Frequencies of Interleukin 1 Gene Polymorphisms in Koreans

To the Editor:

The interleukin-1 (IL-1) family consists of three different cytokines: two pro-inflammatory cytokines, IL-1α and IL-1β, and an IL-1 inhibitor, IL-1 receptor antagonist (IL-1ra). The genes for IL-1α, IL-1β, and IL-1ra, located in a cluster on human chromosome 2, have several polymorphisms. IL-1α has a base-exchange polymorphism at position –889 in the promoter region (1). IL-1β has two base-exchange polymorphisms: at position –511 in the promoter region and at position +3953 in exon 5 (2). The IL-1ra gene has a pentanucleotide polymorphic site in intron 2, containing variable numbers of an 86-bp identical tandem repeat (VNTR) (3). These polymorphisms of IL-1β and IL-1ra have an effect on cytokine production in vitro. In addition, certain combinations of the IL-1α and IL-1β loci regulate the plasma concentrations of IL-1ra (4), which would imply allelic cooperation of these genes in the immune and inflammatory responses.

We studied a total of 640 unrelated healthy individuals (age range, 25–54.7 years; 51.9% female) attending Wonkwang University Hospital (Iksan, Korea) for general check-ups. All participants (all Korean) gave informed consent before participating in the research protocol, which was approved by the ethics committee of the hospital. The genomic DNA was extracted by an inorganic procedure (5). Genotyping was performed as follows. Genotyping for the IL-1ra (intron 2 VNTR), IL-1α (–889), and IL-1β (+3953) in each ethnic group are shown in Table 1. The three polymorphisms fit well with the distributions expected under Hardy–Weinberg equilibrium for our population. The heterozygosity at the IL-1ra locus was 0.15. The observed frequency of allele 2 of IL-1ra in Koreans in this study (6%) was similar to the frequencies reported for Japanese (3.1%) (6) and Taiwanese Chinese (6.2%) (7). The frequency of IL-1ra allele 2 was significantly lower in Koreans compared with Caucasians (6% vs 21–23%; P < 0.001) (3, 7). For IL-1α (–889), allele 2 was observed only infrequently in Koreans (7%), but Caucasians have a significantly higher frequency (30%) (8). For the Japanese, the frequency was slightly higher than in Koreans (7% vs 11%; P = 0.019). For allele 2 in the IL-1β +3953 polymorphism, Caucasians had a significantly higher frequency (24–26%) (7, 8), whereas Taiwanese Chinese had the lowest (1%) (7). The allelic frequency in Koreans was 4%, which was similar to that in Japanese (6).

Our study determined the frequencies of IL-1 cluster genes in healthy individuals from Korea and compared them with the other populations reported. As a result, we found significant differences in allelic frequencies among ethnic groups. The IL-1ra allele 2 was very rare in Koreans (frequency, 0.060). In addition, we also found a significant difference for the IL-1α (–889) and IL-1β (+3953) polymorphisms in Koreans compared with Caucasians. This study provides the first comprehensive report on the IL-1 cluster alleles in the Korean population. These results could provide a valuable reference for inflammatory disease and future disease association studies in Koreans.

References
4. Humre M, Santtila S. IL-1 receptor antagonist (IL-1Ra) plasma levels are co-ordinately regulated by both IL-1Ra and IL-1β genes. Eur J Immunol 1998;28:2598–602.

<p>| Table 1. Allelic frequencies of IL-1 polymorphisms in several ethnic populations. |
|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|</p>
<table>
<thead>
<tr>
<th>Ethnic group</th>
<th>n</th>
<th>Allele 1</th>
<th>Allele 2</th>
<th>Allele 3</th>
<th>Allele 4</th>
<th>Allele 5</th>
<th>IL-1α allele 2</th>
<th>IL-1β allele 2</th>
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</thead>
<tbody>
<tr>
<td>Koreans</td>
<td>640</td>
<td>0.917</td>
<td>0.060</td>
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<td>160</td>
<td>0.956</td>
<td>0.031</td>
<td>0.006</td>
<td>0.006</td>
<td>0.001</td>
<td>0.11</td>
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</tr>
<tr>
<td>Taiwanese Chinese</td>
<td>145</td>
<td>0.931</td>
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<td>0.003</td>
<td>0.001</td>
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<tr>
<td>United Kingdom</td>
<td>70</td>
<td>0.736</td>
<td>0.214</td>
<td>0.036</td>
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<td>American Caucasians</td>
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<td>0.740</td>
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<td>0.003</td>
<td>0.003</td>
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</tr>
</tbody>
</table>

* a,b,c All comparisons of frequencies between Koreans and other ethnic groups were performed by the χ² test (two-sided): *P < 0.05; **P < 0.01; ***P < 0.001.
Detection of Hereditary Persistence of α-Fetoprotein by Conformation-sensitive Gel Electrophoresis Analysis

To the Editor:

The concentration of human α-fetoprotein (AFP; MIM 104150) is used as a marker for several diseases in both adults and children, and it is also systematically measured in pregnant women as a marker of defects in the foetus.

In 1983, a case was discovered of a woman with high AFP expression that was shown to be attributable to a benign autosomal dominant genetic trait, hereditary persistence of AFP (HPAFP) (1). This syndrome shows high expression of AFP, but there is no association with any pathology. Failure to recognize HPAFP can lead to unsuitable treatments. For example, a 20-month-old child with HPAFP underwent surgery for a testicular germ cell tumor (2).

In one family, all affected members exhibited an identical haplotype: a heterozygous G→A substitution (3) at position −116 of the 5′-flanking region of the AFP gene. The same haplotype was also reported in another HPAFP family (4). The frequency of this anomaly is unknown because of the paucity of reported cases. As it is an autosomal dominant genetic trait, the routine inclusion of a test for HPAFP should be seriously considered in pregnant women and patients with high AFP concentrations to prevent inappropriate treatment decisions.

We show that conformation-sensitive gel electrophoresis (CSGE) can detect the G→A mutation in a possibly affected case of HPAFP.

Seventeen DNA samples from members of a family with HPAFP (4), with their mutational analyses carried out by sequencing in our laboratory, were used in this study. This familial study was performed with the formal consent of all members of the family, who were previously informed of the aim of the study.

The promoter region of interest was amplified from genomic DNA; the PCR product was 260 bp in length. The PCR amplifications were done as indicated in the Data Supplement that accompanies the online version of this letter at http://www.clinchem.org/content/vol49/issue12/. The conditions for CSGE analysis were essentially the same as described previously (5). The electrophoresis was performed in a SQ3 standard manual sequencer (Amersham Biosciences).

The results of the CSGE analysis of six members of the HPAFP family are shown, according to pedigree, in Fig. 1. Aberrant bands in the DNA samples corresponded to affected members, whereas only one band was obtained from unaffected members. The extra band corresponded to the presence of the G→A mutation located in the promoter region of the AFP gene at −116 bp.

To exclude the HPAFP trait in those patients with high AFP, we propose the application of CSGE to rapidly and efficiently detect the heterozygous G→A substitution in the AFP gene.

This research was supported in part by the Fondo de Investigación Sanitaria (FIS PI021345). We are most grateful to the proband and her relatives for generously participating in this research. Dr. J. R. Blesa is an associate researcher of the Fundación Valenciana de Investigaciones Biomédicas (FVIB). M. L. Lacalle is a predoctoral fellow of FVIB.

Fig. 1. CSGE results for six members of the HPAFP family, two with normal concentrations of AFP and four with increased AFP.

(A) pedigree of the HPAFP family showing the first and second generations. a, age. The numbers below age indicate the AFP concentrations (μg/L). Arrow indicates the proband. The AFP concentration shown for the proband is the mean of five assays. (B) CSGE analysis of AFP PCR products. The unaffected members show one band (a), whereas the affected members show two bands corresponding to the homoduplex (a) and heteroduplex (b) forms. The bands in the samples of the affected members show lower intensities than the single band from unaffected members, indicating the presence of hetero- and homoduplex forms.

References