broader haplotype, we used the three SNPs for haplotype analysis. Haplotypes were reconstructed by PHASE version 2.1, using previously produced genotype data (Lee et al., 2004).

Of the possible eight haplotypes, three common ones accounted for ≥98% of the estimated haplotypes in the Korean population. Table 1 shows the haplotype frequency estimation in each population. The potentially more inflammatory *IL-1B*-511T/-31C haplotype represented 53.5% of the Korean haplotypes, compared with 33.7% of the Caucasian haplotypes. So far, in many previous association studies, the individual SNP approach, most frequently using *IL-1B*-511 and *IL-1B*-31, has been adopted. To our knowledge, we reported first that the *IL-1B*-1464 polymorphism has allele-specific effects when both *IL-1B*-511 and *IL-1B*-31 were alleles T and C, respectively (Chen et al., 2006). The more informative haplotype 1 (GTC), containing the *IL-1B*-1464 polymorphism, which shows the highest transcriptional activity, represents 9.3% and 6.0% of Korean and Caucasian haplotypes, respectively, whereas haplotype...
Table 1. Common haplotype frequencies of IL1B promoter

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>Haplotype frequency (%)</th>
<th>Korean†</th>
<th>CHB+JPT ‡</th>
<th>Caucasian*</th>
<th>African*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Case (n=433)</td>
<td>Gastrointestinal (n=331)</td>
<td>Diffuse (n=188)</td>
<td>Intestinal (n=133)</td>
</tr>
<tr>
<td>GTC (High)</td>
<td></td>
<td>9.3</td>
<td>10.2</td>
<td>8.4</td>
<td>11.9</td>
</tr>
<tr>
<td>CTC (Intermediate)</td>
<td></td>
<td>44.0</td>
<td>44.2</td>
<td>49.7</td>
<td>37.0</td>
</tr>
<tr>
<td>GCT (Low)</td>
<td></td>
<td>44.8</td>
<td>44.2</td>
<td>40.2</td>
<td>50.0</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>98.1</td>
<td>98.6</td>
<td>98.3</td>
<td>98.9</td>
</tr>
</tbody>
</table>

*Data are from Chen et al., 2006,
†Japanese and Chinese results are from international Hapmap data,
‡Haplotypes were reconstructed using previously produced genotype data from Lee, et al., 2004.

3 (GCT), with the lowest activity, had a higher frequency in Caucasians (64.8%) when compared with Koreans (44.2%) (Table 1). The difference in IL-1B promoter haplotype frequency between the Korean and Caucasian populations was statistically significant (χ²=20.6, p=0.000), and the allele frequencies of the IL-1B-1464 polymorphism (rs#1143623) were also significantly different between the two populations (IL-1B-1464 G allele frequencies for Korean and Hapmap European=0.548 and 0.672, respectively) (χ²=6.38, p=0.01).

It has been suggested that genes that are involved in immune function may be under selective pressure in direct interaction with the environment (Sawyer et al., 2004; Kim et al., 2005). The genes that influence a phenotypic variation between populations are expected to show high Fst values. Compared with the Fst value for the Caucasian-vs-Asian comparison, the Fst values for the African-vs-Asian or A-Caucasian comparisons were remarkably high (Fig. 1).

Previously, we reported that the IL-1B-1464 polymorphism contributes to the development of intestinal-type gastric cancer among Koreans (Lee et al., 2004). As a curious finding in our report, the editor pointed out that carriers of IL-1B-1464 G tend to have a decreased risk of diffuse-type gastric cancer, which is the opposite of intestinal-type gastric cancer, although both intestinal and diffuse types of gastric cancer are related to Helicobacter pylori-induced gastritis (Furuta et al., 2004). Our results showed that most IL-1B-1464 C alleles are linked to the IL-1B-511T/-31C haplotype (Table 1). Considering the level of promoter activity of haplotype 2 (CTC), we cannot exclude the possible association between this haplotype and the risk of diffuse-type gastric cancer, especially depending on interactions with other regulatory factors (Lee et al., 2007). Association studies that use individual SNPs appear to be insufficient, and the understanding of functional haplotype structure of populations could provide potential explanations for IL-1B-related controversies and ethnic-specific associations. Therefore, we believe that these Korean haplotype data will be useful for future association studies between IL-1B SNPs and disease risk.

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References


