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# 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; Kornman *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 underlie 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 differences in nuclear protein binding and is associated with a clinical disease (Lee *et al*., 2004). The biological implication of this polymorphism was supported by *in vivo* studies by Chen et al. that showed that the *IL-1B-1464* polymorphism has substantial 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

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**Table 1.** Common haplotype frequencies of IL1B promoter

| Haplotype IL1B-1464/-511/-31 (Transcriptional activity*) | Haplotype frequency (%) | | | | | | |
|---|---|---|---|---|---|---|---|
| | Korean ‡ | | | | CHB+JPT † (n=89) | Caucasian* (n=900) | African* (n=227) |
| | Case (n=433) | Gastric cancer (n=331) | Diffuse (n=188) | Intestinal (n=133) | | | |
| GTC (High) | 9.3 | 10.2 | 8.4 | 11.9 | 10.1 | 6.0 | 46.1 |
| CTC (Intermediate) | 44.0 | 44.2 | 49.7 | 37.0 | 35.4 | 27.7 | 10.6 |
| GCT (Low) | 44.8 | 44.2 | 40.2 | 50.0 | 53.9 | 64.8 | 42.0 |
| Total | 98.1 | 98.6 | 98.3 | 98.9 | 99.4 | 98.5 | 98.7 |

*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 ($\chi^2$=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) ($\chi^2$=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 -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 of 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

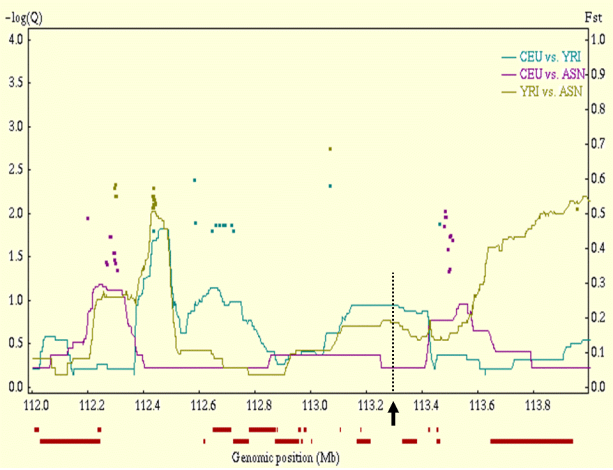


**Fig. 1.** Population pairwise Fst values for the *IL1B* promoter region (113.3 Mb, data from Voight *et al*., 2004.

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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