The IL-1B Genetic Polymorphism Is Associated with Aspirin-Induced Peptic Ulcers in a Korean Ethnic Group

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Background/Aims: Single nucleotide polymorphisms (SNPs) are associated with aspirin-induced peptic ulcers. However, SNPs of specific genes vary among races, and data regarding SNPs in the Korean population are scarce. In this study, we aimed to investigate the relationships between SNPs of the COX-1, IL-1β, IL-1RN, and TNF genes and aspirin-induced peptic ulcers, as pilot research in a Korean population.

Methods: Patients who had been taking low-dose aspirin (100 mg) for at least 4 weeks were prospectively enrolled. DNA was extracted from whole blood, and DNA sequencing was subsequently performed.

Results: A total of 48 patients were enrolled (23 peptic ulcer patients vs 25 nonulcer controls). Three exon SNPs (IL-1β -581C/T [rs1143627], IL-1β -1061C/T [rs16944], and IL-1RN -1129 [rs4251961]) and one intron SNP (IL-1β IVS2+242C/T) were significantly different between the two groups. On the multivariate analysis after adjustments for age and sex, the CC/CT genotypes of IL-1β -581C/T, and the CT/TT genotypes of IL-1β -1061C/T were positively associated with aspirin-induced peptic ulcers (odds ratio [OR], 4.6, 95% confidence interval [CI], 1.054 to 20.303, p=0.04; OR, 4.6, 95% CI, 1.054 to 20.303, p=0.04).

Conclusions: The IL-1β -581C/T and IL-1β -1061C/T genotypes may be associated with low-dose aspirin-induced peptic ulcers in a Korean ethnic group.

Key Words: Aspirin; Polymorphism, single nucleotide; Peptic ulcer

INTRODUCTION

Aspirin is used for the prevention of cardiovascular and cerebrovascular diseases worldwide. However, aspirin is also known to have adverse effects on the gastrointestinal (GI) tract including peptic ulcer disease and bleeding. The annual incidence of peptic ulcers induced by aspirin is approximately 5% to 10%,1-3 and the prevalence is approximately 10%.2 The presence of peptic ulcers can induce a number of serious adverse effects including GI bleeding that may result in death in some patients.4 There are a number of risk factors for the development of peptic ulcers secondary to aspirin use including advanced age, Helicobacter pylori infection, concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin dose, and a past medical history of peptic ulcers.2,5 Additionally, genetic predisposition is also associated with aspirin-induced peptic ulcer.6-8 In order to prevent peptic ulcer in patients taking low-dose aspirin, concomitant use of a proton pump inhibitor is often initiated. However, this strategy does not help to identify patients with a high risk of developing peptic ulcers. Therefore, individual genetic susceptibility may be an important factor in identifying patients at highest risk for peptic ulcer.

Several studies have shown an association between single nucleotide polymorphisms (SNPs) of several genes and aspirin-induced peptic ulcer. These include SNPs of the COX-1, CYP2C9, IL-1β, IL-1RN, and TNF-α genes.9 However, there is racial diversity in these genes, and thus the significance of SNPs as related to specific diseases is also different among races.

We hypothesized that, if patients could be identified as having a genetic predisposition for peptic ulcer before starting aspirin therapy, the development of peptic ulcer could be prevented...
by concomitant use of proton pump inhibitors or alternative antiplatelet agents. Because SNPs of the COX-1, IL-1β, IL-1RN, TNF genes, and SNPs specifically associated with peptic ulcer are still not well understood, we investigated the prevalence of SNPs of the COX-1, IL-1β, IL-1RN, and TNF genes in Korean adults and evaluated the associations between these SNPs and aspirin-induced peptic ulcer in this population, as a pilot research.

MATERIALS AND METHODS

1. Subjects

From May 2011 to December 2012, we performed a prospective case-control study of DNA sequence analysis on 48 patients who took low-dose aspirin and underwent esophagogastroduodenoscopy (EGD). All subjects had been taking low-dose aspirin (100 mg) for at least 4 weeks prior to enrollment, and each subsequently underwent EGD at Myongji Hospital in Goyang, Korea. They were divided into two groups based on endoscopy results including a nonulcer control group (n=25) with no evidence of peptic ulcer and a peptic ulcer group (n=23) that showed evidence of gastric or duodenal ulcer. In this study, a peptic ulcer was defined as a mucosal defect ≥5 mm in diameter based on endoscopic findings. Exclusion criteria included history of peptic ulcer, history of NSAID or steroid use, history of clopidogrel use, history of upper GI surgery, pregnancy, chronic renal failure, history of proton pump inhibitor or H2 receptor blocker use, history of congenital disease, history of autoimmune disease, and malignant disease of the upper GI tract including esophageal or gastric cancer. Blood obtained from subjects was stored in ethylenediaminetetraacetic acid-containing tubes at -40°C and was subsequently sent to a laboratory facility for genotyping. SNP data were compared between groups. Informed consent was obtained from all subjects. This study was approved by the Institutional Review Board (IRB number: 10-076) at Myongji Hospital and all patients gave written informed consent to participate in this study.

2. DNA sequencing

Polymerase chain reaction (PCR) was used to amplify 11 fragments of the IL-1β gene, 10 fragments of the IL-1RN gene, 15 fragments of the COX-1 gene, and eight fragments of the TNF gene. The final volume of the PCR was 10 μL, consisting of 10 ng of DNA, 0.5 uM of each primer pair, 0.25 mM deoxyribonucleoside triphosphates, 3 mM MgCl2, 1 μL 1x reaction buffer, and 0.25 unit Taq DNA polymerase (Intron Biotechnology, Seongnam, Korea). The PCR conditions used were as follows: initial denaturation at 94°C for 5 minutes, followed by 35 cycles of denaturation at 94°C for 30 seconds, annealing at 60°C to 65°C for 30 seconds, initial extension at 72°C for 30 to 60 seconds, and final extension at 72°C for 10 minutes. The PCR products were purified using a MultiScreen 384-PCR filter plate (Millipore, Billerica, MA, USA). The purified products were then sequenced using a BigDye Terminator cycle sequencing kit (Applied Biosystems, Foster City, CA, USA) and an ABI 3730xl automated sequencer (Applied Biosystems). The sequencing primers were the same as those used for PCR amplification. Mutation analyses were performed using Phred, Phrap, Consed, Polyphred 5.04 software (http://droog.gs.washington.edu/polyphred).

3. Statistical analysis

Genotype and allele frequencies were compared between groups using chi-square or Jonckheere-Terpstra test, as appropriate. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using multiple logistic regression with adjustments for age and sex in order to evaluate the significance of the associations between SNPs and disease status. Data analysis was performed using SAS software version 9.1.3 (SAS Inc., Cary, NC, USA). All statistical tests were two-tailed, and p-values <0.05 were considered to be statistically significant.

RESULTS

1. Baseline characteristics

Between January 2011 and January 2013, a total of 48 patients were enrolled in this study, including 23 subjects with peptic ulcer and 25 nonulcer control subjects (Table 1). The mean ages of the peptic ulcer group and nonulcer control group were 66.22±10.85 years and 62.48±9.01 years, respectively (p=0.199). The percentages of male patients in the peptic ulcer group and nonulcer control group were 60.9% and 48%, respectively (p=0.371). On EGD examination, peptic ulcers were found to be located in the stomach (91.3%) and duodenum (8.7%). Thirteen patients (56.5%) had a single ulcer and 10 patients (43.5%) had multiple ulcers (≥2).

Table 1. Baseline Characteristics of All Subjects (n=48)

| Characteristic | Peptic ulcer | Nonulcer control | p-value |
|---------------|-------------|------------------|---------|
| No. of patients | 23 (47.9)   | 25 (52.1)        | -       |
| Age, yr       | 66.22±10.85 | 62.48±9.01       | 0.199   |
| Sex, male/female | 14/9      | 12/13          | 0.371   |
| Ulcer location | -           | -                |         |
| Gastric ulcer | 21 (91.3)   | -                | -       |
| Active or healing stage | 18        | -                |         |
| Scar          | 5           | -                |         |
| Duodenal ulcer | 2 (8.7)    | -                |         |
| Active or healing stage | 1         | -                |         |
| Scar          | 1           | -                |         |
| Multiple ulcer (≥2) | 10 (43.5)  | -                |         |
| Helicobacter pylori infection | 6 (26.1) | -                |         |

Data are presented as number (%) or mean±SD.
### Table 2. Single Nucleotide Polymorphisms of IL-1RN, IL-1β, COX-1, and TNF

| SNP ID | SNP name | SNP ID | SNP name | SNP ID | SNP name | SNP ID | SNP name |
|--------|----------|--------|----------|--------|----------|--------|----------|
| 1      | New      | -1126G/T | New      | -2369G/A | New      | -1837G/T | rs13306710 | IVS3+104A/G |
| 2      | New      | 554G/A | New      | -2091~~-2088CT/CTCTDEL | New      | -1622G/A | rs1799724 | -1037C/T |
| 3      | rs11677397 | -515C/T | New      | IVS3-25G/A | New      | -1337A/G | rs1799964 | -1211C/T |
| 4      | rs16065 | IVS1+26C/T | New      | G46G | New      | -1336A/C | rs1800610, rs80267959 | IVS1+123A/G |
| 5      | rs17042923 | -206C/T | New      | IVS4+509C | New      | IVS7+145G/A | rs1800629 | -488A/G |
| 6      | rs22232354 | IVS4+94G/T | New      | -1468G/C | New      | IVS8+136C/T | rs1800630, rs4645836 | -1043A/C |
| 7      | rs2234676 | -168A/G | New      | -625T/G | New      | -2084G/C | rs3093547 | -1671A/T |
| 8      | rs2234677 | -87A/G | New      | E101E | New      | -1266G/A | rs3093661, rs77222141 | IVS1+54A/G |
| 9      | rs2234678 | -31A/G | New      | IVS5+204G/A | New      | IVS3+265T/A | rs3093664 | IVS3+51A/G |
| 10     | rs2234679 | -12C/G | rs1143623 | -2023C/G | New      | IVS4+52T/C | rs361525 | -418A/G |
| 11     | rs315951 | 681C/G | rs1143625 | -1553A/G | New      | A526S | rs4248160 | -826A/G |
| 12     | rs315952 | S133S | rs1143627 | -581C/T | rs10306117 | IVS2+177C/T | rs4248161 | -752A/C |
| 13     | rs380092 | IVS5+166A/T | rs1143629 | IVS2+242C/T | rs10306227 | IVS3+206A/G | - | - |
| 14     | rs419598 | A60A | rs1143633 | IVS4+64A/G | rs1236913 | R8W | - | - |
| 15     | rs423904 | IVS4+21C/T | rs1143634 | F105F | rs12555242 | IVS5+42C/T | - | - |
| 16     | rs4251961 | -1129C/T | rs1143639 | IVS6+76A/G | rs133044 | -1676C/T | - | - |
| 17     | rs4251967 | -628C/G | rs1143640, rs34159283, rs41294738 | IVS6+111~~+113T/TTTDEL | rs2282169 | IVS3-16C/G | - | - |
| 18     | rs4251968 | -379A/C | rs114364 | IVS6-152A/G | rs3215925 | IVS7+14-JA | - | - |
| 19     | rs4251986 | IVS1-105C/G | rs11944 | -1061C/T | rs3482788 | Q41Q | - | - |
| 20     | rs4252013 | IVS4+132C/T | rs917347 | -400~~-385CT/DEL | rs3482798 | IVS7-45C/T | - | - |
| 21     | rs432014 | IVS4-43C/T | - | - | rs5788 | G213G | - | - |
| 22     | rs442710 | IVS4+158A/G | - | - | rs61757787 | D248G | - | - |
| 23     | rs446433 | IVS4+32C/A | - | - | rs6478565 | IVS8-93A/G | - | - |
| 24     | rs451578 | IVS4-65A/G | - | - | - | - | - | - |
| 25     | rs454078 | IVS5+59A/T | - | - | - | - | - | - |
| 26     | rs45462902 | -1022A/G | - | - | - | - | - | - |
| 27     | rs45507693 | T127A | - | - | - | - | - | - |
| 28     | rs495282 | IVS4+53C/G | - | - | - | - | - | - |
| 29     | rs495410 | IVS4+97A/C | - | - | - | - | - | - |
| 30     | rs878972 | IVS2+8A/C | - | - | - | - | - | - |
| 31     | rs928940 | IVS1-148G/T | - | - | - | - | - | - |

SNP, single nucleotide polymorphism.
2. SNPs of the COX-1, IL-1β, IL-1RN, and TNF genes

All SNPs of the four genes identified in this study are shown in Table 2. The IL-1RN gene had 31 SNPs, of which two (-1126G/T and 554G/A) were newly identified. The IL-1β gene had 22 SNPs, of which 9 (-2369G/A, -2091--2088CT/CTCTDEL, IVS3-25G/A, G46G, IVS4-509T/C, -1468G/C, -625T/G, E101E, and IVS5+204G/A) were newly identified. The COX-1 gene had 23 SNPs, of which 11 (-1837G/T, -1622G/A, -1337A/G, -1336A/C, IVS7+145G/A, and IVS8+136C/T) were newly identified. The TNF gene had 12 identified SNPs.

3. Associations between SNPs and peptic ulcer

Four SNPs had significantly different frequencies in the peptic ulcer and nonulcer control groups: IL-1RN -1129C/T (rs4251961), IL-1β -581C/T (rs1143627), IL-1β -1061C/T (rs16944), and IL-1β IVS2+242C/T (rs1143629). For IL-1β -581C/T, the TT genotype was less frequent in the peptic ulcer group than the nonulcer control group (13% vs 44%, p=0.018) (Table 3). For IL-1β -1061C/T, the CC genotype was less frequent in the peptic ulcer group than the nonulcer control group (13% vs 44%, p=0.018). For IL-1β IVS2+242C/T, the TT genotype was less frequent in the peptic ulcer group than the nonulcer control group (13% vs 44%, p=0.018). Finally, for IL-1RN -1129C/T, the TT genotype was more frequent in the peptic ulcer group than the nonulcer control group (96% vs 68%, p=0.011).

Logistic regression analysis for adjustment of age and sex was performed in three exon SNPs (Table 4). The IL-1β -581 genotype was significantly associated with peptic ulcer. The CT and CC genotype had an OR of 4.625 (95% CI, 1.054 to 20.303; p=0.042) for the peptic ulcer group, as compared with the TT genotype. The IL-1β -1061 genotype was also significantly associated with peptic ulcer, and the CT and TT genotypes had an OR of 4.625 (95% CI, 1.054 to 20.303; p=0.042) for the peptic ulcer groups compared with the CC genotype. The IL-1RN -1129 genotype was not associated with peptic ulcer after adjustment for age and gender. The CT and CC genotypes had an OR of 0.115 (95% CI, 0.013 to 1.049; p=0.055) for the peptic ulcer group.

DISCUSSION

Our study is the first to investigate SNPs of the COX-1, IL-1β, IL-1RN, and TNF genes in Korean subjects, identifying 23, 22, 31, and 12 SNPs, respectively, including 22 novel SNPs. In addition, we aimed to reveal the significant associations between specific genotypes and aspirin-induced peptic ulcer disease. Of a total of 88 SNPs, two of the IL-1β gene and one of the IL-1RN gene were significantly associated with peptic ulcer. C carriers of IL-1β -581 and T carriers of IL-1β -1061 were significantly more frequently associated with peptic ulcer, and there was a trend for association between T carriers of IL-1RN -1129 and peptic ulcer, though this was not significant after adjustment for age and sex.

Aspirin irreversibly inhibits cyclooxygenase-1 (COX-1) in platelets. Genetic polymorphisms of the COX-1 gene can affect aspirin-induced inhibition of prostaglandin synthesis, which

| SNP       | SNP ID  | MAF   | Peptic ulcer (n=23) | Nonulcer control (n=25) | p-value | Functional consequence |
|-----------|---------|-------|--------------------|-------------------------|---------|------------------------|
| IL-1β -581C/T | rs1143627 | 0.4479 | 3 (13.04) | 11 (44.0) | 0.0184* | Upstream variant 2KB   |
|           |         |       | CT 15 (65.22) | 10 (40.0) |         |                       |
|           |         |       | CC 5 (21.74) | 4 (16.0) |         |                       |
| IL-1β -1061C/T | rs16944    | 0.4479 | 3 (13.04) | 11 (44.0) | 0.0184* | Upstream variant 2KB   |
|           |         |       | CT 15 (65.22) | 10 (40.0) |         |                       |
|           |         |       | TT 5 (21.74) | 4 (16.0) |         |                       |
| IL-1β IVS2+242C/T | rs1143629    | 0.4583 | 3 (13.04) | 11 (44.0) | 0.0184* | Intron variant        |
|           |         |       | CT 15 (65.22) | 9 (36.0)  |         |                       |
|           |         |       | CC 5 (21.74) | 5 (20.0)  |         |                       |
| IL-1RN -1129C/T | rs4251961    | 0.1042 | 22 (95.7) | 17 (68.0) | 0.0116* | Upstream variant 2KB   |
|           |         |       | CT 1 (14.4)  | 7 (28.0)  |         |                       |
|           |         |       | CC 0         | 1 (4.0)   |         |                       |

Data are presented as number (%).
SNP, single nucleotide polymorphism; MAF, minor allele frequency.
*Chi-square test with dominant model; †Jonckheere-Terpstra test with allele model.
eventually can result in the development of peptic ulcer. Several SNPs of the COX-1 gene are known to have a significant relationship with peptic ulcer. In a U.S. study, two SNPs of COX-1, A-842G and C50T, were found to be associated with aspirin-induced peptic ulcer. The heterozygous A-842G/C50T haplotype inhibits prostaglandin synthesis by acetylsalicylic acid to a greater degree than does the homozygous haplotype. However, the opposite results have also been reported for A-842G/C50T. A recent systematic review shows no significant association between these SNPs and aspirin resistance. In addition, different results have been obtained in patients of other races. In a Japanese study, the A-842T/C50T polymorphism of the COX-1 gene was not detected in any of the 480 patients studied. Similarly, this polymorphism was absent in 323 Chinese subjects. Variable results have been reported within races as well. One study in a Japanese population reported that -1676T alleles of the COX-1 gene promoter were a significant risk factor for NSAID-induced ulcers, while another Japanese study reported that -1676T alleles are not associated with aspirin-induced peptic ulcer. In our study, a total of 23 SNPs of the COX-1 gene were found, none of which were associated with aspirin-induced peptic ulcer.

The biological role of IL-1β is to enhance the inflammatory response, and the cytokine IL-1β induces the expression of other proinflammatory cytokine genes including TNF-α, IL-2, IL-6, and IL-12. In addition, IL-1β is an inhibitor of gastric acid. Polymorphisms of IL-1β -511 (rs16944) and -31 (rs1143627) have been shown to be significantly associated with aspirin-induced peptic ulcer in Japanese patients. These findings are consistent with those of our study, in which IL-1β -1061T (rs16944), which is the same SNP as IL-1β -511, was significantly associated with aspirin-induced peptic ulcer. In addition, IL-1β -581C (rs1143627), which is the same as IL-1β -31, was significantly associated with aspirin-induced peptic ulcer. T carriers of IL-1β -511 have an associated increased production of IL-1β, which enhances inflammation of the gastric mucosa. In our study, T carriers of IL-1β -1061T (IL-1β -511) had a 4.6-fold increased risk of low-dose aspirin-induced peptic ulcer. In the future, screening for SNPs of IL-1β prior to initiating aspirin therapy could help to identify patients at high risk for ulcer development and bleeding. These individuals should also be administered a prophylactic proton pump inhibitor, although this assumption requires further investigation.

The IL-1RN gene encodes the IL-1R antagonist (IL-1RA), which exhibits anti-inflammatory properties by competitive inhibition of IL-1 receptors. One study reported that the minor allele of IL-1RN -1129 (rs4251961) is associated with decreased IL-1RA production in healthy adults. The C allele of IL-1RN -1129 reduces IL-1RA, which is associated with an increased IL-1β level that in turn inhibits gastric acid secretion. These

| Table 4. Odds Ratios of Genotypes in the Peptic Ulcer Group (n=23) and Nonulcer Control Group (n=25) |
|-------------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| SNP ID | SNP | Unadjusted | Adjusted* | Unadjusted | Adjusted* |
|-------|------|------------|-----------|------------|-----------|
| OR (95% CI) | p-value | OR (95% CI) | p-value |
|-------|------|------------|-----------|------------|-----------|
| IL-1β -581C/T | rs1143627 | TT | 1 | 1 | 1 | 1 |
|       |       | CT | 5.5 (1.219–24.813) | 0.022 | 4.999 (1.068–23.394) | 0.040 |
|       |       | CC | 4.583 (0.733–28.646) | 0.100 | 4.297 (0.653–28.285) | 0.129 |
|       |       | TT (dominant) | 1 | 1 | 1 | 1 |
|       |       | CT and CC | 5.238 (1.231–22.822) | 0.024 | 4.625 (1.054–20.303) | 0.042 |
| IL-1β -1061C/T | rs16944 | CC | 1 | 1 | 1 | 1 |
|       |       | CT | 5.5 (1.219–24.813) | 0.022 | 4.999 (1.068–23.394) | 0.040 |
|       |       | TT | 4.583 (0.733–28.646) | 0.100 | 4.297 (0.653–28.285) | 0.129 |
|       |       | CC (dominant) | 1 | 1 | 1 | 1 |
|       |       | CT and TT | 5.238 (1.231–22.822) | 0.024 | 4.625 (1.054–20.303) | 0.042 |
| IL-1RN -1129C/T | rs4251961 | TT | 1 | 1 | 1 | 1 |
|       |       | CT | 0.11 (0.012–0.985) | 0.025 | 0.135 (0.014–1.272) | 0.080 |
|       |       | CC | - | - | - | - |
|       |       | TT (dominant) | 1 | 1 | 1 | 1 |
|       |       | CT and CC | 0.097 (0.011–0.849) | 0.035 | 0.115 (0.013–1.049) | 0.055 |

SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval.
*Logistic regression analysis was applied to adjust age and sex.
findings are consistent with our results, in that the TT genotype of \textit{IL-1RN} -1129 was found in 95.7\% of patients with peptic ulcer, although this was not statistically significant after adjustment for age and sex. Further investigation of \textit{IL-1RN} -1129 as a potential risk factor for low-dose aspirin-induced peptic ulcer would be valuable.

Our study has several limitations. First, our sample size was too small and thus may not be representative of general genetic trends in the Korean population. In order to find the associations between SNPs and low dose aspirin induced peptic ulcer, we performed the full DNA sequence analysis of these target genes and proposed the several candidates of SNPs related to aspirin induced ulcer. Second, the functional effect of these SNPs are still doubtful. The functional consequences of \textit{IL-1β} -581C/T (rs1143627) and \textit{IL-1β} -1061C/T (rs16944) are known to the "upstream variant 2KB" (Table 3). There is a possibility that they may affect the promoter activity by the differential binding affinity of nuclear proteins, however pathogenic effect of them has not yet been established. Third, the presence of \textit{H. pylori} is questionable in this study. One previous study reported that \textit{H. pylori} infection does not affect peptic ulcer induced by low-dose aspirin;\textsuperscript{19} however, \textit{H. pylori} is regarded as a major cause of peptic ulcer disease and account for a large proportion of peptic ulcers in Korea. Therefore, further investigation including \textit{H. pylori} infection and a functional assay for these SNPs are warranted. Even with these noted limitations, however, this study is the first to investigate the relationships between SNPs and aspirin-induced peptic ulcer in Korean patients, as well as the first to suggest that SNPs may be different according to the population studied.

In conclusion, Korean adults with the the C allele of \textit{IL-1β} -581C/T or the T allele of \textit{IL-1β} -1061C/T had an increased risk of low-dose aspirin-induced peptic ulcer. The polymorphism \textit{IL-1RN} -1129 might also be associated with peptic ulcer, although this trend was not significant. These SNPs may become potential biomarkers for identifying patients at high risk for aspirin-induced peptic ulcer, although further investigation and validation are needed.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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